Immunology
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Lecture - 55
Transplantation or Graft vs. Host Reaction (Contd.)

Hello everybody. So today also in this lecture also we are going to continue about the transplantation and host versus graft reaction. So in previous lecture we tried to explain like slowly like what are the major antigen, what is a minor antigen and the T cell. So in this lecture, we are going to say what is actually happen in different cases and how it is recovered, okay.

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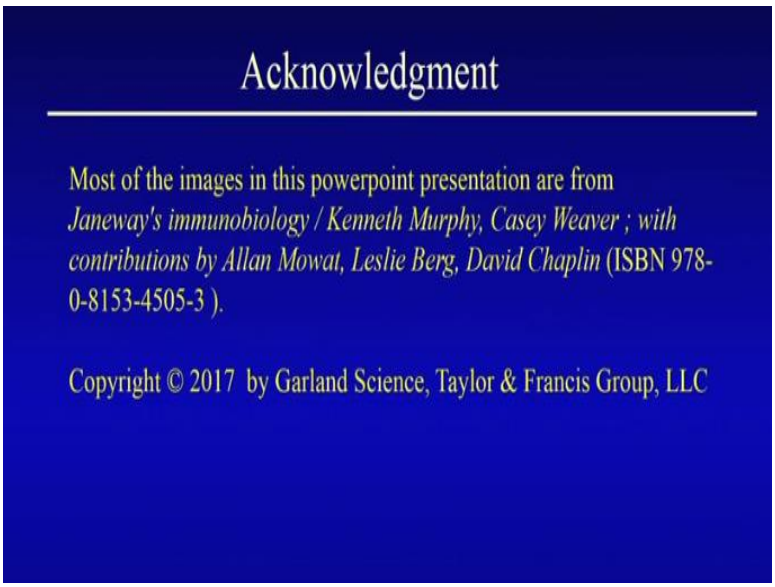

So as usual, this is an acknowledgment that I am using the slides from Janeway's immunobiology book.

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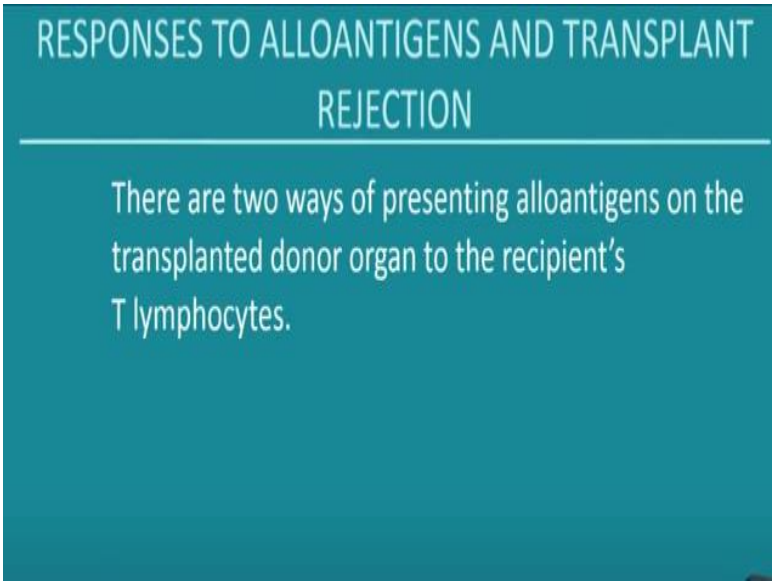

So in continuation with previous lecture, we can say we are always saying like alloantigen and alloreactivity. So how this alloantigens are presented or how cell or the donor can understand? Actually there are two ways of presenting alloantigen on the transplant donor organ to the recipient T lymphocytes. Because what happen or the minor antigen or even if it is not minor, if the donor is widely different genetically.

Normally identical MHC is not possible in the human system except the identical twin. Most of the cases it is different right. So alloantigen recognition is very common and two way it can recognize and who is recognizing, T cell is recognizing.

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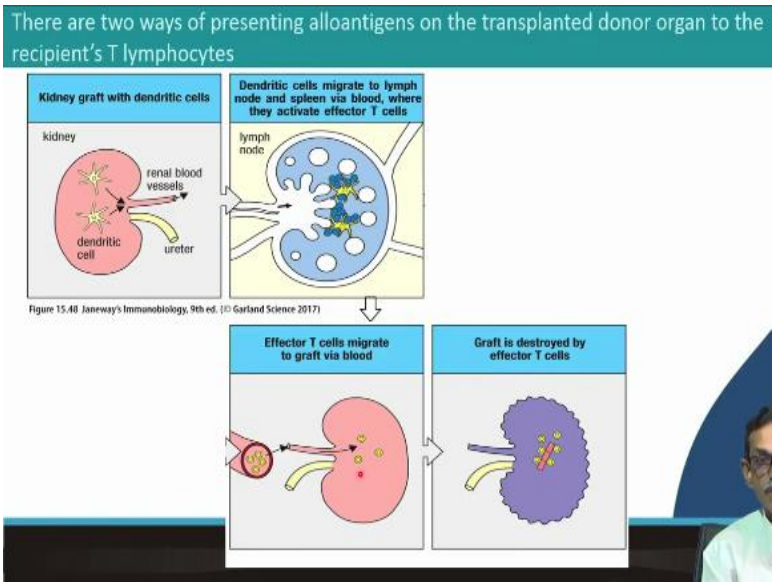

The first thing you know that normally what happen suppose this is the kidney of the donor kidney, okay. So it is transplanted. What happen, when you transplant the kidney, it will bring some dendritic cells along with that, right. It is not just a kidney cell. So there are lot of dendritic cells, which is the donor dendritic cells which contain MHC, which is nonself MHC.

So what will happen these when it is fit and after transplantation and the surgery what will happen, these dendritic cells from the donor will go to the nearest lymph node, which is the recipient lymph node and these dendritic donor dendritic cells will be recognized by alloreactive T cells that 5% and they will be activated, okay. Once it is activated, and that T cell will take time and then after that it will reach to the donor kidney or the donated kidney.

And these activated T cell will find this kidney as foreign, okay. As soon as this kidney is foreign, so with time that kidney cells or the cytotoxic T cell will destroy the kidney and that is how it is going to ultimately it will be rejected. So the donor dendritic cells donor dendritic cells are transported to the recipient lymph node, alloreactive T cells are activated by these dendritic cells.

Because donor dendritic cells will bring the donor protein on their surface with MHC I and this will I mean the activated T cell will come and destroy it.

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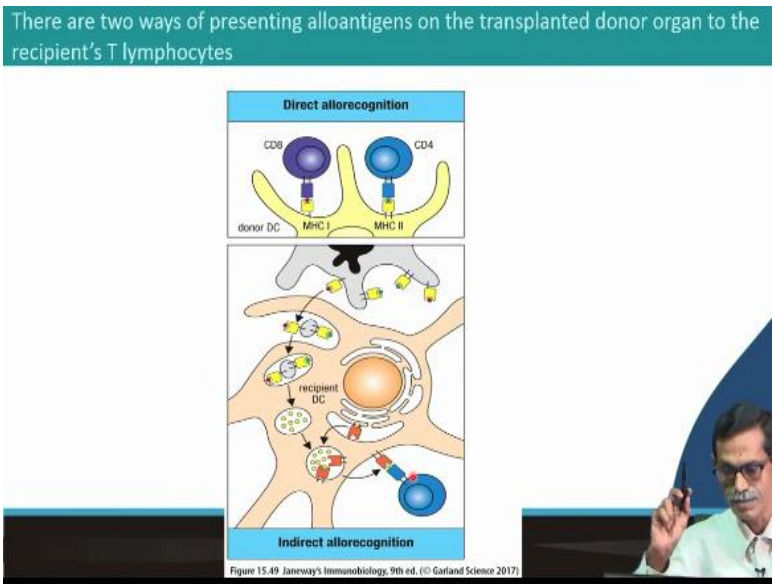

And there is a direct way also. What happen this direct allorecognition is that what has this is the donor dendritic cells, okay. The yellow is the donor dendritic cells which will be directly recognized both MHC I and MHC II and proliferate what we showed last time, and I mean in the last slide actually. So what happen these CD8 cells if it is react with the MHC I, this is alloreactive and this recognition will activate this CD8 which will go and kill.

We just remember the last slide. But at the same time, this one will also kill this donor dendritic cells and these donor dendritic cells will get the signal of apoptosis and this apoptotic cells which is expressing all sorts of foreign or the donor antigen will be engulfed by recipient cells or the macrophage, okay, mostly the dendritic cells. So the dead cell, we do not keep it. So their R scavenger will clean it.

So while cleaning this whole death or apoptotically died this cell will be taken up by recipient dendritic cells. What will happen? So this MHC which is foreign, which is not identical, some at least will do tissue matching, but not hundred percent possible and then this red, green, blue, yellow, all this protein say assume, they will be internalized, chopped and processed.

What will happen just as symbolically you see, the yellow part is MHC part. So MHC part will be expressed by the I mean recipient dendritic cells, which will activate T cells, okay. These T cells will go and help the B cell and produce antibody because this part is this yellow part is foreign. And that will go and bind MHC of recipient cell. So MHC of recipient cell which is in the surface of the dendritic cells and many other cells MHC I also be there.

So that will be in the recipient cell and the antibody go and bind to the recipient cell and then another inflammatory response is going to happen and this is the indirect. So this is direct, which was the previous slide and this is direct, this is indirect because directly recognized cell will be engulfed by our own cells and do the harm or the symptom.

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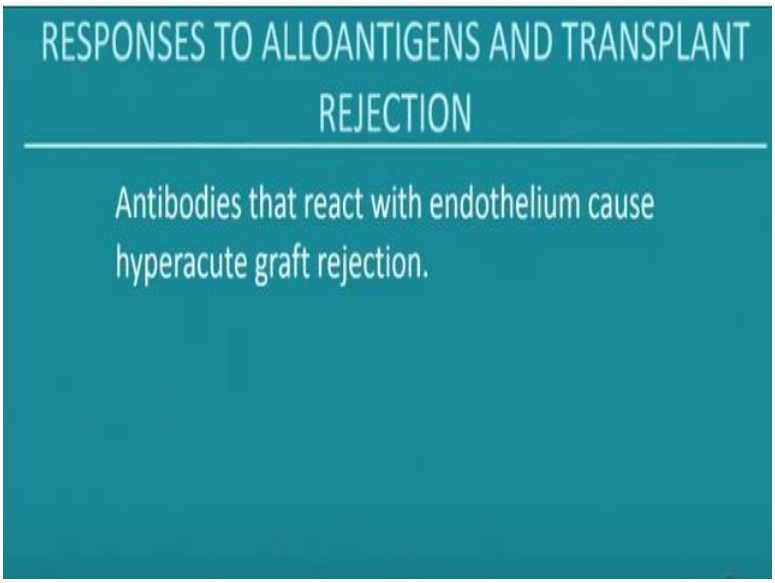

So antibodies that will be generated by the indirect allorecognition will do the hyperacute graft rejection.

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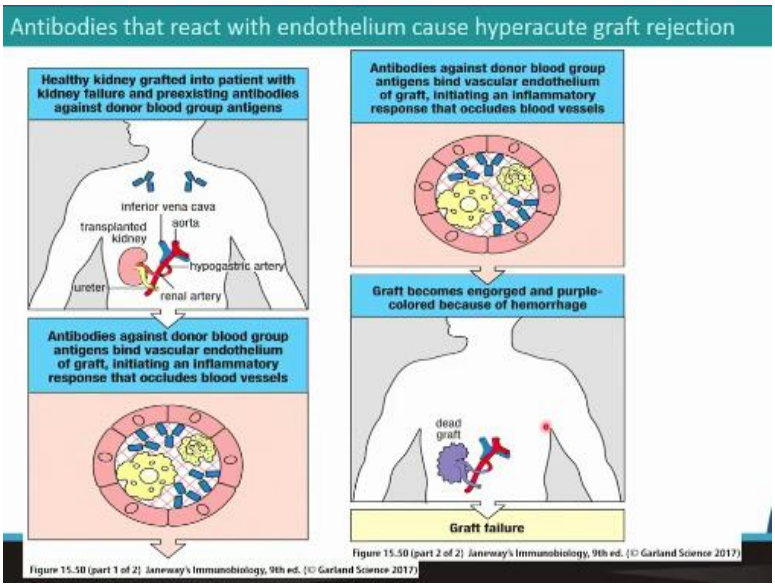

What is going to happen? So you see by that method by the previous method, this cell is helper cells right, alloreactive helper cells because it is MHC II, you can see from there. So that will create some antibody and that antibody will circulate in the blood. And while going inside the kidney, okay wherever the artery is there rest of the artery is the recipients own artery.

But the artery on the blood vessels of the donor cells it will go and what will happen in the epithelial this antibody which is raised against the recipient cell will go and bind in the surface. What will happen? This antibody will bring or call lot of

macrophage and neutrophils and these macrophage and neutrophils ultimately do severe inflammation, okay. And these inflammation will make the whole kidney gradually purple and colored.

Because there are lot of because what will happen these inflammation will make this tight junction loose and lot of blood will and internal hemorrhage will happen. Ultimately, graft failure is going to happen, okay. I hope it is clear. The antibody generated by the indirect I am repeating quickly indirect activation of the dendritic cells antibody will generate.

And then these antibody go and bind the vesicles or the blood vessels inside this donor kidney and cause inflammation and ultimately hemorrhage will happen, the kidney will change its color to purple and ultimately lost its function and there will be a failure, okay.

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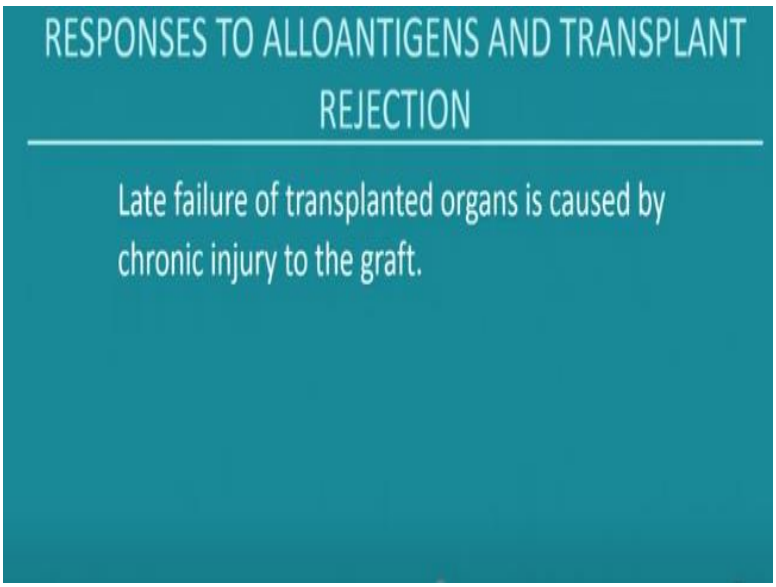

Late failure of transplant organ is caused by chronic injury of the graft, okay. What is that? Same.

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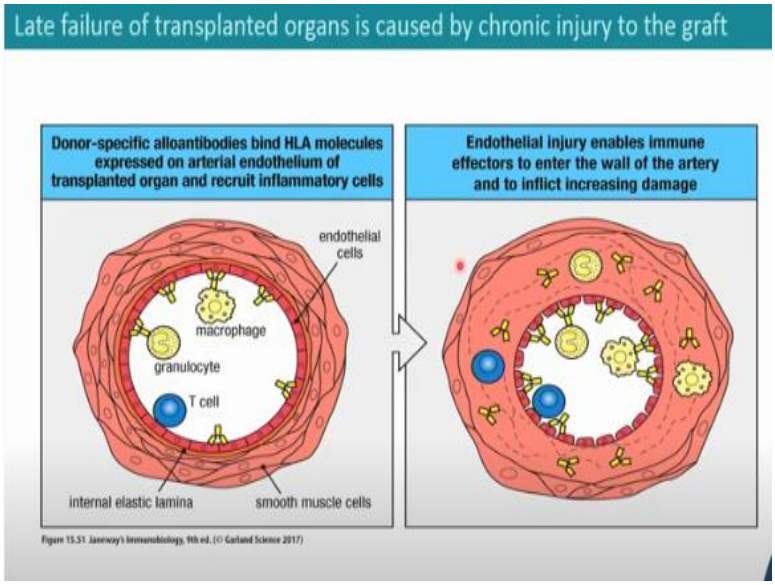

So that particular donor specific alloantibodies against HLA will go and bind the other artery endothelium also and that will cause a similar function and what will happen this antibody will go and bind and different and these antibody will call macrophage, granulocyte, neutrophil. And ultimately, we will see that there will be I mean this tight junction will be lose, again inflammation, okay.

Severe inflammation will happen and it will cause the injury to the blood vessels and many other part, okay. So wherever not we have to remember that this thing is not always for the kidney. Kidney is not the only organ that we transplant, we transplant heart also. So there are lot of other places. Whatever we transplant that particular this kind of thing can happen which will take little more time, but it is going to happen, okay.

So T cell I mean the whole artery you will see lot of antibodies, macrophage, T cells, everything go inside the tissue and create a serious problem.

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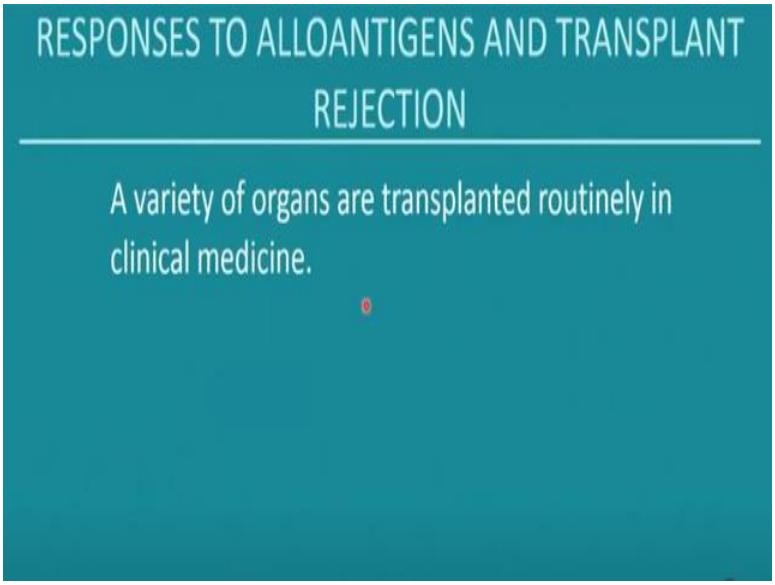

A variety of organs are transplanted routinely. Even after that, even after that a variety of organs are transplanted routinely. It is not that immune system is so strong and so active it is stopped us. Even today, you might have heard like there is a system called green corridor. Green corridor is developed in Madras actually first in Chennai like to make a like a pilot car. So keep the road clean the flight and everything airport, road, airport to hospital.

So what happen if the any person die okay donor are two types actually, one is a living donor, another is the dead body like cadaver which has no person to claim or somebody are organ donor. I mean, all of us can do that right. I can say that okay after my death, if my organs are okay, I would like to donate. And if the information properly reach and even in India, the rule is saying the brain death is also death.

So person who wants to donate the organ. So some something happen in Delhi and somebody needs a kidney here in Kolkata or Calcutta or in Bombay or in Chennai. So what will happen? That need to bring it, it will not survive for days. So immediately it should come and the hospital and everything should be ready from actually one hospital to another hospital bed or the operation theater, it should go without any hassle.

So at least it can reduce 50% of the time and that was practiced and now it is called green corridor. So one person is looking for a kidney for example, another person dead person can donate many organ at a time, heart, brain, lung, kidney, eye, okay. So

that is there is no time of matching the HLA or the tissue typing and all this thing. Normally, if we have time we can do. So even after that if that kind of transplantation is possible, how it is possible?

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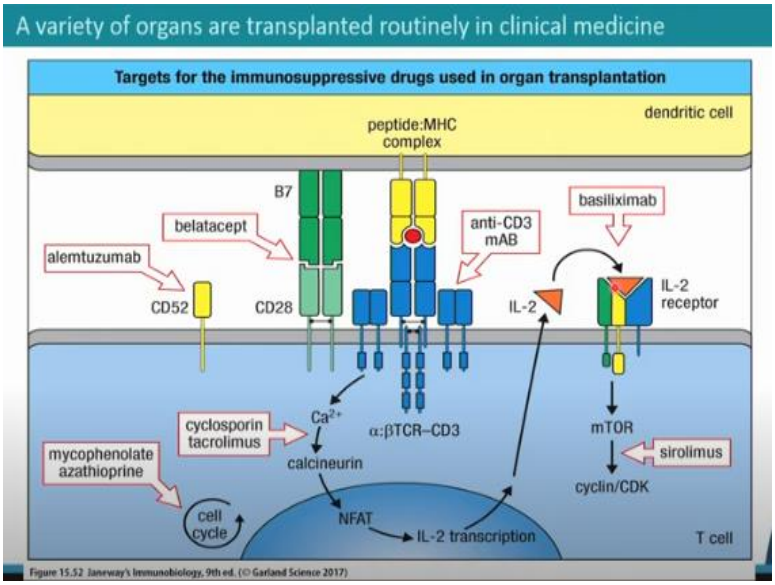

Because there are some good advancement of immunosuppressive drugs, lot of new drugs are discovered, which can really suppress the immune system for long time or long day so that after transplantation for many months, you have to use the immunosuppressive drug, so that immune system does not work properly. The person or the recipient should be very careful because any other infection can happen, immune system is completely blocked.

I am not going to tell you the name of the medicine and what can be done and you have to memorize that. But I am just would like to show you here in this slide. You remember B7, CD28, this is costimulator of T cells. There are nice inhibitor for that, okay. So this CD8 anti-CD3 moclonal antibody, that we will see what is that monoclonal later on, there are cyclosporine which causes.

So every stage like the cell cycle, IL-2 receptor binding inhibition, so wherever T cell activation is there, so that T cell activation is stopped by many different drugs, either single or in combination, which can block. So now MHC matching or tissue typing is not that important, which was 15, 20 years back, okay. That time it was.

And one more thing we have to be careful, I mean, consider actually for transplantation, biology or the medical science progress, like not only this drug development or MHC knowledge or immunology knowledge, we have to have what? We have to have the source. We have to have, now the communication is much more. We came to know what is happening all over the world.

So we immediately know what happened in Delhi and we have a communication, we can bring that organ. It was not there before. Surgery improved a lot. There are lot of new device, new techniques. So the successful surgery is also one of the important factor for transplantation. Even everything is okay if the surgeon is not good or doing his job properly, then there is no point.

Third is this medicine or the immunosuppressive drug discovery. So all these thing made the success rate of transplantation all over the world very high. It was not as before.

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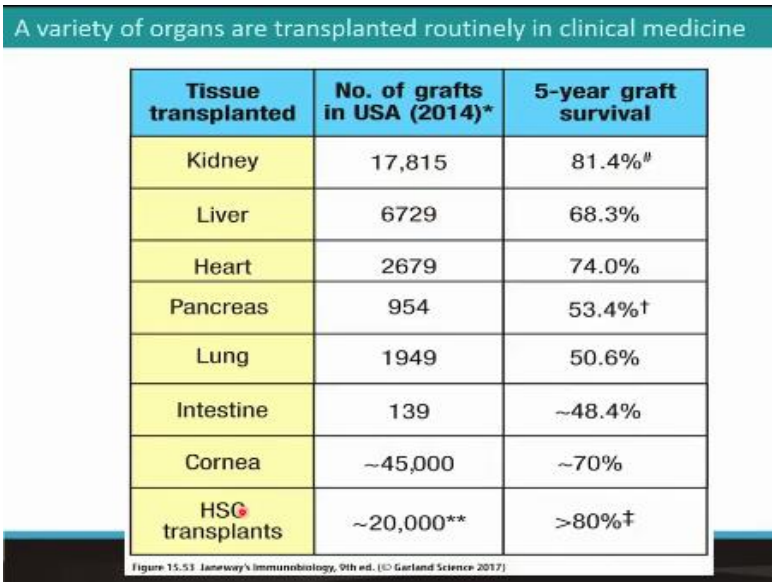

Okay, there are many organ transplantation. This is a report for US. This is a 2014 because you cannot have every year all the time. This is a 2014. You see there are kidney, liver, heart, pancreas, lung, intestine, cornea and hematopoietic stem cells transplantation. So this is these are the numbers of transplantation and this is the five year survival of the graft rate. So I am not going one by one like reading this thing.

You can see that okay, what is the success rate or what is the five years. Five year success rate is good enough. Many cases what happen after five years or six years that individual may need to another transplant, okay. Another transplant is always a problem. It is going to give you a secondary kind of response. So what in the first slide of the last lecture we showed that okay the sensitized so one organ is transplanted means sensitized.

And you will not get a same donor again and it is not possible. One person cannot give both the kidney, right. You have to have a second donor. And best donor is always a relative, because their MHC will be very similar okay. And then nowadays, this is also not required. Because just in the last slide we showed so many new drugs are discovered or the immunosuppressive drug, okay.

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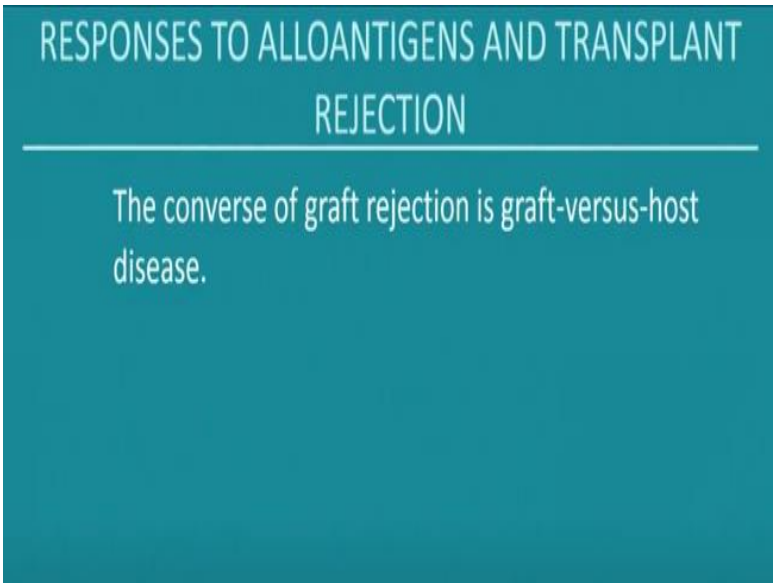

So the converse of graft reaction like what is this. Just reverse is the rejection of graft versus host disease. When you say the graft rejection if it happen reversely it is called disease.

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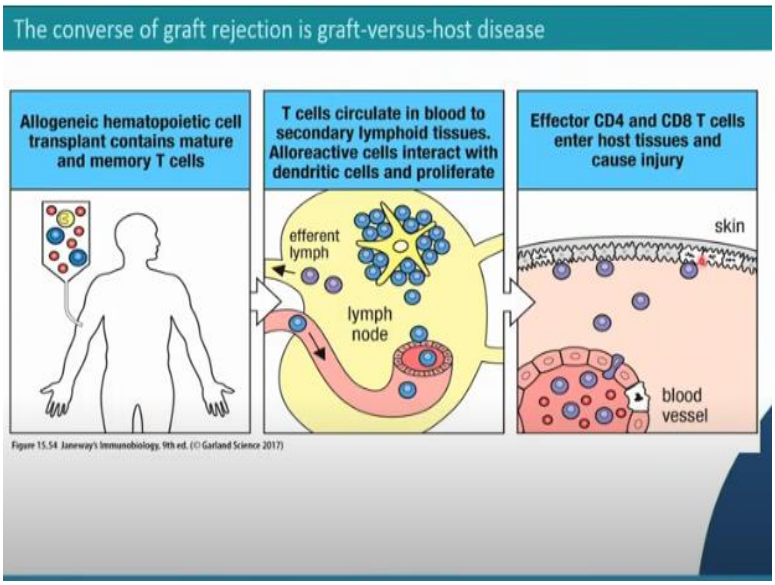

So rejection is one thing, it will reject. But if some reverse or adverse reaction happen separately, then it is called disease. So allogenic hematopoietic cells transplant contain memory T cells, right. So when you transplant the hematopoietic stem cells that stem cells and the blood will contain the memory T cells. And that T cell will be activated in the lymph node, okay and alloreactive again.

So these alloreactive T cells will because donor also has the alloreactive T cells. It will be activated and these activated T cells will go and cause. This is reverse way. Now the donor's alloreactive cells are activated by the recipient, okay. It was like the previously we were discussing recipient alloreactive T cells will recognize the graft and reject it.

Now we are saying that donor's alloreactive T cells are going to activated by the recipient and that donor's T cells will create harm in the tissue or the skin of the recipient and that is also a disease which is called graft versus host disease.

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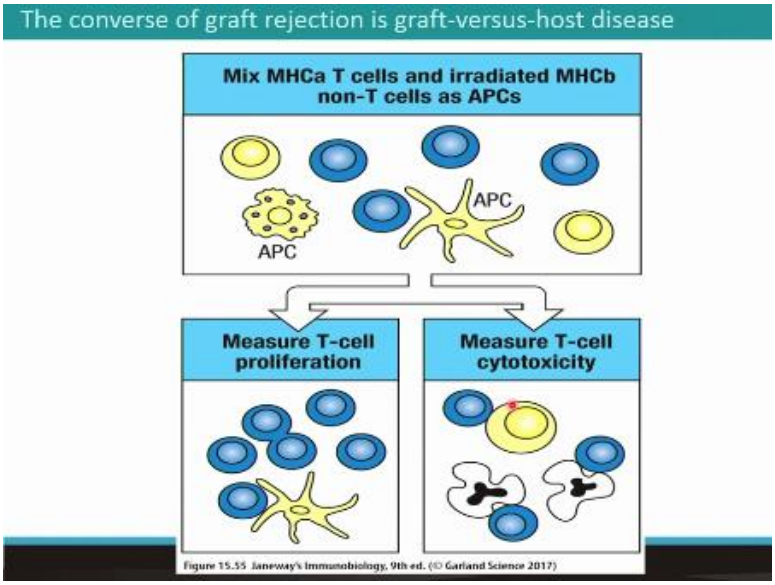

And that we can test actually, whether it is going to I mean happen or not. What we can do is like say recipient in this case, we are trying to say whether the donor has this how much alloreactive T cells are there, whether they are going to activate or not. What I can do is I can take two blood cells, one from donor another from recipient. And recipient T cells we can destroy by irradiation, okay.

We can limited radiation can kill the proliferation activity of the recipient T cell. So if we kill all the T cell of the recipient and then mix the donor T cell and rest of the cell will be okay and mix them and keep them for five days what will happen, if the donor has lot of T cells, which is alloreactive that will proliferate, okay. These are the basically the helper cells. So they will proliferate and we can see that they are proliferating.

That means alloreactive helper T cells are there. Same way cytotoxic T cell because our recipient T cells are all dead or they are not having capability of multiplication or they cannot replicate. So what happen? So if donor has alloreactive cytotoxic T cell what will happen, in five days it will start killing of the recipient cells. So that number of T cells also but this is called actually mixing lymphocytes reaction.

But these cannot give us the real number. There are much better experiment. But this is a very quick experiment, okay. So we can do how much alloreactive T cells are there? If helper cells proliferate and cytotoxic T cell killing the cells that means the percentage of alloreactive T cells in the donor is much more, better not to take okay.

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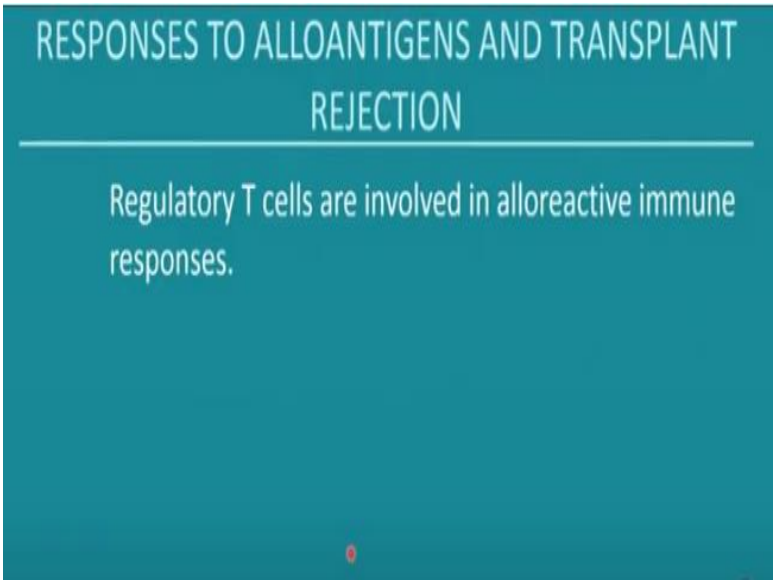

Regulatory T cells. You already we did not say much, but we already said like there is a T regulatory cells, which suppress the active T cells or T regulatory cells also are very important. If that supress or regulatory T cells are much there, they can also repress the alloreactive immune response. But so that is how another treatment is there. If you along with the transplantation if you give some cytokines which will activate the alloreactive sorry regulatory T cells that can also suppress the transplant reaction.

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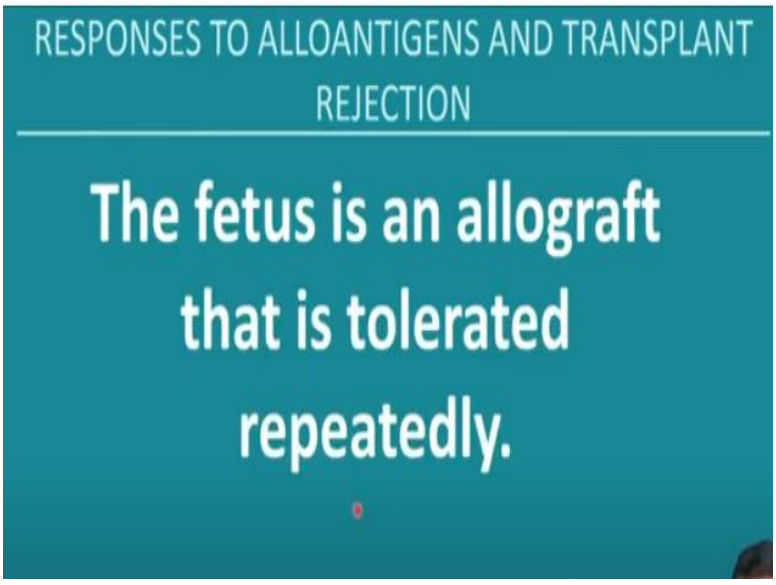

Now the best part of this transplant, fetus. Fetus is an allograft, right? Because it is part of 50% father's MHC, 50% mother's MHC. Okay, so one set completely from father and it is growing inside the mother womb for nine months, at least nine months.

Even after that fetus is not rejected by the mother. It is allograft, but it is not rejected and it is not a single time. Repeated pregnancy also not doing any harm.

So it is a really a great mystery. Okay, what exactly happen? How the fetus is surviving and growing happily inside the mother's womb, even after we have so strong immune system which can identify a skin within 7, 10 days, how the whole body is not. It is still mystery, but still there are some idea or some knowledge I will just share with you.

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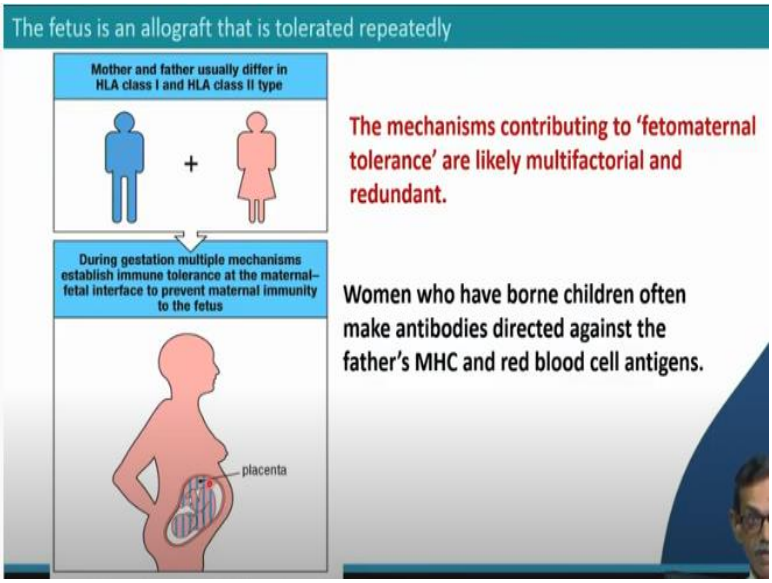

If you see that the it is just symbolically, father is green mother is pink, blue and pink and the baby inside which is the stripe like pink is also there and blue is also there. That means this is the allograft, whatever the bicolour thing is the allograft. Okay, the mechanism how this fetomaternal tolerance is happening is not rare but it is not a single reason. It is a multi-factorial and it is redundant, okay.

Women who have borne children often make antibodies. It is not that there is no immune reaction, okay. During pregnancy every women make lot of antibody against the father's MHC. So antibody, when we do the tissue typing, actually this is the source of anti MHC antibody, okay. So it is not very little. So immune reaction is happening. Anti-father MHC antibody is also found in mother's blood. But they cannot do much or they do not do anything rather. How?

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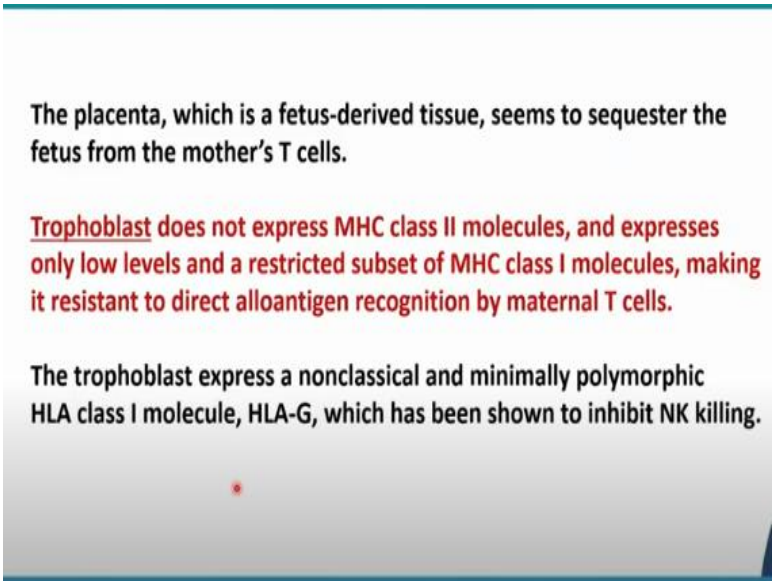

The placenta which is actually a fetus derived tissue, okay. The placenta you might heard about. I am not going to do the physiology part. Placenta actually sequestered the baby okay. So it does not allow many things to get inside and do any harm to the baby, okay. Trophoblast, what is trophoblast? Trophoblast is the outer layer of the placenta. The interface between fetal and maternal tissue, okay.

So that trophoblast actually does not express the MHC II okay. So if there is no MHC II the T cell cannot be activated. And there is a very low level of restricted subset of MHC class I molecules, okay. If you if any particular tissue, I do not know whether myself or Professor Ganguly mentioned it or not. Let me tell it now. If any tissue in our body does not express MHC I, what will happen NK cell will be activated.

NK cell you will find that it is not expressing MHC I means something is wrong, it will kill it okay. So it is restricted level of MHC class I that means low I mean the variety is very little and not only that trophoblast is also expressing MHC class I type molecule called HLA-G okay. So HLA-G is very similar to look like MHC I. So NK cell will not find it again. Okay, so it is fine.

So just to trick the NK cell or to inhibit the NK cell killing, it is not expressing MHC I, MHC it is almost zero. And MHC I is very little along with that they will express HLA-G to avoid the NK cell killing, okay.

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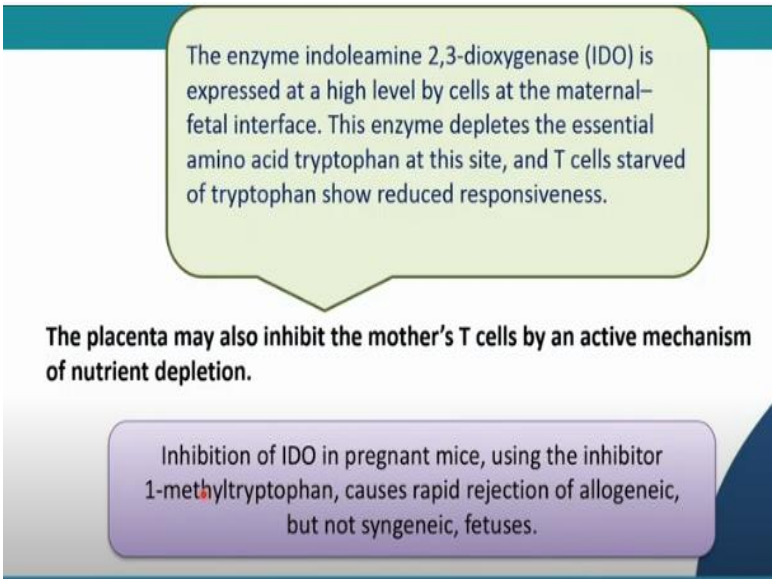

The placenta also inhibit the mother's T cell by an active mechanism in nutrient depletion. So what happen placenta because T cell activation, T cell activation actually need tryptophan, okay. So the enzyme IDO is expressed at a high level in the cell, the maternal fetal interface, what it is doing? It is actually depletes the essential amino acid tryptophan which T cell is need I mean T cell required the tryptophan to be activated or its power function.

So it reduce that tryptophan level and T cells start with tryptophan may not or cannot work properly, okay. And how it is proved? If you see the bottom one the inhibition of the IDO, indoleamine 2,3-dioxygenase in pregnant mice using the inhibitor. That means if you inhibit this enzyme that means no tryptophan starvation and it happen the fetus is rejected, okay. But it is not happening in syngeneic mice.

Syngeneic mice means two identical mice. So that inhibition does not matter, okay. That will not cause any problem because T cell is anyway is not going to reactivate it, okay.

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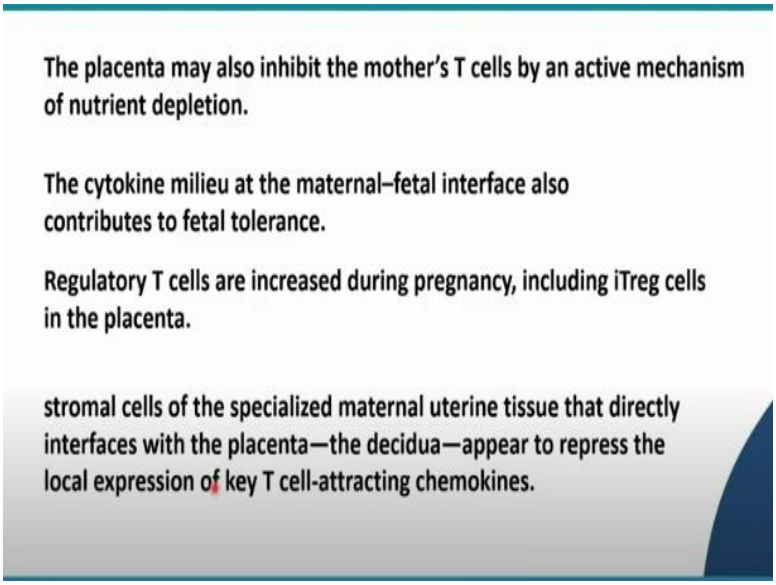

The next I mean these are the few points which is known. I mean, all of them are working but what is exactly happening, nobody knows. The cytokine milieu of the maternal fetal interface also contribute the fetal tolerance. What kind of cytokines it is happening.

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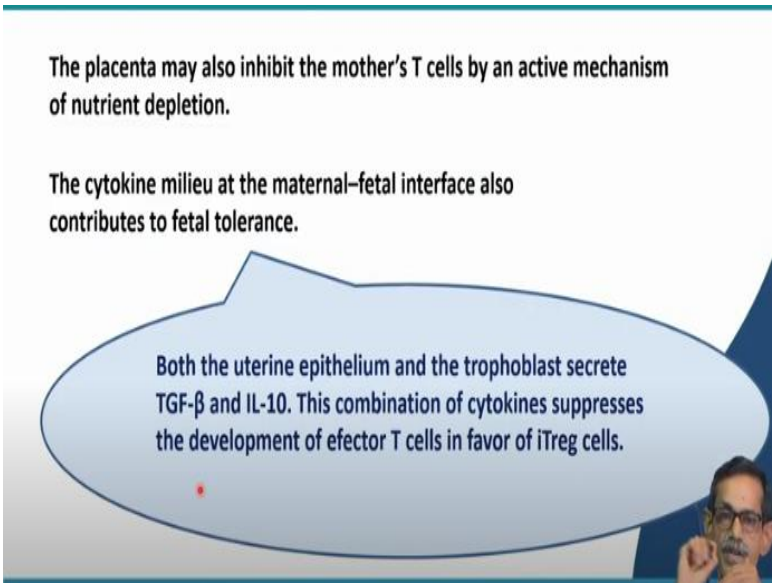

They actually favor the cytokine TGF beta and IL-2, it favors the expression of more inducible T regulatory cells and as long as T regulatory cells number is increasing, the overall T cell activity is going to be reduced. So that particular part is specifically secrete a specific cytokines which favors the growth of T regulated cells. And as a result, other T cells like CD4s and CD8 do not do much because T regulatory cells suppress it, that we already know, okay.

And stromal cells are specialized maternal uterine tissue that directly interface with the placenta and appear to repress a local expression of key T cell attracting chemokines. So cytokines is also there and that particular region the maternal tissue the placenta is expressing or do not express the chemokine which attract the T cell, okay.

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So all these things so far known, both maternal as well as fetal, because the placenta is a fetus derived tissue part together contribute so that even the fetus is allograft, body do not recognize it. So you can say without drug, immune system is completely suppressed. I am sorry, not completely partially suppress, but that part is completely suppressed almost because simple thing can cause rejection or reabsorption of the fetus, okay.

So this thing is really even mystery I mean if we can understand exactly how this thing is monitored, how it is controlled, that knowledge can be extrapolated to the transplantation. So what we are of course, we are doing by the immunosuppressive drug, okay.

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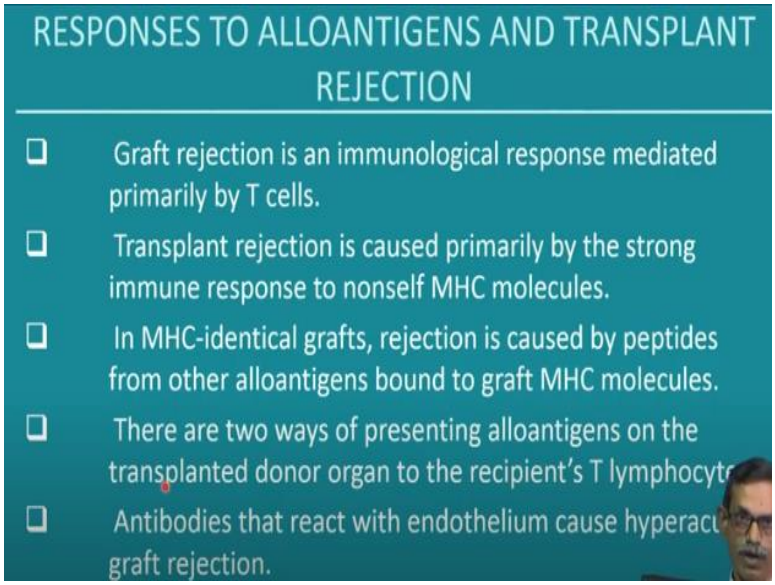

Now these are the all in the last lecture and today's lecture or this lecture, this one, these are the summary point, what we are discussed so far. So just if you remember this and remember your the cartoon or the figure, it is all the transplantation that we have done. Like graft rejection is an immunological response mediated by primary T cells.

Transplant rejection is caused primarily by the strong immune response of nonself MHC molecule that is the alloreaction from the donor side. In MHC identical graft rejection is caused by the peptide so minor H antigen. There are two ways of presenting, one is alloantigen one is direct, another is indirect. Antibody also produced which can cause the hyperacute reaction making the inflammatory response to make the tight junction loose and leaking of blood molecules.

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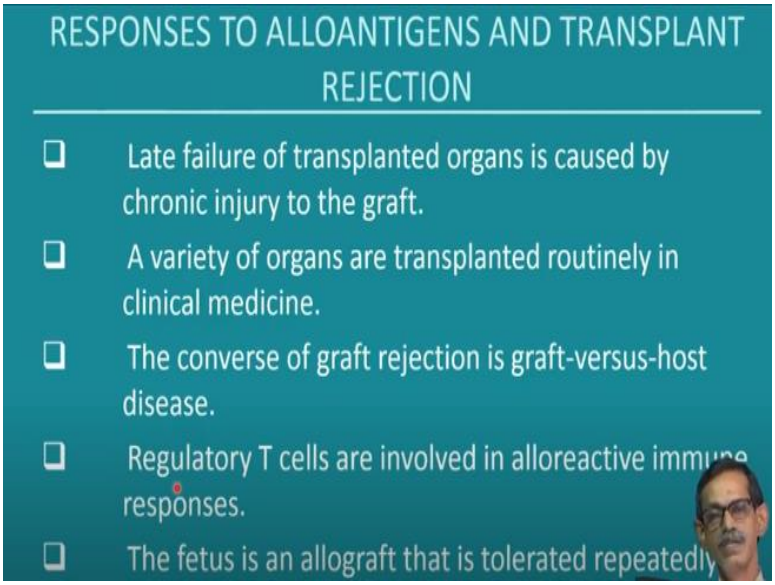

Late failure of the transplant is caused by the chronic injury what we said the same the tissue like macrophage, antibody, T cells will enter into the artery. A variety of organs are transplanted routinely, successful because lot of suppressive drug. Converse graft rejection response is basically the disease. That means, which happen the reverse way. The donor alloreactive T cell can cause harm to the host body.

That is reverse to the rejection but that is going to cause the disease. Regulatory T cells has a important role in controlling the alloreactive immune response. The fetus, we just discussed is an allograft, is tolerate repeatedly. And this is real mystery and we should have to know because lot of information if we can discover from there our transplantation may be much more. Now I am going to take little more time.

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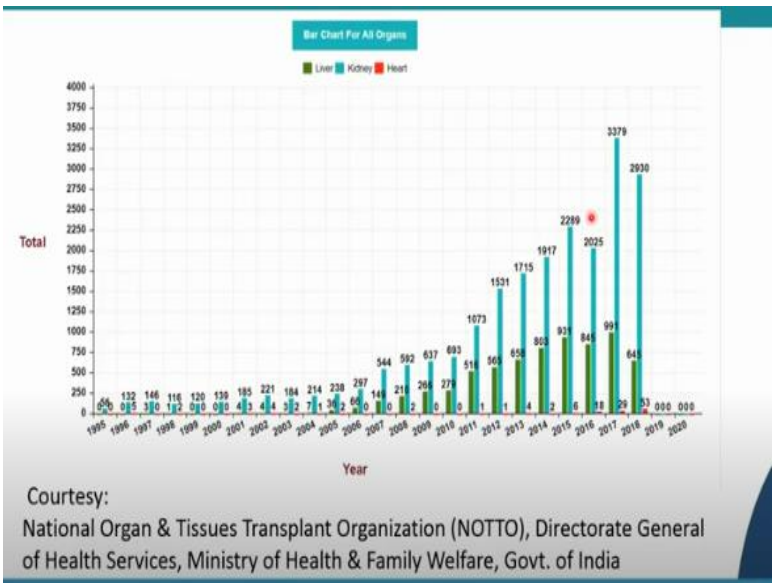

What is the scenario of India, okay. Very recently Government of India, one institution called National Organ and Tissue Transplant Organization okay, NOTTO. We also have five more regional okay Bombay, Calcutta, Delhi, Chennai. So they are taking care of the nearest like the in Kolkata the regional center is taking care of Jharkhand, Bihar, Orissa and this region. We have only five regional center.

And according to the parameter, you can see I am not going to see if you see this the number of transplantation is increasing, okay. Blue color is the kidney one. Kidney is the most transplanted organ. And the green one is a liver and the red one is heart you can see is much less. Definitely, I mean until unless somebody is death someone cannot donate the heart, right? Living donor cannot donate the heart, okay.

So there is no possibility so the kidney donation is maximum. So this is and it is gradually increasing and is a good sign, okay.

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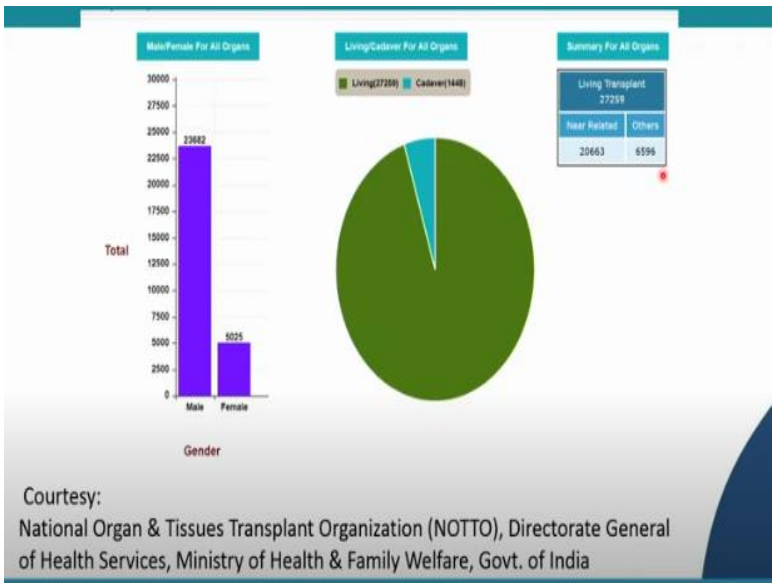

And if you see the number of donor like the male donor is much more than the female donor, gender wise. And this is the distribution. I am talking only in India. This is the distribution and this is between this is actually between 1995 to 2018 data, okay? And 2020 it is not completed yet. And this is if you see the green or the major part in the pie chart major part this is the living donor, okay.

This is a living donor and this is a cadaver, so from dead body and summary of all organ. So you see this out of 27,259, 20,663 are from the near relative. Near relatives

are always better, okay. Because much more chance of having similar MHC than any unknown. Even though there are lot of drugs are discovered, if you have better MHC matching or tissue typing match first definitely blood group need to be matched, okay.

And then they may see if near relative chances of matching is much more higher and this is from others like 6596. So these number just to give an idea, like when we are discussing transplant anyway this is kind of statistics okay. So we can you can have idea. And normally what happen? I mean which has not yet started here. In US long time back even 25 years back also whoever is going for the driving license they used to ask I would like to donate your organ, okay.

And it is used to written like organ donor in the driving license. So just in case nobody knows accident can happen anytime, okay. And after death, if it is already written organ donor, so immediately the nearest hospital will be informed that this thing happened and death happened or casualty happened by accident and the passenger or the driver whoever is the organ donor, okay.

So immediately that hospital will take care and then organ will be utilized by those who really need it, okay. So this, but even this is not exactly happening in India at least so far my knowledge is concerned. Maybe someday it will happen. And we are in progress, I mean lot of successful transplantation is happening in India, different part of the India in different hospitals.

So, so far this is transplantation and host versus graft or graft versus host reaction and this actually the end of immunology part. In next few lectures, we are going to discuss about the implication of immune system or knowledge of immune system, how we utilized in vaccine, vaccine production and different kind of antibody. So immunology as such whatever we are supposed to discuss, this is the last class or last lecture.

Thank you very much. Hope you enjoyed the whole course. Next five class we are going to discuss about different application or the vaccine particularly. Till then, bye.