Medical Biomaterials
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Lecture - 03
History

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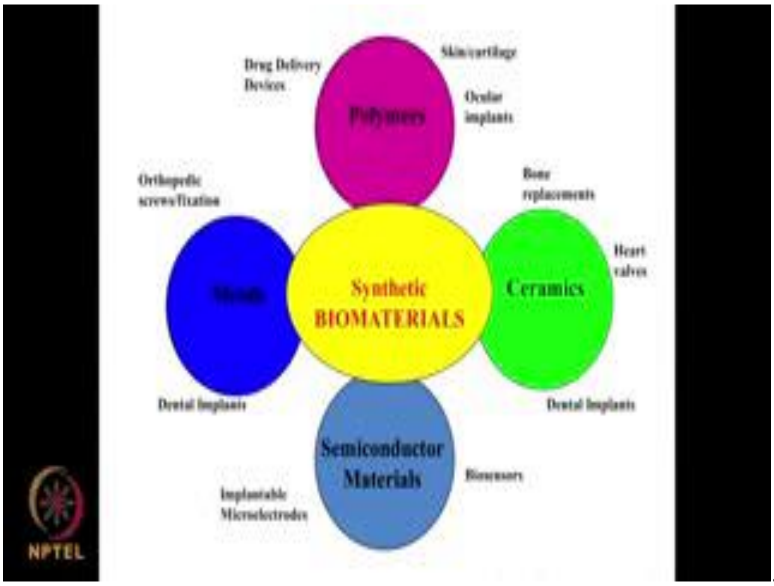

Welcome to the course on Medical Biomaterials. Hello everyone, we will continue on the historical prospective of biomaterials. As I mentioned in the previous class we have biomaterials made up of synthetic materials, it could be metals, it could be polymers, it could be ceramics, it could be semiconductor material, and there could be blends of all these. In addition, we also have natural materials; nowadays, quite lot of interest is being shown on natural biopolymers, which are produced by bacteria or from the plant source.

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So, let us look at history of biomaterials, this takes backs to almost 2000 or even 3000 years back, the Chinese, the Romans, the Indians used gold, silver and mercury in dentistry. They used to have a type of teeth you know even wood teeth, ivory teeth and so on actually. And then aseptic surgery was even practiced almost about 120-50 years back. And after a fracture even bone plates were implanted as early as 1900. Then in the year of 20th century A.D synthetic polymers were started being used in biomaterials. Then poly methyl methacrylate was getting popular are the most popular polymers because it was used in the World War 2, and hence they were also used in biomaterials.

Another material, which was which another polymer, which was very popular was polyester, because polyester was used in many industrial applications as well as in everyday clothing, so that also went into the biomaterials. Then in the 60s polyethylene started coming into sometimes combination of metals coated with polymers, so that especially in hip joints one could have better flow properties one could have better moving properties especially in the joints.

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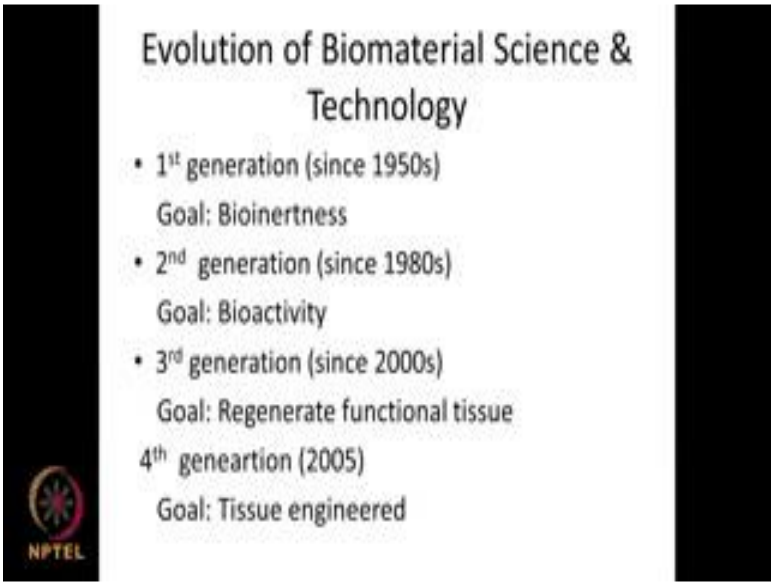

So, the biomaterial could be thought of as four stages or four generations. The very, very early biomaterial the general feeling was the material has to be inert it should not cause any adverse reaction to the host that is all. So, the whole goal was looking at material which are completely inert. The second generation of biomaterials was that material should be active that means, the whole system should be able to respond to the material and the material should be conducive to the whole system. So, the second generation of biomaterials which came around 80s were thought of in terms of bioactivity.

The third generation of biomaterial looking at regenerating functional tissues that was the third generation of biomaterials using nano composites, nano materials and so on. And the fourth generation of materials they started thinking in terms of tissue engineering that means, can I make a different types of tissues outside in the lab and bring it in and use it inside. Can the tissues grow or cells grow on top of these biomaterials without differentiating as a foreign body, so that is how the evolution of biomaterial started, and that is how the thinking with respect to the biomaterials usage and research also started actually.

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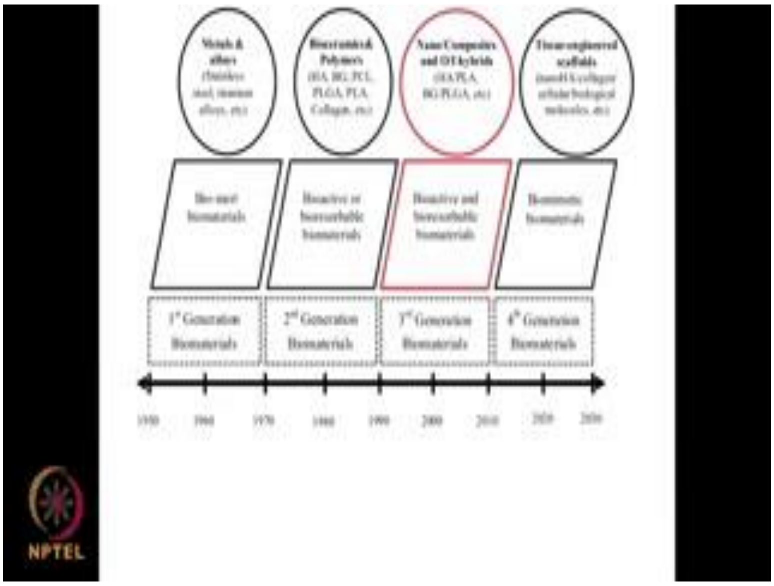

So, if you look at this particular a figure it nicely gives you an idea. So, the first generation I would say of biomaterials we are talking in terms of inert materials. The second generation of bioactive materials bioresorbable that means, materials which will completely dissolve or get absorbed. And the third was bioactive and bioresorbable biomaterials and involving nano composites and hybrid materials. The fourth was biomimetic biomaterials that means, like a (Refer Time: 04:37), scaffolds and so on that is how the biomaterials started coming. And as you can see it is hardly 80 year old research started from 1950s going right up to 2020s and 30s. Although biomaterial was used as I showed you in the previous slide as old as Chinese and Indians and Romans, but that was more of ad hoc and it was just practiced.

So, in the first generation of biomaterials, they were talking about stainless steel, titanium alloys and so on which was very inert, it never caused any adverse reaction to the host. The second generation they started using bioceramics, they started using polymeric material, hydroxyapatite, then polymer polymers like polycaprolactones then poly lactic acids, collagen, poly lactic glycolic acid and so on. The third generation involved lot of nano composites, it was hybrid combinations of polymers and metals, combinations of ceramics and metals and s, on actually, so hydroxyapatite, poly lactic acid and so on.

The fourth generation where we want tissues to grow on the material, so that it does not differentiate whether it is the host natural system or a synthetic system; so we had nano hydroxyapatite, collagen, cellular biological molecules like proteins immune modulators, growth factors. So, the tissues started growing on that. So, lot of research is being done on tissue engineering developing scaffolds, which will allow tissues to grow differentiate and then this scaffold may completely get bio adsorbed. So, the scaffold will completely disappear. So, this is the historical perspective of biomaterial I would say over the past 80 to 100 years.

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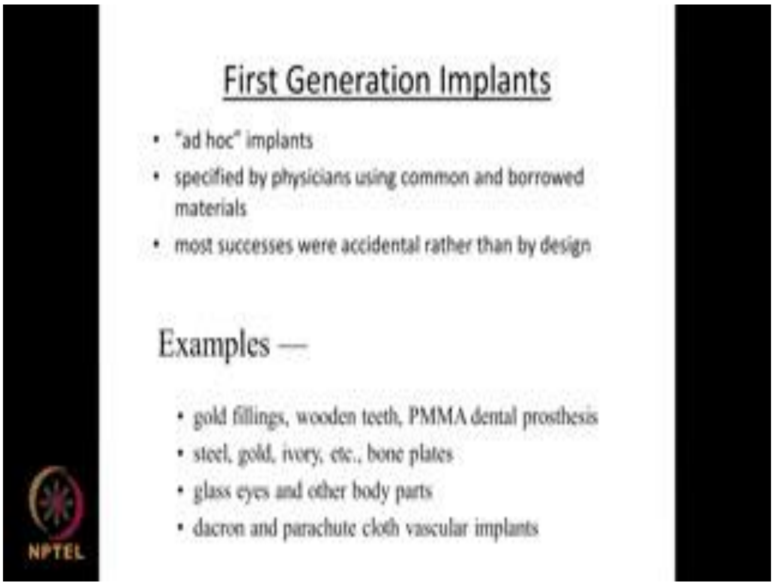

So, the first generation ad hoc implants. So, the physicians used common materials which are found around them or borrowed materials from engineering disciplines. So, it was more like accidental rather than design like gold fillings, like mercury or silver, wooden teeth, poly methyl methacrylate. So, lot of these natural materials were used glass eyes, when the eyes got destroyed due to accident or due to growth. Dacron, dacron like polyesters, parachute cloth, they were all used in vascular implants. So, they are more of accident rather than by design.

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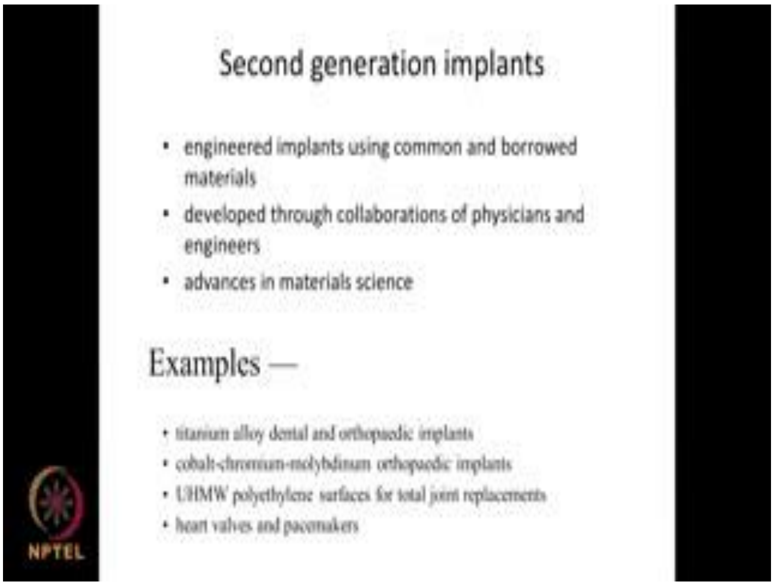

If you go to second generation, it is engineered. So, there is a collaboration between the physician and the medical practitioner. So, the medical practitioner would say what type of materials are desired. So, the engineers would modify certain structures. So, that we get the properties. So, there was lot of advance material science research being done, like use of titanium alloy, orthopedic implants, cobalt chromium molybdenum type of orthopedic implants ultra high molecular weight polyethylene surfaces heart valves. So, all these came under the second generation where there was a lot of collaboration between the physicians and the engineers.

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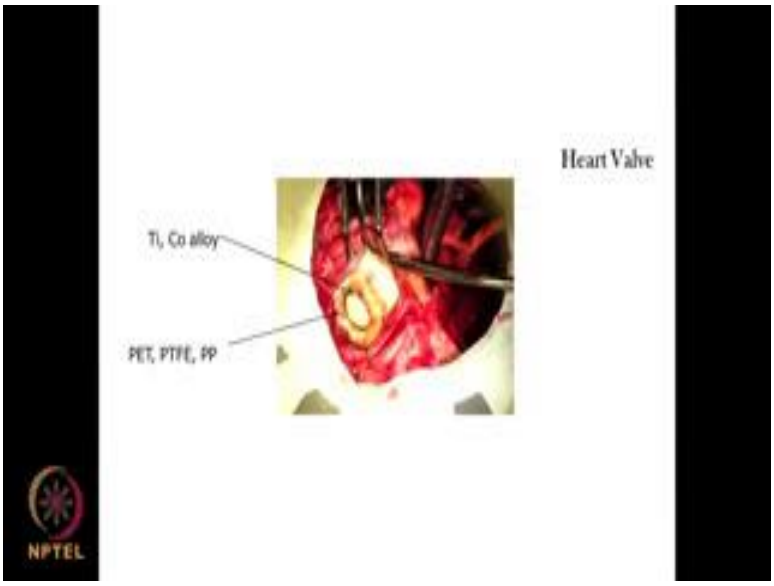

For examples, if you look at this heart valve, so it is got a titanium-cobalt alloy and then ring here titanium cobalt alloy. And here you have a poly teritalate and PTFE - polytetrafluoroethylene. So, it is a combination of two materials and they were all engineered, so that they will do their purpose.

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Or if you look at pure titanium cages, these are used for long bone segmental defect. So, if the bones have defects more than 2 inches, then you cannot just hope that it will cure by itself. So, they have to do some other ways and these are called long bone segmental defect and titanium cages are used to address these type of long bone segmental defect.

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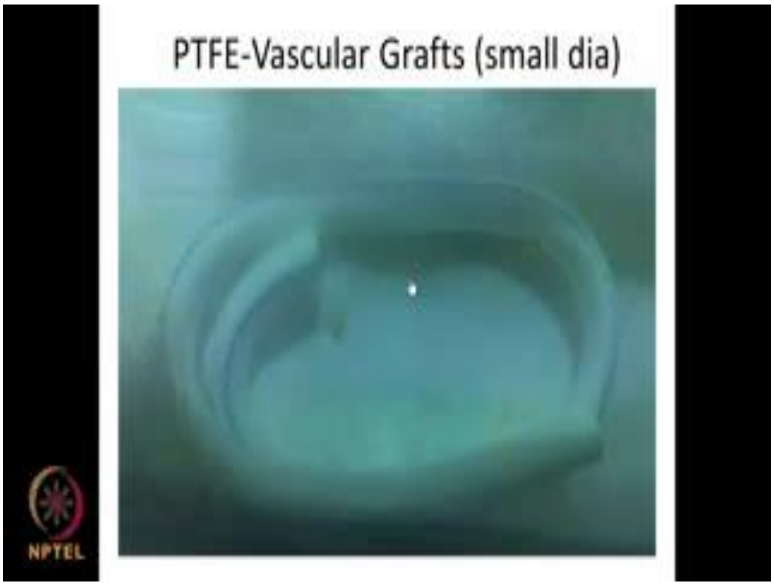

If you look at this, this is a polytetrafluoroethylene vascular grafts. These are small diameters vascular grafts. If the that is about 1 mm or something like that 1.5 mm; if you have 2 mm or 2.5 mm, we can use PTFE or we can use even polyesters. PTFEs are very, very inert and they can also be nicely designed for diameter of interest.

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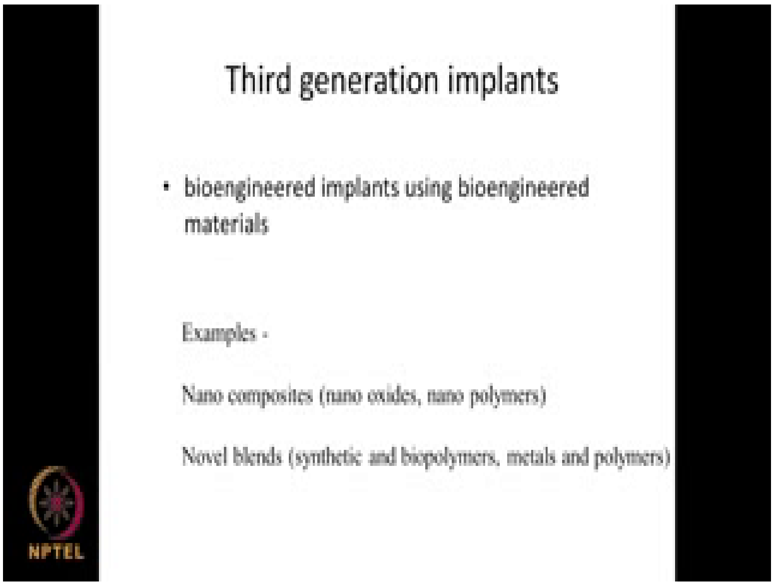

Now, if you look at third generation, they are bioengineered implants using bioengineered materials like nanocomposites like using of nanooxides, nanopolymers in drug delivery it releases the drug, when the nano scale material and then it gets completely biodegradable or novel blends like combination of synthetic and biopolymer or metal and polymers metal and biopolymers. So, combinations of many of these are very much engineered and bioengineered materials. So, they are mostly nano scale. So, they had good interaction with the host system.

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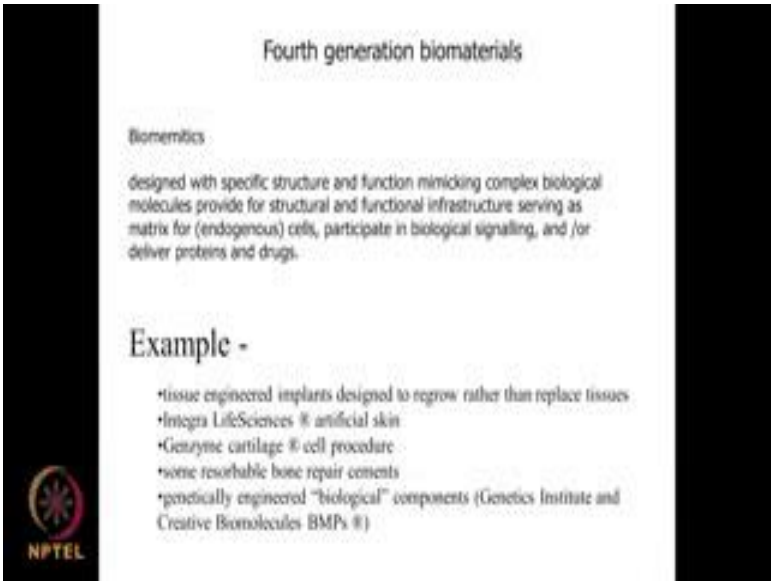

And you go to the fourth generation system, they general feeling is to have biomimetics material. This is a important word you will come across in biomaterials, biomimetic, it is designed with specific structure and function mimicking the biological molecules. So, in the human system, you are supposed to having proteins, you have many enzymes, you have peptides growth factors. So, the biomaterial you are designing should be mimeting these complex biological molecules, and they should provide the structure function infrastructure. They act as a matrix or a base for the cells to grow; they also get involved in biological signaling that means, you sometimes include signaling molecules, which are slowly released inflammatory molecules, which are slowly released so that certain actions take place.

So, you can help in delivering proteins we can use it for gene therapy you can use it for drug delivery and so on actually. So, four generation biomaterials are of recent origin and I think the biomaterial research is going in that direction. These are tissue engineer implants designed to regrow rather than replace tissues, artificial skins being looked at by this particular company. Looking at cell cartilage procedure, looking at bone repair cements they are resorbable bone repair cements. Genetically engineered biological components being researched by these company, so these are called the fourth generation biomaterials. They are biomimetics that means, they mimic the actual body part either in the form of acting as support or acting as a matrix for the cells to grow sometimes giving out biological signals sometimes giving out proteins, genes, drugs and so on actually. And finally, it may completely bioresorb and disappear these are called the four generation biomaterials.

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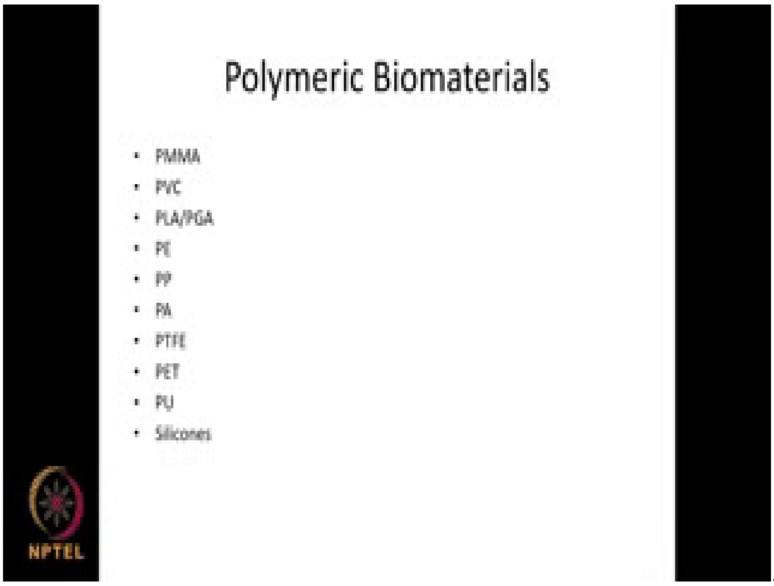

If you look at polymeric biomaterials, many polymers are used as biomaterials. And many of them are approved by the FDA - poly methyl methacrylate, polyvinyl PVC - polyvinyl chloride, PLA - poly lactic acid, poly glycolic acid, PE – polyester, PP – polypropylene, PA – polyacetate, polytetrafluoroethylene, polyester, polyurethane silicones. All these are biomaterials, which are used in different parts of the body and many of them have been approved by the FDA.

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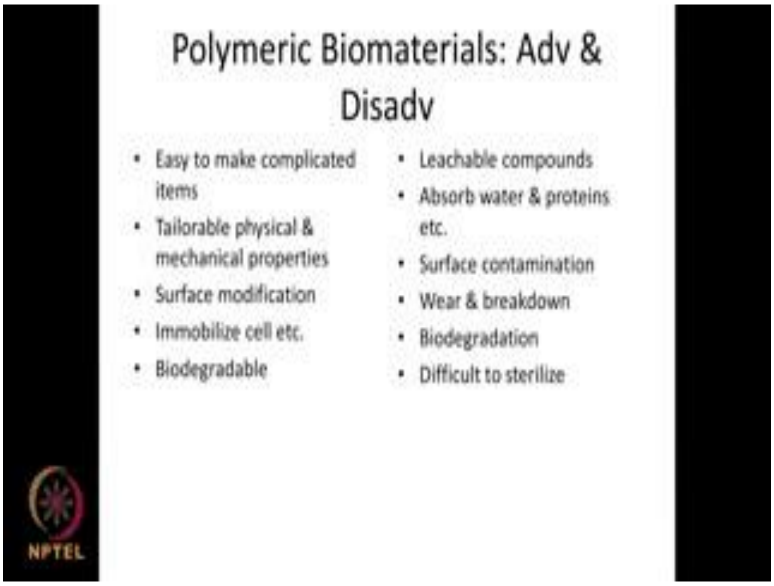

What are the advantages they are easy to make even complicated items could be made we can make it, so that we can tailor the physical and mechanical properties. So, I want a very soft material I can use a polymer I want to have a very hard material I want to have a very strong material like polycarbonate. So, we can nicely tailor we can do nice surface modification, so that the material is biocompatible with the whole system, the material does not cause adverse reaction with the plasma proteins. We can help the material as a scaffold for immobilizing cells; it can be made biodegradable.

If you want to have a biodegradable drug delivery system or if you want to have a biodegradable scaffold, you have to go for polymeric material. But what are the disadvantages leachable sometimes you know n reacted monomers may leach out sometimes, if it is a blend of two, three polymers some polymers may leach out which may be toxic. There is you might be knowing polycarbonate is made up of bisphenol a and diphenyl carbonate, and sometimes this bisphenol a leaches out which is known to have an indecorant disordering property. So, there is a worry about polycarbonate

If we will take poly methyl methacrylate, which is widely used in dental acrylic acid which may be in order of ppm or even very much smaller than that maybe leaching out very slowly which could be toxic so that is one disadvantage. They can absorb water and proteins. Sometimes, this is taken as advantage, sometimes it is taken as disadvantage, because they may absorb and they may swell which is good in some way because it has the water carrying purpose. Sometimes surface contamination can happen while handling oil or other material contamination, they can bear easily unlike metals they can break down because of UV or other gamma rays. They can biodegrade which is an advantage as well as which is disadvantage.

Suppose I am using an ultra high molecular weight polyethylene in joints. I do not want to biodegrade, whereas if I am using stent biodegradable stent, I want to degrade. So, this is advantage as well as disadvantage difficult to sterilize there are different sterilization procedures, which have to be adopted before the material is placed inside the body.

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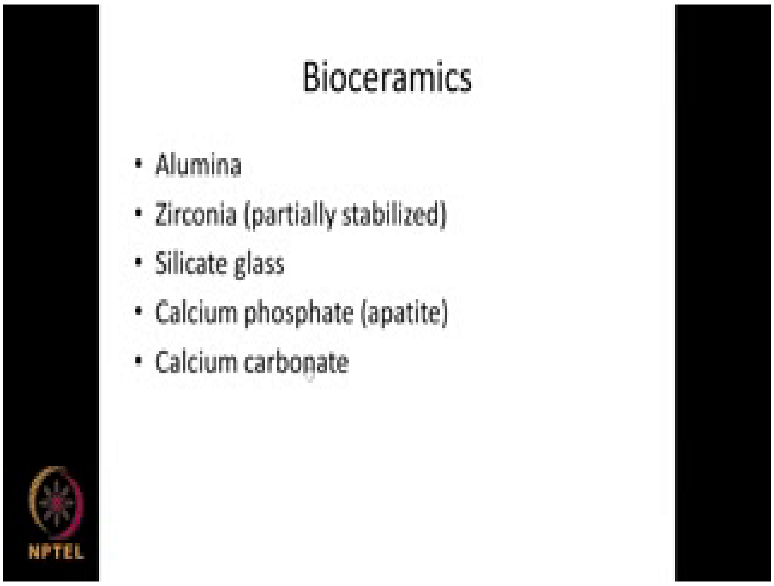

Some polymers cannot withstand certain conditions. So, we will talk about it later as time goes on ceramics they are oxides like alumina, zirconia, silicate glass, calcium phosphate, calcium carbonate, calcium sulphate, they hydroxyapatite. So, there is lot of interest in ceramics because many of our body like bone contain lot of hydroxyapatite. So, they are extremely biocompatible and they are bio resorbables. So, there is more lot of interest in bioceramics.

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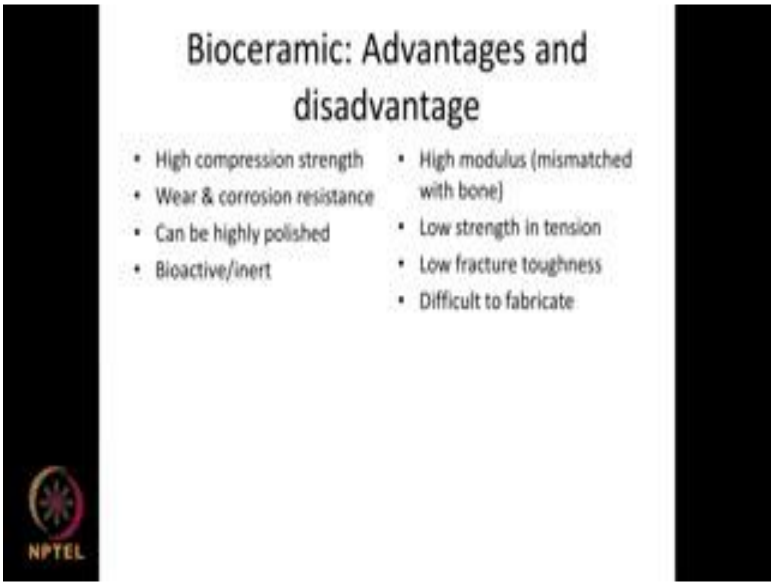

Disadvantage and advantages are there ceramics high compression strength they have good wear and corrosion resistance can be polished they are very bioactive and bioinert. So, the advantage is the system easily adducts the used. So, system is easily adducts to this they have high modulus. So, they do not match with the bone they do not have any tensile tension. So, they easily snap. So, we cannot use it in such situations they have low fracture toughness it is difficult to fabricate. So, you know you have to be very, very careful about that when you are designing. So, it is got some advantages and disadvantages.

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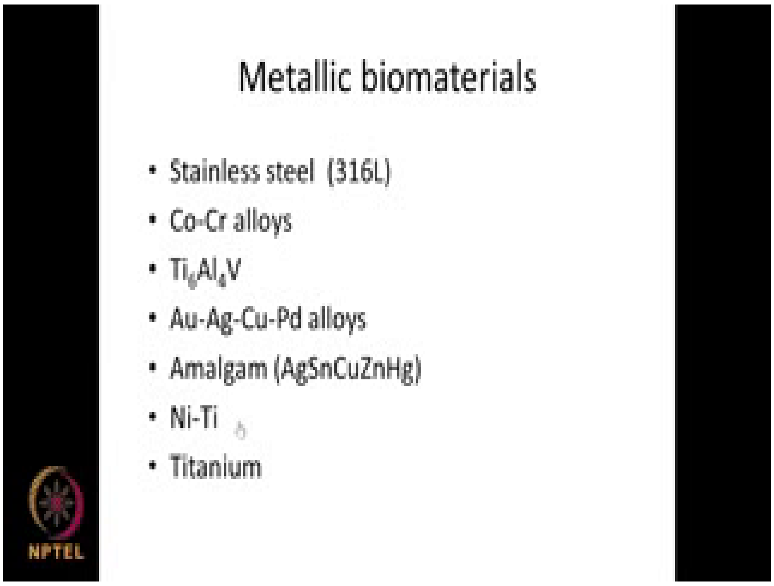

Metallic biomaterials stainless steel 316 L cobalt chromium titanium aluminum silver gold copper palladium alloys amalgam. All of them with different amount of mercury nickel titanium, titanium. So, lot of metals are being used as biomaterials nowadays in different parts of the body.

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High strength, good fatigue strength, resistance good wear resistance, easy fabrication, we can fabricate nicely. And the technology for metals has been there for almost 200 years, so that is the advantage. Easy to sterilize, we can heat it up to very high temperature and bring it down so nothing will happen to metals. Shape memory you can even design material which retains its original shape, these are advantages. High modulus is a big problem these materials are very strong. So, if I am going to use it in place of a bone, when you compare the strength modulus strength of the bone, and the metal there is a mismatch.

Corrosion is a problem because stainless steel can get corroded over a long period of time. Many material metals can get corroded. Metal ion sensitivity and toxicity slow leaching of metals is a big problem, even if it could be in the order of par per billion, some patients may be allergic to metal toxicity. Metallic looking you will always suppose I put metals in the teeth in the oral cavity then you the metal look does not very esthetic. So, there we may have to go to polymeric type of biomaterials.

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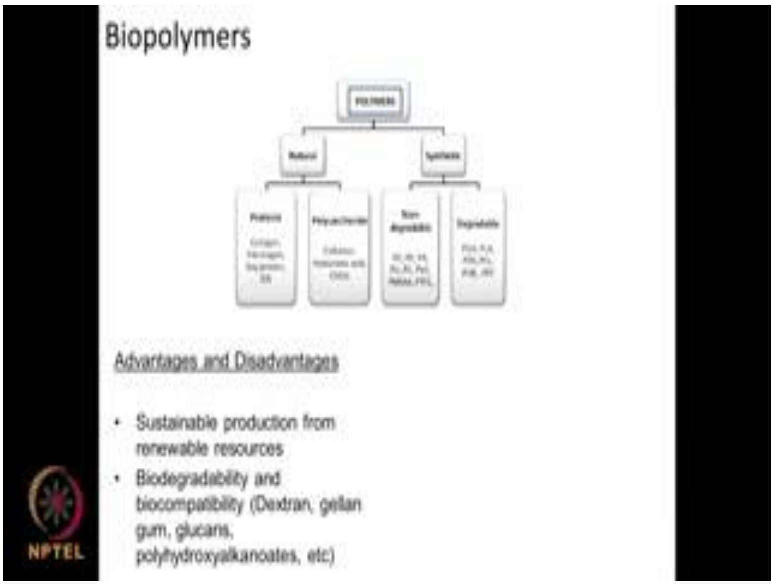

So, many advantages disadvantages of various materials. So, if you look at polymer, we have we are going to spend lot of time later, we have natural polymers, we have synthetic polymers, natural could be proteins like collagen, fibrinogen, soy protein, whereas you also have polysaccharides like hyaluronic acid, cellulose, chitin and so on glucons. If you go to synthetic materials we have non-degradable and degradable; non-degradable is like a polypropylene, polyethylene, polyacetate, polyurethane, polycarbonate, PVC, PMMA. Degradable you can have PGA, PLA, polycaprolactone, polylactic acid, polyhydroxybutyrate and then even aliphatic polyesters. So, they all degrade actually. So, advantages, disadvantages they have sustainable production. So, we can manufacture them nicely using petroleum based raw materials, they are biodegradable, they biocompatible, so lot of advantages.

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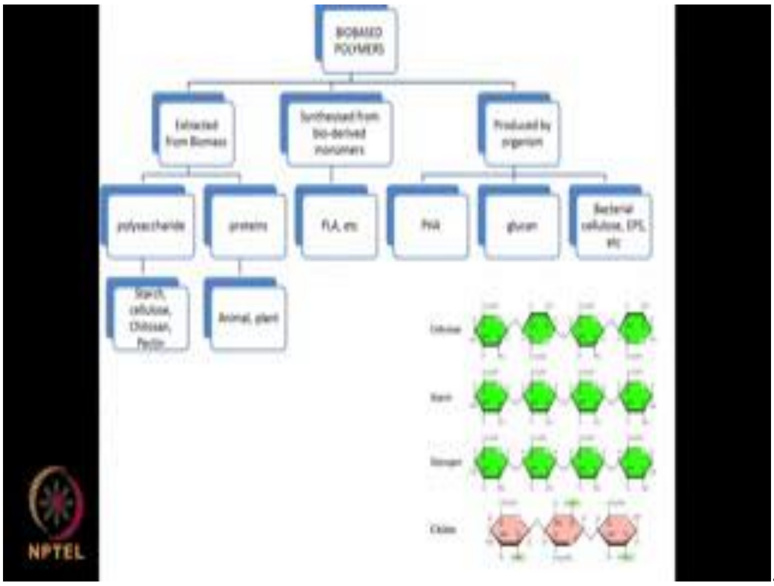

If you look at biopolymers, there are quite a lot of biopolymers polysaccharide based polymers, proteins based then we have the synthetic semi bio derived monomers. So, polylactic acid then produced by organism poly hydroxyapatite then you have the glucon based bacterial cellulose. So, we have extracted from biomass obtained from bioderived monomers or produced by organisms. So, a huge number of biopolymers are now slowly coming and they can be nicely tailored and nicely tailored, we can change the molecular weight. And if it is a bacterial bio based biopolymer by modifying the fermentation condition. We should be able to tailor make the molecular weight of the polymer we can blend it with synthetic polymer to achieve the desired properties because biopolymers might not have the desired strength. So, we can use the synthetic polymer. In addition to achieve the desired strength, and we will be able to use it for making different biomaterials of different size and shape, so that is the advantage of bio based material um

So, huge number of opportunities are there especially for one to do research on bio based material either animal origin either plant based origin or monomers which are derived from biological raw materials. So, there is a lot of interest in biobased polymer systems.

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You need to do surface modification of any material so that it becomes biocompatible. It does not cause any toxicity the whole system. So, the material should not be bioreactive and so on. We will spend more time later. So, there are many physical and mechanical approaches for doing the surface modification. When chemical treatment method for example, if I want to make it very hydrophilic I want to put in lot of hydroxic groups, so I can modify the surface of a polymer to put more hydroxic groups. For example, if it is too hydrophilic I want to make it hydrophobic, I may reduce the hydroxic groups that are present. If it is very if there are too many positive choice, if it is very cationic I want to make it neutral I can put functional group, so that the charges are getting neutralized. So, lot of chemical treatment approaches are there for surface.

Then biological treatment I can even immobilize cells, I can immobilize proteins, peptides, so this surface becomes more biomimetic surface becomes more biocompatible. So, lot of work research possibilities are there especially in the area of modifying the surfaces using biological I can see the cells. So, that bacterial contamination does not happen. I can have a some growth factors immobilized on this surface of the polymers, so that the surface acts as a very good scaffold for growing cells. Again various opportunities are there for looking at surface modification of materials either through physical, mechanical, chemical or biological methods. There is lot of interest nowadays on biological surface modification techniques.

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So, surface properties of materials, when I say surface properties surface is a either hydrophilic or hydrophobic, surface is either ionic or neutral, so we can look at surface charges, we can look at the surface morphology, we can look at either the surface has spore. Either we can look at what type of functional groups are present on the surfaces. So, different types of surface properties are available. We can use different instruments we will talk about instrumental approaches later on, how to look at surfaces, how to look at charges on surfaces, how to look at surface morphology and all those we will be looking at as time goes on.

So, the materials of course, deteriorate with time materials deteriorate because presence of lot of enzymes in the lot of body fluids that are present materials deteriorate, because where it is located inside the body. Bacterial contamination, bacterial growth, release of certain toxic material by the bacteria, all these can lead to deterioration of biomaterials. When I talk about deterioration, it is degradation, leaching out of monomers, leaching out of stabilizers and so on.

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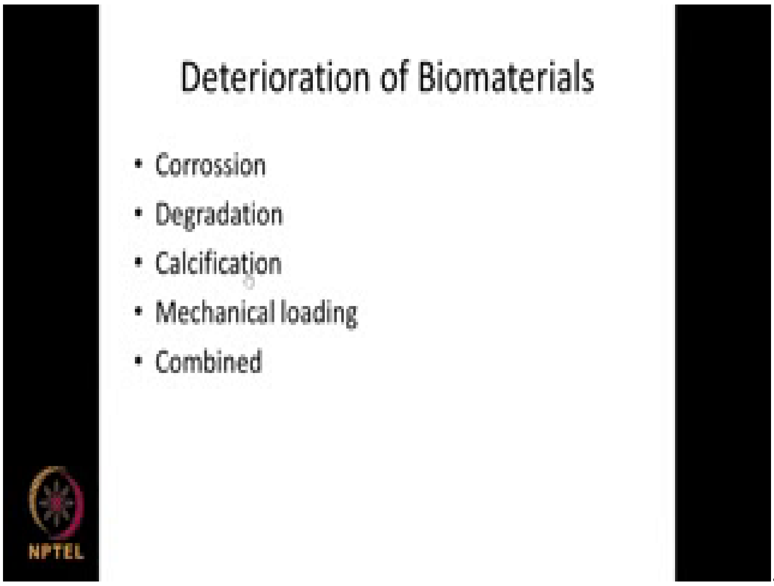

If you are talking about metals then of course, we are going to have corrosion polymers can have degradation, sometimes you can have calcification; in addition, you can have oxidation, reduction, amidation so many types of reactions are possible because body contains lot of enzymes and proteins which can lead to these type of chemical reactions or biochemical reactions. Then we are having to have mechanical loading, especially if it is replacement of a bone long bone segments or replacements of different joints, then we are going to have mechanical loading mechanical wear and tear, leaching of certain metals from these joints. So, all those things are also possible that also leads to deterioration and failure of the biomaterials.

Then we can also have these combined or combinations of all these affects actually. So, there could be a slight deterioration. So, a coating which is present on a metal to prevent certain corrosion gets removed. So, the metal will start getting corroded over a period of time. So, you are talking in terms of combinations of deteriorations we will talk about each one them little bit later on in detail also actually. So, when how do we select materials it is there is no single answer in selecting because as I said some biomaterials are placed in the urinary region, some materials are placed in the blood region, some materials are placed as heart valve, where they actively move continuously. So, some materials are like your urinary catheter are placed for only few hours, whereas if you look at cardio vascular stent they are placed for many, many years. If you are looking at joints, they will they are supposed to last for the entire life. So, if time factor comes in mechanical loading factor comes in the location in the body comes in. So, there is no single answer for selecting a biomaterial. So, depending upon the application and duration we need to have different criteria.

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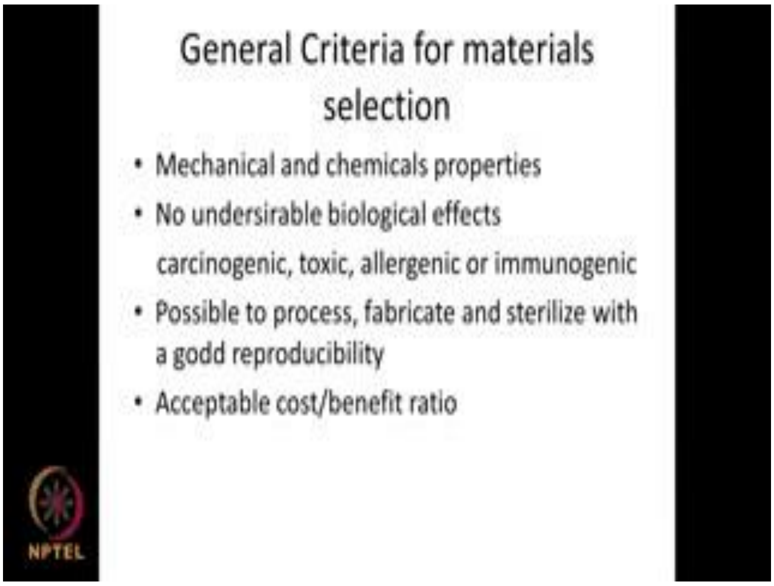

So, we need to consider mechanical properties, we need to consider chemical properties. What type of biological effects that may take place because we do not want any biological reactions taking place, do they we have to consider carcinogenicity toxicity is there any allergic reaction. For example, a chromium plate might not cause allergy to some patients, whereas chromium may cause allergic reactions to some other patients, is there any immunological effects.

How do you fabricate is it easy to fabricate, how do you process the material, is it easy to sterilize. Can we make hundreds of biomaterials, oh, there is a spelling mistake here it should be a good. So, can we keep on manufacturing in large scale with reproducible properties. So, all these also needs to be considered because ultimately we are talking in terms of manufacturing and selling it. And then of course, cost benefit is very, very important. We have to consider is it cheap or its very expensive.

See for Indian scenario, we have to consider how expensive is the biomaterial because India is a poor country and it is not so easy for everybody to afford biomaterials which are very expensive unless you have say medical insurance. So, for example, you have imported cardiovascular stent may cost couple of lakhs which drug eluding cardio vascular stent, whereas your ordinary bear metal stent may cause one and half lakhs, whereas it is just manufactured in India may be much less. So, the physicians have to give all the options to the patients. So, that they can select the biomaterials based on the cost benefit analysis.

So, this goes for many of the products imported products may be if expensive Indian products may be cheaper. Indian products have equally good benefits and that needs to be explained to the patients by the physician, so that the patient can make a cost benefit analysis. Some of the joints hip joints may last much, much longer several years, but it may be very expensive, whereas there could be some hip joints which are cheaper which life may not be as much as those expensive ones. So, patients who do not have an active life can manage with those type of hip joints. So, we need to really educate the patient of different types of possibilities that are available, what are the cost of each one of them and what type of situations are suitable for each one of the product. So, I think that sort of knowledge has to be imparted to the patients, so that they can make a good selection based on many factors. So, these are some of the criteria for some of the material selection.

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So, material properties if you look its huge compressive strength, tensile strength, bending strength. Of course, these properties are not necessary if you are have going to have a passive biomaterial like the catheter or something, but these properties become important when you are talking about hip joint or bone replacement or even your heart valve. Coefficient of thermal expansion is there going to be any changes in the thermal coefficient of thermal conductivity, surface tension, hardness, density, hydrophilic, hydrophobic properties, water sorption, swelling, solubility, surface friction, creep bonding properties. So, all these are very, very important which needs to be considered bonding comes in if when we are having two or different types of materials combined together. So, I have a ceramic combined with a polymer or a polymer with a metal especially in your hip joint. So, there has to be a good joint between these two. So, in such situations, we will have bonding properties to be considered. So, all these properties need not be considered for all biomaterials. So, we will be taking properties which are very specific for particular type of biomaterials and the applications.

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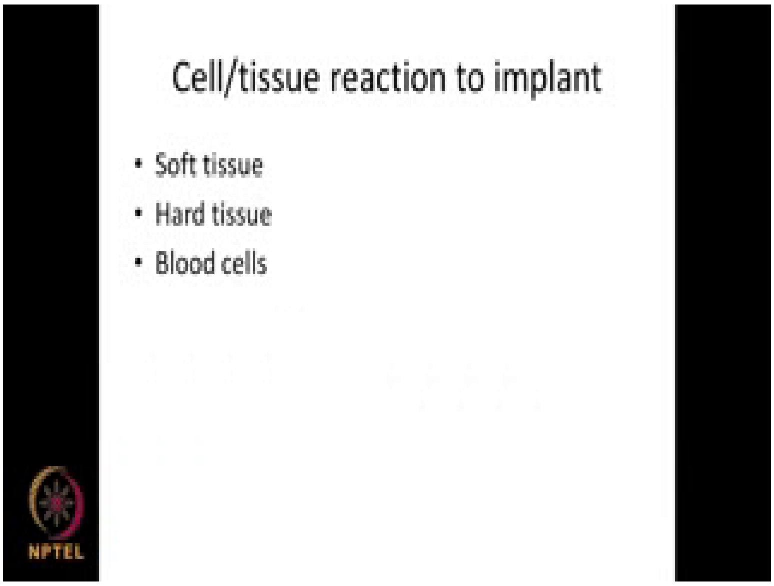

So, one needs to consider also what is the interaction with the cells with the tissues with the biomaterial.

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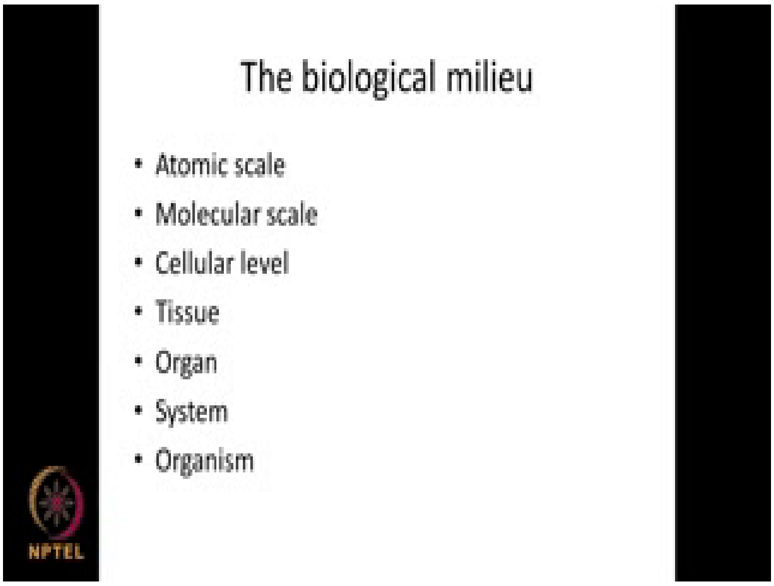

So, many factors we need to consider as we go along, and it gets very complicated and complicated, because the biomaterial has to be implanted and placed inside the body for a either a short period of time or for very long period of time.

Thank you very much and we will continue in the next class.