Bioengineering: An Interface with Biology and Medicine

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Lecture - 27
Developmental Biology

So welcome to the MOOC course on Bioengineering: An Interface with Biology and Medicine. Today we are going to talk about development, especially if you remember from the last lectures we started discussing about cell, cell cycle, different type of cell division, mitosis, meiosis, etc. In the same theme, I think it is important to understand that how 1 single cell could actually evolve into the embryo.

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So first we are going to talk about the development, which is 1 of the most important processes of our life and then in which way modern technologies, biotechnology and tools have really helped us to understand this process so well that we could detect many of the defects at the early stage and try to make some sort of predictions based on those understanding.

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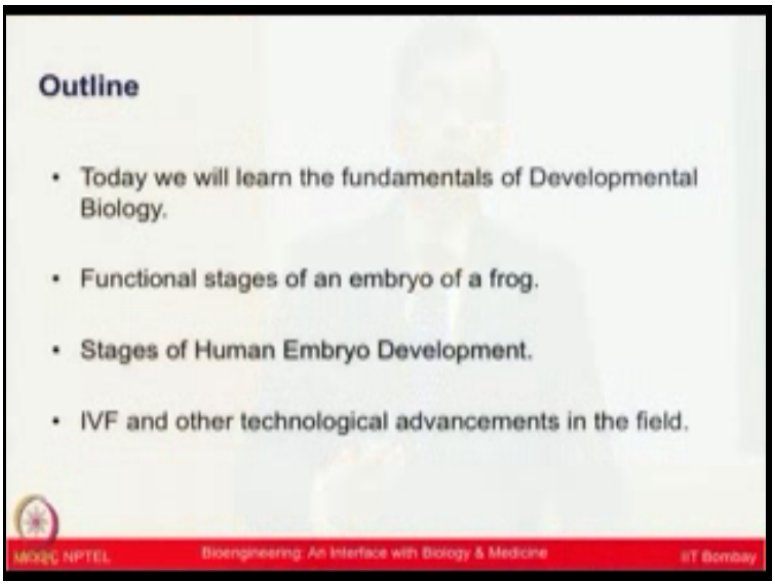

Let us first start with discussing about development. You know another way of thinking about cell is that you know in which way know that same cell could actually give rise to an embryo and then finally birth to a child right. So we are still discussing in context of cell, but today major focus is the development part. How did a single cell develop into the embryo. So now some of the concept I think we have to correlate from the previous lecture. We have to continue in that.

If you think about meiosis, remember we talked about gametogenesis process. The gametes formed in meiosis, sperm and ova right. So in this process now we are going to continue on that to see the fertilization followed by developmental stages, but the very first question, which should come to your mind that you know why at all we should study development.

And there are many reasons to study development. Of course, it is you know one of the such a crucial process that which tells how we evolved and still for many of the crucial links you do not have clear answer that how we got involved in the evolution chained right. It is also now important to learn that you know what are the different profile happens over the period of the entire gestation period during development of features.

What could be going you know, which we can monitor that it is going smooth or is there some sort of you know aberrations are happening, some sort of you know mutation might be happening in the embryo, how to actually check those out and how to rectify those. So many of

the errors can be already diagnosed at the newborn level or even just before that you know because you have to then take a decision whether this is right embryo to continue or not.

So understanding more of them actually probably can reduce the burden of many of the disorders, which we may see that of course there are a lot of ethical issues and many you know controversial issues could be debated about it, but broadly I think it is good idea for us to know that what is going on at the embryonic stage level and is that normal process or some sort of aberrations are happening.

So many of the diseases people do check at the very early stage itself, including different type of you know heart related disease, neural defects, club foot, etc and with more and more advancement of technologies that now you will see that during the pregnancy there are 100s of tests being done to ensure that you know a variety of parameters are in place or not and that differently needs you know a good integration of knowing about biology what we want to measure and using engineering skills to ensure we have sensitive devices.

We have very robust modeling system, very robust data analysis system to really do those predictions.

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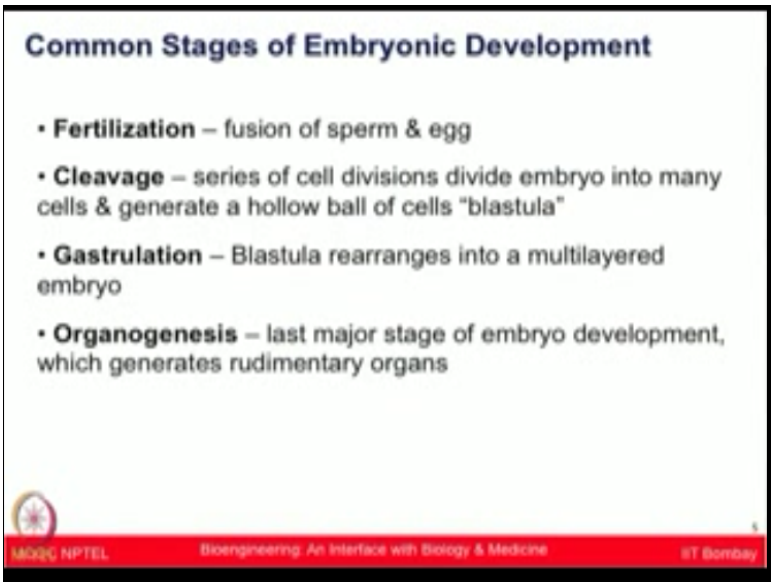

So you know before I come to the actual developmental cycle, let us kind of you know familiarize you with some terminologies. Fertilization process of fusion of both the sperm and egg, which we have seen in the meiosis and mitosis when I was talking to you about the cell cycle part. Cleavage when series of cell division happens and that you know the sperm and ova fuse now and that one cell is now dividing to 2, 4, 8, 16, 32, 64, morula, blastula, gastrula.

Many of these you know stages are following for development to happen. So all those divisions are part of the cleavage and eventually it generates like a ball, which is surrounded with the cells, which is known as blastula. Gastrulation is the process when this blastula has already rearranged the cell into multiple cell layers and interestingly the inside part is pretty hollow and that has some liquid. So it is mainly surrounded with the outside multi-layered cells.

And then of course the organs has to be formed in a process known as organogenesis. So now what is interesting to note that you know while newborn will come after 9 months' time, but even much ahead of time, the fate of the organs already get decided and once you start monitoring those at a very early stage of the embryonic development itself. Let us first you know go back to little you know simpler organism, talk about frog.

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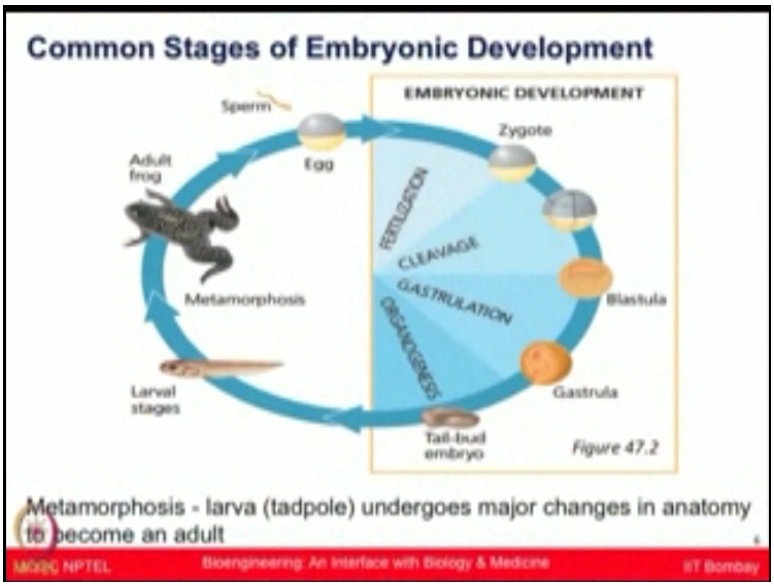

So frog embryonic development, a little interesting, because if you think about from the evolutionary point of view, although you may not have a steady revolution in detail, but at least

you would have monitored that you know in a rainy season, you would have seen some tadpole in the pond or you know some sort of water tanks and those after sometime result into a frog which just jumped and you know reaches on the land.

So same organism can actually survive in 2 conditions and that is what is known as amphibian, right. So it can live both in water and in the land and there are lot of evolutionary adaptation, which it may have, therefore it is also very crucial. People feel that it is a important evolutionary link in which way from the water the life may have evolved on the land.

But it is interesting here that you know all the early stages from zygote to the blastula, gastrula formation or even early stage of the embryo formation, these stages are pretty similar to what you would observe even in human or other vertebrates, other organisms like fertilization, cleavage, gastrulation, organogenesis. All of these are very common stages. Now additionally this additional thing happens here.

This larva is now changing to the adult form and many changes are happening because it contains a tail, which is required for its water life, aquatic life. Now this tail has to somehow you know disappear through process of apoptosis and then it is going to change to the adult frog. This process is known as metamorphosis. So this is one of the very elegant example of a simple organism showing a different developmental cycle and also interesting from the evolutionary point of view, also showing you in which way the same you know genetics set of makeup could result into 2 different type of morphologies.

So metamorphosis is a process where the larva, tadpole in this case undergoes major changes and transforms into the adult frog. Let us think about the egg and there are factors which dictates the polarity of the egg. So 1 pole is known as animal pole and second pole is known as vegetal pole and again many of these things you know are not random. They are pretty much fixed even in a quite early stage.

So even when meiosis is happening, oogenesis is happening, that time itself the fate is decided, at which part of the ova is going to transform into the animal pole, which part is going to form the vegetal pole.

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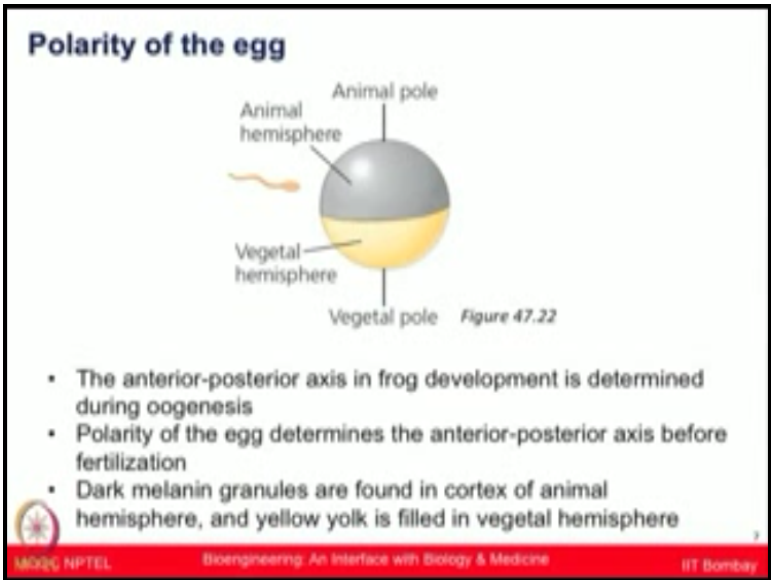

Of course the animal pole is much rich in the dark melanin granules and the vegetal pole is much rich in the yellow yolk size. So these 2 you know just orient the cell in that format and now many of the division, which has to subsequently happen will happen in this particular type of orientation in the anterior-posterior axis. Now let us come to more of the human fertilization and development process.

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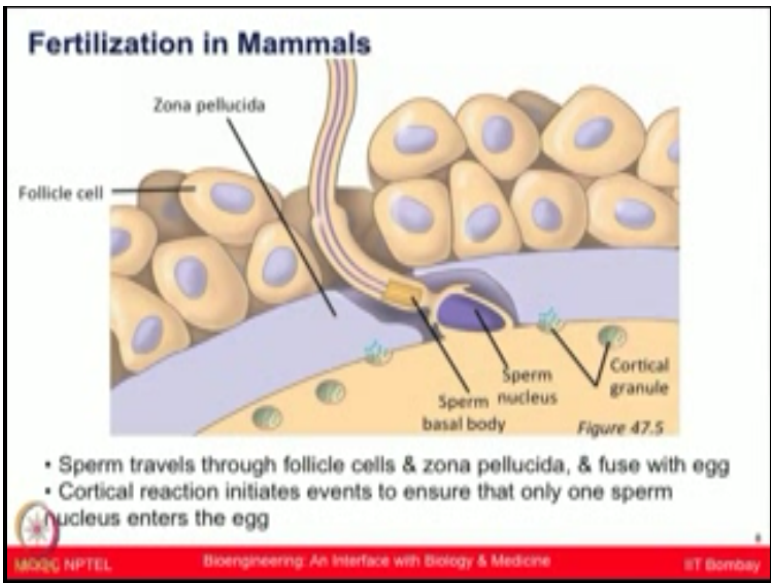

During the time of fertilization, coming from the follicle cells and zona pellucid layer, the sperm travels here and now try to reach and nuclei have to fuse to the ova, ova nucleus. Now there are many sperm which are simultaneously traveling and they are trying to compete to fuse with the nucleus of the ova. As soon as the first nucleus of the sperm with ova nucleus get fused, a reaction starts which is known as cortical reaction.

Coming out of the cortical granules they disperse on it and kind of put a coating, a solid coating on top of those fused nuclei, just so that now other sperms cannot compete. So therefore you know it is only one sperm nucleus with one egg nuclei is going to get fused with one ova and then that is going to further result into the embryonic development and this process is controlled, you know there are many factors involved.

So again I am just trying to give you a very simplified picture here. There are a lot of things also involved including the role of calcium, in which way it kind of changes some of the potential differences over there as well as many granules coming out of the cortical granules, which has stopped this reaction. So many things together ensure that multiple sperms are not fusing with the same egg or you will not see multiple fusion happening.

So when that process happens and let us say that process result into a successful fertilization event.

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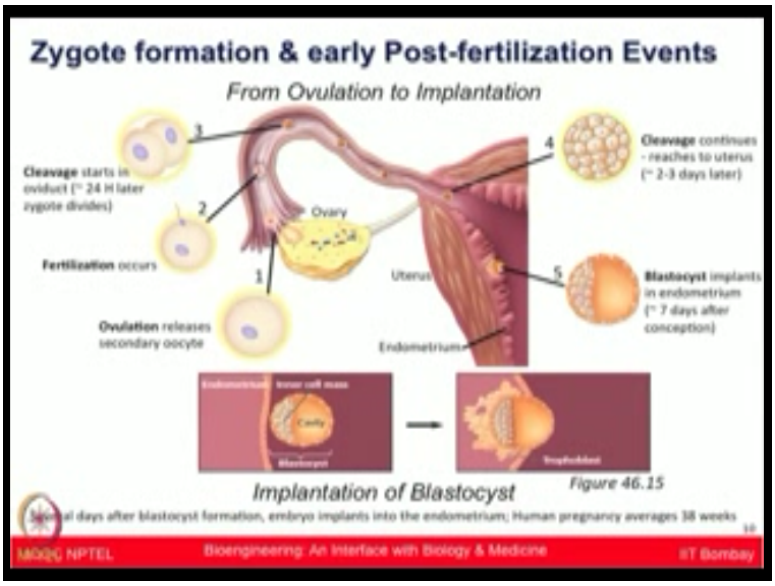

I am going to now a list out couple of events from ovulation to implantation. So very first thing is the release of secondary oocytes from the ovary, which is going to happen. Now the fertilization occurs the way I showed you in the large image. One of the sperm is going to fuse its nucleus with the ova and then the cleavage process starts. Immediately in fact even within 24 hours' time, it starts forming different cells and it is all moving it inside the uterine layers.

Now within 2-3 days' time, it is trying to reach to endometrial layer, so that it can reach and make a place for itself where it can start getting all the nutrition which are required for further embryonic development. So after almost 7 days, it reaches to the endometrial wall of uterine layers and then implants into the endometrium, which is known as blastocyst. So around 7 days after the conception, this process happens and this is required to get the nutrition for these cells to further divide.

And of course then if this have been successfully implanted which you know depends on many factors, which are governing it, then it will continue for you know several weeks and almost 38 weeks has to be continued over there for the full embryo to develop.

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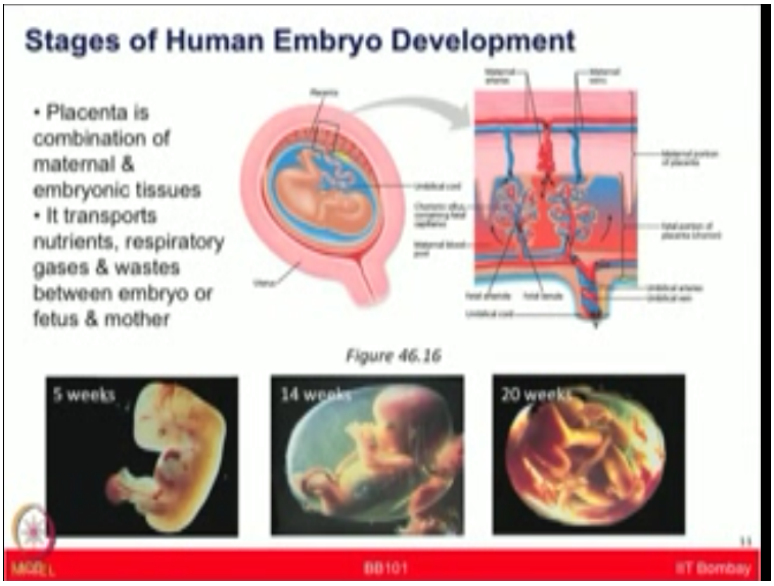

So these are some of the images shown at different weeks, 5 weeks, 14 weeks, 20 weeks, you know the organs are keep developing. Organogenesis are happening, what is important here that this embryo is totally developing on the mother's nutrition and that environment and to connect that it has the placenta and those placenta is actually providing all the nutrition from the mother to the child is coming and all the gases all the oxygen requirement and so with all kind of its excretory material, which has to go out also just being connected from the same layers.

So everything it is utilizing and transporting through mother with layer of the placental membranes some of the embryonic tissues, which are involved in doing that and there are set of those tissues which are known as extra embryonic membranes.

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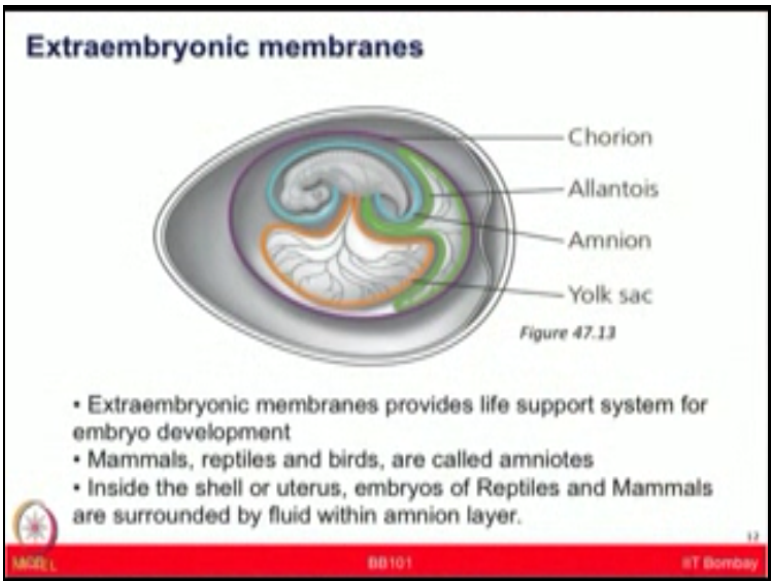

One could term 4 of them clearly, one is chorion, allantois, amnion, yolk sac. Amnion is quite close to the embryo as you can see here. It is just you know close here, the blue one. Now within this, there are some fluid available and that fluid is known as amniotic fluid and that fluid provide lot of you know nutrition for the life-support of the embryo. So this is closest to the embryo whereas there is you know good role of each one of these membranes.

But this is the kind of characteristics, which one would observe mainly in the vertebrates and especially in the mammals, reptiles and birds and therefore they are also called as amnoides. I think it is good idea to even they are you know difficult terminology; I think good idea to still keep in mind. What are amnoides? Amnoides are some of those vertebrates which contains these extra embryonic membranes including amniotic membrane.

Inside the shell or uterus, especially embryos of reptiles and mammals, they are surrounded with the fluid in within the amniotic layer. Now these things have quite a important role, which we will talk how people have made use of this information with the technologies for all kind of detection as well as the monitoring the progress of the embryo, because that is the time when it is you know you want to really monitor the progress very closely.

At the same time, you do not want to touch embryo, you do not want to harm embryo. So another interesting fact is that you know if you think about cell division, we talked about you know

cancer cell uncontrolled growth happening right. These are also cell here and they are also growing right, but they are not relating into the uncontrolled mass like what we would have discussed something in the context of cancer cells right.

So there are certain distinct thing happens during the cleavage process, which makes it different than the normal cell division process and those differences are here.

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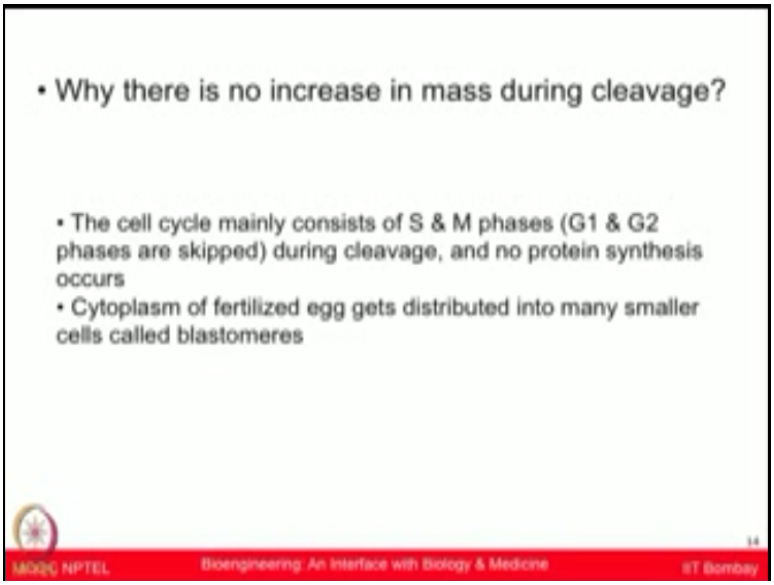

That it mainly consists of S phase, which is required for the DNA replication and M phase or the mitotic phase. It has very shorter G1 and G2 phase and almost no protein synthesis happens. So some of these are actually not the same cell cycle pattern, but I have talked to you about in the normal cell cycle right. So some of these things are slightly distinct features here and then cytoplasm of these fertilized eggs, they are getting distributed into many of these smaller blastomeres, a smaller cells.

So as a result it is not relating into the uncontrolled growth like what you know, we would have talked in the context of normal versus cancer cell, but here the lot of divisions are happening, but these are is still very ordered division and that result into a cleavage process. So these germ layers, there are you know as I mentioned, the fate of which layers are going to derive which organs actually pretty much pre-destined. It is already decided quite ahead of time.

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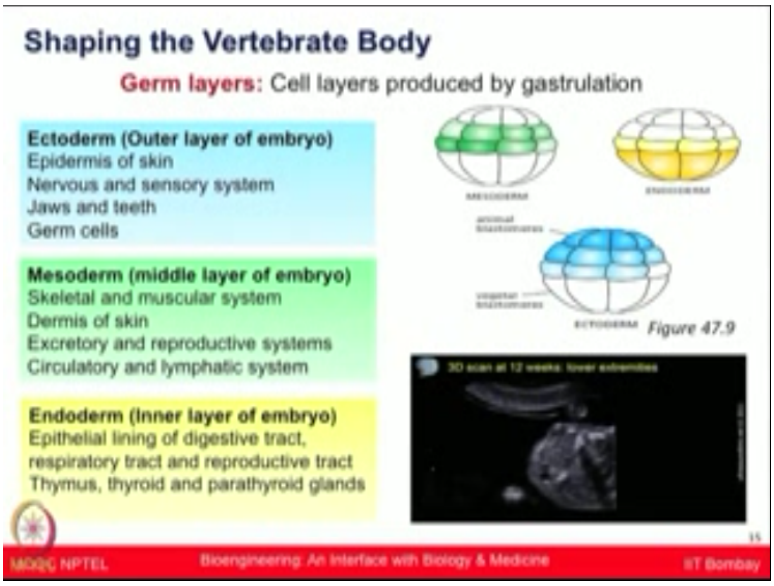

And if you look at this particular you know part, outer part is ectoderm, which is shown in blue color here. So ectoderm is going to derive couple of organs, which includes epidermis, nervous and sensory system, germ cells, jaw and teeth, etc. Terminology wise you know what is, ecto means outside, meso means middle, and endo means inside right.

So now if you look at the middle part which is mesoderm shown in green color, already decide that this layers are going to form eventually its skeletal and muscular system, dermis of the skin, excretory and reproductive system as well as circulatory and lymphatic systems and now if you look at endoderm, the inside part, they are going to dictate formation of digestive tract, respiratory and reproductive tracts as well as some of the glands, including thymus and parathyroid glands.

So now at the very beginning itself you know the fate of the cells already decided at which part of the cells are going to form which organs and therefore if you see some anomaly happening during the development in those cell itself you may have some prediction that you know, why it may dictate to some of the organization's process and which organs might get affected. So morphogenesis or the conversion of you know this embryo into the full shape now.

Where organs has to develop many things happens, especially in the later part of the embryonic developmental stage where gastro has already been formed now and many of the cytoskeletal

elements which we talked they are actually getting reorganized, because they have to give a strength to the baby now and it has to come out and it has to have its own skeletal system. So many of the cytoskeletal system dictates quite a bit of development at that point.

And more importantly there are series of programmed cell death or apoptosis that also happens.

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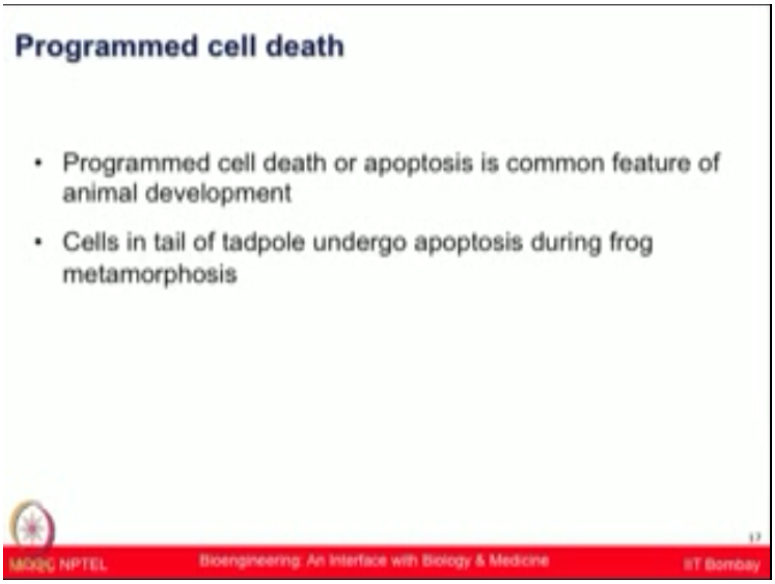

So programmed cell death or apoptosis is common feature in the animal development and more so immediately if you think about the context of frog development from the tadpole larva to making the adult frog, the tail was disappeared right. It means that part has got destroyed and then resulted into the, you know some of those constituents and energy were used for other part of development. So this is known as apoptosis.

Along with these concepts acting what is also important, as I mentioned while there are many things which one would assume that you can build something further, but somehow at these things you know you have to feel there is somewhere you know that eternal power there, which actually dictates many things already and something is predefined somewhere right, because you know some people suffer from certain deficiency or some sort of disorders.

Probably those cells in the beginning itself would have got some issues and which then becomes very difficult for medical science to actually cure or rectify later on. So people have tried to do

some experiments when they try to see are the layers what we are talking right now, the cells from the mesoderm, ectoderm, endoderm, etc. are those cells already defined with the kind of you know what output they may give.

Or you can change their location and they will change their phenomenon right. So for example if you take a cell from the ectoderm layer and move it inside the mesoderm, ideally 1 would assume that because now you have changed the location, then probably it should now behave like mesoderm, but because the kind of nature of those cells, which are derived from those layers they have, they are still showing the same properties from which layer they came from.

So people did 1 experiment and that experiment was known as fate mapping experiment. When they tried to trace the ancestry of the embryonic cells, can you trace the ancestry of these cell from which layer they were derived and as you can see in some of these colorful images they try to take, you know let us say the yellow colored cell and try to place it in a different place, but still the phenomenon, the properties came same.

So it is I think interesting concept to note that embryonic cell stages, they have already pretty much defined their fate which organs are going to develop and these layers are pretty much worked in already a distinct manner. Experimentally derived the fate of map of embryos, they show that a specific regions of zygote can develop into the specific parts of the older embryos.

You know there are a lot of as I said you know, I will try to keep the core concept slightly at the lower level just so that your interest level is still high and you are not feeling bored. Let us think about how some of these you know, I am sure development we can study a lot. We can study quite more in detail. Let me not go too much in detail more further now, but just think about how some of these basic understanding has already started making an impact for the actual practical scenario.

So think about we have studied something about in the context of cell, organelle mitochondria, role of mitochondria right. We know mitochondria have their own DNA and you know they play some essential role at the maternal DNA level. Now there are some disorders, some diseases

which are only happening from the mitochondrial dysfunction. So if there is some defect in mitochondrial DNA, child may carry some of those genes and those properties and they will have some defects.

So in UK, this is one of the interesting study when they figured out then there are you know some women, which have the deficiency of you know certain kind and their mitochondria is having some sort of defects and now if the child is going to be born, they will have some of those issues right. So can they overcome this thing. So by understanding the developmental biology so well and by knowing the role of mitochondria and mitochondrial gene.

Now people are able to you know someway dictate if not totally play with it at least try to make an attempt to play with the nature and try to overcome some of the barriers, which are already there. So let me try to show you what they did in this particular study, but this is not a research study it is actually you know actual patient care example.

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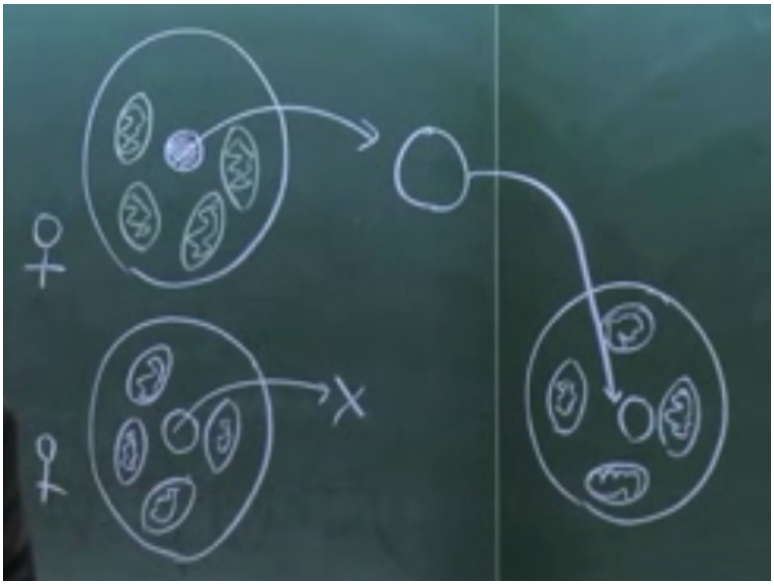

So just imagine that you know you have this cell, ova cell and that is a nucleus there. I know you have many mitochondria inside and now these mitochondria, which I showed you in green color they are defective mitochondria. Now you know if these parents you know, so this female and her husband they have decided that they do not want you know this defective mitochondria in their child and they are ready to take help of another woman.

So in this case what happened, so they took the nucleus from this ova out and now we have another female, another woman who has the normal mitochondria. I am showing in white only here, you remove the nucleus here as well and now destroy this nucleus. So now this particular female you have only mitochondira, and which are normal mitochondria. So now can you move this particular nucleus inside here, which will provide the normal mitochondria and normal nucleus both alright.

So it means you are taking help of 3 individuals a male and female and another surrogate woman to overcome those deficiency and is still trying to get a child, which is healthy both from the normal genetic point of view as well as the mitochondrial defects point of view. These are the I think interesting study I came across and not that is it for research purposes mainly they are trying for the patient care for the infertile couple or for the people who have the child is carrying some defects.

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So they are actually trying now whether this thing can be allowed legally in UK and then whether this could be become a law. So I will elaborate on this particular concept, which I just talked to you.

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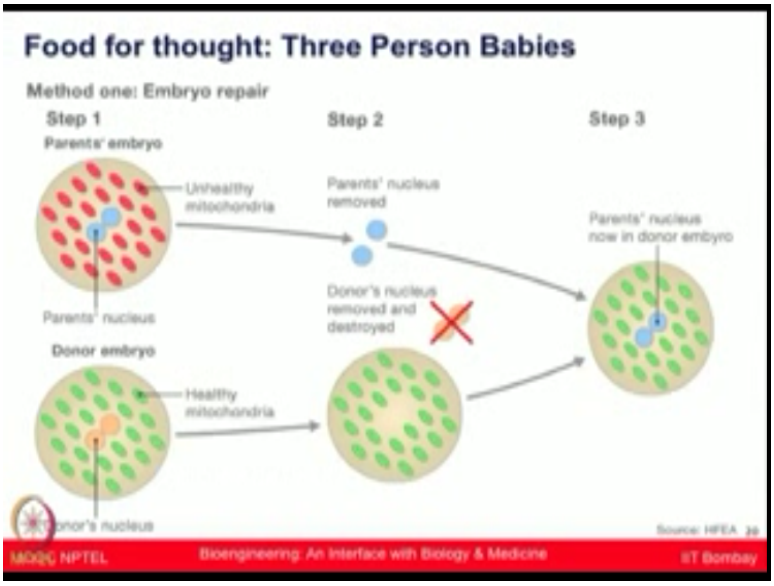

It can happen at 2 levels. It can happen at the ova level directly where what is shown here that you know you are or it can happen in the embryo repair level. So at both the levels, they have tried that you know if you want to even change the embryo, you are removing again the nucleus from there and now using the donor embryo and then fusing those 2 together and then further you are keeping it back in the same original woman.

Or in this case egg repair has happened. So both way they tried embryo repair and the egg repair and that related into quite you know I think interesting and healthy child, which should have overcome those issues. So some of these things are just kind of, you know concept to give you feel that the basic understanding, which we talked the basic concept which we talked understanding those.

And the technology development is actually making lot of difference, especially when people are encountering certain issue that the you know infertility, reproductive care, etc. Let us kind of look at some of the reproductive technologies, and I must say that you know one of the area, which has witnessed and got immensely help from the engineer discipline is this area of reproductive and developmental biology.

Because at developmental level, you have literally no clue, you cannot do any biology experiment at that time. You are totally relying on technologies to tell that what is going inside.

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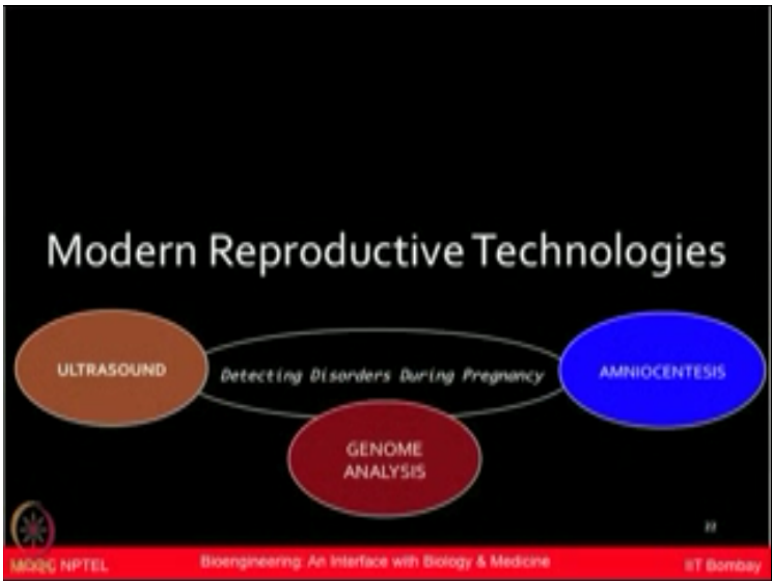

So as a result you are using ultrasound, people are also doing some of the test based on the fluids, which is known amniocentesis. I will talk to you about that or now more recently people are doing genome analysis, to look at the entire gene profile. So let us look at this image. I am sure at least you would have you know read these kind of things somewhere or would have seen somewhere that in which way people are able to monitor the growth of these fetus using ultrasound imaging.

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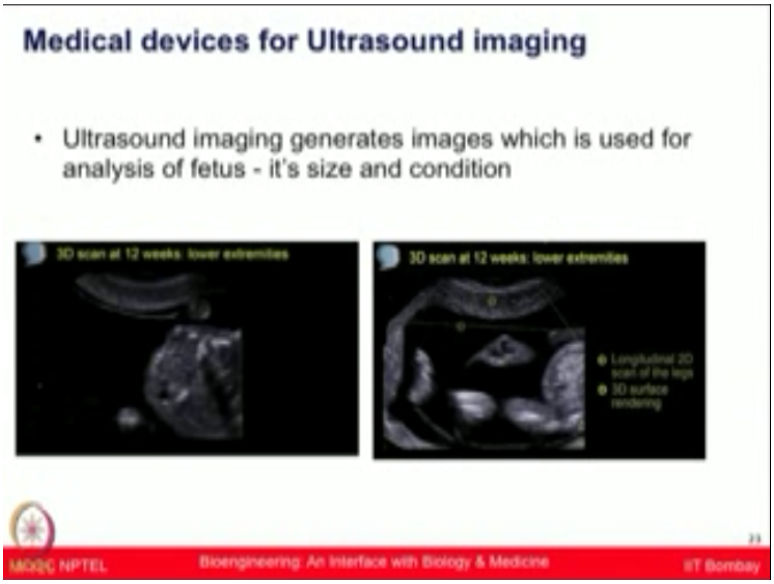

And it is very you know I think good to highlight that in which way people in the medical imaging field are really contributing so heavily, because all these things are you know you are

making some 3D models and you are trying to you know analyze those images and then make prediction that which part is actually is, you know is going to form the foot, which part is going to form the heart, etc. and then your keep, you know also you are doing measurements.

So you are actually now making some, they will doctors will do some scales over there and then you have some you know formulas, which can actually extrapolate to tell that what is there you know actual growth, how many centimeters it has grown, all those details and very, accurately being done. So this area of you know the biology field has definitely benefited very immensely from the engineering tools and very robust technology.

Because you cannot have the wrong predictions at this time right. So you know many people who work in the you know imaging area or the Medical Physics area, I think they you know will feel very happy that this kind of technologies have become very robust and already being used in the clinics. Then coming to the more innovations in biology, more innovations in genetic engineering field, they are also making big impact for you know all of these type of issues which 1 would may encounter.

So people want to test their fetus for the many of the genetic defects and those defects they want to look at their, you know, how their chromosomes look like?

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Are the chromosomes normal, is there any aberration, any defects in any chromosomes are there? That is known as a process known as karyotyping, you are analyzing all the chromosomes. One of the tests which is commonly being done is known as amniocentesis and I will tell two or three tests and then I will actually you know move around to ask your understanding about these tests right. So I am sure you are careful.

So amniocentesis as I mentioned in the beginning, you are having the one amniotic layer right, extra membranes which we talked one of the amniotic layer that along you know inside the embryo, outside the embryo. So from embryo within the amniotic layer, there is some amniotic fluid there and those automatic fluid you are trying to take out from this fetus.

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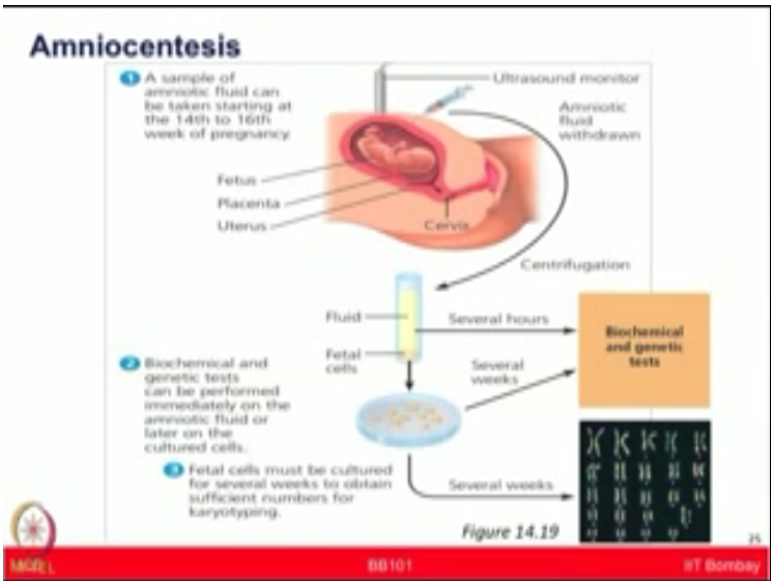

And at the time of 14 to 16th week of pregnancy and you are just taking out the fluid, a small few micro liter. You are doing the measurements on a very, very small scale. You cannot take in the mls right, you have to take just take few microliters and from those microliters you are assuming there might be some cells present and those cell you can use to extract some DNA out. So it is possible that you may have you know only one or two cell and you may not have been lucky to get enough cell out of it and at this stage, which is early stage you may not assume too many cells to be present there.

So people are trying to get some of the amniotic fluid out and then you can concentrate those, you can do centrifugation process to ensure all the fluids that you taken out, only the cells are actually filtered down and now those cells you want to make multiple copies of those cell because then only you can have some DNA. So they can culture those on the nutrient mediums. So that these cells can grow and make many copies of those cells.

And now from those cells, then they extract DNA, then they look at their entire chromosome profile, how the chromosome pattern looks for this child. So this thing takes some time because you cannot just take the cell and do the analysis right away, you do not have sufficient DNA. So you have to wait for the cells to grow further outside, you know when which you are doing in the lab and then after that only you can do some sort of genetic test on that.

This process is known as amniocentesis, because you are using amniotic fluid, right. Names look tough, but like I said not too much, if you use some logic. Second test is known as chorionic villus sampling or CVS.

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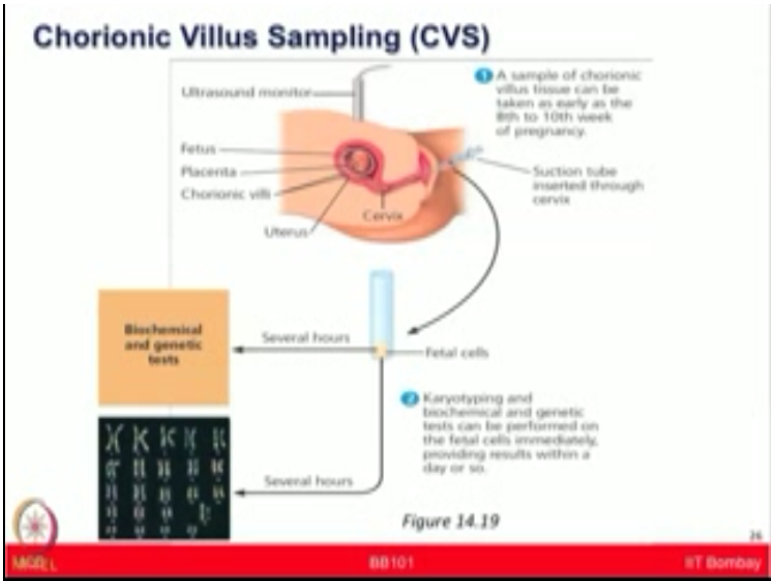

In this case, the first one we talked about fluid, the second case they are taking some of the chorionic villus tissue, a small bit of the tissue, of course you do not want to damage the fetus, you are just taking a small tiny bit of the tissue over there and then from that tissue, you will

have much more cells as compared to the fluid what you would have taken. If you suspect, you know that child might be carrying any of the genetic disorder.

If the parents have you know some sort of disorder to begin with; they are suffering from (()) (30:10) or Down syndrome etc and if they feel that they want to test for their child that at the early stage and they want to take a decision, they want to continue the pregnancy or not then they want to do it much early, much ahead of time. So in this case they are you actually using the tissue, but they can do 8th to 10th week itself.

Keep some of these timelines in mind okay. It is a pretty valid for me to ask you, you know, at different contexts on a developmental stage, what kind of test should be more preferred and I am sure they know, if you pay attention to these things you have much more cells available from the tissue, you can do much early. So CVS can be used at much early stage. Amniocentesis can be done slightly at a later time point.

So in this way again you can do all the biochemical testing, karyotyping, etc. Now much more newer approaches, as we are going along I will have a full lecture on the biotechnology tools and technologies that we are progressing and how they are making a huge impact for the medical in many applications, but just to know brief you again, how to sequence the DNA, all the genetic material what we have, we have made huge progress in that.

Now we have you know those sequencing technologies which can sequence all your genes in three or four days' time, which was earlier not possible people did bigger projects and they try to sequence one human in 15 years' time. Now over the time period again in a lot of engineering revolution has happened, a lot of technologies have come into the place. Therefore, now you know sequences can be much faster, much more accurate, much more cost-effective, one could do sequencing much faster.

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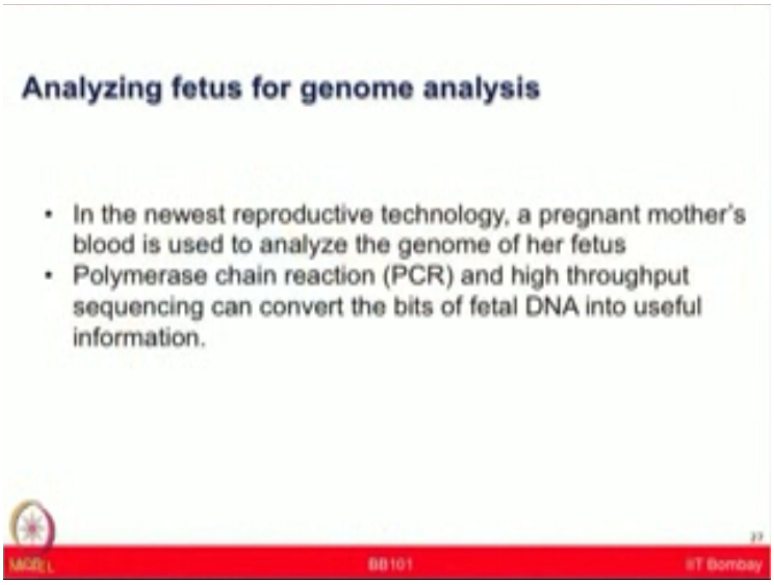

So people are using sequencing technologies as well as polymerase chain reaction, which can amplify the DNA and then you can do DNA analysis and some of these technologies, they are looking at, so they are using the pregnant woman's blood sample, extracting DNA out of it, assuming that you know fetus would have exceeded some part of their cells, which is part of the mother now and then you are making an assumption based on these facts by doing the much intense DNA analysis.

Many times you know if couples are not able to do proper fertilization, they feel that you know they have to take some medical help and again there is an area in-vitro fertilization.

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Which has really solved problem for many infertile couples and you will see lot of you know interesting examples happening how the IVF technologies have been used heavily. It is costly technology, but in this case you are still following the normal rules of the development. You are taking a sperm and ova from the individuals who want to have a baby and then you are using the laboratory condition for the fusion to happen properly.

Because there is some reason for which the fertilization is not happening successfully. So then you are trying to monitor change in those conditions and in this case you are actually moving the nucleus out from the ova, you are removing the nucleus from the sperm cell, you are trying to fuse them together and once in the beginning for you know several cell developmental stage. Once you have observed it going fine, then you put it back in the women for the normal development to happen.

Or sometime it can also be kept in a different woman, which is known as surrogate mother where it is not you know from the same parents, somebody somewhere else. I am sure you would have heard some celebrity examples, where you know they would have use of surrogate mother for their child to happen right and there many times you know if woman are older and they have got some complication. So then they again they can take this kind of help.

So this field has really, you know, resulted into practical you know help to many couples who were not able to conceive properly and they have infertility problems.

And just by doing the simple ways of knowing how to you know take out the nucleus from the ova and what can be the good culture conditions for it to grow all of those have resulted into these successfully overcoming this medical disorders alright. So today we try to understand the development process in a very simplified way taking examples of frog first and then we talked about some of the processes involved in human development.

I also tried to give you some sort of brainstorming ideas, some food for thought concept about understanding in which way our cell organelle and mitochondrial defects as well as trying to do the developmental biology together could actually result into some normal progeny even from

the parents who may have the defect in the mitochondria. I gave you case study on that. Additionally, we have tried to understand how modern reproductive technologies have made some difference in the different individuals or patient's life and also try to overcome some of the infertility issues.

We discussed about some of the basic concepts of comparison of genome, which is static information versus proteome, which is much more dynamic protein information and how one could elegantly see those information in the cases of frog development, as well as butterfly development. Let us continue our discussion about cell development, cell cycle and reprogramming in the next lecture. Thank you.

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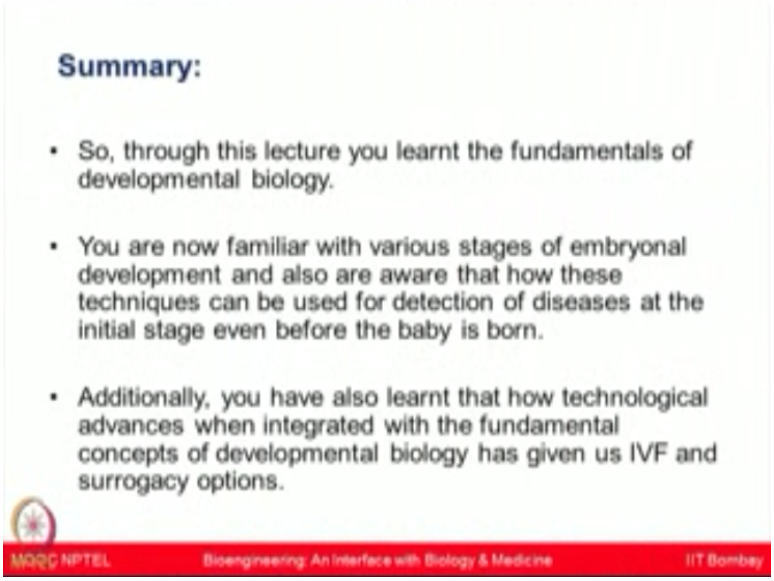

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