Medical Biomaterials
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Lecture - 02
Background History

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Welcome to the course on medical biomaterials. As I mentioned yesterday, biomaterial is any substance it can be a synthetic or it can be a natural or a combination of both, it is used maybe for a short period of time or very long period of time or forever. You know into the human body it is meant to treat or augment or diagnose or replace any tissue or organ or any bone of the functions of the body. So, it could be a replacement of a knee joint or hip joint, it could be a stainless steel plate which will support broken bones or it could lens which is ocular lens, which is placed inside after an eye surgery. It could be a cardio vascular stent which has to remain inside for a very long time, or it could be urinary catheter which is placed for a few hours. So, that the urine from the patient gets drained.

So, it could be very few hours duration or it could be many years. And it could be a synthetic material or it could be a natural material. So, when I talk about a material it could be a metal like titanium stainless steel cobalt chromium or it could be a polymeric material, like poly methyl methacrylate polylactic acid, glycolic acid or it could be a polyvinyl alcohol poly ethylenes poly teritalites, or it could be a ceramic like hydroxide appetite calcium sulfate magnesium oxides or it could be a biopolymer like glucan cyclodextrin and so on actually.

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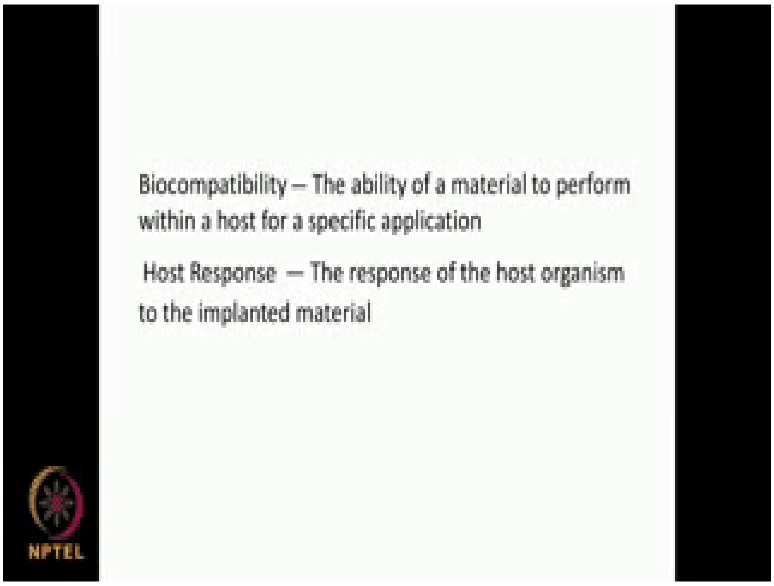

So, we are going to see all of them in the course of time. So, the most important points we need to consider, when you are designing biomaterial is the biocompatibility; that means, the material has to perform, within the host of for the specific application. And without creating any problems to the host like toxicity different types of toxicity that are possible local toxicity systemic toxicity. And what is the response of the human when the material foreign material is placed inside the body.

So, that has also to be considered, when you are designing a biomaterial the material, maybe coming in contact with the host tissues blood membranes proteins and various parts of the bodies. So, it should not cause adverse reaction whether it is short term or long term.

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Ah this is a good book to follow, have a look at this book biomaterial science an introduction to materials in medicine. It gives a lot of information on biomaterials as I goes along I will suggest some other books also, but this is a good book to follow.

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It is an interdisciplinary area it involves expertise of bioengineers, material scientists polymer chemists polymer technologists metallurgists immunologists. Because the material could cause immune response. So, you need to consider that it involves chemists who may be synthesizing new surfaces modifying surfaces. It will involve biologists it will involve physicians and surgeons. So, as you can see it is extremely interdisciplinary it starts with engineers scientists medical practitioner.

So, that is why as I said yesterday it is going to be exciting time for the area of biomaterials, especially research as well as in the manufacturing of new materials and product.

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These are some of the journals we can see a large list of journals if you are interested to read more the current topics as well as if you are interested in publishing your research, a large number of journal are given some of them are very specific to biomaterials and some of them could be interdisciplinary some journals like advanced functional materials biomaterials tissue engineering part b biomacromolecules acta biomaterials. So, you can see that they some of the journals may take studies on metals, some of them may be on polymers, some of the are blended, some of them on the immunological aspects tissue engineering aspects and so on actually. So, huge number of journals are now available where you can think of publishing your research also.

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Some of the companies which work in biomaterials royal DSM, wright medical technology, Corbion Zimmer, Bayer, Carpenter Technology, Covalon Technology, Evonik BASF, Invibio, Berkeley, Advanced Biomaterials, Cam Bioceramics, Collagen and Depuy Orthopaedics, Dentsply International, Biomet Dsm, Biomedical Noble Biomaterials as you can see large number of companies located in US and Europe you will be coming across and these names if you are interested in purchasing samples and so on actually.

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The biomaterials market is going to be huge. It is predicted in the year 2020 it will touch approximately 130 billion US dollar. So, the market is divided either based on the material or based on the type of application.

So, when you are talking about materials metallic, ceramics, polymers or natural biopolymers or biomaterials. If you are look you are looking at applications then it would be cardiovascular applications, orthopedic applications, dental applications, plastic surgery wound healing neurological applications, tissue engineering, ophthalmology application. So, you can divide the market either based on the materials or based on the applications.

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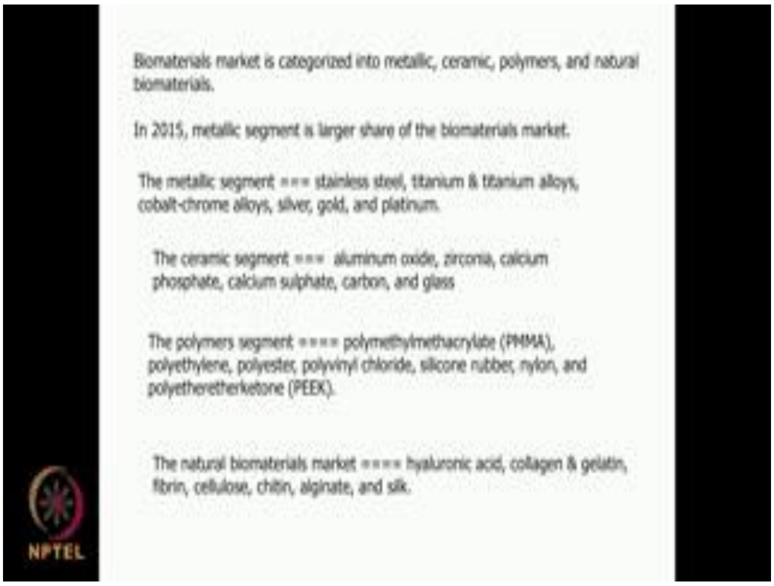

So, the biomaterials market is categorized into metallic, ceramics, polymers and naturals. Like I said you know and metallic segment is very large especially in the year 2015. Like I said huge number of metals have come into the biomaterial area. So, the metallic segments could be involving stainless steel, stainless steel is used in orthopedic plates titanium. Titanium is used quite a lot in stents again in orthopedic joints then titanium alloys different types of metals are added to titanium to improve certain properties. Cobalt chrome alloys, silver, gold, platinum.

So, lot of metals are used as biomaterials for different applications for antibacterial properties, for where taking care of wear and tear, for with standing high tensile strength and so on actually. If you look at ceramic segments these are aluminum oxides, zirconia, calcium phosphate, calcium sulphate, carbon glass. All these come under ceramic segment and nowadays there is a lot of interest in ceramics because they are extremely biocompatible and they nicely fit into the system human system without causing any adverse effect. Especially as you know hydroxyapatite calcium phosphate calcium sulphate they are all part of the bone and various tissues. So, they are extremely biocompatible.

If you look at the polymer segment, we have huge number of polymers there is a lot of interest in polymer biomaterial because of many properties. Polymers are very flexible polymers can be biodegradable, polymers could be made into different shapes and sizes polymers could be blended with other polymers to get very specific property polymers could be surface modified to improve. It is biocompatibility and antibacterial property hence polymers are widely now being used polymethylmethacrylate especially the oral and teeth contains lot of polymethylmethacrylate. Polyethylene is used in joints rotatable joints polyesters are used in grafts vascular grafts, polyvinyl chloride again being highly inert material, it is also used quite a lot inside the human system. Silicone rubber is used in urinary catheters urinary stents, the nylon is used in stitches again nylon is extremely strong and has very high tensile strength.

So, it is used in the areas where you require strength. Polyetheretherketone it is called peek; these are very specialized polymers which have many applications. In addition, other polymers like PLA poly lactic acid PVA poly vinyl acid or poly vinyl alcohol. Then we have the PLGA poly lactic glycolic acid. So, these are more polymers and many of them are approved by the FDA for use in the human system. Then the forth type of biomaterial market is natural; that means, it is either produced by bacteria or cells or found in plants and so on, like hyaluronic acid collagen gelatin fibrin cellulose chitin alginate silk. And the beauty of these biomaterials they are very biocompatible, hence they will not have cause in systemic problems, but they may have some disadvantages like strength tensile strength or flexural strength and so on. So, what industries do is they prepare blends of an natural polymers and synthetic polymers to arrive at a desired property, but the natural polymers are highly biocompatible. So, they are also finding applications quite a lot nowadays in the biomaterial market.

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So, the biomaterial market if you look at it based on application, cardiovascular orthopedic, dental, plastic surgery, wound healing, tissue engineering, ophthalmology neurological other applications like drug delivery systems, gastrointestinal bariatric surgery, urinary applications. Out of this the cardiovascular is larger shade of the biomaterials. Because we are talking about stents we are talking about shunts we are talking about diaphragm valves, we are talking about heart valves, we are talking about heart patches and so on actually. So, cardiovascular is the biggest segment in the area of biomaterial market. This is followed by orthopedic because orthopedic when we talk about we are talking about areas like bone replacement, joint replacement, augmenting after a fracture bone, plates bone screws wire different types of metals and polymeric blends are used.

So, the orthopedic takes the second largest application the year 2015, and the cardiovascular is the largest share of the biomaterial market as far as the application is concerned.

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So, as I said yesterday that just like drugs the biomaterials, once it is designed in the lab and tested in vitro has to go undergo just like drug animal trials and then human trials. So, lot of animal trials have to be performed like rabbits, guinea pigs, mice, crabs, pigs, bacteria. Sometimes you have to test the actual material or sometimes we need to test the extracts or elutants that is coming out of these to see whether the leachents coming out of the biomaterial is causing any cytotoxicity or problems like that, and then finally, it has to go through human volunteers for long term studies.

So, different parts of animals could be tested depending upon the type of application at for which you are looking at. If I am looking at cardiovascular area, then I am I may not be using small animals I may be using larger animals like pig or even dogs. If it is biocompatibility or cytotoxicity I may go into smaller animals. So, depending upon the type of application we may test in small or big animals actually before it actually goes into the human volunteer studies.

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So, there are many testing labs are there. Everybody follows this association for assessment and accreditation of laboratory animal care international. So, they do lot of testing on animal like rabbit pyrogen, US pharmacopeia class testing sensitization implantation sub chronic and chronic effects toxicity effect intracutaneous reactivity irritation necropsy histology. Then in vitro testing could be on cell lines different types of cell lines cytotoxicity hemolysis; that means, what happens effect of biomaterial on the blood. Then compliment activation PTPTTAMES mutagenicity, carcinogencity. Generally, all these labs follow all the usual guidelines based on say USP or ISO or JP or European or British pharmacopeia, FDA food and drug administration or ASTM standard that is American standard for testing of materials.

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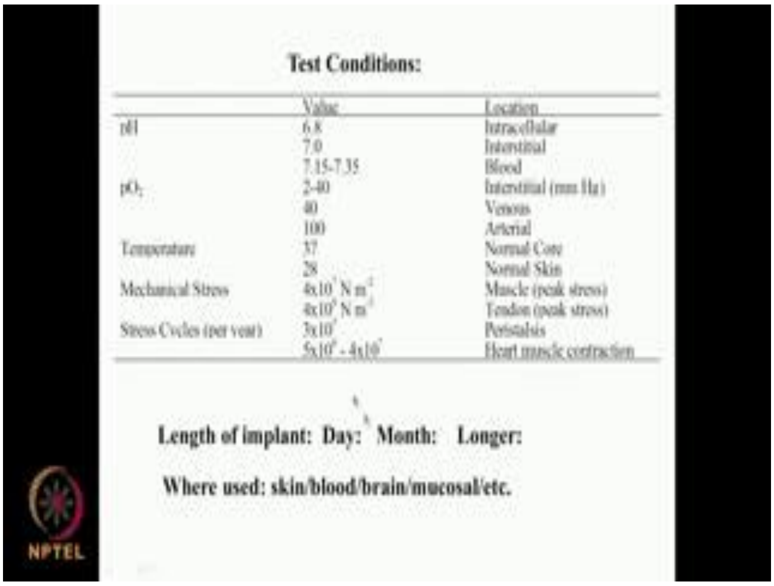

So, the test conditions could vary. Because like I said yesterday I told you the biomaterial may be placed in a area which is contact with the blood. So, the pH of the blood is 1.4. So, the material will be coming in contact with the plasma of the blood, maybe the red blood corpuscles white blood corpuscles. Whereas, if the biomaterial is urinary catheter or (Refer Time: 15:35) stent, it may be the pH may be neutral, but it may be in contact with the salts present in the urine, like calcium oxalate, magnesium salts and it may be in contact with the bacteria like equali and protease metabolize.

So, the biomaterial has to be tested depending upon it is application. So, the pH as you know varies quite a lot in human body. If it is going to be region of stomach, then we are talking about very acidic pH. Whereas, if it is inside the body in the blood plasma we are talking about 7.4. So, material has to be tested at various pHs depending upon what you are looking at, then oxygen this is also very important especially if you are talking about ocular lenses, permability of oxygen is a very important factor. So, oxygen diffusion oxygen partial pressure needs to be looked at and depending upon the location whether it is interstitial venus or artery. Temperature 37 degree centigrade or if it is skin it is much less 2.8 degree centigrade. Mechanical stress, if it is tendon the peak stress could be almost 10 power 8 newton per meter square, whereas, if it is muscle 10 power 7 newton per meter. Square stress cycles because we are talking about joint which may undergo lot of cycles or we are talking about diaphragm valves which maybe undergoing lot of cycles, heart muscle contraction, you are talking in terms of 10 power 6 that is million per year cycles, whereas, if it is peristalisis it could be 10 power 5. And then the length of the implant could be vary between days months or even much longer depending upon the application and also it maybe just placed below the skin or in the blood region or it could be in the brain region or mucosal region depending upon what type of study we are trying to undertake.

So, the test conditions vary quite a lot the locations where the biomaterial has to be implied implanted varies quite a lot, the duration also can vary quite a lot. And there are some FDA and ISO guidelines FDA mandates based on test contact; that means, it could be 24 hours 1 to 30 days or greater than 30 days.

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Ah ISO 10993 is the European union certification. So, on needs to consider the FDA and ISO guidelines for testing of biomaterials, classification of biomaterials is very important I briefly did mention about classification of biomaterials.

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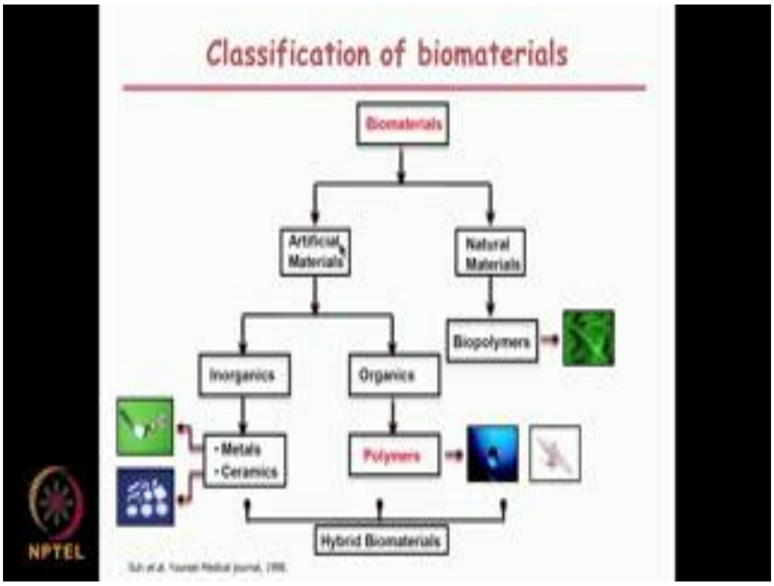

Let us look at it more detail. So, we have the artificial materialism we have the natural materials, natural materials could be biopolymers like I mentioned it could be alginate, it could be glucons, it could be dexrins, it could be halurenic acids. These are all produced by bacteria or fungus or cells or even derived from plants or animal origin, like some of the collision or it could be artificial; that means, I make it in the lab. The artificial materials can be inorganic or organic. Organic based that is using carbon, hydrogen, nitrogen, oxygen, sulphur. So, organic biomaterials are generally made of polymers PET PMMA PTFFE or PLGA PLA PBA and so on. These are all polymers. Or it could be metals stainless steel titanium chromium tickel. Or it could be ceramics calcium sulphate hydroxiapitite oxides of magnesium and alumina or it could be a combination.

Nowadays there is a lot of interest in hybrid materials, can I combine the strength of metals with the flexibility of the polymers and biodegradability of polymers. So, can I design a biomaterial which may have a metal core, but on the surface there could be a biodegradable polymer, which will have some drug and the polymer slowly degrades over a period of time. So, the drug gets eluted and maintains the biocompatibility of the material.

So, nowadays lot of combinations of materials are coming. And can I quote say hip joint with the polymer layer. So, that the friction is reduced and so on actually. So, there is lot of a interest now happening on hybrid type of biomaterials, where you are combining materials with polymer ceramics with metals ceramics with polymers and so on actually. So, we will look at some of them as we go along slightly in more detail.

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Some commonly used biomaterials. Silicon rubber silicon used has been used in catheters tubings quite a lot, they were also used in urethral stents then comes dacron. Dacron is nothing, but aster polyester, that is used in vascular grafts large diameter vascular grafts. So, there are many vascular vessel needs to be replaced because of infection or because of damage then dacron type of polymers are tubes are used to replace that we are talking terms of 2 to 3 mm in diameter. Cellulose this is a natural polymer.

They are quite quietly used in dialysis membrane especially if a person has problem with the kidney or and dialysis as to be performed you know with the salts and other toxins accumulated in the blood. They use performs something called dialysis and there cellulose membranes are used to remove the salts and the toxins from the blood. Poly methyl methacrylate this polymer widely used in dental applications, it is used in lenses bone cement polyurethanes there are very flexible almost like rubber. So, they again used on catheters, they are made used in pacemaker leads. Hydrogels, they are used in optholmological devices they are extremely hydrophilic. So, they can detain water they can swell in water and so on. They are also used in drug delivery system because it is extremely they are extremely hydrophilic. They do not cause any adverse reaction and they can swell and the drug that is present inside the hydrogel because of the swelling gets released.

Stainless steel. Because of it is strength it is used in orthopedic devices, it can use for replacement of bone parts, and it can also help in maintaining growth of bone after fracture. So, stainless steel is used there, also it is used in stents of course, cardio vascular stents. Nowadays use extremely hybrid metals like titanium nickel and so on. Titanium is very biocompatible. So, it is used quite a lot in orthopedic it is got good strength both tensile strength and compressive strength. It is also used in dental devices like screws alumina, because it is ceramic or inorganic material. It is very biocompatible. So, it is used quite a lot in dental devices hydroxyapatite after all or bone contains only hydroxyapatite. So, it is widely used in orthopedic. It is extremely biocompatible and bones grow nicely especially after filling bone defects with hydroxyapatite. It is also used in dental devices especially filling up gaps and also for facial surgery.

Collagen, this is derived from animal, but it is reprocessed it is used in wound dressings, opthalmological applications. As you can see this slide just gives you a brief show of what type of materials, that are used for different applications, as you can see metals come into the picture nonmetals, like inorganic metals come into the picture polymers come into the picture also biomaterials come into the picture. And there is always a overlap of applications of these materials in different areas of biomaterial design.

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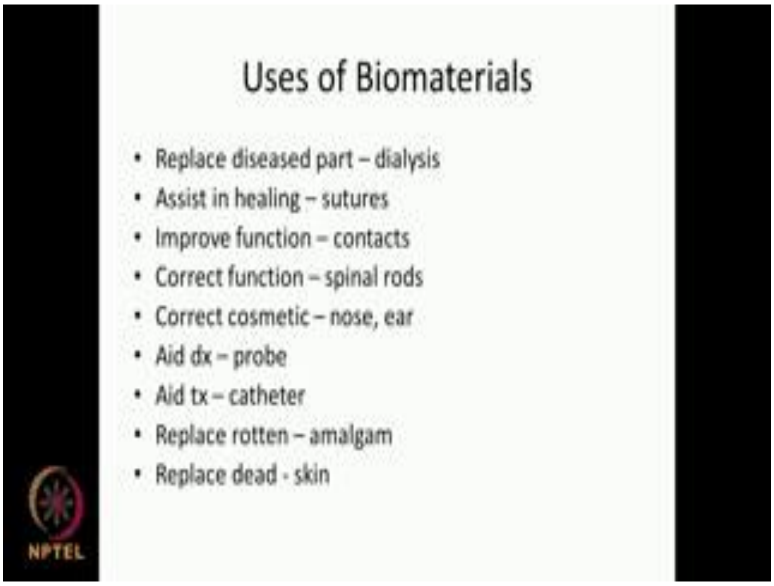

So, what do biomaterials do, more in detail. They replace diseased part especially if you are doing dialysis. Assist in healing for examples sutures we tie the skin using nylon or biodegradable material improve function. So, they are in contact, correct function like in spinal rods especially if there is a spinal defect. They place a long metal stent or tube correct cosmetic. This if for cosmetic surgery when if one is talking about surgery of nose or ear either after a an accident or because of cosmetic. Then we are thinking in terms of using a material like polyurethane or silicon mostly a polymeric material, which will exactly appear like the human tissue and they are flexible soft and, So, they nicely fit off after an accident or for a cosmetic surgery. Aid in detection like a probe like if I am interested to have a implanted glucocenture or implanted device, which will automatically correct your heart beat irregular heart beat then that is a probe. Aid transaction like catheter replace some rotten position like amalgam you know based on mercury replace dead skins. Artificial skins are now coming into research areas after a burn injury or after an accident can we tissue engineer the entire skin and replace the diseased skin or damaged skin using a tissue engineered externally tissue engineered skin.

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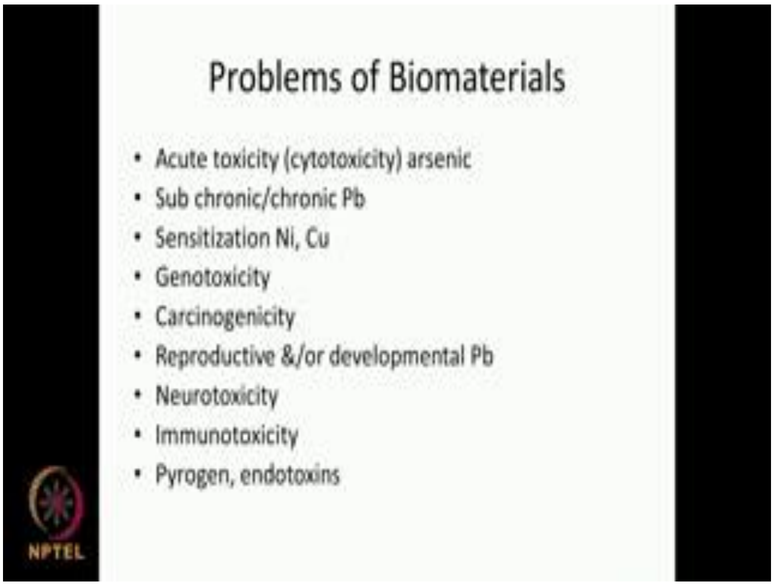

It could be a exterior portion or it could be even a interior tissue engineered portion. So, what are the problems of biomaterials. Acute toxicity cytotoxicity, that is a big problem because we are processing the biomaterials. So, they, So, there could be toxic chemicals which may create adverse response on the cells. So, cytotoxisary is a very important point. For example, arsenic could be causing cytotoxicity. Sub chronic or chronic toxicity like blood sensitization. So, sometimes the metals like nickel copper chromium which are used either as lead wires or which are used in joints may slowly get leaching leached out, and go into the blood stream. And this maybe in terms of the parts per billion, but still it could cause certain sensitization to the host

Genotoxicity, carcinogenicity sometimes it can cause cancer, the biomaterial reaction can lead to inflammation local inflammation it is cancer. reproductive and or development reduction in development like led it is a lot of talk about lead products which contain led may affect both the developmental stage of the embryo or even the reproductive stage. Neurotoxicity can the material hurt the neurological functions, can the material cause immunological damage immunotoxicity pyrogenic or endotixin. So, can the material lead into these. So, all these can happen. So, when we are designing the material, we have to be very careful it has to be approved by FDA saying that it does not cause any of these toxicity. So, we need to perform if it is not approved by a FDA, we need to perform all these tests before it can be approved by FDA.

So, it is much more involved and complicated than drugs. Because in drug discovery drug performs it is actions maybe few hours and then it gets completely eliminated from the human system. Whereas, in a biomaterial some of the materials have to stay inside the human for very long periods of time years and years, so we need to consider all these factors when you are designing a biomaterial.

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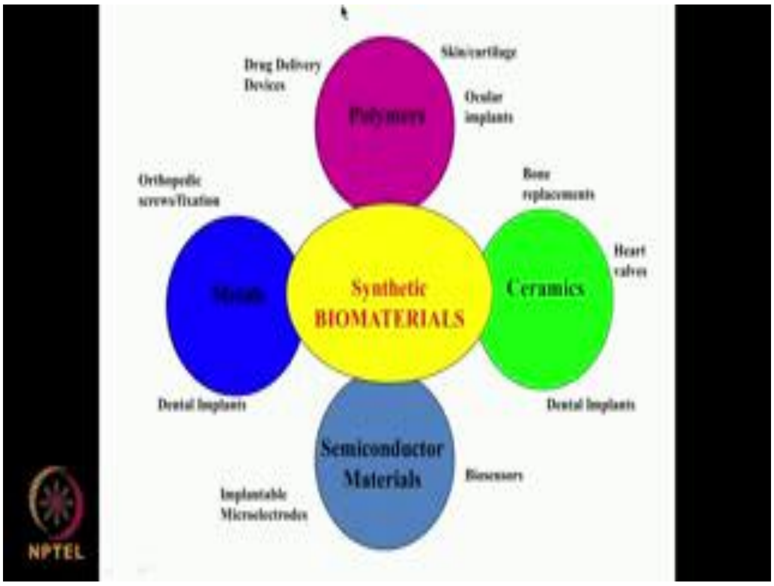

So, we have polymers, we have ceramics, we have metals, we have semiconductor materials, and then we have synthetic biomaterials. So, all these sometimes used on it is own or sometimes they are used together. For example, polymers used in skins and cartilage, when we when we talk about polymers, here we talk about both synthetic and natural ones ocular implants polymers are used drug delivery devices biodegradable drug delivery devices.

Ceramics are used as for bone replacements. Bone surgery like your hydroxyapatites heart valves, ceramics are used dental implants ceramics are used here. Metals we are talking terms of orthopedic fixation like stainless steel screws, like metal screws then dental implants sometimes titanium is used in dental implants metals are used quite a lot, they teeth cap sometimes metals are used semiconductor material like biosensors implantable microelectrodes. So, you see large all these applications, we have all these base material which are used either on it is own, or it is used in combination to achieve certain function. And there is no hard and fast tool that one cannot use a particular type of biomaterial, from other application depending upon the needs of the application the materials can always be tailor made to satisfy that material application. So, we will continue in the next class more on the biomaterials.

Thank you very much.