Introduction to Biomaterials

Prof. Bikramjit Basu

Prof. Kantesh Balani

Department of Materials and Metallurgical Engineering

Indian Institute of Technology, Kanpur

Module No. # 01

Lecture No. # 03

Concept of biocompatibility, host response, structure-property of biological cell

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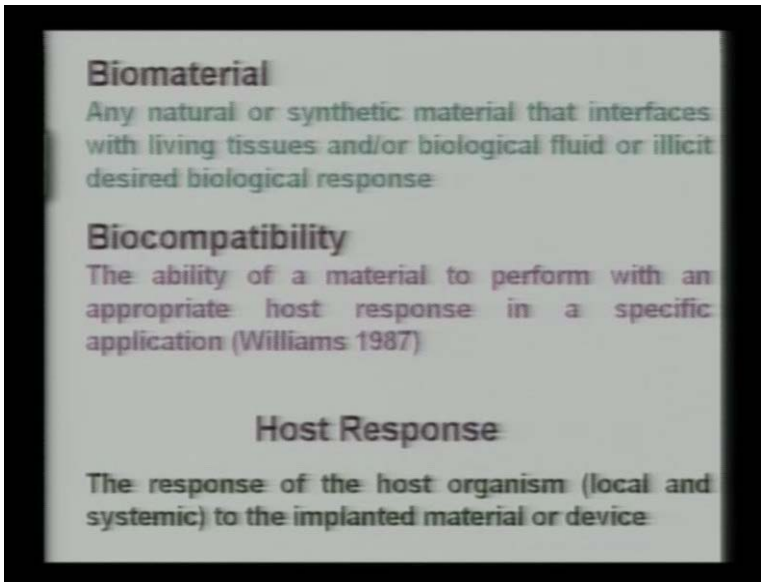

In this lecture, I will first discuss the concept of Biocompatibility and I will give you some definitions, useful definitions, which are related to biocompatibility, and host response and I will also discuss that, what are the different property requirements for a given synthetic material before the biomedical application can be realized.

So, biomaterial the way it is defined it is as that, any natural or synthetic material that interfaces with living tissues. So, I highlight here the synthetic material, because synthetic material means, it is a bone replacement material and this material is fabricated outside the body environment in laboratory or in industry or in research labs and so on.

And this material does not contain any biological substances like you know sales, proteins etcetera, and this is purely synthetic material it can be organic material like polymer base material or it can be inorganic base materials like, metals or ceramic base materials. And some of the important things in this definition that you need to follow is that, it should have a good interface with living tissues that means, the synthetic material it is expected that, when it is implanted inside the body environment that it will it will establish or it will good interface with living tissues, now this tissues these are nothing but, actually self organization of multiple type of cells.

So, you can note down this what, like this self organization of different cell type in a particular passion, and then this is called biological tissue. So, therefore, a synthetic material when it will have interface with tissues in other words, it will have interface with the self organize layers of different cell type or biological fluid biological fluid can be serum, biological fluid can be plate, biological fluid can be you know blood serum, and etcetera and it should illicit desired biological response. Now, the way desired biological response means, it can be different for different type of biomaterials just to give an example, when you are talking about total hip replacement, it is suppose to bear the load, when you talk about the heart parts, then it is suppose to facilitate the blood flow in the heart.

So, artificial heart valve for that mechanical property is not important, but total hip replacement for that mechanical property also important, after the biocompatibility property. The second thing is that, artificial any artificial bone replacement material that should have a good cell (()) property and tissue formation property.

But when you talk about the artificial heart valve, then it should have a property, which should not allow blood cells to adhere on that artificial heart valve. So that, blood cells cannot calculate, blood cell cannot for a minute thrombus on that heart valve surface, do you understand? So, biocompatibility is a broad term and then it is also applications specific, so for bone replacement materials or total hip replacement, whatever you call it biocompatibility that kind of concept is not valid when you go to the artificial heart valve applications, so these things should be taken into consideration when you design a particular biomaterial.

Now, second important definition is that biocompatibility that is ability of a material to perform with an appropriate host response, now what is host here, whenever you talk about host, host is the human patient. So, host response and host whenever you talk about host means, it is a human patient or any animal for example, and appropriate host response means, like this host will not suffer some kind of implantation, just because of the implantation of the material, so that is what is important and in a specific application.

Now, what is a host response, the response of the host organism local and systemic to the implanted material or device, now host organization means in the knee joint application, it is the tissues around the knee or if it is hip joint that is tissues around the thigh region of human patient that is important; how those tissues will react to the implanted material that is what is known as the host response. So, now you have launched three important definitions, number 1 what is meant by biomaterial, number 2 what is meant by biocompatibility and number 3 what is meant by host response.

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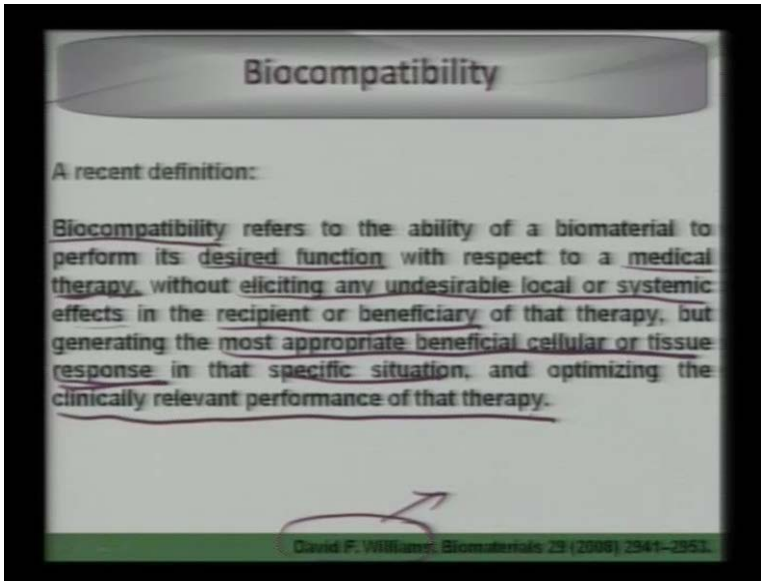

Now, this definition of biocompatibility is more detailed and I am now, giving a more recent definition that is proposed by David Williams who is currently the editor in chief of the zonal of biomaterial, so the biomaterial that is a journal and David Williams is the editor in chief.

Now, what he proposed the definition of biomaterials is that, biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy. Medical therapy means like, in a particular application that you are developing this biomaterial for without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy; who is the recipient or beneficiary; that means it is the host that is the human patient.

But generating the most appropriate beneficial cellular or tissue response in that specific situation, means most appropriate beneficial cellular tissue response means, whatever is required like you know for bone replacement you want that blood tissues or tissues to grow inside the material or any other material bioresorbable material means, like you want the material to dissolve and degrade with time in (()) condition, then it should be replace with the natural tissues which is surrounding that material.

So, what is saying is that, it should have a good cellular response or tissue response in a specific situation and optimizing the clinically relevant performance of that therapy. That is what; I was trying mentioning to you a few minutes ago, that whatever biocompatibility property required for the heart valve application is different from whatever biocompatibility property that you require for hip replacement and knee replacement for example.

So, these two things should be very clear, for any for many students who pursue that research biomaterial, they always think biocompatibility means it is always the cell adhesion, test emptily, cell (()), but that is important for orthopedic applications, but not for cardio hospitalize application, cardio hospitalize application means like heart valves that I have mention, for that different type of phase is required that is called blood compatibility, so it is not biocompatibility, but it is an again blood compatibility case is required. So, now you understand roughly what you know, what is the concept of biocompatibility and why the biocompatibility concept is different for, different applications.

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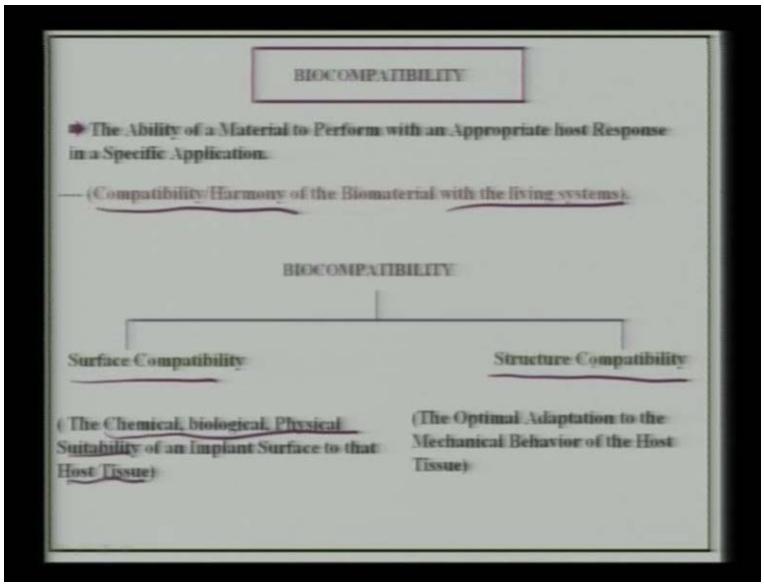

Now, here is it been little bit more defined or described that you know that ability of material to perform, that compatibility harmony of the biomaterial with the living systems, living systems means that is the human being system. Now, there are two type of compatibilities, what they have defined here is one is surface compatibility, and one is the structure compatibility.

Now, surface compatibility means like now, let us go back to the example that I have given you in the earlier lecture, like where I have discussed the total hip replacement you have the titanium steam and on the top of you have this hydroxyapatite surface coating. So, the pal composition is titanium surface composition is hydroxyapatite, so what I am meaning here by surface compatibility is that, it is not the biocompatibility property of titanium here is not important, but it is important whatever hydroxyapatite coating you are putting on the surface of title, that is what i am trying to say here.

So, that is the chemical, physical or biological suitability of the implant surface to that host tissue that is important. So, here host tissue will not see the titanium directly, here host tissue will first experience the hydroxyapatite coatings, before it will see the titanium surface. The second one is structure compatibility, structure compatibility means, that is the optimal adaptation to the mechanical behavior of the host tissue; mechanical behavior means, like you know what is the response, mechanical response of the tissue or bones surrounding that, that is what I was mentioning in the last lecture, that

you have the elastic modulus of the cortical bone that is 3 to 8 gigapascal. Now, if your elastic modulus of the implant is too high, then the implant will be almost the load not the bone, and as a result your implant will be detached from the as surrounding bone.

So, that is what it is important, that your optimal adaptation to the mechanical behavior of the host tissue or host bone, bone is nothing but a hard tissue, so this bone how this is optimal adapted as per is the mechanical property is concerned, that is what meant by structure compatibility. Now you see that, there are two things, one is the surface compatibility, and one is structure compatibility; structure compatibility mostly means for the load bearing implants, how mechanical adaptation process is possible.

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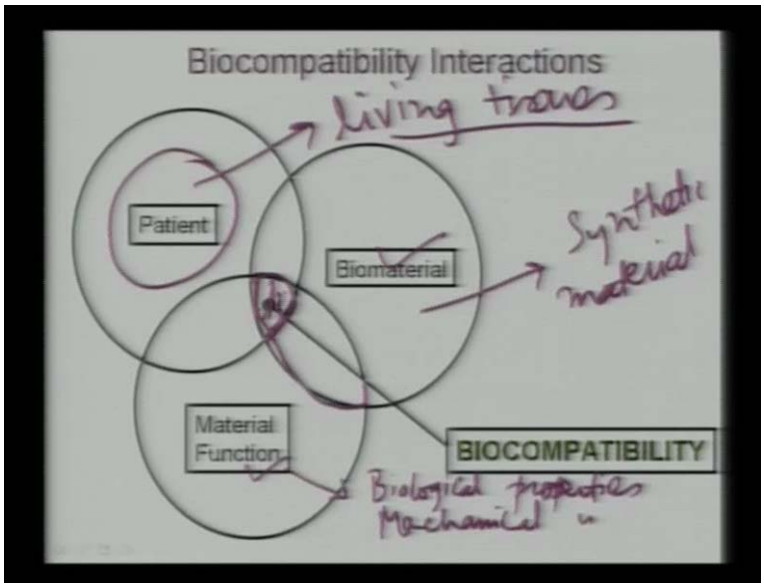

Now, here is a biocompatibility interactions, what I have shown here that one is a biomaterial and one is a material function, material function can be your two things, one is the biological function, biological properties; biological properties means, what is the you know that how the sales will grow on the surface or how this (()) will be adhering on the surface etcetera. And you have the mechanical properties also, like what the elastic modulus strain etcetera, and then one is the patient, patient is your human patient.

So, patient is your living tissues or living organs, so in biological terms you can replace the patient by living tissues or living organs, material function means that is your biological properties mechanical properties, your biomaterial means it is your synthetic

material right. And this synthetic material you are actually fabricating outside the human body, and this synthetic material what is the manufacturing processes, that I have explained to you in last lecture, that is in for meta-city the standard costing, rolling etcetera, for ceramic it is most powder base methods like, you know processing like product processing, (()) and so on.

So, now there is an intersection of these three, and these intersection region is this one, what I have been now shaded, now this intersection is nothing but, what is your biocompatibility properties is important; where biomaterial it should have a suitable composition, it should have a suitable or desired material function like in terms of biological properties, mechanical properties, and that should match with the specific tissues or specific biomaterials organs, where you are implanting this biomaterial into the human patient, you understand. So, that is that common area or common subset of these three actually will reflect in the biocompatibility property.

So, I am giving you all these slides, so that you can have a fairly good understanding of this, what is meant by the biocompatibility property, but in your laboratory scale experiments you do not use any patient things right. So, that is why it is called in vitro, in vitro experiments means, like it is a stimulated environment of the patient's one.

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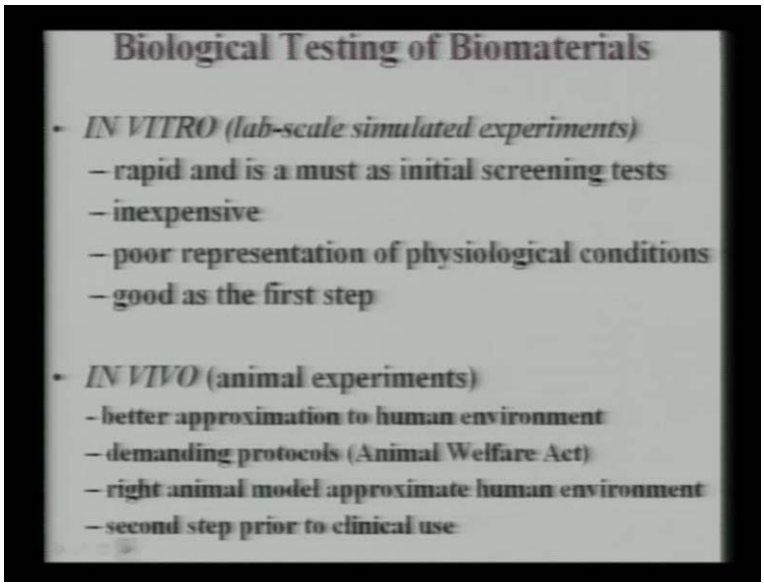

So, as I said that, what is the in vitro and in vivo now typically, in literature you will find that there are lot of in vitro experiments, and in vivo experiments are not that significant in numbers compare to in vitro experience, because in vivo experiments that required you know in ethical committee clearance and then animals which is not very easy to handle and so on.

So, in vitro experiments, the way it defined as that, it is laboratories scale simulated experiments, now what is meant by simulated, you are essentially trying to simulate as close as environment possible which is prevailing in the human patient or human body. So, therefore, as I have explained to you in 1st lecture, that human body that core temperature is 47 degrees celsius, the PH of the blood is maintained as 7.4. And therefore, most of the in vitro experiments that you carry out whether it is cell culture or whether it is in vitro dissolution everything, there the temperature is always maintain at 47 degrees celsius, PH is always maintain at 7.4, and to give you further details, like cell culture experiments they are maintained as 5 percent Co2 level and 95 percent air why because that, that also simulates exactly that Co2 level inside the human body.

So, human body if the Co2 level is more than 5 percent that means, your human organs are not functioning well, that is why Co2 level has increased. So, that is optimum level of Co2 that is always available inside the human body and that is the reason you require 5 percent Co2 in your cell culture experiments right. So, laboratories scale experiments no animal involved and also this in vitro experiments, the other thing is that it is very rapid and most initial screening experiments, because the animal means you are sacrificing some animals for your in vivo experiments, and that is not good right, so you should first prove the in vitro experiments, you select the best material out of these in vitro experiments, then you do in vivo experiments, that is the logical sequence of doing the biological testing.

It is inexpensive in vitro experience and it is poor representation of physiological conditions, why it is poor representation, because I have mentioned in the last 2 lecture, that in a human body environment your PH of 7.4 is only maintained that blood, but that PH also changes depending on whether it is iodine whether it is gastric environment of gastric fluid etcetera etcetera. So, PH 7.4 is not constantly maintained all the time inside the human environment, and second thing is that temperature 37 degrees celsius is also

not maintained throughout the human body, so again that is also grossly grossly poor representation of the physiological environment.

Third point is that, normally all human tissues they are actually aggregate of different cell time, but your cell culture or bacterial culture you are always using only one cell line, you are not using multiple cell lines together during your cell culture or bacterial culture experiments right. So, all these things actually shows you that, it is a poor representation of the physiological conditions; however, it is always a good as the first step, then in vivo experiments like animal experiments, animal experiments means like you can use rabbit, you can use rat, you can use mouse, before you can go for the human try.

Now, you you always start with a smaller animals, smaller animals means like rat, then you go little bigger animals like rabbit, then you can go further largest animal is called largest animal is called human being. Now, why I am putting this stress on the small animal to intermediate animal to large animal, because if you talk to any cleans or medical practitioner, they always tell you that rabbit model experiments; rabbit model experiment means, that is the intermediate animal model of experiments that you are doing in the rabbit, in case of rabbit because smaller the animal lesser the complexity of the body environment in terms of PH variation in terms of temperature variation and so on.

Larger the animal, larger will be the larger will be the variation, because the larger then animal more the volume of the body that you are dealing, the smaller then animal it is the smaller volume of the body environment that you are dealing, so the variation will not be that significant when you are talking with the help of the human being. So, that is what is meant by you know, that is the different in vivo animal models that you really want to use, now it has a demanding protocols like animal welfare act you have to follow, you have also get the clearance of the article committee and so on.

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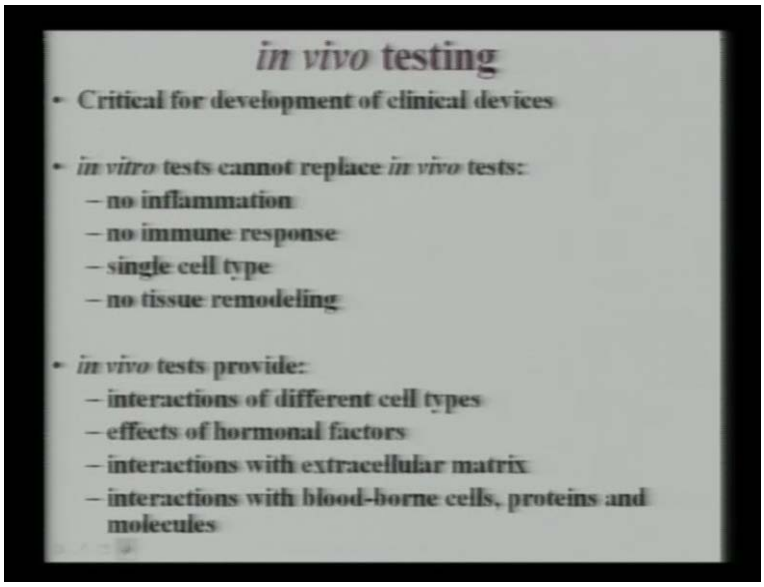

The right animal model actually approximate human environment and it is a second step prior to the clinical use, clinical use means like in the human beings. Now, in vivo testing in vitro test cannot replace in vivo test why, because in the in vitro test you cannot simulate the, whether that is an inflammation and not, inflammation can only be realize when you put the material inside the human body or inside the any animal.

Second one there is no immune response, immune response means you are not dealing with any immune system, immune system means that is the inside the human body or inside any animal. So, there you cannot you cannot study any immune histological response of any material, hard point that I have already mention that in vitro test always deals with the single shelter; let say it is the connective tissue cells like fibroblast, if it is a bone cell type that is osteoblast cell, but it does not it does not invoke multiple cell types in the single experiment, that is what is missing in the in vitro experiments.

Number 4 is the there is no tissue remodeling, tissue remodeling means I will come back to this later when I will discuss little bit of the tissue engineering concept, this tissue remodeling means, you are not giving enough environment or enough biological environment. So, that there is an ECM that is the extracellular matrix formation and that is remodeling of the extracellular matrix composition all the time dynamic, so no dynamic changes in the extracellular matrix that is possible in the in vitro experiment.

Now, in the vivo test whereas, provides interactions of the different cell types that I have already mentioned, effects of hormonal factors, interactions with extracellular matrix that is not possible in the case of in vitro test, interactions with blood-borne cells, proteins and different biological molecules; all these things makes in vivo experiments much more meaningful and much more complicated.

So, in summary I must mention here, that whenever you do the in vivo test you cannot definitely say on the basis of your in vitro test, the TS this material will be extremely suitable for in vivo applications, because you are in vitro test can be very positive, but that does not ensure that you are in vivo test also will be positive. Because, in the in vivo test you have some additional parameter which will be involved and that will significantly influence the biological purpose or biological properties of any biomaterial.

So, the underline thing this is like very final level understanding that you are in vivo test only can say that in this stimulated environments this material has good biological properties, it does not ensure that this material will be clinically successful for some load bearing implants or some from blood valve sorry from heart valves and so on. So, for that you need to use the suitable in vivo test you know particular animal model, and you can start with the small animal go to intermediate animal, go to the large animal model experiment.

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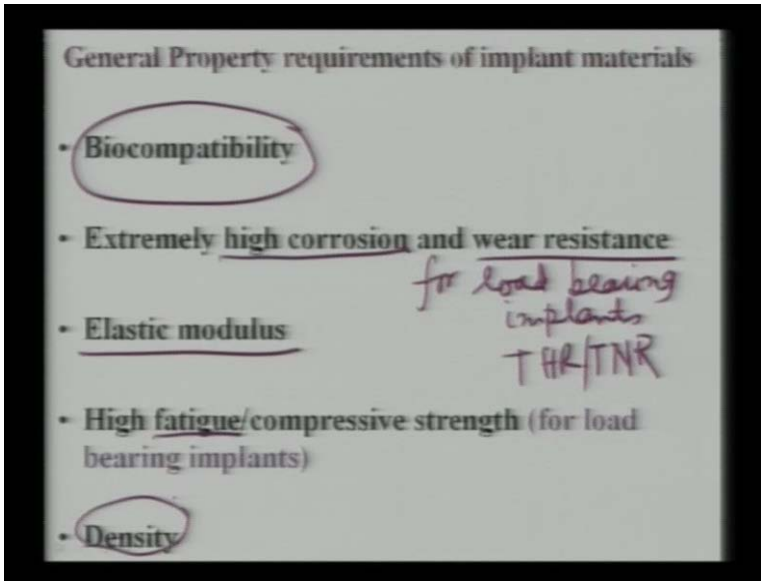

Now, general property requirements of the implant materials, as I have been mentioning right from the beginning, the biocompatibility is the most important properties, that a material must have before it can be used for biomedical applications. Now, biocompatibility property you now have broadly understood that what is meant by biocompatibility, what is the text book definition of biocompatibility, how it is properly define.

The second one is it should have extremely high corrosion and wears resistance, now this is more appropriate for load bearing implant, because in the load bearing implants your material also many times experience some reciprocal emotion like in the ace tabular cup femoral ball those kind of combinations, which I have mention for THR or total knee replacement, so total knee replacement or total hip replacement your wear resistance is also important.

Third one as I said elastic modulus, so elastic modulus matching with the neighboring bone or cortical bone that is important, forth one is the high fatigue and compressive strength again I has told you for load bearing implant. So, fatigue strength I have shown you remember the fatigue strength in the, if you do the normal laboratory environments without sea water, you can measure high fatigue strength, but when you use the sodium chloride with sea water, what kind of environment then you are bound to have much lower fatigue strength compare to that in air.

So, again the material which experiences very high fatigue strength in air that should not be the design criteria, design criteria should be what would be the fatigue strength in the simulated body fluid environment, last one is the density I also mention that density just to give you an example or to refresh our memory that steel base material, that has the density of 7.8 whereas, alumina is has a density of 3.9 which is just half that of the steel.

So, therefore, same volume of implant will weigh less, if you use ceramic compare to metal and if the weight is less, the patient will be feeling more comfortable for the same implant if it performs well; this is thus you know kind of a snap shot view of the part of the property requirements for biomaterials.

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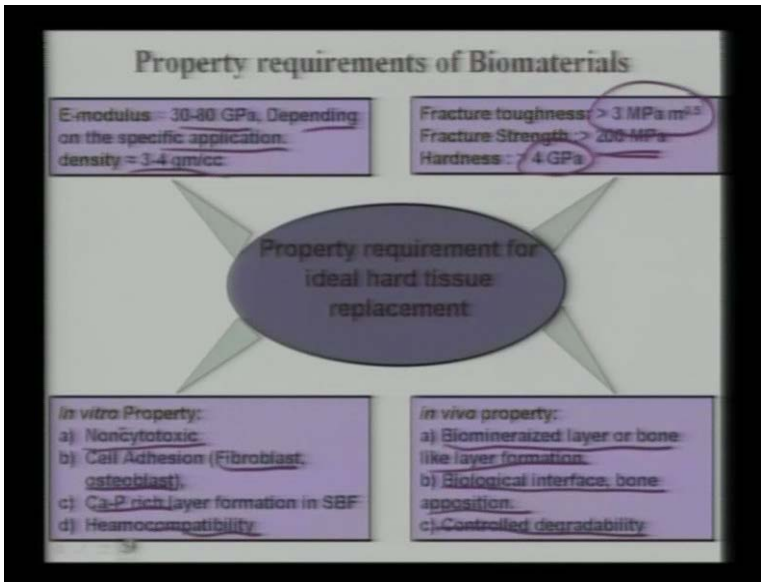

Now, here I have mentioned that elastic modulus is around 30 to 80 gigapascal this is depending on what is the kind of specific application, now density is 3 to 4 gram per CC that is more relevant for ceramic base materials, fracture toughness it should be more than 3 MPa square root meter, because if you remember your cortical bone the fracture toughness that varies around 2 to 12 MPa square root meter. So, if it is more than 3 MPa square meters it is better fracture strength it should be as high as possible.

So, that it can be use for load bearing application like 200 MPa hardness should be more than 4 gigapascal (()), because the typically bone at short and bone does not appear good a very high hardness proper. Now, in vivo property first one it should be noncytotoxic, noncytotoxic means, cyto means cell, toxic means it should not have any undesirable toxic effects, so it should not have any cytotoxic properties that mean, the cells should survive well, when you will sit these cells on this material surface. Then second point is cell adhesion like fibroblast or osteoblast cells, now the type of cells also depend on what kind of application that will be using.

For example, fibroblast cells are the most connectivity tissue cells and this connective tissue cells are actually the cell lines which comes to the wound side, very fast, very promptly before the osteoblast cell line. Osteoblast cells are born forming cells osteo means born, osteoblast means bone forming cell; fibroblast means again fibro means, it

is a cells of the fibro tissue the connective tissue, so that way you can remember these typical biological names.

Third one is the calcium phosphate rich layer formation in SBF right, whenever you do any in vitro desolation experiments you first check whether this biomaterial is capable of forming any calcium phosphates rich layer formation; irrespective of the composition if that biomaterial can have calcium phosphate rich layer formation, then what will have, it will have very good astrological or it will it will have very good biological response when you put it in in vivo conditions.

Because in vivo conditions also, it will first form calcium phosphate rich layer formation. If it is calcium phosphate rich layer formation, then what the neighboring tissue bones will feel, because each bone also we have 65 percent calcium phosphate. So, the bone will find as if the similar composition is existing next to the synthetic material, and therefore, it will have good bonding or good biological bonding with between the issue and bone along with the synthetic biomaterial.

Forth one is the hemocompatibility, hemo means blood, blood compatibility, but again that is only applicable for the heart valve applications, not for the other type of applications; it is not the primary criteria. In vivo property means it should have a biomineralized layer or bone like layer formation, it should have a biological interface or bone apposition and it should have a controlled degradability.

So, I will show you later that when a biomaterial you implant inside the human body, then this biomaterial should have good bone formulation neo bone, neo bone means, that is new type of bone which does not exist before you put the implant in the human body, so if this neo bone is form, then it should have a good in vivo biocompatibility property. So, like you know this are the you know over all view of the different property requirements of the biomaterial, this is like more details about the is the different bone analogue materials.

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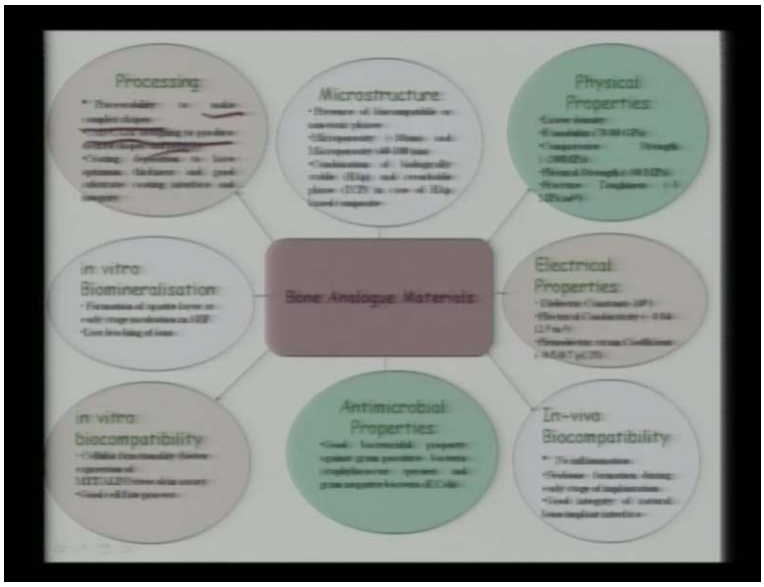

Now, the property requirements for different bone analogue materials it can be, so there are you know 3 plus 25 plus 8 circle surrounding this, so that means, eight different aspects you need to take care, when you are actually developing bone analogue material; bone analogue means, it is like bone replacement materials you are developing materials for using as a like a natural bone.

First one is a processing, now processing means it should have a good process ability to make complex shape, remember bone does not have very simple shapes like rod like shape or typical circular type shape, but bone can have a very complex shape. So, whatever material that you are producing the laboratory scale, you should be able to produce it in a much more complex shape than simple shape. Second one cat cum base designing to produce desired shapes and porosity, cat cum means computer aided design and computer aided manufacturing, so this computer aided designing you can develop the materials with control ferocity using the cat code, the computer aided design code or computer aided manufacturing process.

Third one whenever we use the hydroxyapatite coating, you should have a optimum thickness and you should have good subset coating interface and integrity; that must be ensure before good processing, before this material can be used in real applications. When it comes to micro structure it is important that whether you have a presence of biocompatible or non toxic cells, because if you have alpha, beta, gamma phase, if one of

the alpha, beta, gamma phase has a toxicity effect then the entire material will have a cytrototoxic effect. So, you cannot use this material in real applications, then second one is the microporosity, microporosity porosity means any force which is less than 10 micron and microporosity means any force which is in the range of 40 to 100 microns.

So, if it is less than 10 micron for city, then it is very good for initial cell adhesion property, if it is greater than 40 to 100 micron porosity then this is macro porous then, it is very good for nutrition and nutrients and blood channels everything to entire and tissue formation and tissue in growth also to take place.

Third one for the hydroxyapatite based materials, it is important to have a combination of hydroxyapatite and PCP phase, what we call it as BCB that is a dicalcium phosphate phase; and this dicalcium phosphate phase is important for these hydroxyapatite based materials. Now, coming to the physical properties, physical properties means lower density that I have mentioned, elastic modulus 7 to 8 gigapascal that I have mentioned why it is require, for many load bearing applications compressive strength is important as well as flexural strength is also important. Fracture toughness means it is the resistance to the crack growth and this resistance to the crack growth should be as high as PNA square meter or more.

Now, coming to the other properties is like electrical properties, now the question is that why electrical properties is important, bone itself is a physic electric composite of the organic and inorganic pair, and physic electric composite means this bone analogue material should have a dialectic constant which is around thousand or more; it should have electrical conductivity property, it should have a 0.04 ohm per meter and it should have a physic electric coefficient which is somewhere around 0.05 to 0.07.

So, this combination of properties, if it is ensure in this synthetic biomaterials then what will happen this biomaterial would be an ideal bone material; now these four is mostly from the physical and electrical and functional and mechanical properties as well as the processing. Now, these four in vitro properties and antimicrobial properties, in vitro properties is more is the bio-oriented properties; now these are all like physical and biological, physical properties mostly as well as the processing.

Now, in the biological properties, first point to note here is the in vitro biomineralization, in vitro biomineralization means, first of all in vitro means laboratory scale stimulated environment, biomineralization means it should ideally may be able to form hepatite layer at the early stage of incubation in SBL, many times some biomaterials they take four weeks before they can form, calcium phosphate rich layer formation.

There are two or three type of materials say ABC, some material they take one week form that calcium phosphate rich layer formation, another material they take three weeks, another material they take six weeks, but the first material which it takes one week of one week for the formation of calcium phosphate rich layer formation, that material is highly biocompatible compare to other two materials; there is no way that you can quantify or there is any quantification index or how could biomaterial is bio active or not, but this is the way you can roughly find out that how, you can evaluate the biomedical potential of a good biomaterial.

Then second one is the less leaching of irons, like you know if the irons are leached and it irons can cause some toxic effect that is also should be avoided. So, therefore, the less leaching of irons should be proffered. Coming to the other part of the biological properties is called in vitro, biocompatibility property like first one is the cellular functionality, cellular functionality means it is a better expression of entity which is a cellular viability property or ALP that is the osteogenic differentiation or osteoblast differentiation and osteoclast and that is the bone mineralization property. Now, all these essays I will be dealing with it much later in more details, now there is a good cells and processes like whenever you will sit the cells on the biomaterial, it should be able to migrate cells should be able to migrate, cells should be able to differentiate on the contact with biomaterial, cells should be able to proliferate also. So, all this is called in combination like proliferation, migration or adhesion or differentiation, all these properties together is called cell fate processes.

So, this is like a biological terms cell fate is nothing, but combination of proliferation then migration, differentiation and cell adhesion. Next one is the antimicrobial properties, last lecture I have mentioned that hydroxyapatite is the most biocompatible material, the most bioactive material, but a problem with the hydroxyapatite is that it does not have any antimicrobial property, antimicrobial property means whenever you see bacteria cells on this hydroxyapatite surface then what will happen, this bacterial

cells can easily adhere and they can easily survive on the biomaterial surface. So, that can cause infection in the, whenever you are implanting in the human body, but if you add some silver to hydroxyapatite they should be able to kill all the bacteria, so you get a material with antimicrobial property. Third one is the in vivo biocompatibility property, like it should not cause any inflammation, it should ideally cause neo bone formation that is new born, that is form during the early stage of implantation and third one is the good integrity of the natural bone or implant surface.

So, that integrity means there should not be any gap suppose this is your biomaterial and this is your human bone, so this interface should be continuous, there should not be any gap between the biomaterial as well as the natural bone, so this is what I meant by good structural integrity at the natural bone implant interface. As I said that biological tissues they contain self organize aggregates of the multiple cell types and a large number of cells in a particular fashion, so therefore, it is important first understand the properties of the cells, and what is meant by cell, biological cell?

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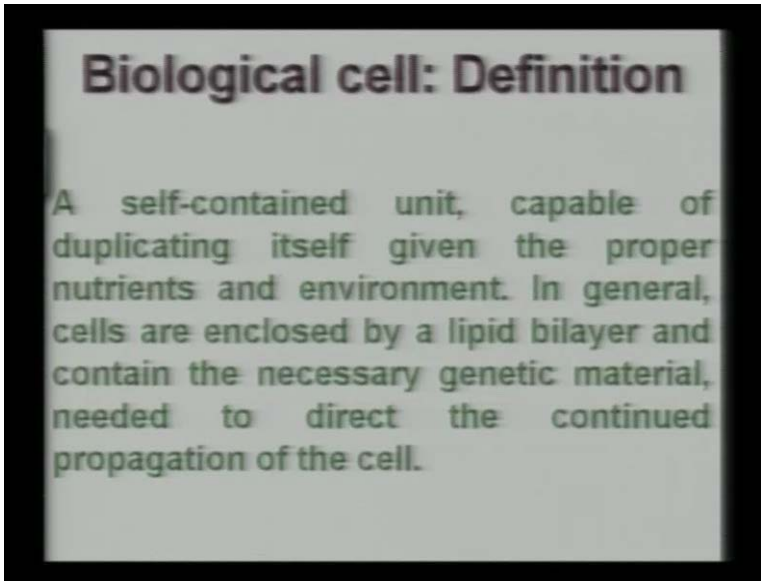

Now, here I am giving you a definition, biological cell is a self-contained unit, which is capable of duplicating itself given the proper nutrients and environment. And in general, cells are enclosed by a lipid bilayer, so that is important, because cell membranes they have a lipid bilayer, and they contain the necessary genetic material, now this necessary genetic material it is enclosed in the nucleus, so that is the DNA, RNA right. And these

genetic materials can direct the continued propagation of the cell; continued propagation of the cell means, the cell will go through a cycle right, cell will differentiate, then cell will go to the death or cell necrosis and so on.

So, that entire entire cell cycle is also governed by that how this genetic material they will perform, so there are two things here you can find out that you know cell membrane they contain lipid bilayer, and cell is a self contained unit which is capable of duplicating itself, because it contains a necessary genetic material.

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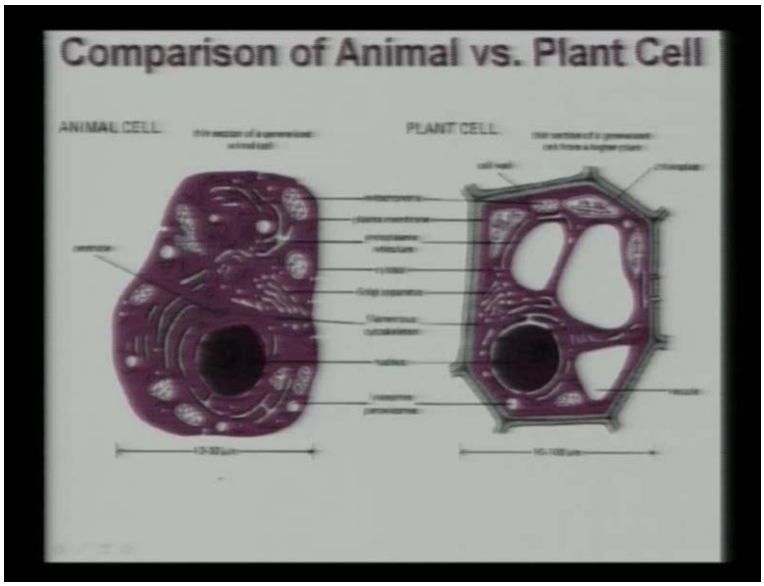

First let us see, that how this plant cell and animal cell them look likes, now this plant cell typical as a very regular type of structure whereas, animal cell it has it does not have any regular structure, it is more like irregular structure; this you are seeing like a thin section of a animal cell. Now, it also has a nucleus and nucleus is enclosed by nuclear membrane, you have the cytoplasm which is inside the cell, you have the mitochondria, you have the Golgi body all those things you can see in the next slide.

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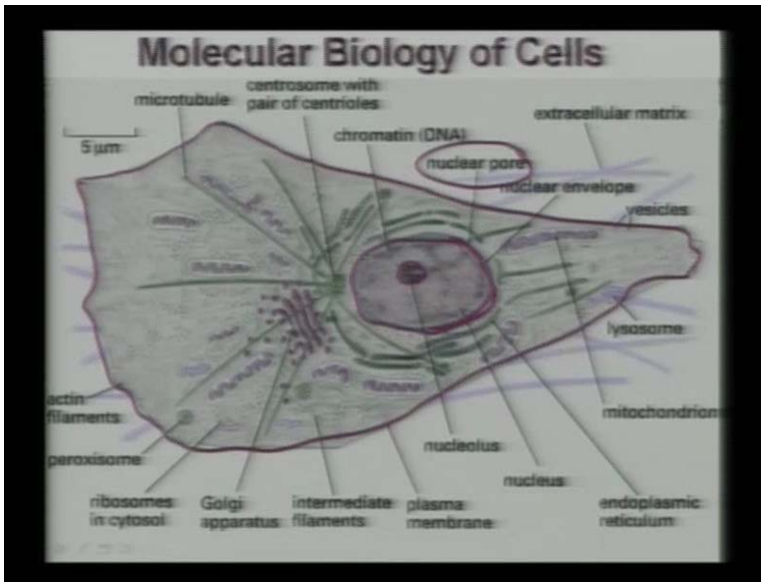

This is the molecular biology of the cell, so you have the lipid bilayer that it is the cell membrane right, it is contained by the cell membrane which is nothing but, a lipid bilayer here, and this lipid bilayer also has a particular property, so that I will come later. Now, this entire cellular, entire cell it is the matrix of the cell which you can call it as the matrix which is called the cytoplasm, so essentially cytoplasm means that it is actually the entire matrix of the cell then you have the one of the important organics is the nucleus, now nucleus again is enclosed by nuclear inhaler and it is a nucleus and you have the entire material, which is inside the nucleus is called nucleoplasm. Now, this nucleus I will come back to later, that nucleus also has a nuclear pore or that means, these membrane whatever you are saying it is not a very compact layer it has also some pores inside the nucleus.

There some of the important organelles of the of these inside the cell, which are called cellular organelles for examples this is called microtubules, so these microtubules are contained in the cytoplasm. So, it is one of the component of the cytoplasm, other component of the cytoplasm is called acting filament, so these are like called acting filaments here.

Then you have the ribosome then what is the called protein synthesis, then you have called Golgi apparatus, now this Golgi apparatus is as closed to the cell as possible and you have the large number of mitochondria here, and mitochondria is called the power

house of the cell right, because it is used in the ephedrine synthesis and ephedrine synthesis will lead to the more anarchy that the cell requires for its survival.

What are the other things that you have seen, that you have the intermediate filaments you have the acting filaments and you have the, this is intermediate filaments, this is the part of the mitochondria cytoplasm, you have acting filaments that is also part of the cytoplasm. Now, there is the other things these organelles this irregular shape organelles these are called ER, which is called as the Endoplasmic Reticulum and you have the mitochondrion here, you have this chromatin that is contained that is nothing but, DNA which is inside.

So, you have the three component of the cytoplasm let me summarize, these components one is the microtubule, acting filaments and intermediate filaments. You have the other important things is called Golgi apparatus, then other important cellular organ is called endoplasmic reticulum, from the energy point of view it is important to have the mitochondria in the material. And the outside you can see that is called extracellular matrix, what is known as the ECM, it is designated as the ECM, because many times later on I will refer this ECM, and ECM is actually essentially means it is extracellular matrix.

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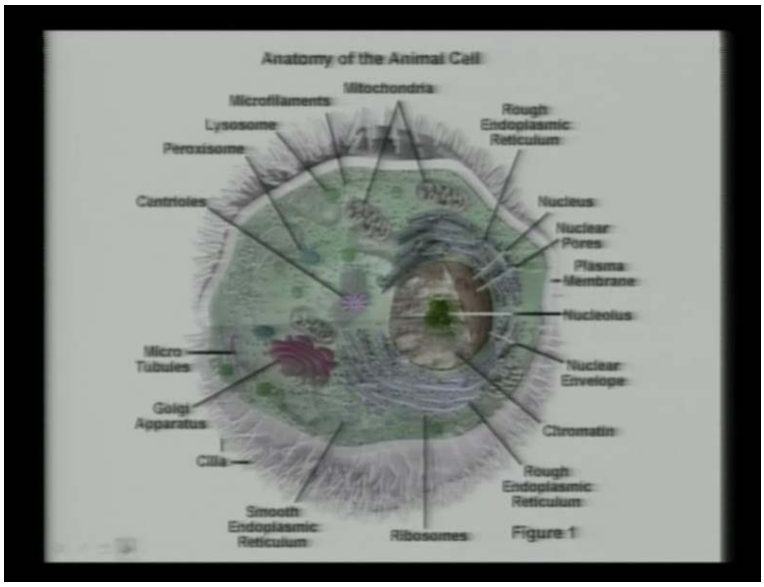

This is also another cell type, I mean for different type this cellular surface of cell size or the cell morphology is also different, it does not necessarily mean that all the cells will have this kind of unique size or shape and this size you can see this is like 5 micron this is the size, so the entire dimension of the cells can be as I as 100 micron or little higher than 100 micron.

Now, here you can see this is the more kind of regular circular type of cell morphology and what is more important you can see, that this cell membrane which contains this lipid bilayer these you can clearly see here, now again you can see more clearly the Golgi apparatus, you can see the mitochondrion this here and also the endoplasmic reticulum which is which is surrounding the cellular nucleus, and you have the nucleoplasm here inside the nucleus. So, nucleus contains the genetic material that is required for the gene related activity like DNA, RNA etcetera.

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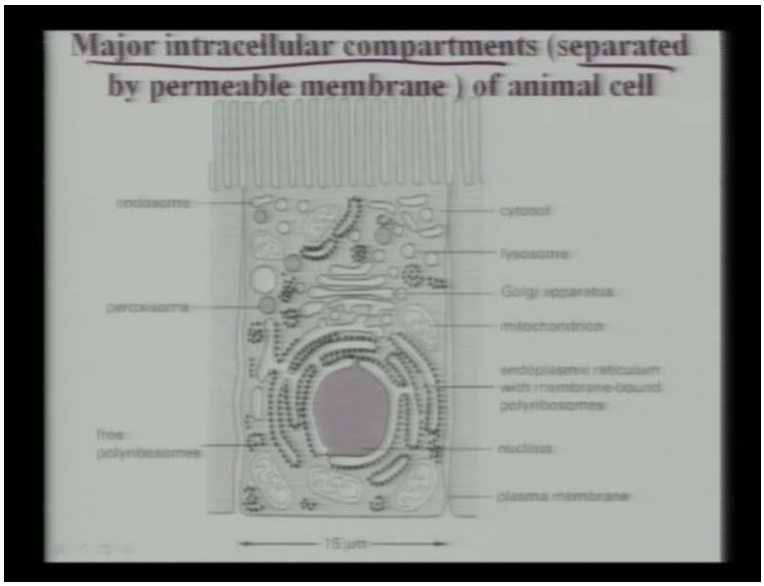

Now, those you have also started in your school biology, but this is important to recall all the important features of the cell biology here, now other things is that major intracellular compartments they are kind of separated by permeable membranes.

Now, if you go back to this particular view graph or here you can see mitochondria, if you look at the mitochondria morphology here, the mitochondria is also contained by a inhaler, which differentiates from the cytoplasm here. So, each mitochondria you can see

a membrane, just like a cell is enclosed by a membrane similarly, all these cellular organelles also are enclosed by some membrane. Also if you see here the Golgi apparatus and nucleus that is another important cellular organelles and this nucleus is also enclosed by a nuclear membrane, so that is also another membrane. So, that is what is meant by here the major intracellular compartments, they are separated by a permeable membrane and this has been shown here, like you know this is plasma membrane, this is a nucleus, this is AER that is endoplasmic reticulum, this is you have a mitochondria and you have the endosomes here, which are also some small elements you have the cytosol, cyto means cell, sol means it is like a you know matrix of the cell.

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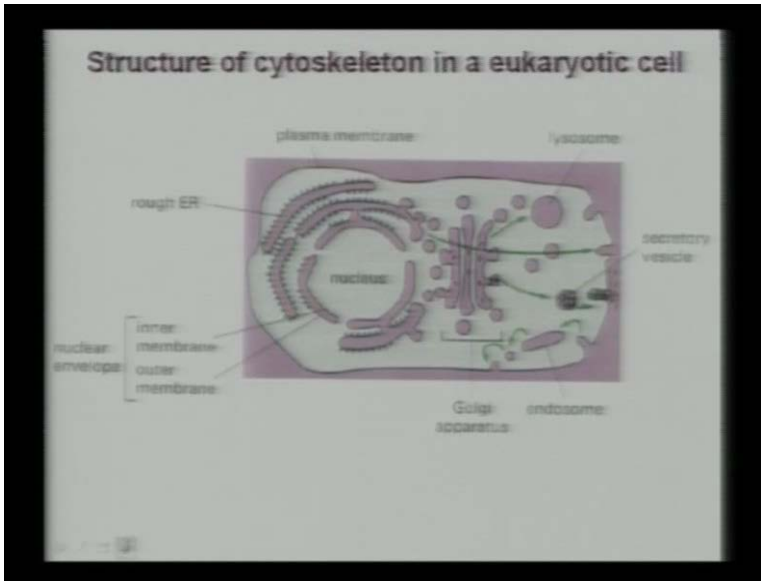

You have a Golgi apparatus, you have a endoplasmic reticulum with membrane bound polyribosome you have the nucleus; this is the structure of the cytoskeleton in a eukaryotic cells and this cytoskeleton it has a different organelles, as well as this entire structure of the cytoskeleton, it has three different components. As I said that it contains the acting filaments, then you have the intermediate filaments, and then third one if you go back to the slide I have already mentioned that it is a microtubule, these three components is actually microtubules is a third component, these three components they contain in the cytoskeleton.

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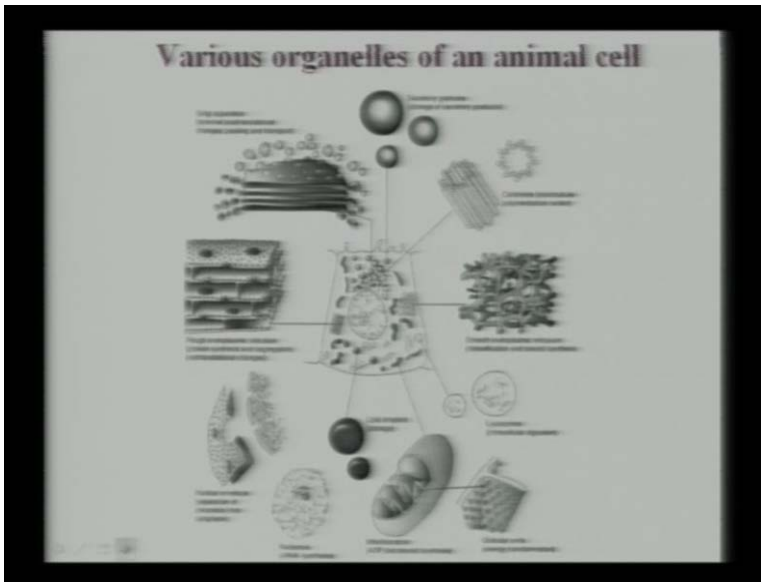

Now, here it shows that how this various organelles they actually look like in reality, so this like a more like a shoe type of morphology in the mitochondria, and it is the power house of the cell you have the RRA in the synthesis region, and you have the nuclear inhaler. Now, nuclear inhaler you can see these are these contains lot of pores, either it can be macro pores, it can be micro pores you have the smooth endoplasmic reticulum it has a very complex type of structure, which is also there and it have the rough endoplasmic reticulum, which does not have a very smooth surface it is moved like a rough surface here.

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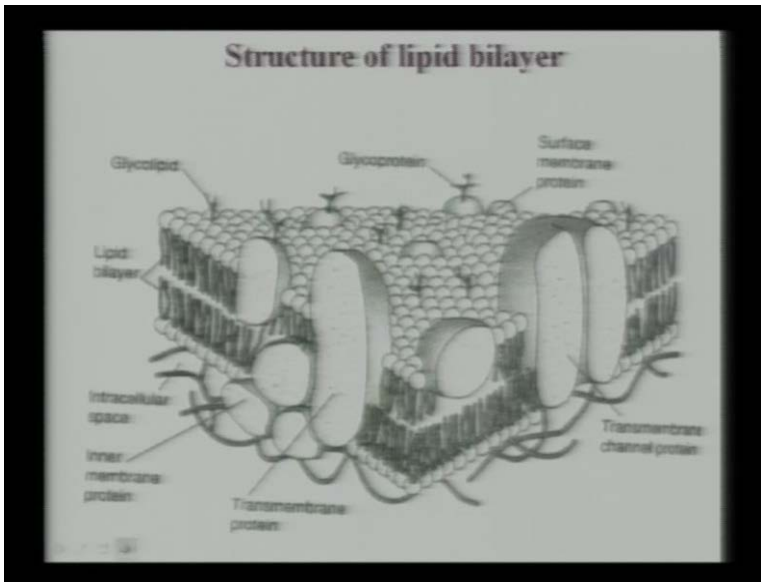

This is a structure of a lipid bilayer, which is the part of the cellular membrane and this membrane actually contains lot of proteins, you have a glycoprotein's which is part of this cellular membranes, we have the trans membrane channel protein, what is meant by trans membrane channel protein, like this protein is actually part of one cell as well as the part of neighboring cell. So, like it is shared between two neighboring cell that is why it is called trans membrane cell protein, then you have the inner membrane protein and you have this this is called the lipid bilayer; bilayer means as the name suggest it has two layers it is compose of two layers, one is the top layer, one is the bottom layer and each layer contains a number of different type of protein molecules which they contain.

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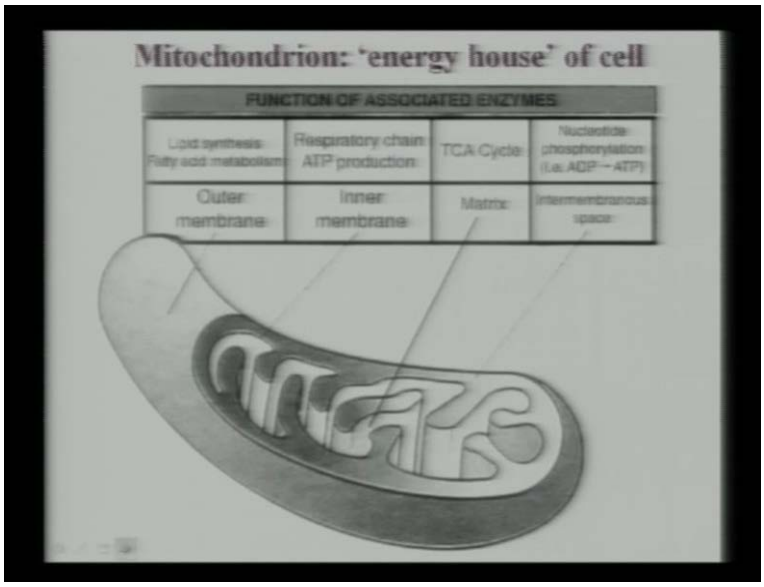

Mitochondrion, it is called the energy house of the cell, now you have the outer membrane which is essentially used for the lipid synthesis or the fatty acid metabolism you have the inner membrane. So, it has the two membranes again structure, so one is the outer membrane, one is the inner membrane; now inner membrane actually is useful for respiratory chain or ATP production, you have the matrix here this is used for the TCA cycle and you have the inter membranous space, which is used for the ADP to ATP conversion, ATP means adenosine diphosphate to, adenosine triphosphate that conversion, that releases the energy and which is used by the cell right.

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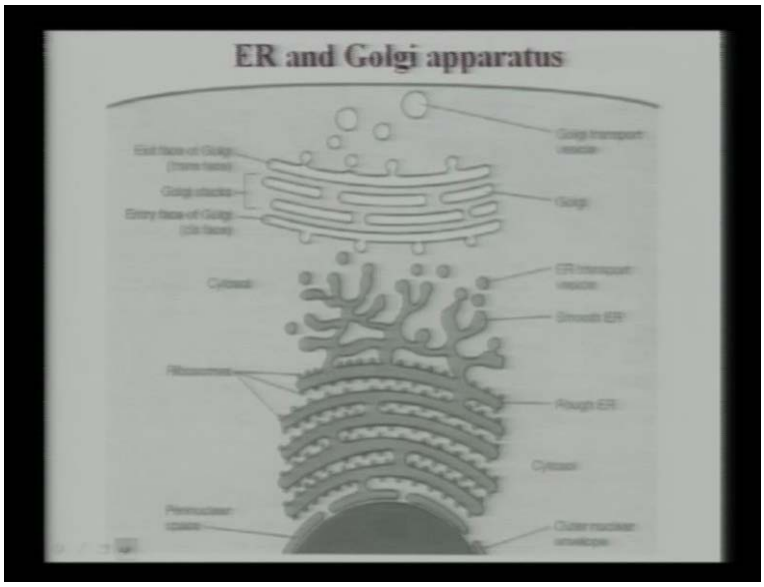

So, this ADP to ATP conversion takes place only in the inter-membranous space, so that is the region where this energy is produced. Now, endoplasmic reticulum and the Golgi apparatus this view graph shows they are actual morphology, now this entire things which is very near to this cell this is called endoplasmic reticulum, you have some rough endoplasmic reticulum that is ER and you have some smooth endoplasmic reticulum, then you have the Golgi apparatus which is also kind of a inter connected layer like structure, and you have the entry phase and the exit phase of the Golgi apparatus.

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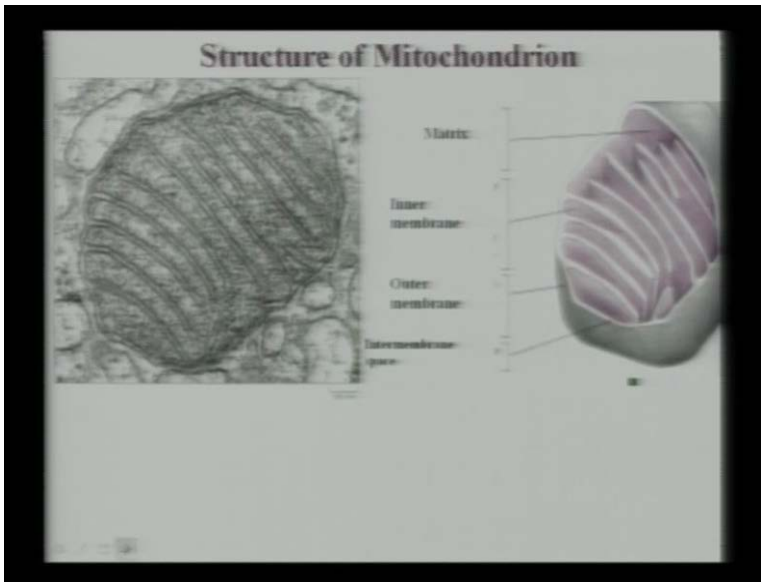

You have the structure of the mitochondrion, which is very clearly shown here this is TEM image, and this TEM image essentially tells you what is the typical dimension this micron body is kind of hundred nanometer that means, this length would be roughly around 1 micron. So, his is the 1 micron that is the typical size of the mitochondria.

Sometimes this size is also important, because this size will tells you to identify when you look at the cells structure that, how fine or how small this mitochondria would be in real life right. And then inside this mitochondria you see this is the inner membrane space that where this ADP 2, so this is the between these two membrane where the ADP to ATP synthesis takes place and that releases energy, and this is actually reflected here in the series of the parallel kind of a concentric kind of lines here in the mitochondrion structure.

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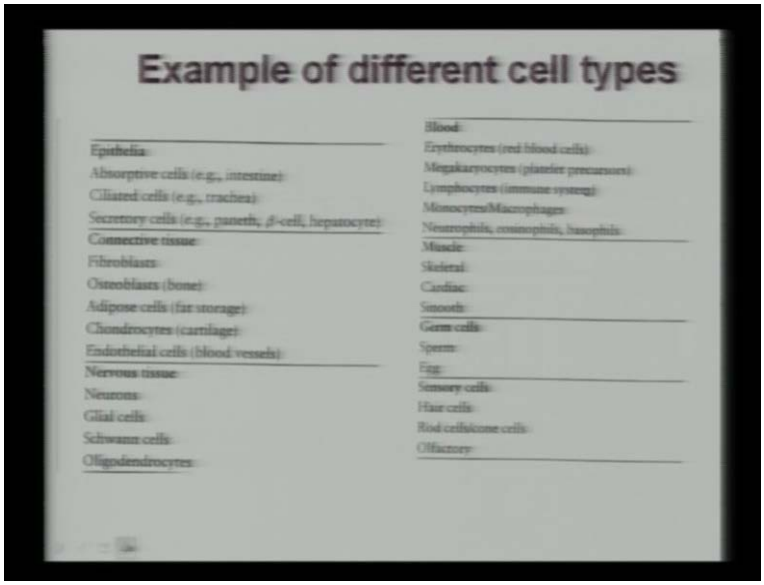

Now, examples of the different cell types, now here I have, I mentioning that what are the different cell types that are possible, now if you start with the blood cells you have the RBC which is called erythrocytes, you have the lymphocytes which is the immune system and you have the monocots or macrophages. In the connective tissue the first cell lies which is important is the fibroblast, you have the osteoblast, osteo means bone a bone forming cells is known as osteoblast, chondrocytes that is the cartilage tissue cells, so cartilage tissue cells are known as chondrocytes.

Now, you have the endothelial cells that is called blood vessels, now you have the neurons which is part of the nervous tissue you have the epithelia that is either secretary cells or absorptive type of cells. You have the muscle, that is the skeletal, cordial or smooth muscle cells and you have the sensory cells like hair cells or rod cells etcetera. So, out of these are the important thing for you to remember like erythrocytes here it is called fibroblast, the connective tissue cells osteoblast cell lines chondrocytes cell lines endothelial cell lines and neuron cell lines, because in biology you will experience or you will see n number of terminology, n number of differential times it is not it is not easy to remember for a non biologist to really remember all the different cell type.

So, whatever important cell types that you would experience in your research or in your study that is enough and that I have marked it by the star. Again I repeat fibroblast cell line, osteoblast cell line, chondrocytes cells, endothelial cells, erythrocytes, monocytes these cell lines are important for you to remember.

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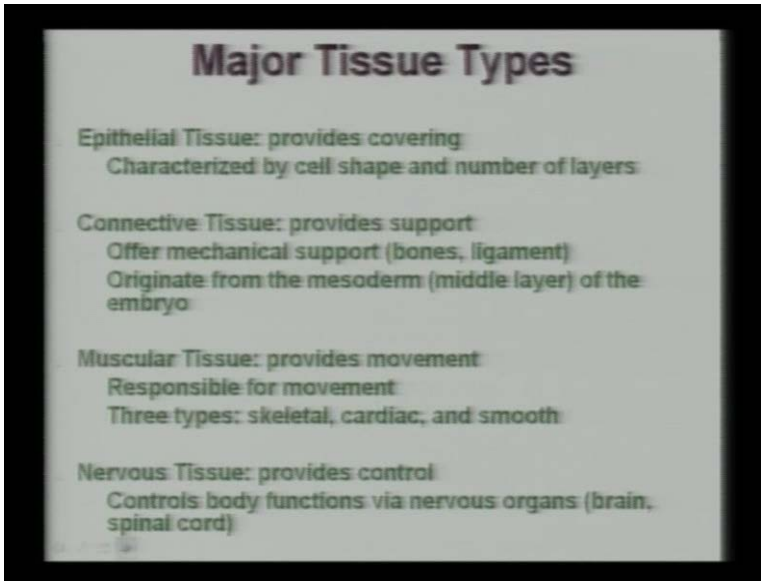

Now, again here these major tissue types like endothelial, epithelial tissue, connective tissue, muscular tissue these are important and this thing I have mentioned here. So, epithelial tissue provides covering and these are characterized by cell shape and number of layers connected tissue actually provides support. So, and this support system actually that means, it can offer mechanical support for example, bones and ligament; it can originate from the mesoderm that is middle layer of the embryo and muscular tissue it is

responsible for movement, like skeletal, cardiac or smooth muscle cells. So, epithelial tissue actually it is like a forms like a protection from the outer environment, connected tissue it offers you mechanical support, muscular tissue it offers you like skeletal or cardiac tissue and nervous tissue it provides you control, like total control like the way you move, way you run everything is controlled by your nervous system sorry, it provides the control of the body functions.

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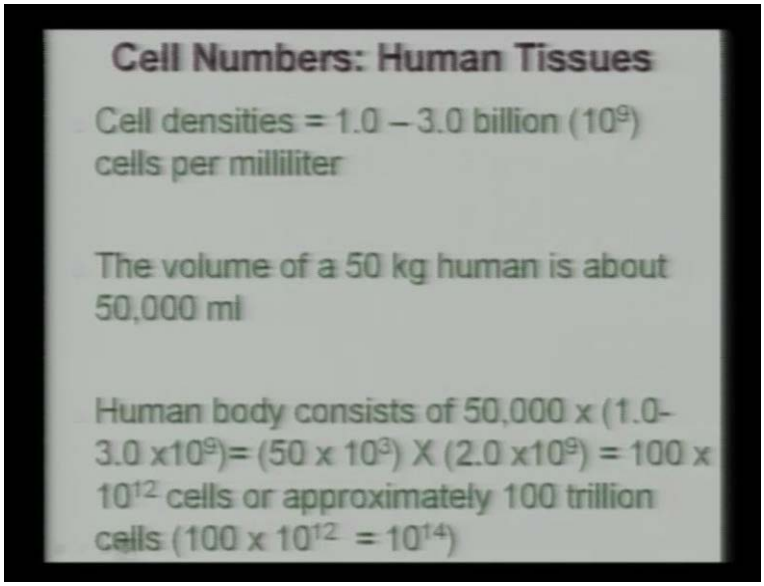

Now, what is the typical cell numbers on human tissues, sometimes these numbers are important, so that you have a feeling that what are the typical cell densities, cell densities can be 1 to 3 billion, like 10 to the power 9 cells per milliliter that is the typical cell densities you have; now the volume of a 50 k g human is like 50000 milliliter. Now, 50000 milliliter, now if 1 milliliter contains let us say, you talk about 3 into 10 to the power 9 cell lines, and you have 50000 milliliter, so that is again 5 into 10 to the power 4. So, total you have roughly equals 15 into 10 to the power 13 that is the number of cells that you have in the typical human body.

So, when you talk about cells, now this 15 into 10 to the power 13 cells they are of all different types, like you have some connective tissue cells, you have some osteoblast cells and so on. So, around 10 to the power 10 to the power 13 numbers of cells are they are in the human body, it also depends on what is the weight of the human body and

accordingly total number of cells also will be changed. So, roughly for a 50 kg weight human body you have roughly around 10 to the power 13 number of cells.

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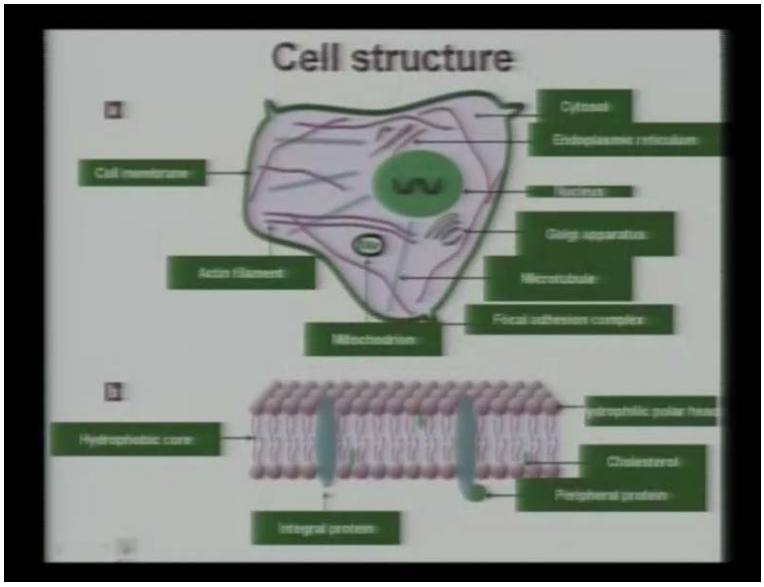

Now, this shows a typically more kind of very schematic picture of the cells and here it shows again clearly that what is the 3 t important components of the cytoplasm that is our cytoskeleton, that is acting filament microtubule and there an intermediate filament and all other typical, most important cellular organelles like Golgi apparatus as well as mitochondria everything they are mentioned here. In the bottom part of the slide what you were seeing is the lipid bilayer structure and this lipid bilayer structure contains one is the integral protein or peripheral protein and then you have the cholesterol here, and then third one is the you have the hydrophobic core, so this is the hydrophobic core region, you have a born layer protein here, you have a another layer of protein here, and that is why you have different lipid bilayer proteins.

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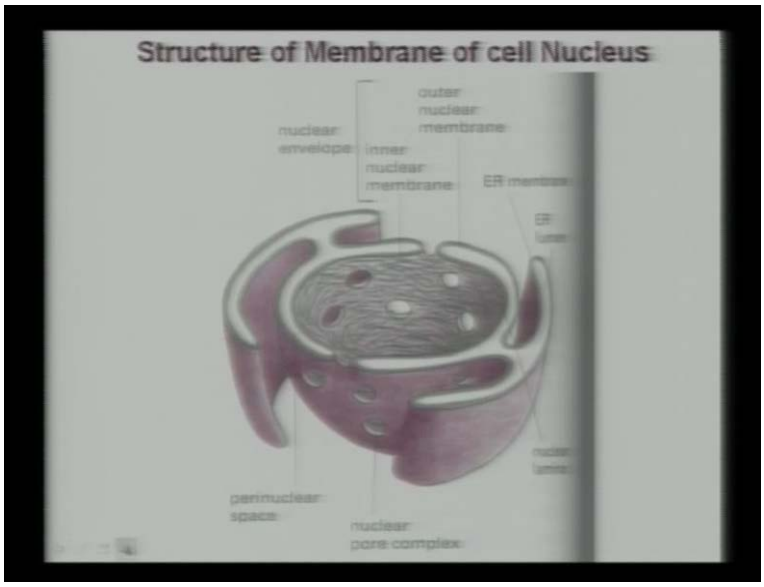

This is what earlier I have told you about the nuclear membrane or nuclear membrane what is the typical structure, again if this membrane also has a typical bilayer type of structure, you remember mitochondria also have a bilayer structure, and also the some of the other materials also a bilayer structure. In the nuclear membrane you have the outer envelope and you have the inner envelop and you can see this small pores here this small pores are actually called, actually found nuclear pore complex NPC, and these NPC through this pore channels your proteins can be transported to and from the nucleus. So, either the protein can be transported to the nucleus or protein can be transported out of the nucleus.

So, this internal structure or biological structure of the different cellular organelles is important for you to understand, the different kind of mechanisms that you will see in the future slides, that so that you will understand that and you can correlate, how they can be correlated with the internal structure of the cellular organelles.

So, remember nucleus just like mitochondria also has as a bilayer membrane, and you have a outer layer membrane and you have a inner layer membrane, and the inner layer of the nucleus contains the nuclear pore complex that means, a finally divided pores it is here distributed in the nuclear pore.

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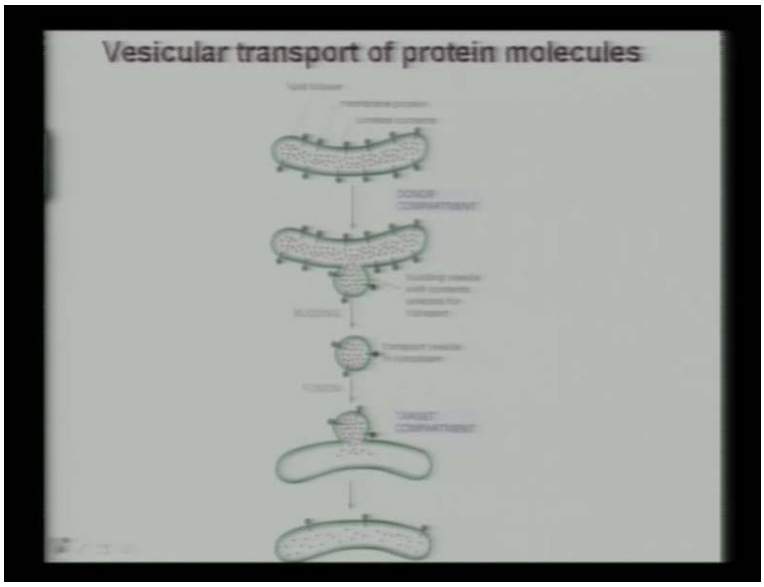

The other thing that is important to understand that you know, that inside the cell or from one cell to another cell the protein molecules they are transported, throughout the living humans system. Now, how this protein molecules they are transported for example, if you have a lipid bilayer and in this lipid bilayer all this protein molecules are presented or present one of this protein molecules are in critical number, then it form a physical and this small physical can be transported and it can be attached to the another cellular organelles and so that, it can be transported to the inside the cell.

So, essentially this can go to the, from the donor compartment to the target compartment, donor can be one cell type, target can be another cell type. So, from one cell to protein to another cell protein that is possible biological.

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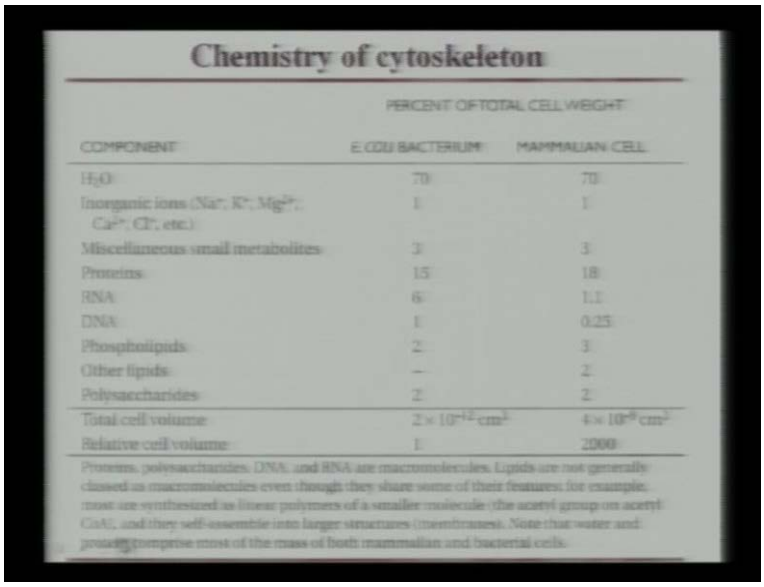

Now, what is the chemistry of the cytoskeleton, typically we have shown here one for mammalian cells like fibroblast or osteoblast cells and one is the e coli bacterium. Now, water contain is around 70 percent, so all the cytoskeleton is essentially a water rich environment then what is important here, the protein content he has the 15 to 18 percent and the rest is you have the polysaccharides or phospholipids or DNA or RNA. So, in case of the e coli bacteria your DNA and RNA are all they are in the cytoplasm, but in case of the mammalians cells your DNA and RNA are mostly enclosed in the nucleus.

So, essentially you have the water and this water plus protein, this is essentially the major constituents and they make like 85 to 88 percent of the total cell volume, rest is that either DNA, RNA or some phospholipids and small metabolites, so that is it that is the content for the cytoskeleton.

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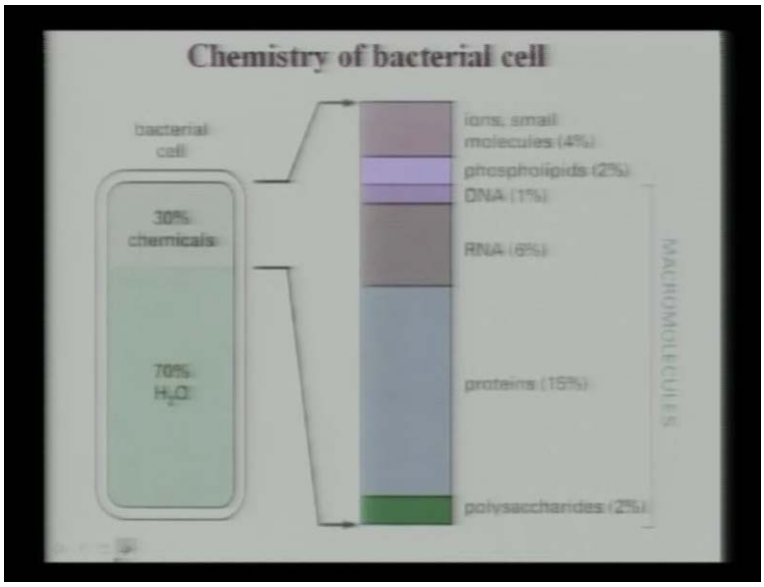

Now, this is like a chemistry of a bacterial cells here you have the 70 percent water and 30 percent chemical, now 30 percent chemicals means, out of that you have some irons you have some DNA and you have some RNA. So, RNA is 6 percent and DNA is 1 percent and you have protein content is the majority or 50 percent of the other chemicals is protein and that is means, so 14 percent is 15 percent and you have polysaccharides are 2 percent.

Now, all this proteins DNA, RNA they are called as macromolecules, so essentially these are like polymeric materials, and polymers means it is like number of mar units they are coming together and they form is macromolecular structure; this actually clearly shows, this view graph clearly shows that what is the typical structure of the cytoskeleton.

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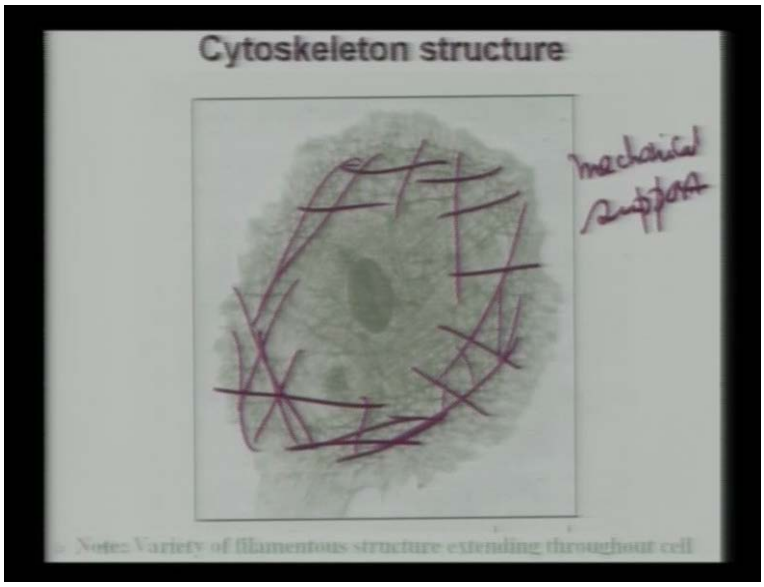

Now, cytoskeleton if you remember that you know it is a very oven need kind of formation it is like a net, you have seen the net in the net you have this all this either square type of net or circular type of net. So, this kind of, it is like a fibro structure like acting filaments, intermediate filaments or microtubule and this fibro structure they are also inter connected, but they are like cross fibro structure and this kind of fibrous arrangement any kind of physical object which is a fibrous arrangement they can support or they can bear lot of load, so that is the reason this kind of cytoskeleton structure they essentially provides mechanical support. So, mechanical support that is possible, because cytoskeleton is essentially you has an extremely fibers and well need well interconnected kind of structure.

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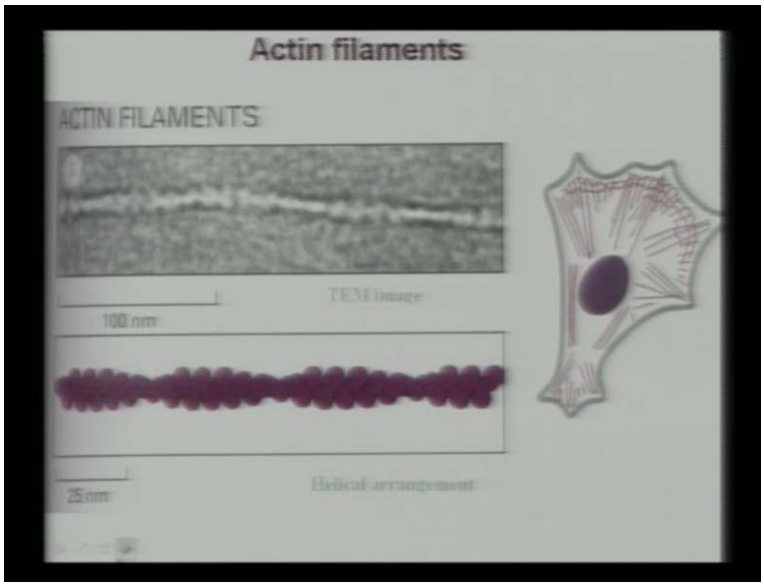

This is the typical arrangement of the acting filaments, you can see it is like a long chain like molecules like macromolecules structure, and this is here it is shown that how the different mod you need, they are connected to each other and they are attached to each other. And here it shows that how inside the cytoplasm, how these acting filaments they really form a very close need fibrous like structure, which is distributed uniformly almost throughout the cells surface.

And if you see that more relatively description of this acting filament, it has a more like helical type of arrangements and if you look at that dimensions of this acting filaments, if it is 25 nanometer, so each long chain can be somewhere around 200 nanometer, 200 nanometer means it is roughly around 0. 2 micrometer. So, that is the typical length of this acting filament structure and what is the typical mechanical property of the acting filament?

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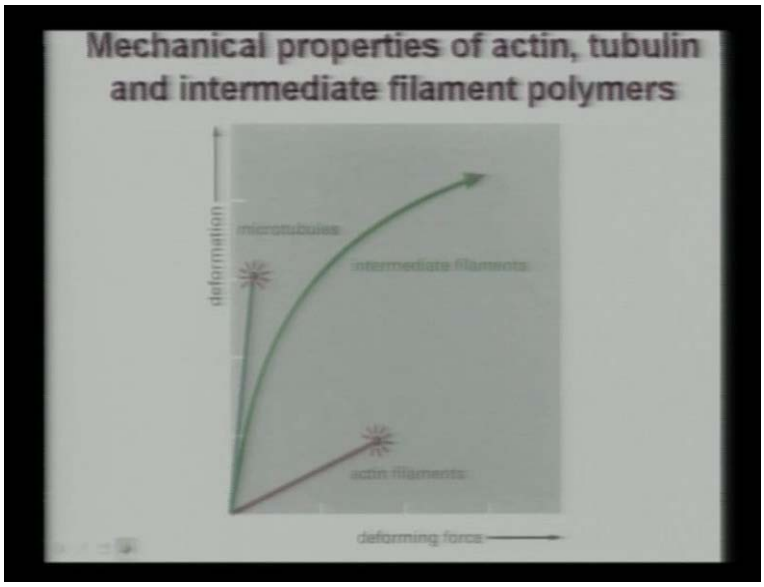

So, here it is a deform force and here is the deformation, and what you see the acting filament it has a more linear type of behavior, like a brittle behavior, microtubules also as a more linear type of behavior goes to fracture and intermediate filaments, has a more initially linear and then non-linear behavior. So, non-linear behavior are more strain to fracture that is possible in the intermediate filaments, but all the acting filaments on microtubules they have a exactly like brittle behavior and which is more like a classical brittle behavior, classical linear type of behavior. I think I will stop here, and in the next lecture I will continue with these differential properties.