Immunology
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Lecture - 52
Autoimmunity (Contd.)

So welcome, welcome everybody. We are continuing autoimmunity.

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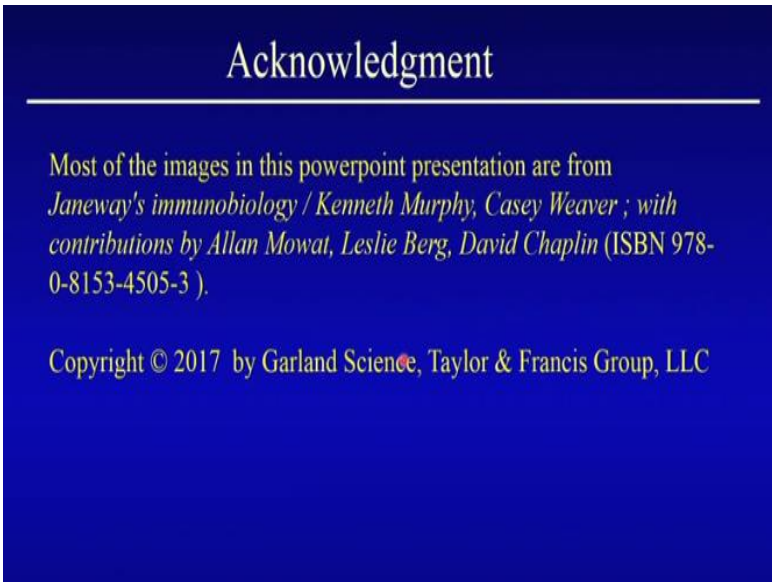

And today in this lecture actually, this lecture we are going to talk about the second part like in the beginning we said that in autoimmunity there we divided into three different part.

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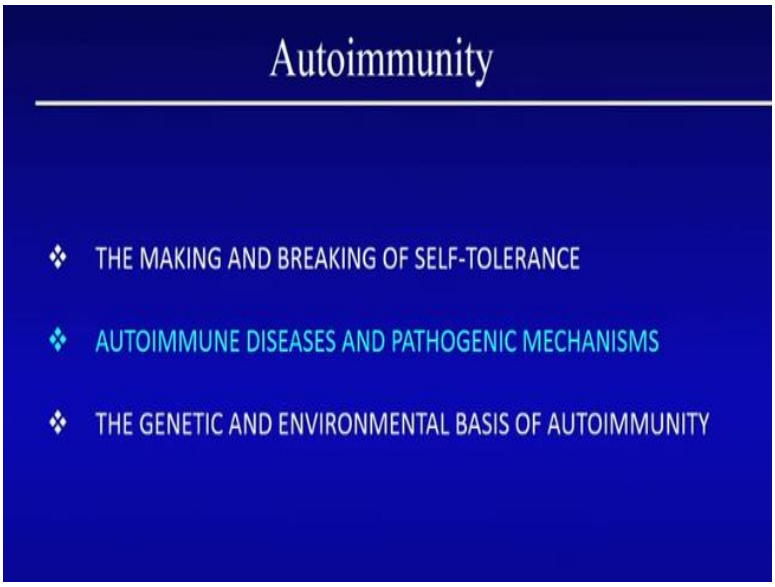

And in this part we are going to talk about autoimmune disease and pathogenic mechanism. We already discussed the making and breaking of self-tolerance. That is, that was basically a summary of what we knew before with some new information like the AIRE kind of thing, which was not discussed before but mostly you knew. And we summarized like these are the tolerance mechanism. If it breaks, then autoimmunity come.

Now in this lecture, we are going to see what is happening in autoimmune disease. How different components are involved in doing this pathogenesis or cause the disease, okay.

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Specific adaptive immune response to self antigen can cause autoimmune disease. Any immune response or adaptive immune response to our own protein or self antigen cause autoimmune disease. Here there is a difference. In infection what happen, in infection if any infectious organism enters into our body, our immune system work on it and remove it, okay.

Whether the toxin or virus or bacteria, eventually we are cured, we will be cured by help of immune system. But that means no antigen will be there anymore, okay. That will be removed. But in case of autoimmune system, the problem is antigen is always there, okay. In foreign pathogen as long as antigen is there immune system is activated or upregulated.

And as soon as it is gone it gradually go down and remain in a very basal level like the in memory cell memory B and T. We would not see the active immune system against that antigen. But in autoimmunity antigen is always there and that is a problem. Immune system is always active. And unfortunately, there is no medicine because if we block the immune system by any medicine, our immunity will go down.

So we will be prone to many diseases, okay. So generally and it is very, I mean lot of every possible attempt are made like to get rid of this autoimmune disease. People are still trying. Just to discover for that what you have to know? We have to know the immune system much more detail. We have to study more detail at molecular level what exactly happening so that specifically we can block something so that the disease can be slowed down or gone.

But the thing is, immune system are so interconnected, if you block one thing many other thing will be blocked. So that is one problem, okay.

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Autoimmunity can be classified in two ways. It may be organ specific or maybe systemic.

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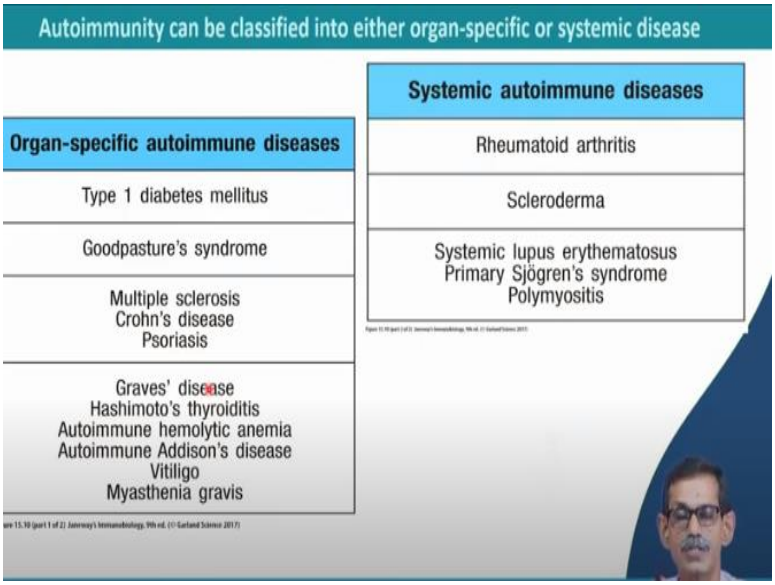

Organ specific means organ specific means type I diabetes mellitus, because it happen in pancreas only. So all these thing like Graves' disease, Hashimoto, these two are thyroid related. Myasthenia gravis is nerve cell related. So that means specific organ, specific organs are affected by the autoimmunity.

But if it is systemic, that means if it is spreaded all over the body, it is not a specific place or site of the body then it is called systemic autoimmune disease like rheumatoid arthritis okay that happen in all the joint and pain okay. Systemic lupus erythematosus, which is in short called SLE, which is not that uncommon, okay. Then Sjogrens syndrome. So these are common or it is spreaded all over the body.

You can see why. I will not tell every detail of all the disease. At least for example I will tell you some. So these disease are all over the body. That is why it is called systemic, okay.

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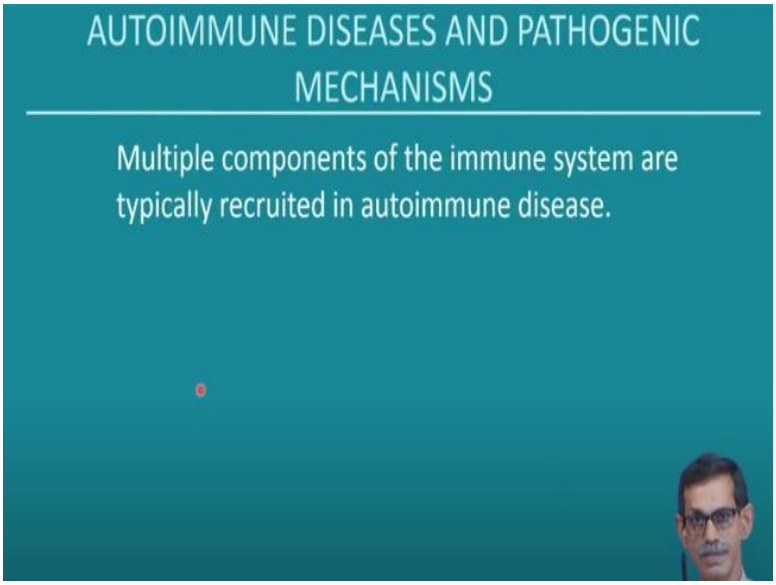

Multiple components are responsible like for any disease, multiple what are the components of immune system?

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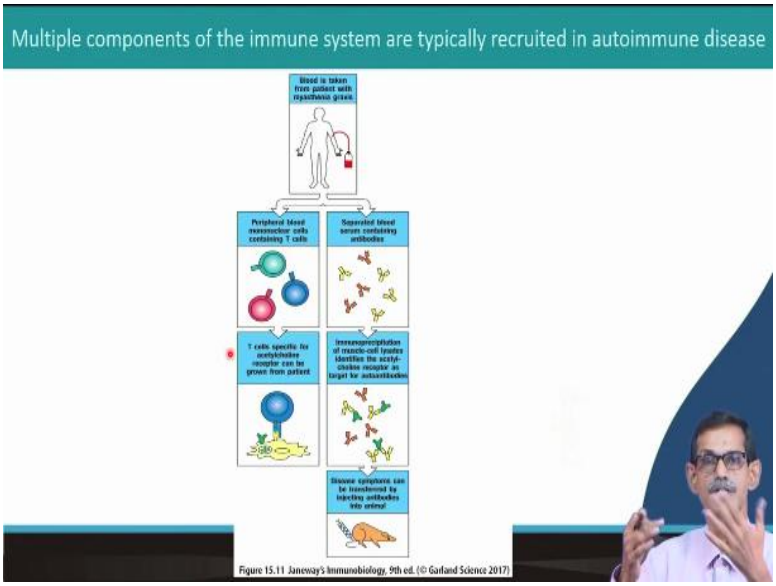

Major component of immune system is the T cell, okay and B cell. B cell directly is not involved. What part of the B cell? B cell produce antibody. That is responsible for the autoimmune disease, okay.

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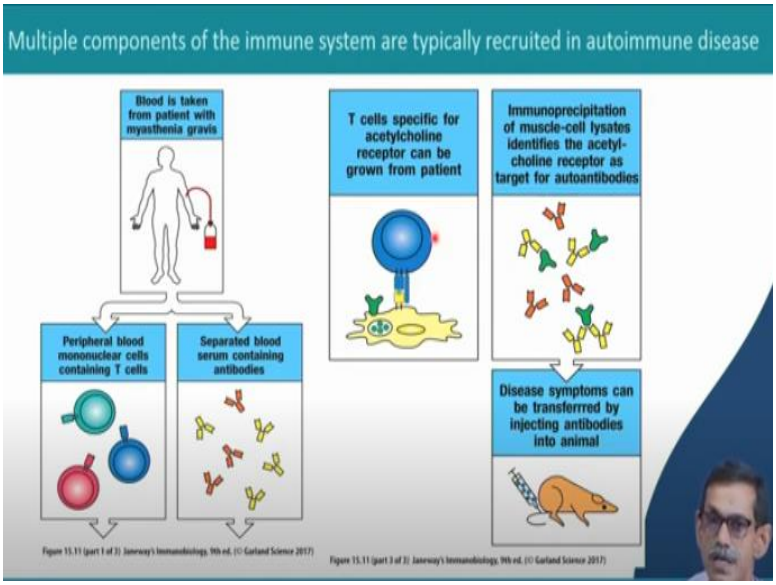

So what happen? So suppose this is a disease called myasthenia gravis, I will tell you what is that. For the time being you just say that myasthenia gravis is a disease, autoimmune disease. So if you take blood from this patient, what will be there? There are I mean immune cell will be T cell, different T cells will be there like TH 1, TH 2, TH 17, Treg all will be there and there will be some antibody, okay.

So if you take this T cell separate it from this patient's blood and you have some antigen presenting cell. Suppose you have a macrophage culture which is expressing this receptor. What is that receptor, acetylcholine receptor, okay? Acetylcholine receptor is a target for this disease. Acetylcholine receptor what it is doing? I will show you later and many of you know also. It is transmit the neural signal, right.

Acetylcholine release and it binds to the receptor and in through synapse it goes to the next nerve neuron and then next to next. And that is how the signal goes from one end to another of the nervous system. So what happen? The receptor find this acetylcholine, T cell receptor finds acetylcholine receptor as a target. So it will bind. So T cell isolated from this patient it is found that it binds to acetylcholine receptor.

Not only that, the antibody also interacting with the acetylcholine receptor. So these two thing is proving that acetylcholine receptor is a target, okay. And these acetylcholine receptor and human acetylcholine receptor and mouse acetylcholine receptor are many places they are similar in sequence, okay. They are not identical, but their similarity is very much, okay.

So what happen? Same antibody which is raised in human acetylcholine receptor can also act with mouse acetylcholine receptor. So it was also found that if you isolate the antibody from this myasthenia gravis patient and inject into mouse then that particular mouse also get are showing the symptoms of the myasthenia gravis. That means, what this experiment or this experiment or interaction between this is telling?

It is telling that these particular disease just example, many other disease you can have like this both T cell as well as B cell is responsible. So I can I mean if you see the title of this slide, the multiple components of the immune system are typically involved in autoimmune diseases. This is just one example. Many autoimmune disease you can have and can see the similar example.

And in this lecture or in autoimmunity, we are not going to discuss all the disease. Whichever is easy and easy to explain easy to understand, I will try to explain that, okay.

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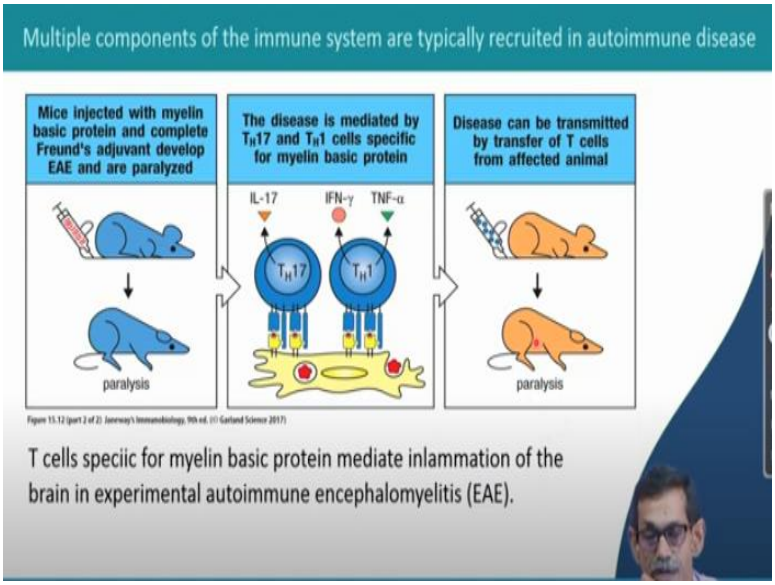

Another one is multiple components of immune system typically recruited in autoimmune disease is that if you see that EAE that is encephalomyelitis is a short form EAE. What happen? Mice injected with myelin basic protein. So what you can induce this disease. This is the myelin protein, okay. If you inject with the adjuvant, adjuvant is I will discuss. For the time being I am not going to spend time on this.

Adjuvant is normally induce the immune system much more where when we will discuss vaccine maybe next week, you will listen that. So when we will discuss vaccine, how to develop vaccine we will discuss adjuvant. What happen you take the myelin protein in mice mix with adjuvant and inject in too much. What will happen? Even if it is a self antigen, it will act as if foreign antigen, okay.

So that particular mice will develop the autoimmune disease and ultimately it will be paralyzed, okay. What was shown that T 17 and TH 1 are responsible for that. So if you inject this, develop the disease, purify the T 1 by again that flow cytometer with the fluorescence activated cell sorter if you isolate the T cell and inject a fresh mouse that itself can cause the disease.

That means, T cell is enough both is cause this disease of autoimmune encephalomyelitis, okay. So this means both varieties of T cell TH 1, TH 17, CD4 that follicular helper cells and antibody everything is responsible for autoimmune disease.

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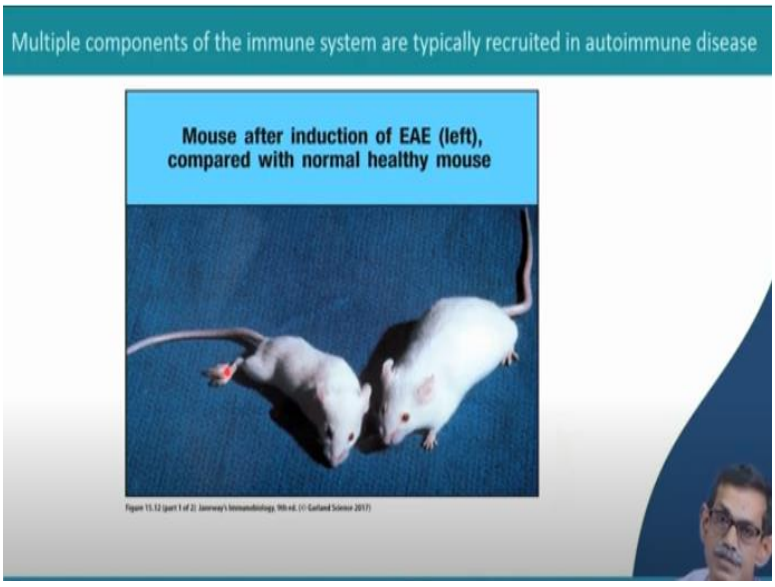

And next one I will just show you the picture how it looks. So this is a normal mouse and if the disease become they become paralyzed. You see their leg. I mean their muscle cannot work because their nervous system is nerve transmission and neural transmission is hampered. That is why they become paralyzed.

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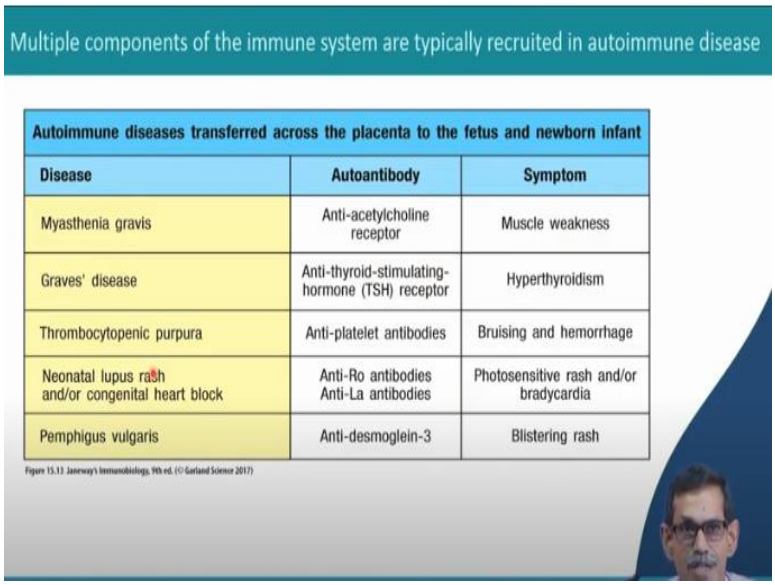

So multiple component, these are the table I told you just too. But here there are table like myasthenia gravis, acetylcholine receptor is the are autoantibodies generated. And these Graves' disease and all other like lupus, rash, there are many other diseases where antibody is responsible.

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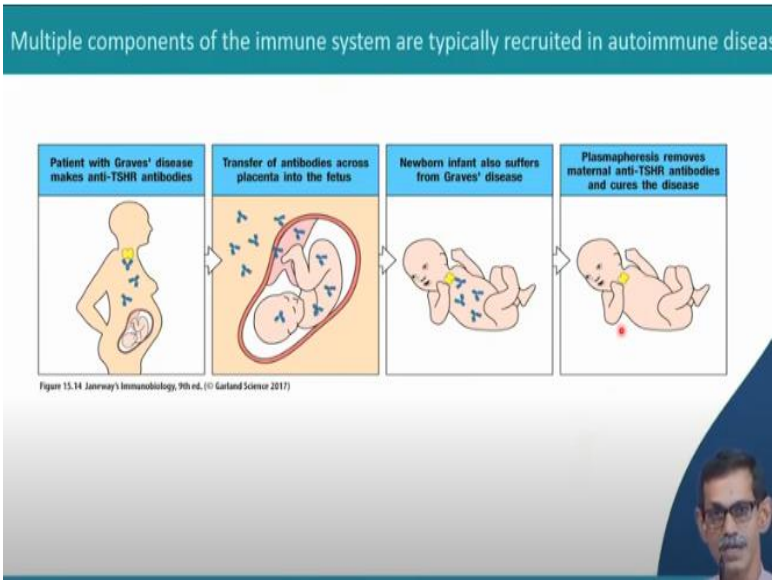

And these antibody can cause temporary disorder like multiple I mean, what kind of say suppose mother having autoimmune disease okay, in this case, it is a thyroid. It is called Graves' disease. I will tell you what Graves' disease is, I mean in this lecture only. So mother with Graves' disease have autoantibody. In the previous slide also you see Graves' disease is autoantibody against what?

Against thyroid stimulating hormone receptor okay, TSH receptor. So antibody against TSH receptor, okay. So if mother has the autoimmune disease of this Graves' disease that means anti-TSHR antibody what will happen? This antibody will go to baby, okay.

So when baby is inside mother's womb baby will show the disease because the same antibody is going to react with the TSHR of that growing fetus. Just immediately after birth also that baby will also show the disease because some antibody will still left. And you know every antibody has a half-life and this is mostly IgG. So IgG half-life is say 30 days.

So that individual will show the symptoms of this disease about 30 days, clear. I am assuming that I mean I do not remember exactly what is half-life, most likely 30 days. So if it is 30 days, so this 30 days that baby will have the symptom of this diseases. But eventually when the existing antibody will go away that baby is normal. There is no autoimmune symptoms. So the baby will normal.

So existing so if any this can happen suppose any Graves' disease any individual having Graves' disease or the blood donor. If you if I take blood for any reason from a person who is having Graves' disease, that blood will contain the antibody.

And as long as that antibody will be there in my body not only in this case this is regular but in the blood donation also autoimmune disease, individual donate blood the recipient also will show the symptom for certain days okay, as long as that antibody remain in the system, okay.

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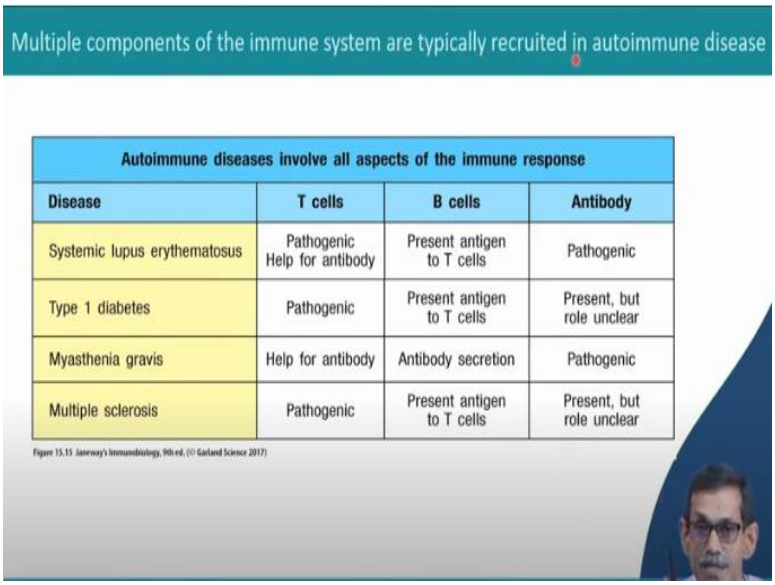

So these are the list. I am not going and spending time. This is the different disease where T cell is responsible, B cell is responsible, antibody is responsible, okay. B cell means B cell and antibody what is the difference? When a B cell is activated and produce antibody that is the cause. But B cell also antigen presenting cells. So sometimes B cell act as the antigen presenting cells also in the autoimmune disease.

So both T cell, B cell and antibody all are responsible. That is why we said in the top that multiple components of the immune system are typically recruited in autoimmune disease.

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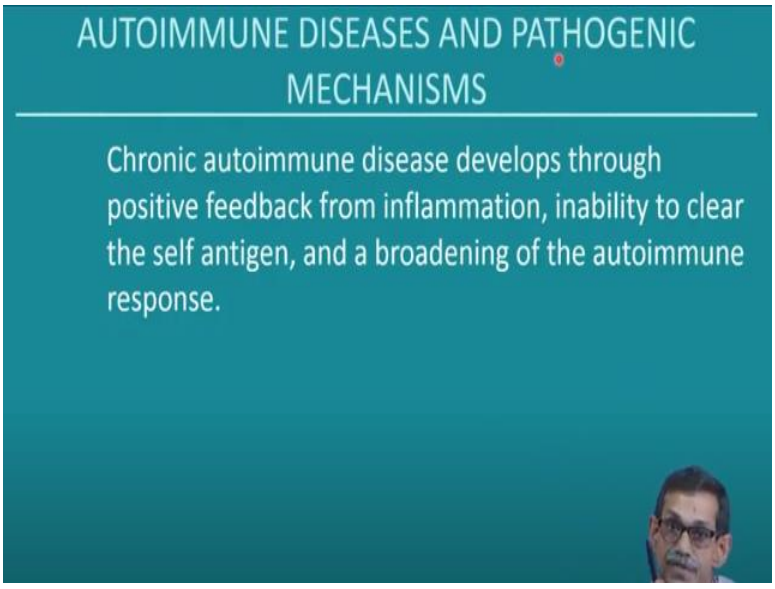

Chronic autoimmune disease develops through positive feedback from inflammation, inability to clear self antigen and a broadening autoimmune response. What is happening? Let us see the example.

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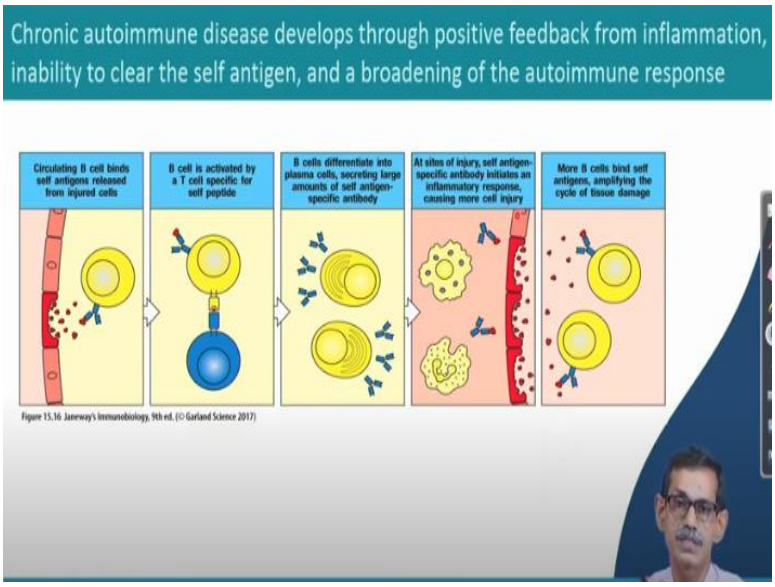

Suppose normally what happen in skin tissue okay, that or in any tissue, the B cell do not see the antigen because it is inside, internal antigen is not exposed to it. All our internal proteins that resides always inside the cell B cell is not going to see them. But if it breaks, some damage, tissue damage happen. The antigen come out, B cell can interact or B cell receptor can interact.

That can present this through MHC II, activate the T cell. That T cell itself will activate again the B cell and convert to plasma cell okay. That plasma cell will produce lot of antibody. What will happen? That antibody will go and try to infect more cells, okay. So more tissue injury. More tissue injury means more macrophage, more neutrophils, so continuous inflammation.

So it start with a single cell. It was not there. So only tissue damage cause this initiation of this disease. And it will start with a very small region or a single cell and gradually it will spread all over the region and cause serious inflammation or a continuous inflammation of the disease. That is also one way that autoimmune disease can happen. So compartmentalization of the antigen or self antigen is also very important.

So our immune system do not see most of the protein normally because they do not stay in blood neither they are in the lymph node or the spleen, okay.

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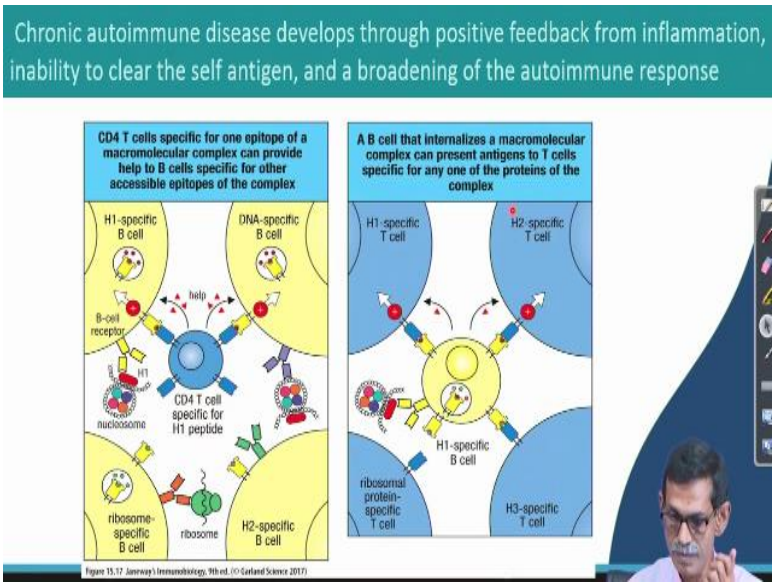

So this is another very do not see do not it is not a very complicated slide. It looks very complicated but it is very straightforward and simple. How? See in suppose one cell damage happen not only the antigen or the protein will come up, the nuclear protein or nuclear material will also come and nuclear material and similar material what is there? They are our ribosome, which has RNA and protein.

They are nucleosome, which has lot of histone, histone 1 histone 2 and DNA, right. So what happen? So suppose there are four B cell, okay. There are four B cell and these B cell receptor can recognize H1 that means histone 1. This B cell is ribosome specific. This B cell is histone 2 specific. There are histone 1, histone 2A, 3B, 3, 4, right to B specific. And this is DNA specific, okay. Four B cell are four different antigen specific.

But these T cell, these T cell can activate almost all of them. Because this particular B cell that MHC II will put H1B. This will put H1B because whole complex are going to be internalized, okay. This whole complex which contain H1, H2B, H2A, H3B, RNA, protein, everything is going to so whole complex of DNA are going to internalize. Everything will be processed and each one will be displayed okay.

So these T cell but these I mean this receptor is HIB specific, but when it is interact this suppose this red bacteria like thing is the H1, okay. It interact with that. That whole complex will go inside, processed and displayed. Same way if it is taking ribosome, all protein and RNA will be taken up. Here this particular B cell is recognizing DNA but whole complex is going.

So if 50 proteins are getting inside all will be processed and displayed. But the receptor is single type okay. So each one may be different, but this T cell I mean each one can activate the one T cell like H1 peptide specific. These two both can activate the H1 type T cell, right. So one T cell can activate multiple B cell. Why this thing happening? Because the antigen is a mixture of many things okay, it is a complex protein.

Just same way one B cell after eating this whole complex can activate multiple T cell because here they are activating H1, here they are activating H2, okay. Because each the suppose there are four different proteins. After processing all will be chopped. So in one MHC II there will be H1, another MHC II there will be H2, another MHC II H3. Some MHC II some other part of the protein, okay.

So all will be exposed in different way and therefore, one B cell can present the antigen to multiple T cell. So this is a very complex situation and this happen in SLE, systemic erythematosus lupus okay. But this is common, but in that case, there are a lot of symptoms are there for these disease. But it is not happen very easily because how the cell will rupture and then all this nuclear material will come and displayed in the peripheral bladder system the ribosome.

So this is possible, but this is not very common. Not very common means this is not happen easily. But it is not that rare also.

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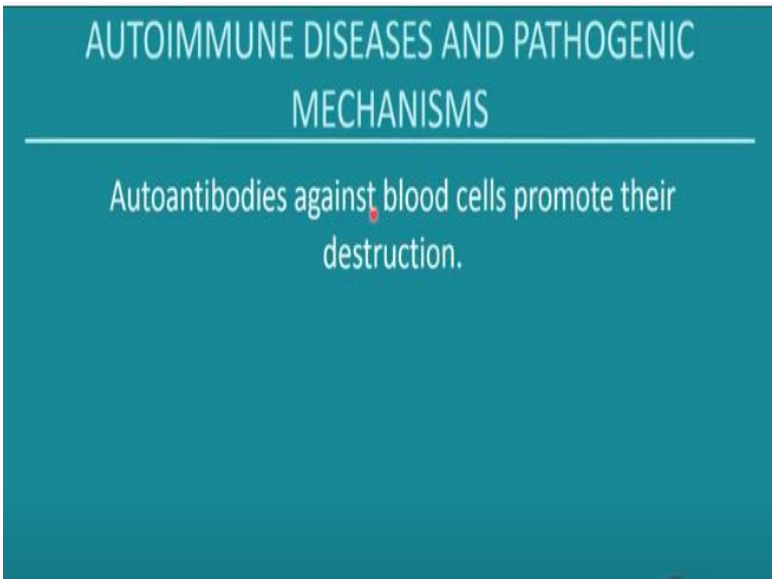

Both antibody and effector T cells can cause tissue damage in autoimmune disease. Both antibody and effector T cell can cause tissue damage in autoimmune disease, okay.

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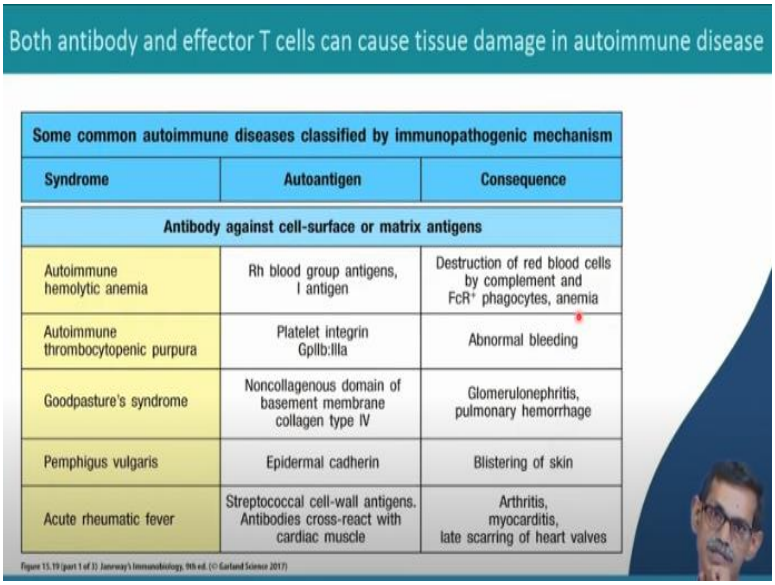

So here is a list of disease. This is autoantigen what is actually cause I mean reacting with the immune system. And this is the consequence what is happening, okay. This is I am just showing that there are many, okay. So some are bacterial I mean some will come and show you.

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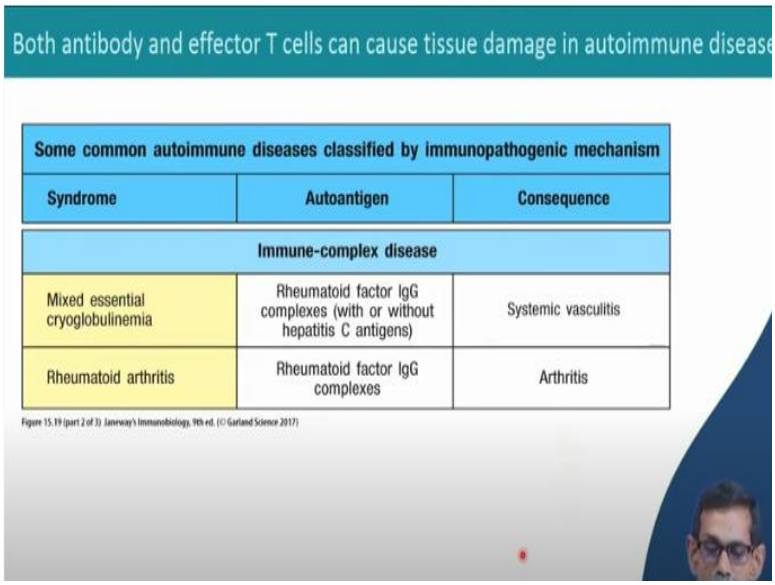

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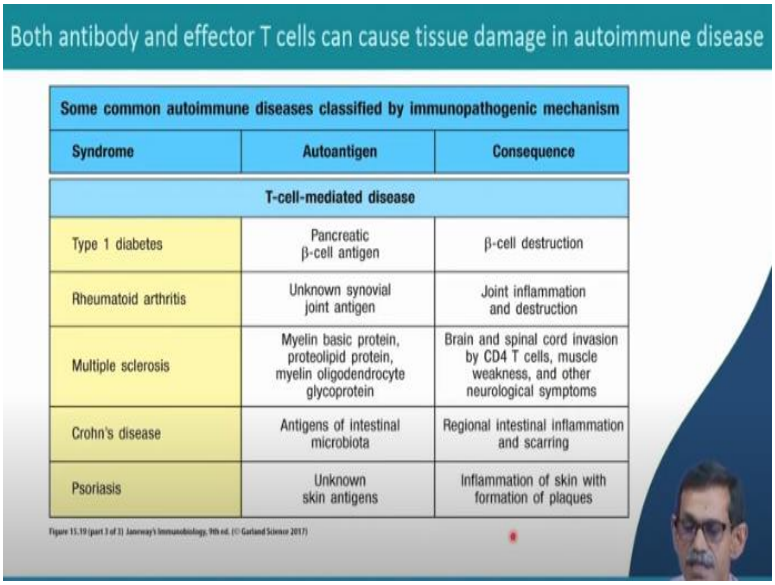

Then there are T cell mediated like type I diabetes is T cell mediated. We are going to explain that okay, what is happening.

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So this was the list. I did not go for the detail. Now we are going to see what is happening. Autoantibody against blood cell, what will happen? Or antibody binding in blood cell activate the complement action. You now know the detail about complement, right. What is going to happen?

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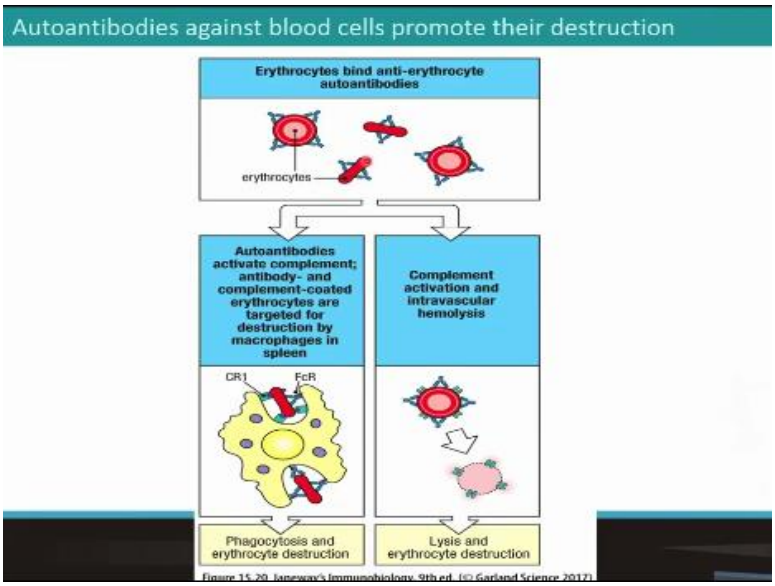

Say this is RBC okay. This is flat I mean this is sidewise. Antibody binds to it. So if there is antibody against RBC what will happen? As soon as antibody coat it, it will act like opsonization and whole RBC will be taken up by macrophage and destroyed. Or same way if after binding antibody if complement binds to it, because you know that complement that is how the name came, okay. What will happen?

RBC lysis will happen, complement mediated lysis. That is also the effector function of antibody. So this is opsonization and this is complement mediated lysis. In both the case what will happen? The number of RBC will be going down very drastically. As a result severe anemia, right. So this is possible. So if any antibody against RBC this can happen. So now I will show you few examples.

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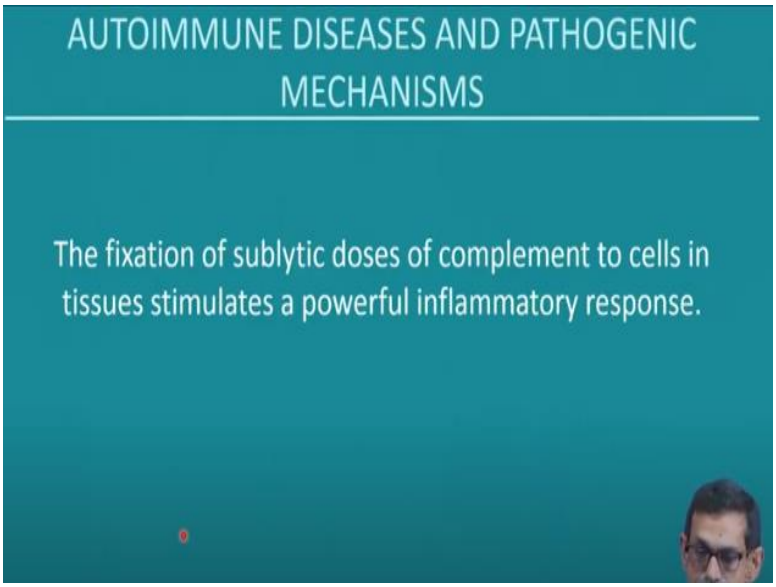

The fixation of sublytic doses of complement to cells, that we already say that, also can cause inflammatory response okay. This complement interaction there are many part after complement processing, there are small part you know that 3HEB. So that small part 3a, 4a, 5a, these also give the inflammatory response in complement. So when complement mediated action is happening, so some inflammatory response is also happening at the same time, okay.

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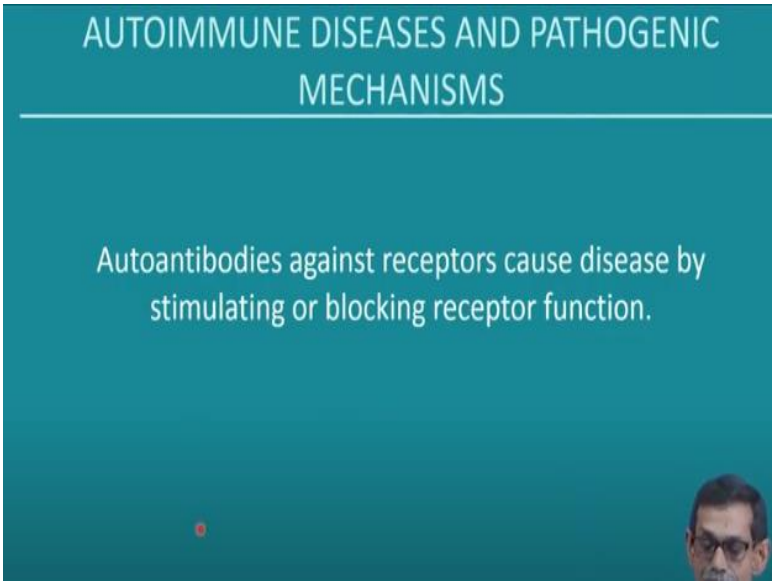

Antibody against receptor that we was discussing the Graves' disease, the receptor against thyroid stimulating hormone and the receptor against the acetylcholine. Now I will discuss like how this happening. So antibody against receptor also cause the disease. And this is very common, okay.

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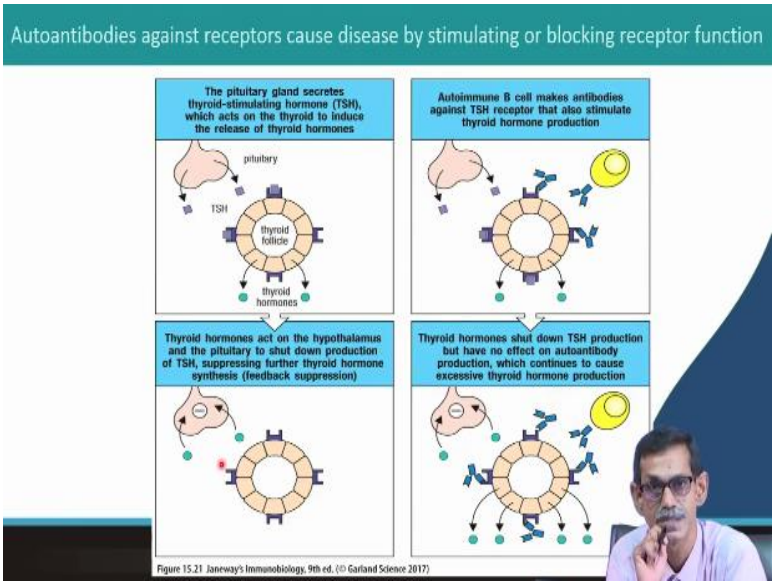

What happen? You have to go back to your school level as well as those who have biology in higher secondary, if you remember. But what happen we always have a thyroid hormone is very important hormone for our system. All the hormones are important, but thyroid is one of the very important hormone too. So what happen? Thyroid hormone is secreted by thyroid gland. Who is controlling that? It is controlled by pituitary, right.

So pituitary gland is releasing TSH. Pituitary gland is releasing TSH, thyroid stimulating hormone that binds to the receptor present in thyroid gland or thyroid follicle. So when we need thyroid hormone that means suppose there is supposed to be levels should be maintained okay. As soon as it goes below we need thyroid because that level should be maintained.

So as soon as it goes below, signal goes to pituitary, pituitary release TSH, it binds to thyroid hormone gland and thyroid released, okay. So when we need thyroid hormone, pituitary do something. What it is doing? It is producing TSH, binds to its receptor and thyroid hormone it is released okay. So it is releasing I mean it is producing thyroid hormone. So as soon as it reach the level if it is continuous it will go up, right.

So that is also not wanted. I mean the level should be maintained. If it is below it is problem, it is above then also it is a problem, right. So you know goiter will happen. So that means how it is controlled? As soon as it reach the level it gives a negative feedback. It tells pituitary well, we are fine, we do not need any more TSH. So as soon as TSH stop, this binding will not be there. So no more thyroid hormone.

That is how it is regulated. So when it is down, we pituitary release TSH, it binds to thyroid hormone gland and release thyroxin or thyroid hormone and then as soon as it reach the level it again giving a negative feedback to pituitary and pituitary stop TSH. As soon as TSH is not there no more hormone secretion is also there. That is the regular function. What happen in autoimmune disease that is a Graves' disease, antibody is developed against this receptor, okay. What is going to happen?

Antibody binding or the ligand binding the TSH binding receptor will not understand what is happening. It will see that something binds to me. As soon as it antibody binds, it will realize that TSH came and bind. So it starts synthesizing thyroxin or thyroid hormone, okay.

That thyroid hormone production will give the negative feedback to pituitary. Pituitary stops producing TSH. But antibody is not controlled by that. What will happen, antibody is continuously remain attached to it and thyroid gland is

continuously produced the thyroid hormone. So what will happen? Hyperthyroidism. So that individual will have lot of thyroid hormone because that regulation by TSH and pituitary is gone now.

Antibody is continuously produced and give this problem. This is Graves' disease. This is also autoimmune disease. I hope you understand this.

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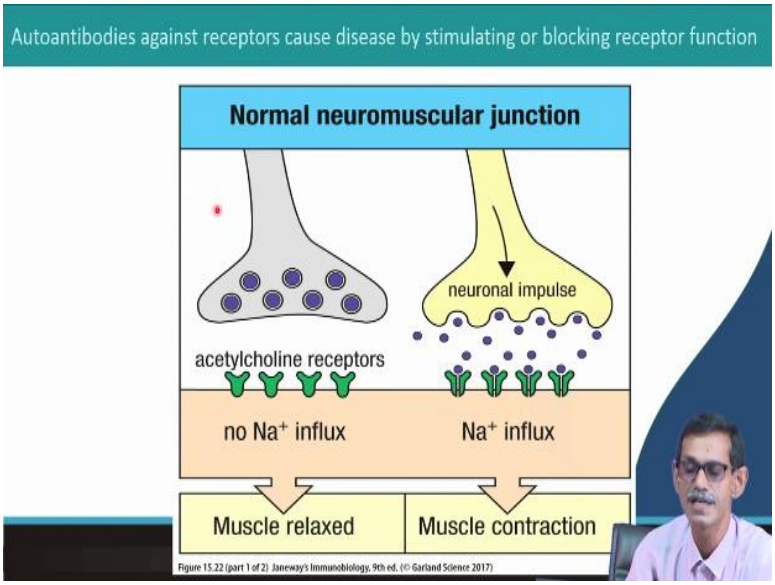

Similarly, myasthenia gravis. This is a disease which is antibody against acetylcholine receptor. Normal case what happen? This is the nerve end, okay. These vesicles are full of acetylcholine. Whenever some impulse is coming what happen? This neural impulse, this acetylcholine is released, all this dots. So these acetylcholine is going to bind with this receptor, okay and give the signal to next nerve or the end that is what is called.

So when there is no acetylcholine here, muscle is relaxed. When muscle contraction is there, whether it is voluntary or non-voluntary, we need acetylcholine. What is going to happen? This muscle contraction will happen. But, this is normal case, this is normal neuromuscular junction. This is muscle, this is nerve end. So finally, motor nerve come and give the signal and muscle get relaxed or contract depending on whether acetylcholine is releasing or not releasing.

This is normal biology, normal individual is going to do that. But in autoimmune disease what happen? I mean again the antibodies developed against this receptor, okay. What is the result?

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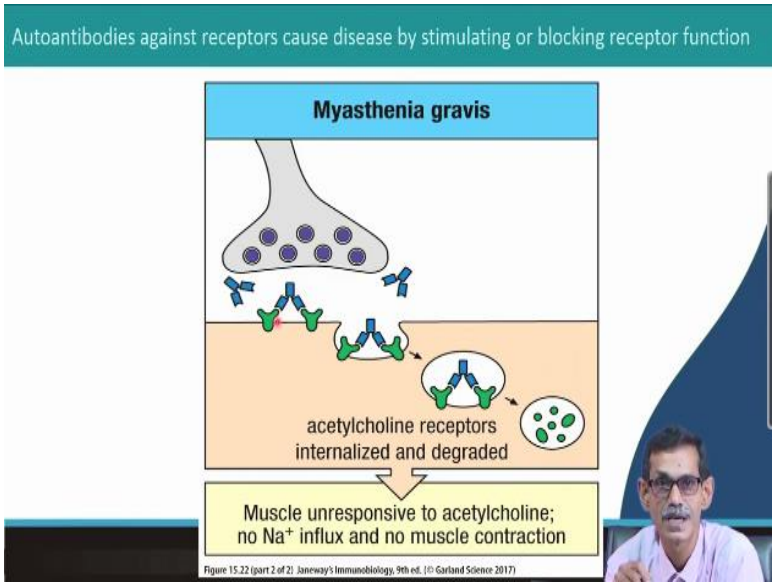

The result is in even there is no acetylcholine release no impulse from brain this antibody is going to bind and crosslink. As soon as antibody is going to bind this will be internalized by receptor mediated endocytosis, okay. And as a result what will happen? You know that everything will be degraded. That is normal process because cell will not understand whether what happened because normally receptor mediated endocytosis does not happen if single like if single molecule attached to it.

But if you see this, this is a cross link. That means one antibody cross link two receptors. When this thing happen cell did not realize that is the normal binding. As soon as crosslinking happen endocytosis will happen. And this endocytosis will reduce the number of acetylcholine receptor here. So as a result what will happen? Suppose this nerve end is perfectly alright. It is loaded with acetylcholine vesicles, okay.

And nerve impulse come all this acetylcholine released but in this place there is, in this place there is no receptor. What will happen? Muscles will not get the instruction for to contract. So if continuously that thing happen muscle cannot contract. It will be completely relaxed forever or as long as possible, is not coming. As a result what will

happen? Again paralyzes because your muscle I mean if I cannot do this contraction or relaxation, then muscle will not work.

And as a result that particular part will be paralyzed, okay. So this is these are the two very unique example of antibody mediated autoimmune disease and definitely antibody there means definitely T cell is there, okay T cell mediated activation is there. So there definitely antigen presenting cells are presenting this and which is activating T cells, which is activating B cells. So those part are common.

So if by any chance that regulation or this mistake happen, we will see these kind of diseases. Two very nice example and there are some other but we will restrict to this kind of like receptor, anti-receptor antibody mediated autoimmune disease, okay. So we will discuss some more disease in next lecture. Okay. But till then thank you very much.