Essentials in Immunology

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Module No. # 17

Lecture No. # 32

Autoimmunity

So, today's class is going to be on auto-immunity. It is one of the cases where the immune cell actually rebels against the host and what you have is a generation of immune response against host cells which herds the host. Now, under most cases, the immune responses are directed towards pathogens, tumour cells and so on. It is to help protect the host, but in some cases, the immune system goes awry and then attacks itself. Then in this case, what we will try and do, is try and understand the mechanisms around it.

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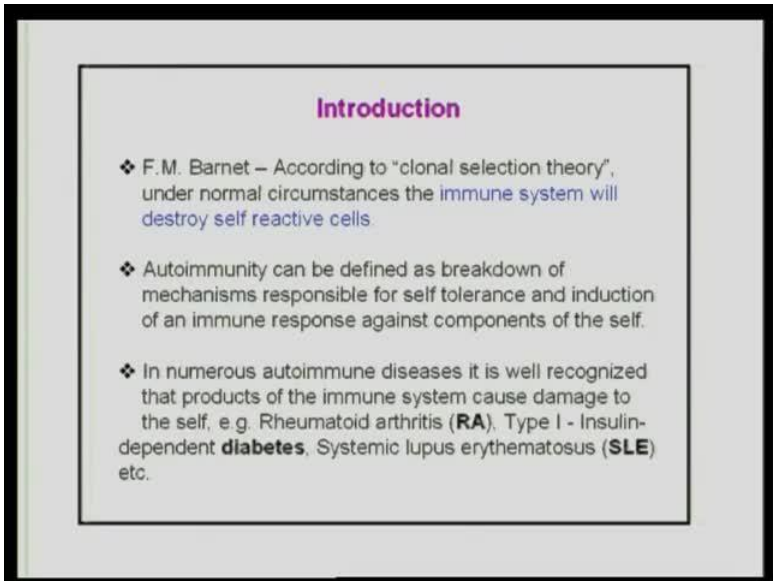

So, if you see in the first slide, Barnet - the famous Macfarlane Barnet - when he coined the clonal selection theory, one of the tendency of the theory was that dealt with the fact as to how came the host cells are able to protect themselves from receptor that might recognize self and this was dealt with the aspect on tolerance where whereby immune receptor again self would be eliminated, so that the host does not generate a response against itself.

Now, we know that by enlarge the immune system does a good job of protecting itself but however, in some cases the immune system turns itself upon the host and that is what this class is all about. So, basically auto-immunity is defined as a breakdown of mechanisms responsible for self-tolerance and that is the essence of auto-immunity. So, how does this occur? So, we will try and figure it out. The other aspect is what are some examples of auto-immunity are and I am sure if you look around your own family or whole friend or society, you will see these cases quite clearingly.

One of the first one is arthritis, especially rheumatoid arthritis where you have a generation of immune system has gone bad and it had the joints especially. So, you have inflamed joints and people are unable to function properly. So, how does that occur, we will be studying that aspect. The other is Type I dependent diabetes. Now, if you remember in terms of diabetes there are two types, Type I and Type II. In Type I is the insulin dependent diabetes. Over here, you have immune cells that target the beta cells of the pancreas and kill the beta cells preferentially. As a result of which insulin is not produced and since the insulin is not produced, the blood sugar levels in are very high, as a result of which leading to diabetes. In Type II diabetes, insulin is there but they are not responsive, the insulin receptors are not responsive. As a result of which glucose does not get pumped inside the cells.

So, the one the diabetes that we are talking about is the insulin dependent Type I diabetes. Then the other example is systemic lupus erythematosus, a disease that often a flex women and this manifests cells after they turn about 25 years of age so on.

So, and if you look around and we will be studying more diseases and we obviously cannot study all autoimmune diseases but at least some diseases we will be studying in somewhat greater detail.

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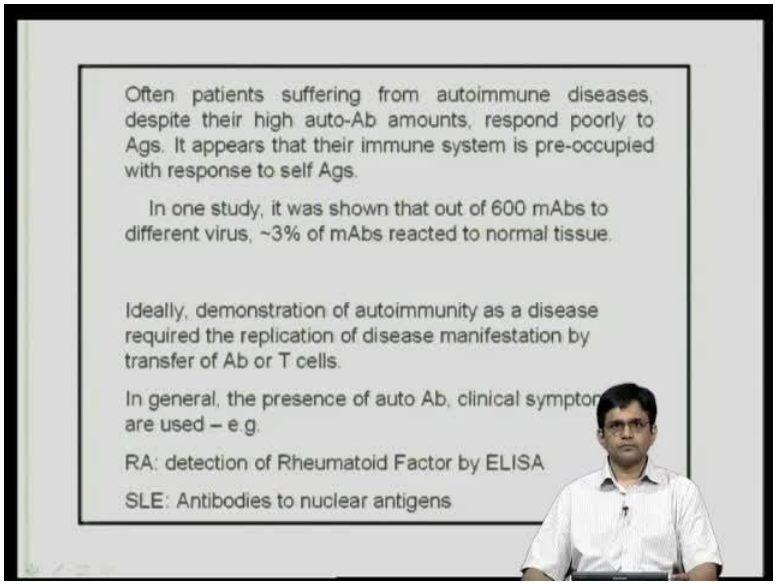

Now, the other interesting aspect about auto-immune diseases is that there are high amounts high titer of antibodies that are produced again self and despite this, the ability to react to pathogens and all is compromised and it would seem as if their entire effort or the entire in these auto-immune patients is directed towards immune responses again self. So, clearly if such a lot of effort goes in generating immune response again self, then some of it is compromised and especially the person becomes more susceptible to infections because the immune receptors and the mechanisms are sort of directed towards self-access. When such situation occurs, it does not help because the direction against non-self also gets affected.

Now, in the process of generating immune responses, it is possible that in some cases a small minority of these immune responses are directed toward self. In fact, when 600 monoclonal antibodies where studied against different viruses, it was found about 3 percentile of these monoclonal also cross reacted with normal tissue. So, it tells you that this occurs but as I said there are mechanisms in place by which the host manages to keep these and these auto-reactive immune cells under check. So, they do not actually manifest themselves in terms of disease, it is only in rare cases that the immune system as I said goes a little bit awry and you have reaction that manifest itself in terms of a disease in patients.

So, but since if since this does occur, it is very important to study as to why this happens and therefore, one can take preventive steps or therapeutic applications can be found out which can sort of keep these in check and these are very well studied by now. So, how does one determine whether a person is suffering from auto-immune disease or so? Usually in terms of theoretical scenarios, it would require replication of the disease manifestation by transfer of

particular antibody or transfer of T-cells but in general the presence of an auto antibody for example, rheumatoid factor. In case of arthritis or clinical symptoms, legions in the brain etcetera are taken as a diagnostic measure.

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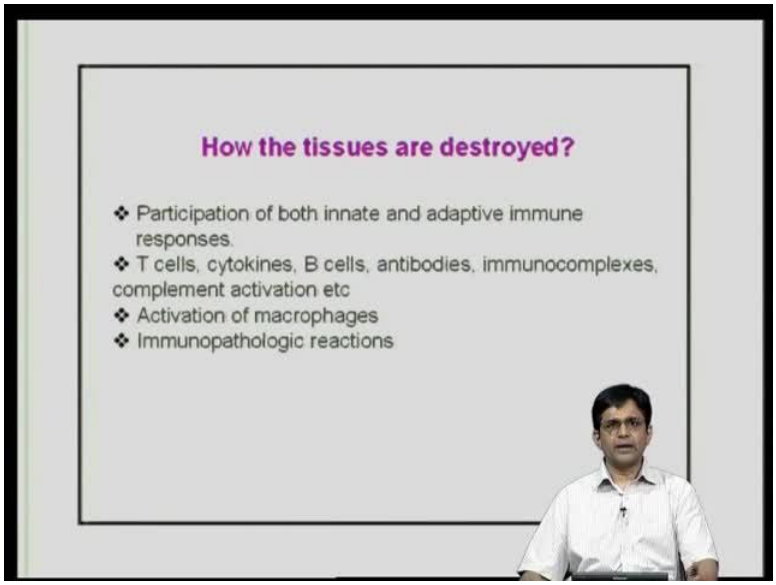

So, for example in rheumatoid arthritis are mentioned, you have detection of rheumatoid factor by eliza and in case of systemic lupus, you have antibodies to a nuclear antigens that are diagnosed. Now, what happens is once you have this auto-antibodies being produced or you have T-cells that start recognizing self-tissue, there is damage. There is damage because you have an inflammatory situation where both innate and immune cells come together and especially with antigen antibody complexes you also have complement activation which will further result in lyses of cells, you have macrophage activation. Basically, it results in immuno-pathology and that is what it results ultimately in terms of a disease and once you have that, then it is a question of trying to control this and trying to reduce this.

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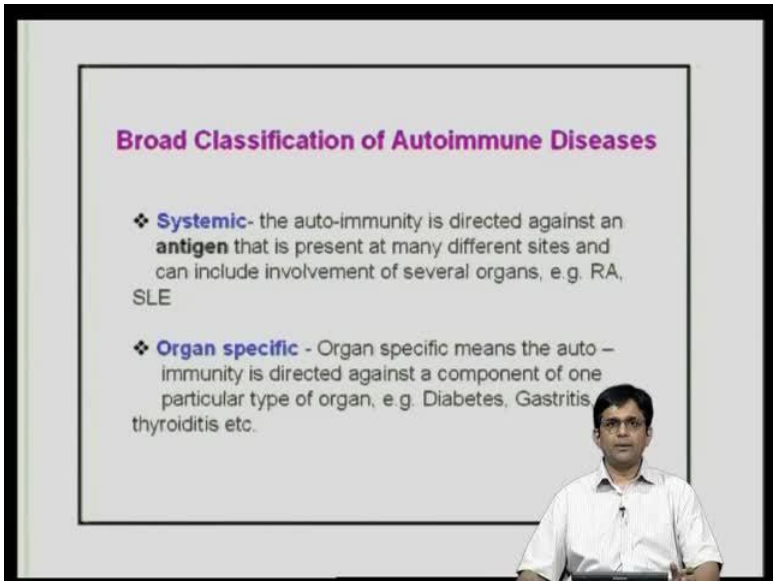

So, in order to be able to do this, we need to understand the mechanisms by which all these occur. Now, in terms of classification of auto-immune diseases, there are two broad classifications. First is systemic. Systemic is that means it is all over, it is all in different, in different organs, different sites. For example, in rheumatoid arthritis you have it in several joints of knees, fingers, elbows and so on systemic and then you have a systematic lupus. So, well systemic lupus erythematosus again you have it afflicting different parts of the body but in systemic lupus, especially the moment it gets serious when you have a antigen antibody complexes deposited in the kidney and because of this, you have the filtration is affected. Your kidney function is affected once, kidney function is affected and your health is at serious risk.

You had one broad classification. You have the systemic and other, you have the organs specific. In case of organs specific, the one that comes into mind is diabetes for example and it is here where you have an immune response against your beta patriotic cells which produce insulin. So, that becomes a problem. Then you have thyroiditis where you thyroiditis is affected and gastritis where the gastrointestinal track is affected and these are something that we will be studying in this class.

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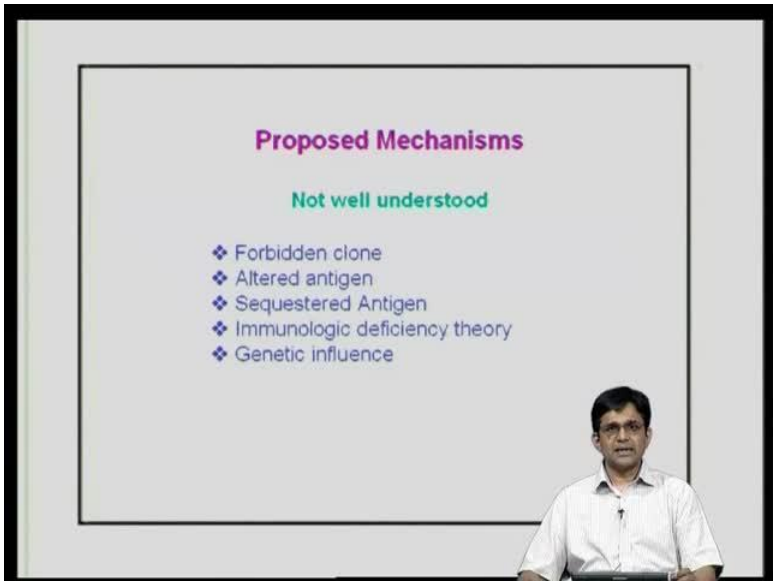

Now, how does this occurs? Now, there are there are several mechanisms proposed. It is not clear exactly what results. There are is a whole list, there is a forbidden clone, altered antigens, sequestered antigen, immuno-deficiency genetic influence and we will be studying these in a little bit greater detail.

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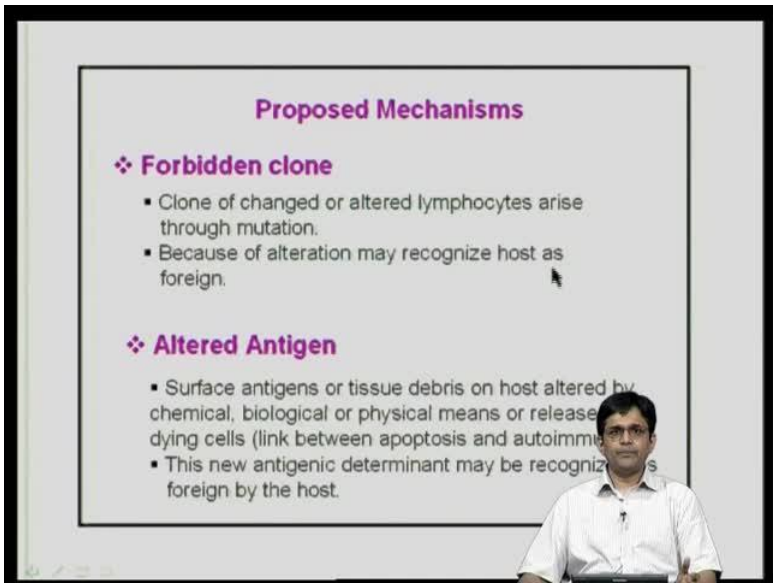

So, the first mechanism that we will study is the Forbidden clone. Now, over here what happens is the clone has mutated oppose selection, there is there is some mutation or altered lymphocyte receptor as has been generated through mutations and because of this, it is now star recognizing the host as foreign. So, this this may certainly occurred because if you remember, in especially in case of your B cells there are somatic mutations that take place

and because of this it is possible that receptor is generated which star recognizing self-tissue. Then this amplifies itself because of recognition it will star amplifying itself and this results into and this may result into an auto-immune disease.

The other scenario is an Altered Antigen. Either, you have surface antigens or tissue debris or antigens or molecules that are released by host by dying cells and there is a link between increase number of apotosis and auto-immunity. This antigenic determine may now be recognize as foreign because usually it is kept, it is not recognized because of this change that is occurred. It is now recognized as foreign and you have a generation of an immune response against this.

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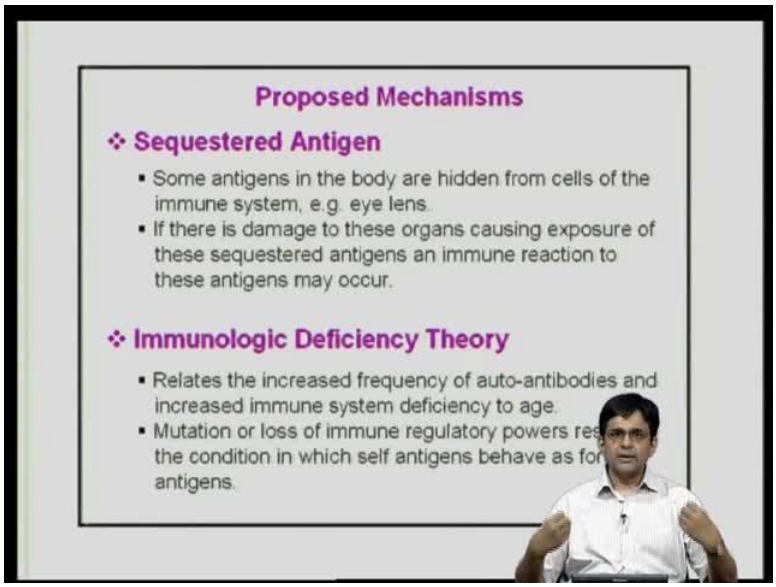

You have the other possibility is that you have a Sequestered Antigens. So, what a good example of a Sequestered Antigen is actually the eye lens. The eye lens does not come in contact directly with blood but in case of damage, it would come in contact with circulation and then you would generate a sort of a response against it. So, this would be good example of Sequestered Antigen.

Then the other one is that of a Immunological Deficiency Theory which means as people age, the receptor becomes more and more what has been found is that there is a narrowness or there is a limitation in the number of receptors that is observed in these people and because of this, you have increase number of auto-antibodies. An increase because the receptors that have gone so specific perhaps because they are recognizing now some self-tissue and they

sort of increase in numbers and after a point this sort of can take over and generate auto-immunity.

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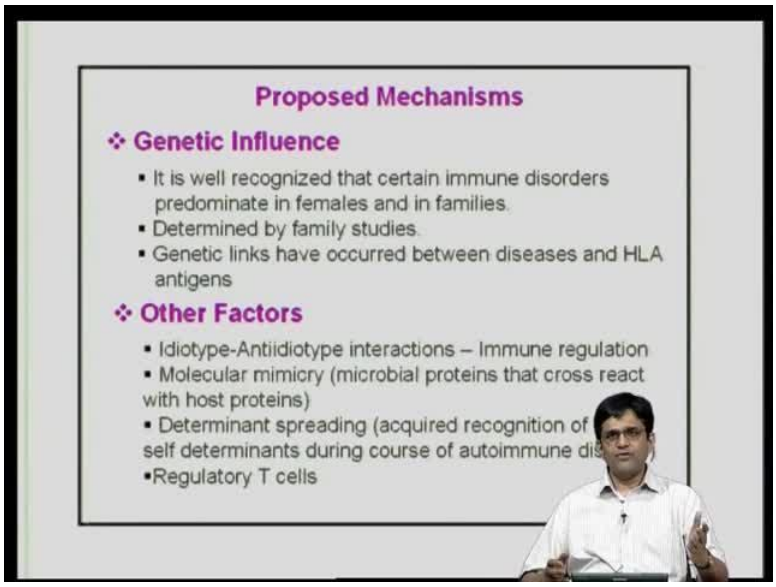

The one of the major factors is Genetic Influence. Now, in some auto-immune disorder, it is clear that that genetics plays an important role. So, for example in case of or in case of some auto-immune diseases, MHC molecules predispose, so the type of MHC molecule that will have predisposes you to be either sensitive or to be resistant to certain diseases. This we had discussed during our discussion in MHC and obviously, the MHC molecules play an important role.

Now, apart from these, there are other loci that play an important role and these are some that we will be studying as we discuss a different aspect in the class. Now, in terms of other factors there are several other factors, so one is the Idiotype, Anti-Idiotype interaction. This comes under the category of what is known as immune regulation. What is an Idiotype? You remember the antibody molecule will recognize a particular antigen and the part of the antibody molecule that recognizes this antigen is known as the Idiotype. Now, because if you have lot of these antibodies being generated, that recognize a particular antigen, you would have what is known as in terms of immune regulation. You would have an Anti-Idiotypic antibody that is particular to this part of the antibody molecule.

So, often you have Anti-Idiotype interactions and if you have a lot of this, this means you have antigen antibody complexes. So, you have antibodies reacting with antibodies because

of Idiotype and Anti-Idiotype interaction. Hence, as a result of which you have these immune complexes and if you have too much of these immune complexes, these are a problem because as I said these immune complexes are a problem in a kidney because they are harder to separate out. They will clump up and they will clog up the filtration process in the kidney.

Now, the other aspect is Molecular mimicry. Now, in the here there has been a thought that often auto-immune auto-immunity results after a particular infection. So, in this case, what happens is let us say you are exposed to a particular pathogen and the body reacts to this particular pathogen and some of these antibodies or may be T-cells that that are generated also cross react. Now, with a self-molecule because the molecular pattern that is present in the microbes is cross reactive with something in a self and this sort of results in it which is known as Molecular mimicry and this result in the generation of a auto-immunity. So, these are the different factors that have been proposed.

The other is Determinant spreading. Now, what we mean by that, so you have a particular determinant and you have an antibody response to it. Now, as with during the course of the immune response, the anti-body response changes and the determinant starts that is a spreading that means it enlarges and your antibody response also enlarges. During this process, it is possible that you generate some cross reactive antibodies against again self.

Finally, Regulatory T cells. Now, by enlarge one of the main mechanisms by which auto-immunity is kept under check is by Regulatory T cells. In fact, what has been shown is that and the we covered bit of covering during our course on T cell subsets that if you remove regulatory T cells, the amount of auto-immunity increases because so you so the basic point is that there is a basil level that that our immune system is not that perfect, that we cannot generate a completely fool proof system.

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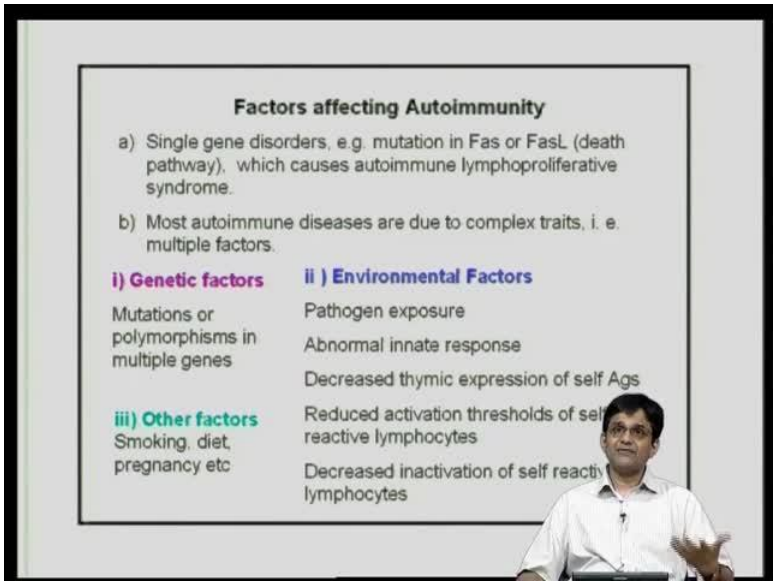

So, there is basil levels of auto-immunity but that is kept in check because of the regulatory T-cells, so only after that is over come if that you are able to generate an immune response. So, the generation of an immune response, therefore must be accompanied by severe by informatory reactions which will overcome the enabution by the T-rex. So, by enlarge basil immunity or auto-immunity is kept in check by Regulatory T-cells and we had discuss this part and it is a very important aspect of T-rex and auto-immunity sort of go hand in hand.

So, we will discuss some other aspects among the several factors affecting auto-immunity. Again, you can have two main groups, one is you have single gene disorder and b, you have the other is the complex traits where multiple loci and multiple factors are involved. In terms of single gene disorders, the most important one is our mutations in Fas, FasL or the death receptor or a mutations occurring in the death receptor are pathways. For example, certain gas basis.

This aspect was covered very well in our course on T-cell differentiation selection. Over here, what happens is if there is a mutation in the death receptor like Fas, the Fas receptor or the Fas ligand, it results in what is known as an auto-immune lymphoproliferative syndrome. What is seen over here is that the normal process by which death sort of removes these T-cells is not taking place where the death path way removes this T cells is not taking place. As a result of which they accumulate, so you have that is why word lymphoproliferation because they proliferate. The lymphnodes are bigger, the spleen is much bigger because the cells are accumulated and because they accumulate, they cause this auto-immune lymphoproliferative syndrome.

However, most auto-immune diseases are due to complex traits that is multiple factors. What are some of these multiply factors? The first is the genetic factors. These are mutations or polymorphisms in multiple genes and that can occur in different loci. We will discuss these different genetic factors in for example, in diabetes where it was shown that MHC is important but also the amount of insulin that is produced is important. You also have molecules like CTLA4 which play an important role in diabetes. So, again because that is a complex trait, you have different factors being involved in the actual generation of a disease.

You also have environmental factors. We talked about pathogens exposure. May be there is some cross reactive, a molecule between the pathogen or a microbe with self-molecules and the process of generation of a immune response against this. There is some cross reactive proteins, you have you generate response against cross reactive proteins which results in disease.

You have abnormal innate responses or for example, you have decrease thymic expression of self-antigens. You also have reduced activation thresholds. Now, here the strength of a signal is important because you have these self-reactive lymphocytes. Now, if for example the lymphocytes see something with greater ability, you would generate a reaction and may be that would get eliminated. However, if the reaction is of much slower in or it is a low affinity antigen, so the reaction would be there, it would keep this lymphocytes but it would be a it would generate responses against cross reactive.

So, that is always a possibility which may increases chances of auto-immunity and you have decrease inactivation of self-reactive thymocytes. For some reasons, you have inactivation of the self-reactive thymocytes and we have we have seen this case especially in when we were studying our in the class on thymic differentiation where you AIRE is a gene which is expressed in the thymus and which is important in terms of expression of peripheral antigen. So, that T cells are recognized these peripheral antigens are eliminated from different tissues. In case, you have mice or humans that lack AIRE, then you have this higher amount of auto-immunity. So, AIRE is a good example of that which controls the expression of peripheral antigens in the thymus and in the absence of that you generate auto-immune receptors which will cause disease, subsequently after these cells move into the periphery.

You also have other factors. For example, smoking, diet, pregnancy. These also affect auto-immunity. So, for example what has been found is during pregnancy for example, there is

some sort of suppression of auto-immunity feature, so that sort of perhaps that is accompanied as overall response to other antigens may be going down. Especially, you remember the features is also considered as sort of antigens, perhaps during pregnancy there is a lowering of these responses to allow the pregnancy to fully take place. So, the babies born but as a consequence of this, auto-immunity features also go down. Smoking also seems to have a negative effect which means it increases chances of these immune reactions and cause increase inflammation. So, that would correlate in a sort of negative sort of way, there is pregnancy sort of suppresses these auto-immunity features.

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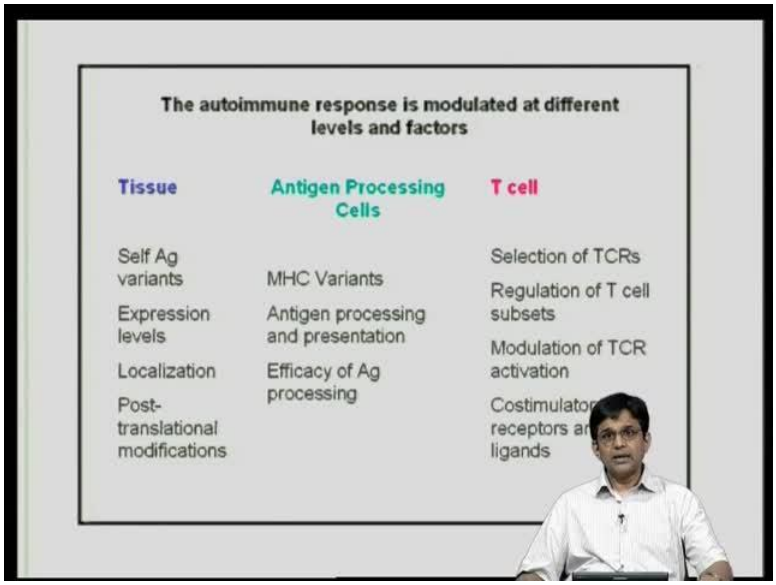

So, we will consider the different aspects that we study. So, what are the ways by which these could occur? So, in terms of tissues you can have the antigenic self-antigen variance in different tissues, perhaps which may generate auto-immune reaction. You have expression levels as I mentioned in case of diabetes you have insulin. The amount of insulin that is produced is important in again generation of manifestation of diabetes, localization of a tissues specific antigen and then post translational modification. With respect to antigens and their expression in tissues, there are different factors that are involved which are listed down here.

With respect to APCs, you have MHC variance. Now, remember MHC variance, MHC molecules are polymorphic and they will have different affinity for different peptides. So, depending on a type of MHC that you express, it might have it might have an effect. You

have antigen processing and presentation, remember we discussed these aspects. You have the MHC, the proteasome components. These all may contribute to differences and class two, you have the DM molecule so on which would again sort of apart from MHC. You have other components which might help the result in variance or if different kinds of peptides that are sitting on MHC molecules which will have implications in generation of a T cell response and then you also have efficacy of antigen processing.

Now, with respect to T cells which are really a key over here, you have selection of the T cell receptors type of T cell receptors that are selected play obviously an important role because it depends on the amount of cross reactive ones that are generated. Regulation of T cell subsets very important aspects because the T helper differentiation phenotype plays a critical role and as we will see is that there is no real correlate as to these as to what happens because in case of you generate a T helper, Type I responses, T helper Type II responses and in some cases beneficial in some but hurtful in other. So, there is no generalization about TH1 and TH2 responses in terms of auto-immunity and in terms of EAE as will be seen, the T helper 17 responses play an important role.

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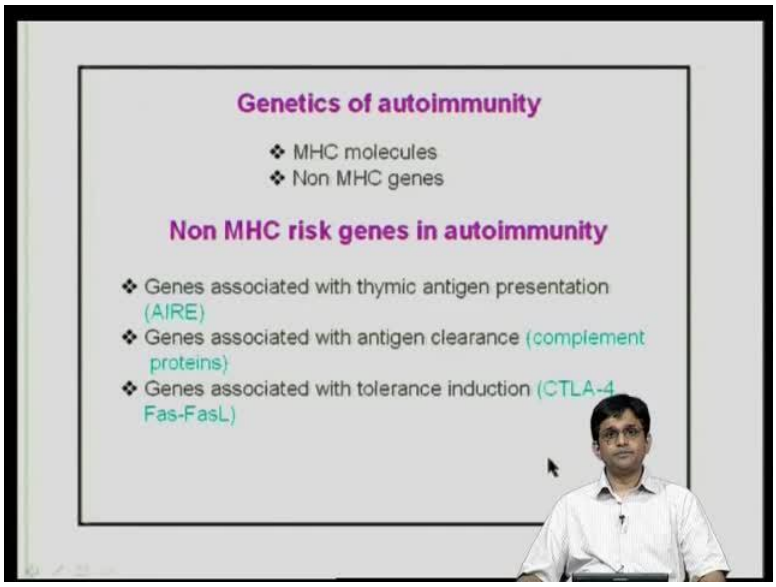

Modulation of TCR activation, I had talked about the strength of signal playing an important role over here, high strength of signal T-cell response strongly. You generate a you either you generate a good reaction and often it might result in animation, however with low strength of signal, the T-cells are there and that will help generating against cross reactive antigens. You

of course stimulatory receptor and ligands expression of CD80 86 and then subsequent one like icos and the program that receptor. These all play an important role in this process and actually take part in auto-immunity that is something that we will study in the next class.

With respect to genetics of auto-immunity, we have the MHC molecules. As I have clearly stated molecules play a very important role in this and I have given examples of this and Non-MHC genes, the one of the most important one says AIRE. This is with thymic selection and this is something that I had covered in and you must look this up genes associated with antigens clearance. Remember, antigen antibody complexes are recognized by complement and which results in lyses of cells. It might also cause greater tissue damage.

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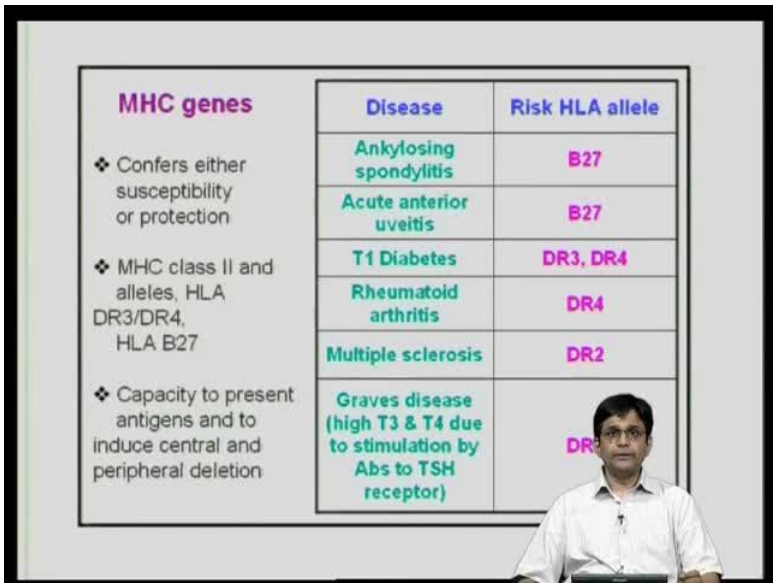

So, complement protein are clearly important, genes involved in tolerance induction, Fas FasL is clearly important. So, if you have mutations in Fas FasL, it results in lymphoproliferation phenotype. Also, if you have CTLA4 lacking a mice, if you have seen auto-immune phenotype because CD4 positive cells go haywire, they proliferate like crazy because there is no brake to sort of their activation as and consequently, it results in greater auto-immunity. Now, with respect to MHC, I have said that it can either be beneficial in some cases or can be harmful in other cases.

Now, you can see that there is a whole list of molecules or the variance of MHC. For example, HLA B27 is associated with spondylitis. Very high association HLA B27 is also associated with UVI. It is now with respect to Type I diabetes; you have a association with

DR3 DR4. Now, you will remember that these they are molecules are MHC class two molecules with rheumatoid arthritis. Again, you have a association with DR4 multiple sclerosis with DR2 and then you have graves disease. Now, in graves disease what happens is that you have higher amounts of the thyroid hormones, T3 and T4 being produced. Now, why are higher amounts produced, that is because you have antibodies to the TSH receptor and these antibodies sort of stimulate the TSH receptor. So, they bind to TSH receptors, stimulate it and this stimulation results in higher production of thyroid stimulating hormone which will go on and stimulate higher production of a T3 and T4. As and as a consequence of which if you have higher amounts of T3 T4, it results in increased B cell metabolism which will have its effects. So, that is an important aspect that needs to be considered.

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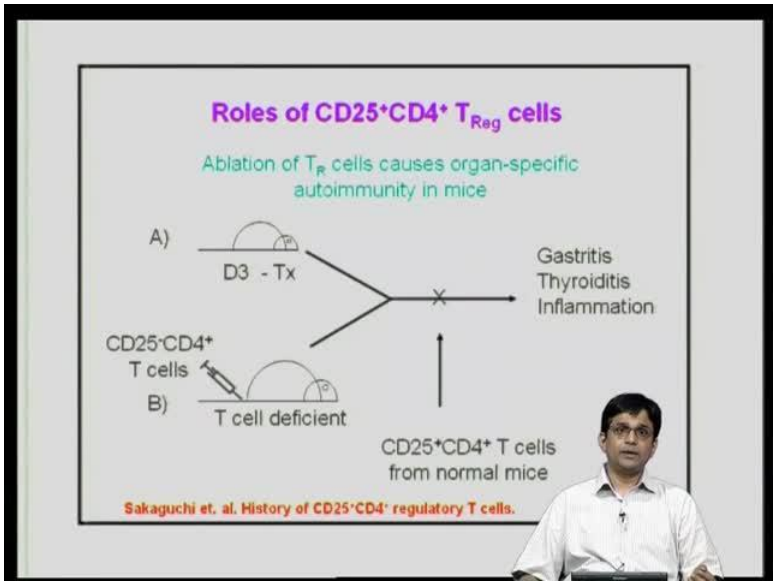

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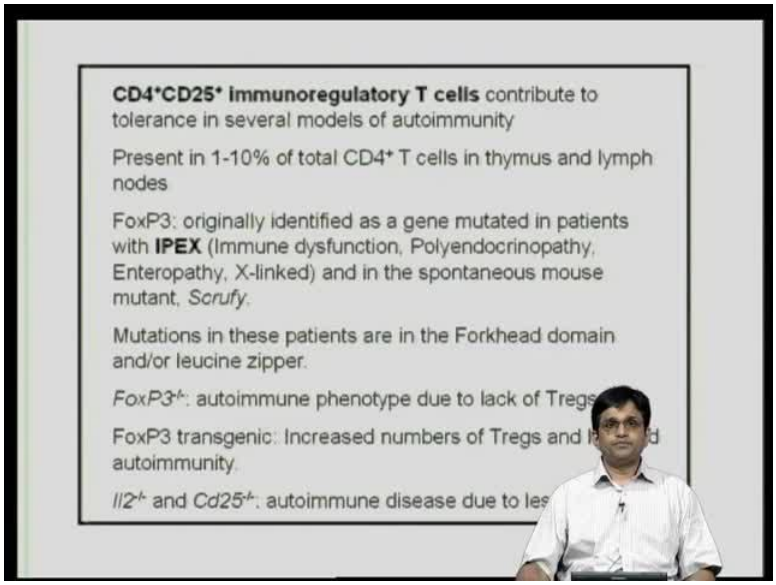

So, it has effects in terms of disease phenotype. This I have mentioned the example of Regulatory T cells that plays such an important role and that is what is shown over here. If thymectomized D3, thymectomy is done in this case or in the T cell deficient mice if you inject these cells, these results in gastritis or a thyroiditis and this is because of the lack or reduced number of regulatory T cells. Now, however if you give these cells and you remember from the previous class that we had discussed, the T reg phenotype is CD 25 plus CD4 positive and then you are able to block this generation of auto-immune diseases. So, clearly there is a big link between Regulatory T cell and auto-immunity and we have to thank Sakaguchi who was a discoverer of the T regulatory cells and because that has certainly informed or there has played a major role in our understanding of auto-immunity.

Now, auto-immune T cells have been covered in the past class but I will briefly quickly go over it. The numbers of CD4 positive, CD25 positive regs are present in small numbers you know 1 to 10 percent in the thymus and lymph nodes. Now, the key thing over here is the expression of a transcription factor as fox P3 and in patient that lack fox P3, it results in disease known as IPEX which is immune dysfunction. So, they have multiple disease phenotypes, immune dysfunction polyendocrinopathy, enteropathy x linked and or and if you see the similar phenotypes in mice that lacks fox 3 which is known, which is defined by the mutation known as Scrufy because that is how they look.

Now, apart from fox P3, just to keep regulatory T cells, just for the survival and maintenance of regulatory T cells IL2 and IL2 receptor, alpha is required. So, if you have mice that are mutants in IL2 or CD25, then you again see auto-immune phenotype and that is because of

the lowered numbers of T regulatory cells. So, clearly regulatory T cells there is a big link between regulatory T cells and auto-immunity and the different genes are involved over here, fox P3 because that is a key transcription factors and IL2 and IL2 receptor which play an important role.

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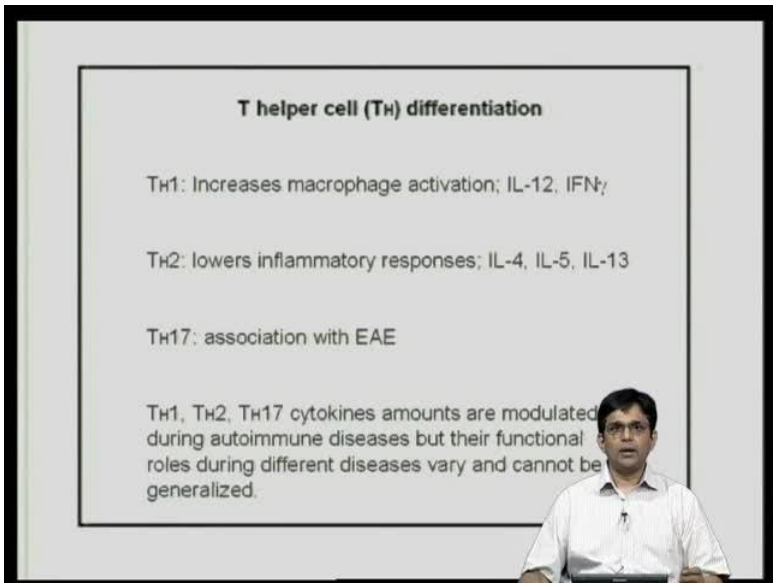

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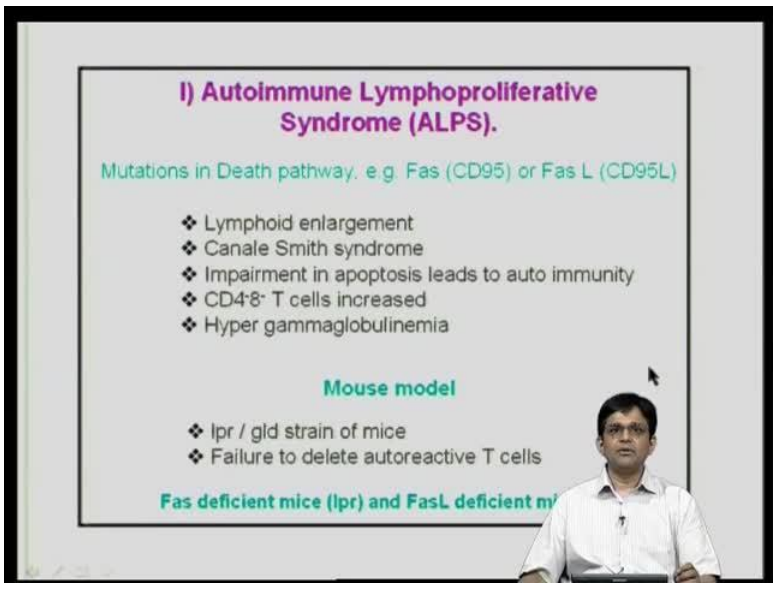

Now, we had covered different T helper differentiation pathways and you should be very well aware about the TH1 TH2 TH17 pathways. Now, as mentioned previously, these T helper phenotypes are there and they vary with different auto-immune diseases. However, there is

no generalization can be can be made because for different diseases, we see TH1 playing a beneficial role or harmful role. So, while clearly cytokines are modulated in different auto-immune diseases in terms of the function roles they vary, so one has to look at each auto-immune disease and try and determine what is responsible or what is playing a functional role in that in these scenarios. In case of TH17, there is an association with experimental auto-immune encephalitis and that is something we will study little bit later.

So, in the first, now what we will do is we will study different examples of auto-immune disease because I think that is very important for students. So, the first one that we will study is the auto-immune lymphoproliferative syndrome. We have already covered this these results in mutations in Fas FasL or may be, other mutations in the death receptor pathways which could be Fas phases which but the main one mutations that are obviously uncovered are ones in the death receptor ligand and humans is known as the Canale Smith Syndrome. This results in large increase in size of the lymphoid organs or you have increase in the double negatives hipper gammaglobulinemia in the mouse model is the lpr/gld. What is interesting is lpr is lymphoproliferative, gld is the generalize lymphoproliferative disease. This is the Fas, lpr is the Fas mutation in the Fas receptor, gld is mutation in the Fas ligand and phenotypes that are seen both in humans as well as mice are somewhat similar. Basically, it involves failure to delete auto-reactive T cells which results in this condition.

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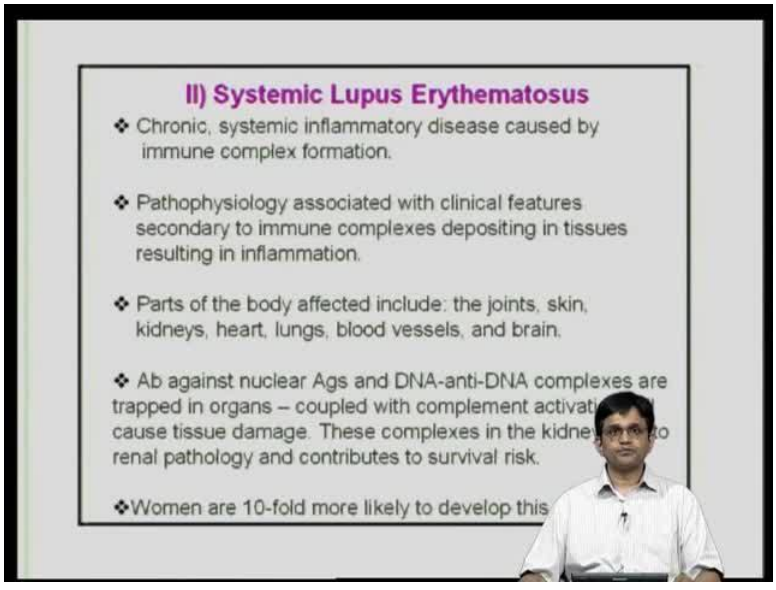

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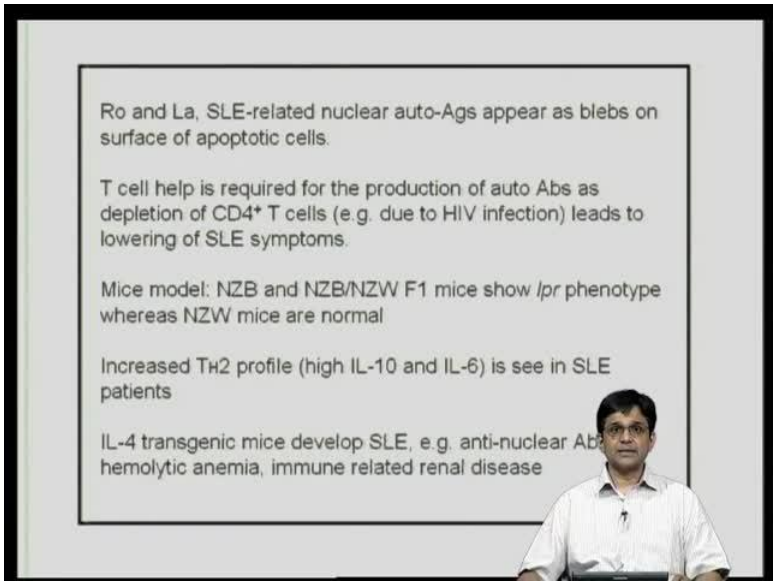

Then second disease is the systemic lupus erythematosus as I mentioned that women are more likely to come down with this disease and it manifests after they turn about 25. It is a systemic inflammatory disease and what happens over here, you have the antigen antibody complexes or the immune complexes depositing themselves on tissues resulting inflammation. So, you have inflammation in different parts of the body joints, skin and kidney. Here, what is important in SLE is that you have antibodies against nuclear antigens and in fact that is a diagnostic feature of SLE. So, once you have deposition of these antigen antibody complexes, they are coupled with complement activation and these cause these cause damages, I mentioned and this especially, this ones the kidney function is affected because of accumulation of this large amounts of antigen antibody complexes followed by complement activation. Then the patient is at great risk and what is known is the nuclear antigens, especially Ro and La are the important ones and they appear as blebs on the surface of apoptotic cells and lot of the antibody response is against these nuclear antigens.

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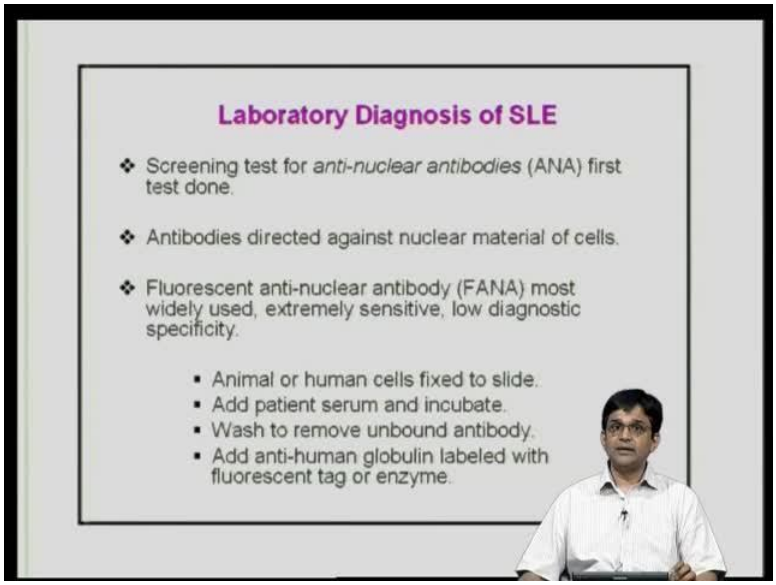

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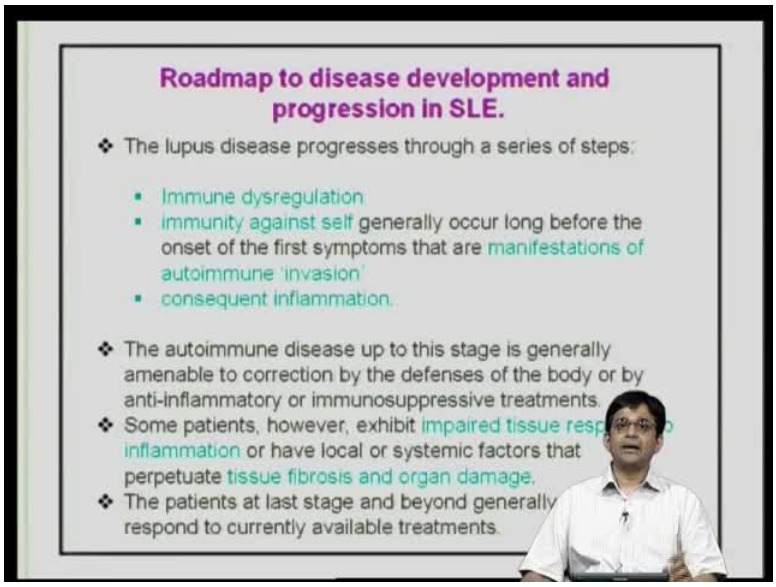

Now, T-cells are clearly playing an important role because if the CD4 number is go down as has been seen in case of HIV patients, then it leads to lowering of SLE symptoms. So, clearly T cells play an important role over here. The mice model that has been used are the NZB and NZB, NZW F1 mice, so this is the F1 mice and this is the NZB. Now, what is interesting to note is the NZW mice by themselves are normal but the F1 along with NZB or the NZB themselves are shown lpr phenotype. What has been seen over here is that there is an increase TH2 profile, in fact there is high IL10 and high IL6 and in fact IL4 transgenic mice, there is those express those mice expressing lot of IL4, develop SLE on their own, especially antinuclear, antibodies and renal disease is observed. In terms of laboratory, one of the

distinguishing features of SLE is this generation of antinuclear antibodies and that is what is often used you have you have a method to detect these and which is has a diagnostic benefit and the way this is done, you have animal or human cells fixed to the slide and with the patient serum you incubate them, wash off and then you stain with a anti-human globulin linked to a fluorescent tag. Then you are able to check for especially if you have fluorescent anti-nuclear anti-body that is that that is seen. So, the important feature of this is with SLE is the anti-nuclear antibodies that are seen.

Now, in terms of the different generation of disease in case of SLE there are three main. Once, first is it starts form immune dysregulation and then you have obviously you need to start off with immune dysregulation because that is how you generate the response. You have the response going then you have the immunity again self and then there are manifestations of auto-immune invasion. Finally, you have hugely inflammatory scenario that is developed and once you have that huge inflammatory scenario, it becomes difficult to control the disease.

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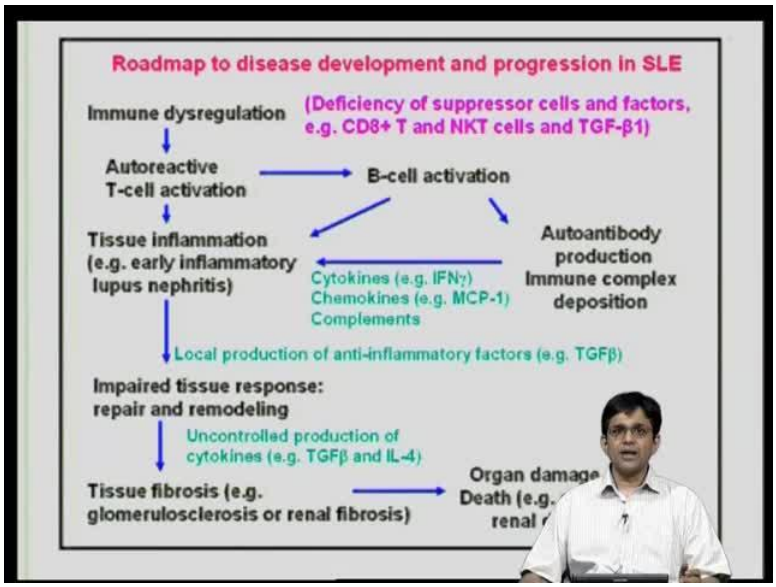

So, it is easier to control the disease in the first two steps and that is an important aspect. So, that we will see it over here, you have immune dysregulation, you have the auto-reactive T-cell activation which will go on and then turn on the B cell activation. Then subsequently, you have tissue inflammation, you have auto-antibody production and then you have different cytokines that are that are turned on because you know what you have is an inflammatory

scenario. Then you have impaired tissue responses because now, because of the excessive inflammatory reaction your organ and tissue functions are getting compromised. They are not able to repair themselves as well, you have tissue fibrosis, you have organ damage and then over all, you have real manifestation and a full bloom, a systemic lupus erythematosus going on.

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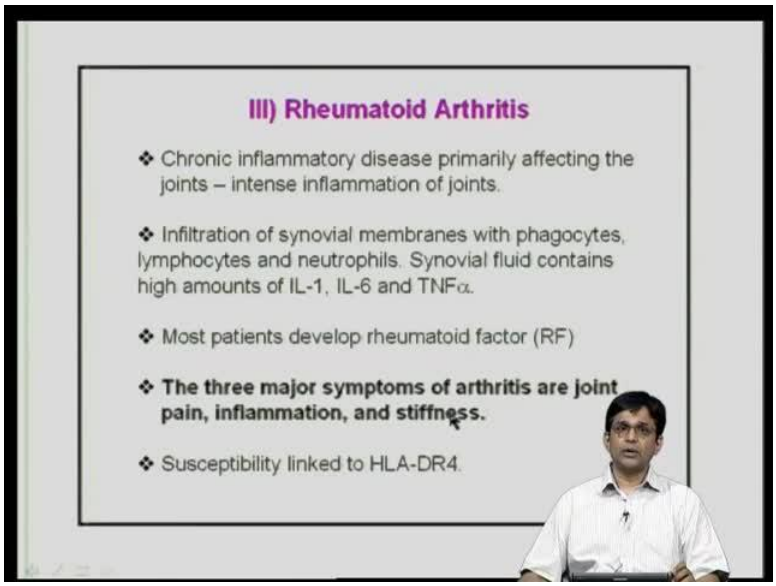

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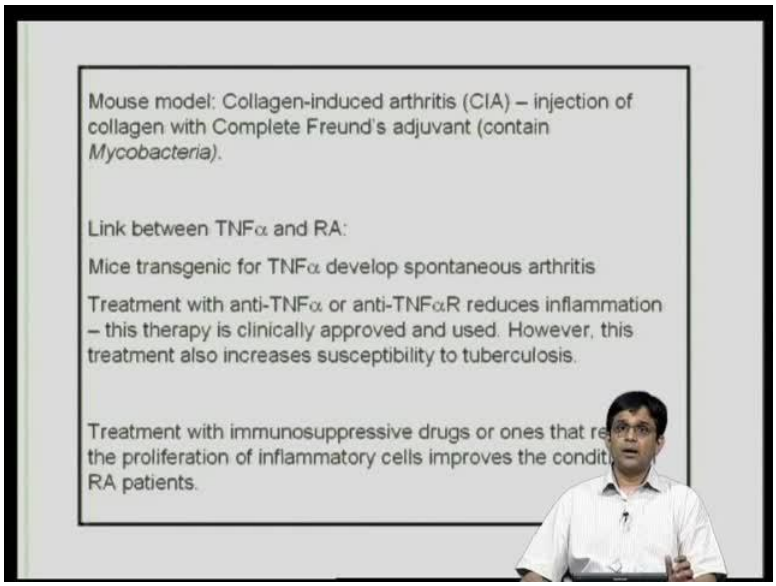

How does one control these diseases? That is again something that we will be discussing. Again, for different diseases you have different strategies and by enlarge there are some

common ways by which these are taken care. The third disease that we will that we will go over is rheumatoid arthritis and arthritis as you know is inflation of the joints. The major symptoms are joint pain inflammation, stiffness because your joint function is affected. What is interesting to note is that you see that it is a immune reaction because in these in these joints if you take the fluid, they will contain high amounts of the cytokines IL1, IL6, TNF because these are being produced by the immune cells was as was mentioned previously. Rheumatoid arthritis is link to MHC. The mouse model is a collagen induced arthritis where you take Type II collagen and you mix it along with complete Freud's adjuvant and then this generates an injection of this generates a disease.

Now, let me ask students a question. Why is it that you need to inject with complete Freud's adjuvant? Now, this is something that we had discussed in the first classes on innate immunity because what happens over here, collagen is the self-protein and if you want to generate an inflammatory reaction, if you want to generate a good immune reactions, it needs to be inflammatory in nature. So, the way that is often done is to is to mix it along with mycobacteria and your able once you are able to do it with these dead mycobacteria, the adjuvant potency is increased and you are able to generate a good reaction. In this case, this reactions leads on to the breakdown of tolerance and it will generate auto-immune disease. So, this is a mouse model and these are useful because when people study for different therapies so on, these become useful. In terms of RA, what there is a link between tumour necrosis factor and rheumatoid arthritis, so mice that are transgenic again producing large amounts of tumour necrosis factor develops spontaneous arthritis.

So, clearly this cytokine is responsible in a large part for arthritis. So, consequently if you treat patients with anti-TNF or anti-TNF receptor, then it reduces inflammation and in fact, this is a clinically approved form of therapy. Now, what is interesting is TNF also important in terms of immunity, so when once you star lowering TNF, it has other affects and one of the affects is that you see increased susceptibility to mycobacteria tuberculosis. So, very interesting scenario over here I think for immunologist, it is a very important aspect.

So, when you tuque or when you try and use therapeutic regimens, especially targeting important cytokines like TNF, you will have some consequences of it. So, one has to be careful with these aspects of the immune system because what you are doing is you are reducing important cytokines. So, obviously and this cytokine is protective, so the pathogens

especially mycobacteria tuberculosis takes advantage of this situation and tends to tens to take over these patients. So, one has to be careful about these aspects.

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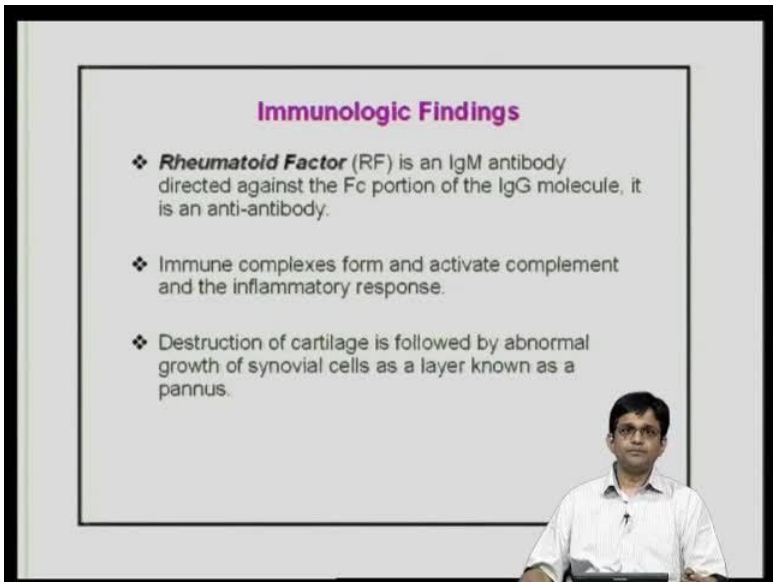

Now, with respect to RA, you have treatment with immuno-suppressive drugs or the one's that that suppress the proliferation of immune cells and this again helps. This is again part of a regime that is again autoimmune diseases. One of the diagnostic features of rheumatoid arthritis is detection of rheumatoid factor. Now, what is rheumatoid factor? Rheumatoid factor is actually IgM antibody and which is detected against the Fc portion of ig molecule. So, it is an anti anti-antibody in that sense, so detection of rheumatoid factor. The rheumatoid factor levels increases with the rheumatoid arthritis and also along with some other auto-immune diseases but it is correlation with RA is very good and it is it is used in terms of diagnosis.

Now, as was mentioned, immune complex is activating complement followed by the inflammatory reaction and this will follow by damage. Often what is seen over here in case of rheumatoid arthritis, you have destruction of cartilage. Remember, cartilage is what buffers actual the bone tissue and it is followed by the once cartilage is disturbed, you have a you have proliferation of cells that try and take over which is known as the Pannus but Pannus unfortunately is abnormal growth of these cells and which is not particularly good.

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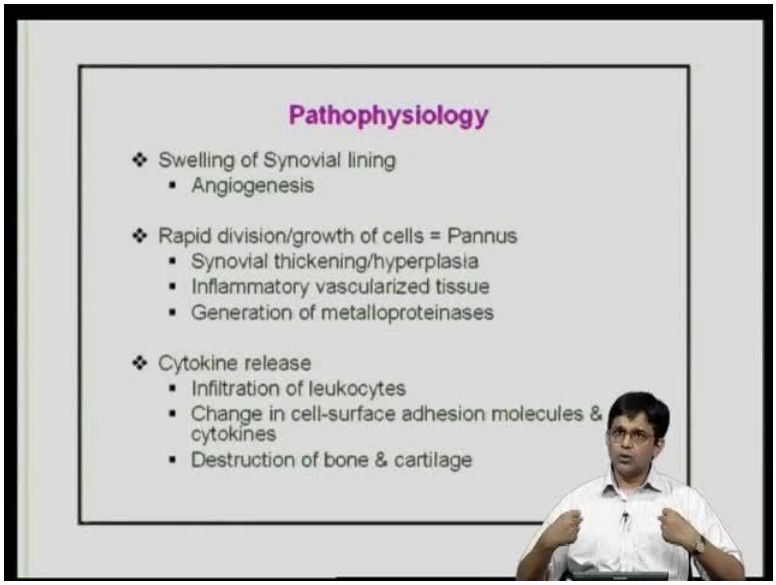

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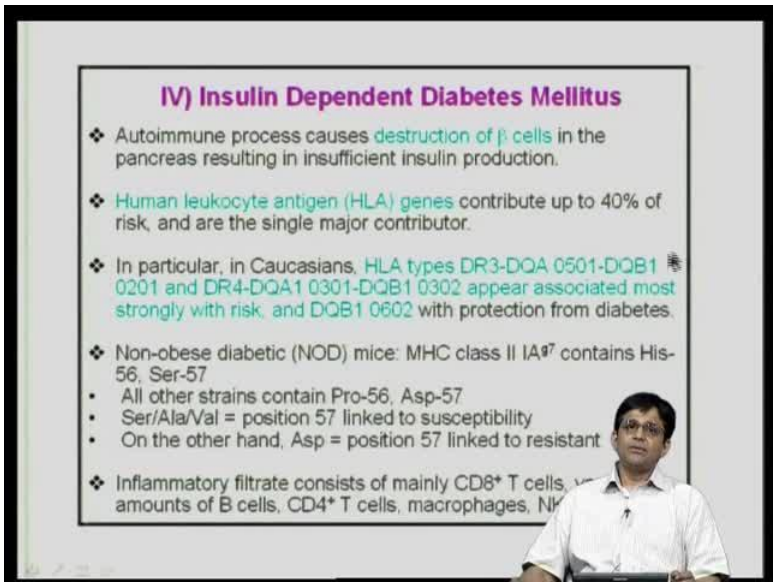

Now, in case of the pathophysiology, your swelling of the synovial lining you have rapid division of cells which is what gives rise to Pannus and then you have Cytokine release infiltration of leukocytes, destruction of bone and cartilage. So, not a good not a good scenario and all these contribute to arthritis which is why you are there is pain, there is swelling, your there is stiffness and so on.

The next disease that we will study is insulin dependent diabetes as was mentioned over here that you have destruction of the beta cells of the pancreas. Now, over here actually plays an important role and a people have shown that it contributes to 40 percent to the risk factor. You have different HLA molecules that are protective or that that appear to make you more

susceptible to disease. What is interesting in mice, you have these mice known as non-obese diabetic mice or nod mice, these are known.

Now, nod mice have a very interesting MHC class two and there the haplotype is G7. Over here, the MHC class two molecules, it contains histadeen at 56 and serine at 57. What has been seen is in all other strains which are not at susceptible, they contain aspartate at 57 instead of a serine and in fact, what has what has been shown is that if you contain a serine, valine or an alanine at position 57 is linked with susceptibility. On the other hand, aspartate is linked with resistance. You can see a single residue is important in determining in MHC class two is important in determining susceptibility to diabetes or resistance, so a very important aspect. Again, inflammatory filtrate that is that is seen especially in the pancreas. It contains primarily your CD8 positive cells, different types of B cells, again there is a lot of killing, so have the catalytic once are generated CD4 positive cells macrophages and so on.

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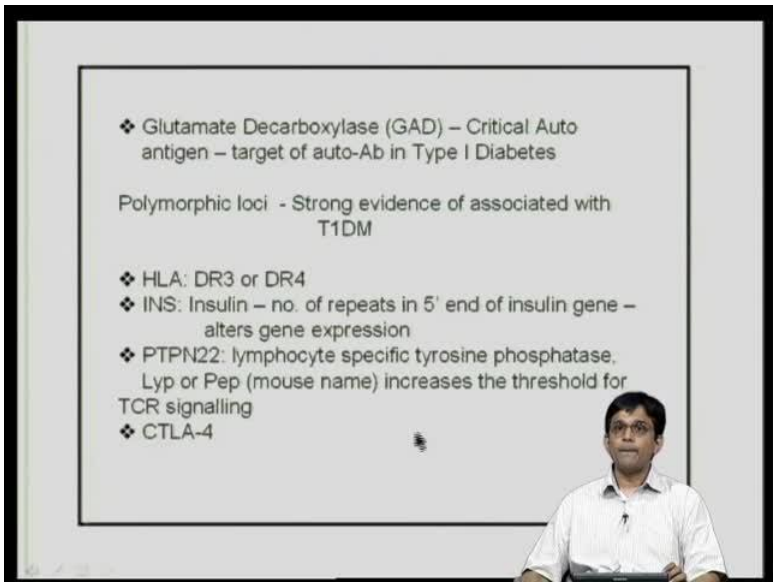

One of the antigens that have been found that generates a lot of auto-antibodies is glutamates de-carboxylase and along with MHC what are some other molecules that are linked with disease progression? Remember, diabetes is a complex strait as a complex disease, so you have different genes that are involved. One of which is insulin, apart from MHC class two you have insulin. So, the number of repeats at the 5 prime end determine is important in terms of expression, so that is important. There is lymphocyte specific tyrosine, phosphatise, lyp or pep which is also important and then you have CTLA4 has also been shown.

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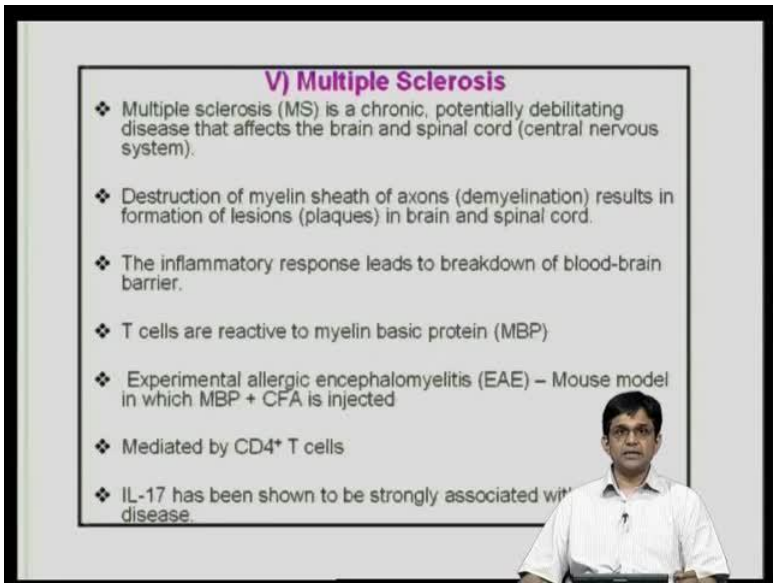

So, these together these 4 genes are play important role in determining resistance or susceptibility to diabetes. The next disease that we will study is a multiple sclerosis. So, what is multiple sclerosis? So, over here you a T cell response and the generates lesions in the brain, so you have lesions in the brain which show up and because of this you have the myelin sheath gets destroyed and you have demyelination and it forms these plaques in the brain and spinal cord. Again, this is inflammatory response; the T-cells are reactive to myelin basic protein. In fact, in the model that we have often discussed EAE which is the experimental allergic encephalomyelitis, over here, myelin basic protein is mixed along with CFA to generate multiple sclerosis. It is mediated again by CD4 positive cells and again as IL17 has been shown to be playing an important role.

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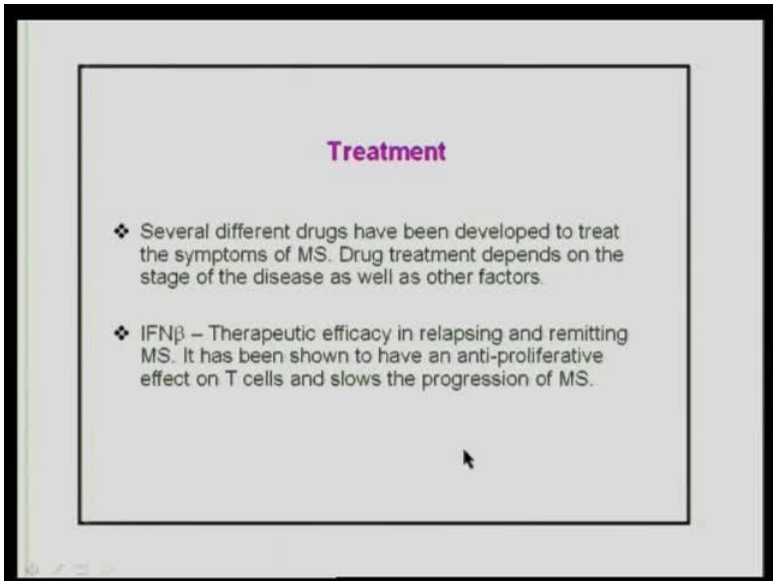

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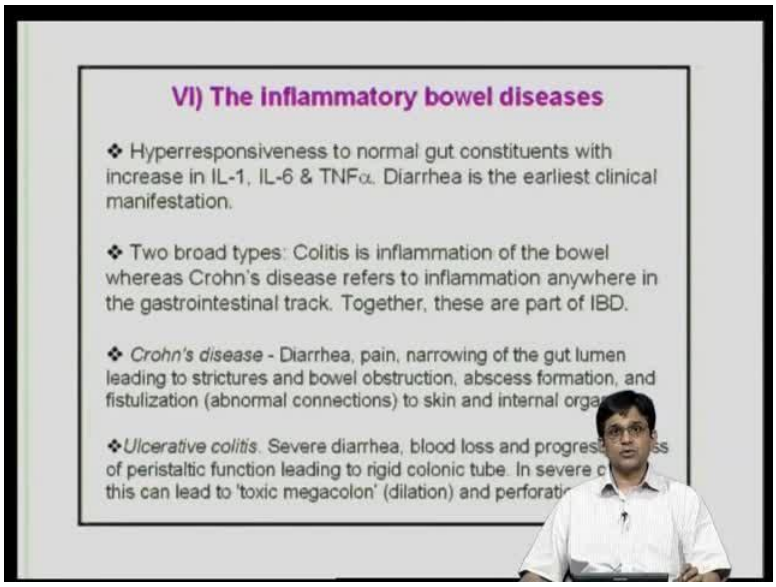

Now, in case of multiple sclerosis what has been found is interferon beta has been found to slower the disease and how does it slow down multiple sclerosis because it shows it has been shown to have a anti-proliferative effect on T cell and sort of helps. In fact, so interferon beta is therapeutically used to slow down multiple sclerosis.

The other disease that we will study is inflammatory bowled disease and this is a very painful disease because it causes lot of anguish in patients. There are two main, in fact Diarrhea is a most common manifestation of it but there are two main ones. One is Colitis which is inflammation of the bowel which is the end of the large intestine as such. The other is Crohn's disease where inflammation can result anywhere in the gastrointestinal track and

together these form a part of IBD or inflammatory bowel disease. In terms of Crohn's disease, there is a diarrhea pain, there is narrowness of the gutter lumen, so it leads to bowel of obstruction formation and fistula which is actually an abnormal connection between the skin and internal organs. You have colitis on the other hand as a severe diarrhea blood loss. It results in what is known as megacolon formation or the dilation perforation, so a very painful disease.

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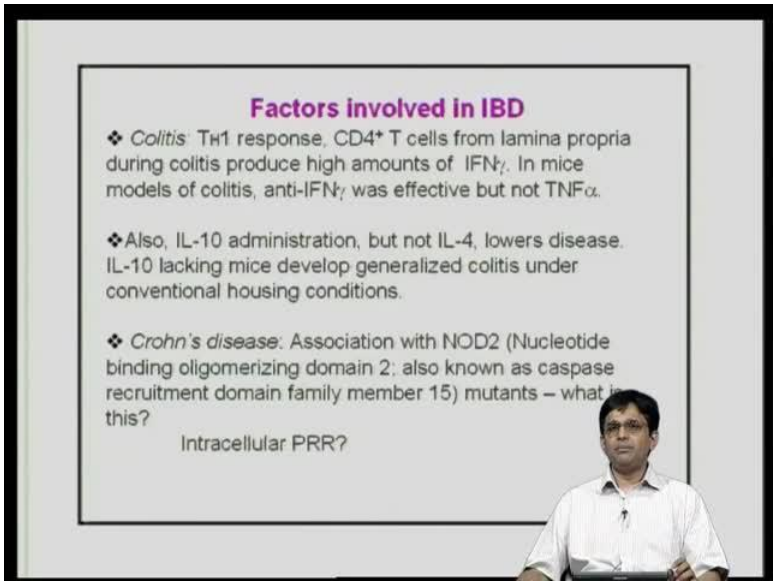

Over here what has been shown is that gamma plays interferon, gamma plays an important role. So, anti-treating mice at least with anti-interferon gamma has should be shown to be useful. IL10, again IL10 sort of is important over here in lowering a disease and if in mice that lack IL10 these generalize these develop colitis under conventional housing conditions. Now, crohn's disease, we there is a link between a particular gene known as nod two. Now, we had discussed nod two again in the innate immunity class. The nod two stands for the nucleotide binding oligomerizing domain 2. It is part of the pattern recognizing receptors, remember you have the TLR which are present on the surface and the nods which are intracellular pattern recognizing receptors.

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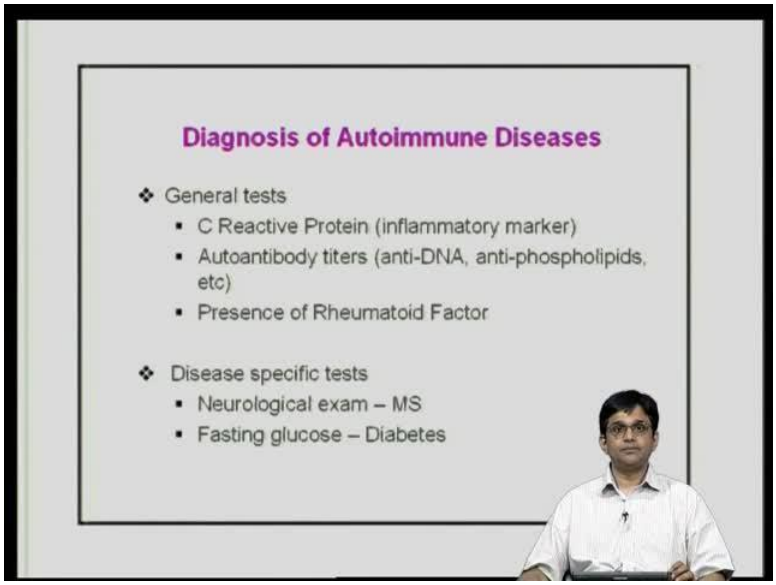

So, one of them is nod two. It sort of it is recognizes the murine paprido, the bacterial paprido glycan and so that plays an important role in generation of responses. So, nod two is a link between nod two and Crohn's disease. Now, we mentioned that what are the different ways by which that you can diagnose auto-immune diseases that general test. So, you can have C reactive protein which is an inflammatory marker, you have auto-antibody titers, anti-DNA in case of SLE nuclear antigens and you also have presence of rheumatoid factor. Rheumatoid factor level goes up especially in case of rheumatoid arthritis.

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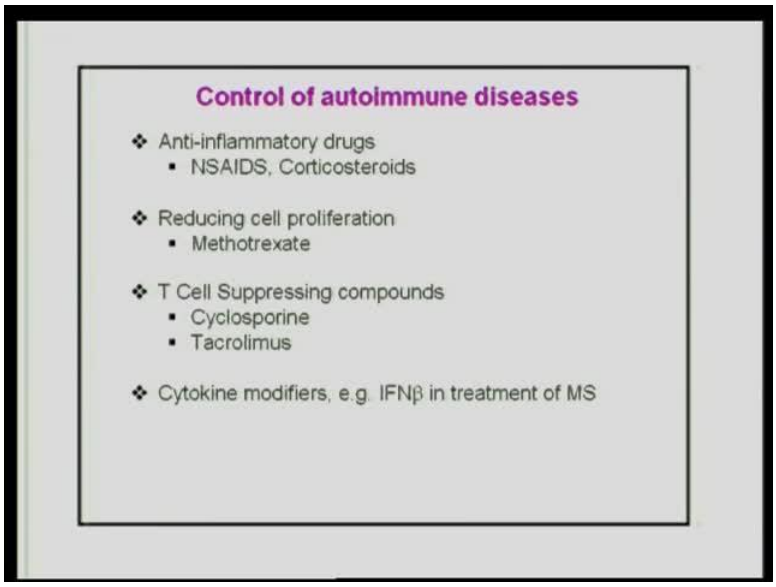

So, have these different elizas that can be that can be done. You also have specific ones, for example neurological examination will tell us whether there are lesions in the brain,

especially with respect to multiple sclerosis. In case of diabetes, fasting glucose is one of the easiest ways by which it can be determined. Remember, diabetes is a major problem in India with increasingly population is coming increasing numbers are coming down with diabetes. So, one has to be little bit careful about these. Now, how about the control about auto-immune diseases? Now, the anti-inflammatory drug, so see one aspect that people need to understand is that once you have auto-immune, it becomes difficult to manipulate especially at the end stage.

So, the easier thing that can be done is one has to manage auto-immunity and in order to manage auto-immunity, there are different ways. One is to reduce inflammation, so often corticosteroids are used but remember steroid treatment results in other effects. So, the non-steroidal anti-inflammatory drugs are often tried initially. In case they work, corticosteroids croticosteroids might be used. Corticosteroid is much more effective but it has side effects. The other way is to reduce cellular proliferation; especially in rheumatoid arthritis in these cases you have lot of immune cell proliferation.

So, you can reduce these cellular proliferations using these drugs such as methotrexate. You have T cell responses again. You can suppress T cell activation using cyclosporine, tacrolimus. These remember, cyclosporine, tacrolimus both are important in acting on the affinity pathway, so that is certainly used and then in case of in case of multiple sclerosis, you have treatment with interferon beta.

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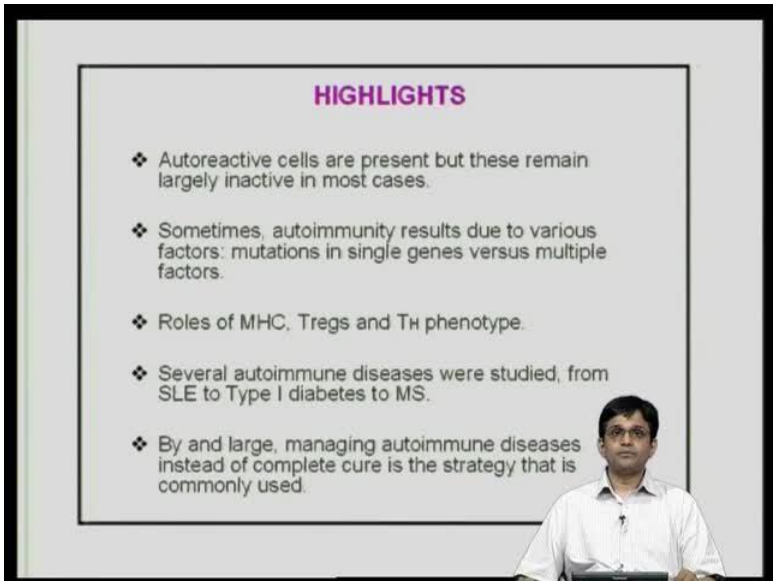

So, we will just briefly go over some of the highlights of today's class. The first important thing that we need to discuss is that by enlarge the immune system works very well but only in minority of cases, it actually results in auto-immune disease. This is not to say that the immune system is perfect. We do have auto-immune cells within us. In the process of generating an immune response, perhaps some auto-immune cells are generated but those do not take over and results in disease. It does so only in the minority of cases, by enlarge it works quite well and there are mechanisms in place to keep this as in check. The primary cell the that plays an important role in this case is your regulatory T cells over here.

Now, in some cases perhaps due to environmental factors, perhaps due to mutations in genes, you have manifestation of auto-immune diseases and we had discussed here the roles of MHC, especially MHC class 2 molecules in predisposing either susceptibility of resistance to different auto-immune diseases. Regulatory T cell obviously plays an important role and the role of fox p3 IL2, IL2 receptor cannot be over emphasized and then you have the TH1 TH2 TH17 cells which play an important role over here. So, together you have different factors that seem to play a role. What we have also done in this class is to study different examples of auto-immune diseases and they all differ in their manifestations and in their reasons.

For example, in SLE the major diagnostic feature is your generation of anti-bodies against nuclear antigens, whereas that in Type I diabetes you have destruction of the pancreatic beta cells. In case of multiple sclerosis, you have primarily T cell response that is that recognizes a myelin basic protein and that causes lesions of plaques in the brain and spinal cord. So, there are different ways to diagnose these auto-immune diseases. On was, Eliza is very good tool you can check for rheumatoid factor in case auto-immune or in case of rheumatoid arthritis. One can check for anti-nuclear anti-bodies. In case of SLE, you can check for general inflammatory markers in C reactive protein, also check for disease manifestation specific once. So, for example fasting blood glucose levels and in case of diabetes and so in terms of cure there are the way that this is done is you can reduce inflammation by using non-steroidal anti usually that is tried and then subsequently, quadrasol therapy is done because of side effects. Then you can prevent the proliferation of immune cells as I said methotrexate is often used because that sort of reduces. Then you have in case of T cells specific diseases you can reduce T cells activation by using agents such as tacrolimus, cyclosporine which will affect the IL2 pathway, which will result in blocking T cell activation because blocking IL2

pathway and in cases like multiple sclerosis, you can use interferon beta which has been shown to be extremely useful in slowing down multiple sclerosis.

Over all what this class has dealt with, actually it is case of a rebel scenario in which auto-immunity results by certain rebels. So, the question is why does this occur? Why we have seen different factors that are involved in place but there are one has to emphasize that auto-immunity is impossible to get rid of auto-immunity. One has to learn to deal with auto-immunity and try to keep it in check because once auto-immunity is completely full blown, it becomes very difficult to control and contain.

So, therefore during the initial stages or initial manifestation of auto-immunity these need to be diagnosed early as possible and need these needs to be controlled. There are different therapeutic mechanisms in place that can sort of help us control auto-immunity. Further studies in this area may help us to understand for the factor and come up with potential therapeutic targets which will help us control auto-immune diseases in a much better fashion.

Thank you