Essentials In Immunology

Prof. Anjali A. Karande

Department of Biochemistry

Indian Institute of Science, Bangalore

Lecture No. # 16

Autoimmunity

Autoimmuno-deficiencies f the B cells

So, in today's class, I will continue with the subject of tolerance and immunity.

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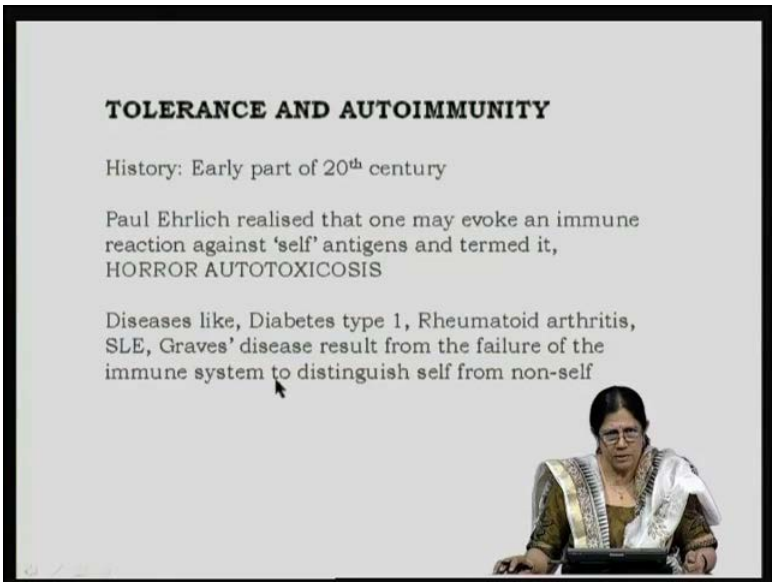

I had already introduced to you, what is autoimmunity. Just going back to the history, to a sometime in the early part of the 20th century, that doctor Paul Ehrlich realized, that one can evoke an immune reaction against self-antigens and he termed this condition as Horror Autotoxicosis because we always believed till then, that the immune system has the capacity to mount an immune response only against non-self antigens. Now, obviously, if the antibodies or T cells start attacking self-antigens, naturally this would be a process, which would be continuous unlike in case of pathogens, where the immune system is activated only till the period that the pathogen exists in the body.

There are several diseases that can be studied under this autoimmunity, diseases like diabetes type 1, rheumatoid arthritis, systemic lupus erythematosus, SLE for short, Graves' disease, these results from the failure of the immune system to distinguish self from non-self. We will come to, how this situation happens and how is it, that a small percentage of people get affected with these conditions? Before that, we will just go over what, what are the different autoimmune diseases, which are common?

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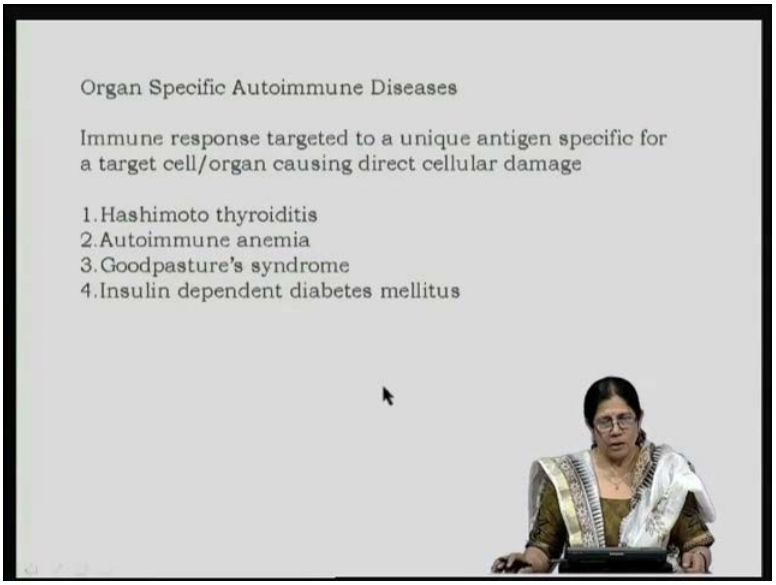

Now, autoimmune diseases can be both, organ specific or systemic. Now, of course, as the name suggests, organs specific would be the immune response, which targets unique antigens, which are specific to a particular target, cell or an organ, and this of course, would cause cellular damage directly. There are 4 diseases that I am going to talk about under this: one is Hashimoto thyroiditis, autoimmune anemia, Goodpasture's syndrome and IDDM or insulin dependent diabetes mellitus.

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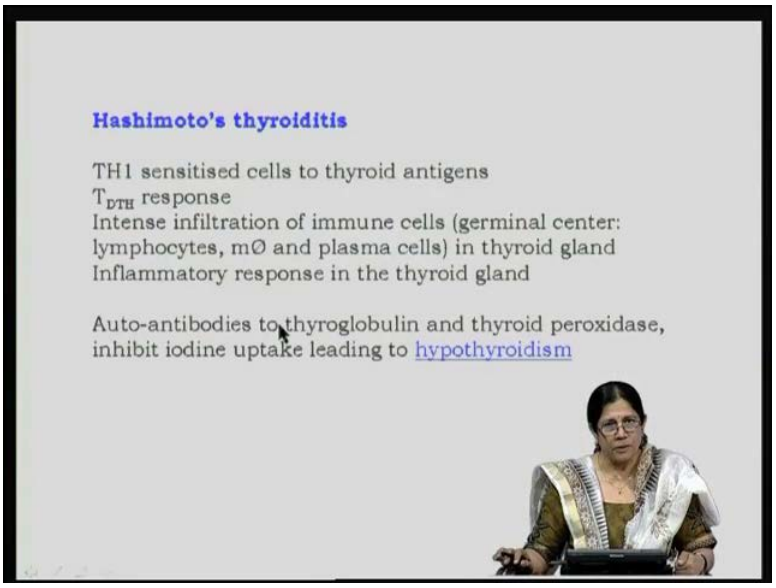

Let us start with Hashimoto's thyroiditis. In this particular condition, of course, the organ involved is a thyroid, again as the name suggests, this is because of auto-reactive sensitized TH 1 type of cells to thyroid antigens. If you remember the class on hyper sensitivity, you would remember, that the type 4 hyper sensitivity is because of T DTH cells, which are well, TH 1 cells. At these cells are the causative factor for Hashimoto's thyroiditis, there is intense infiltration of immune cells in the thyroid gland and there is therefore, an inflammatory response in the thyroid gland.

Now, whenever there is T DTH response, it is associated with inflammatory response. So, imagine that now all organs, of course, will have immune cells, for example, macrophages all the time. Now, imagine a case where this intense infiltration of lymphocytes, which would be TH 1, mostly macrophages activated, as well as, plasma cells, because in this particular condition there are also autoantibodies generated to thyroglobulin and thyroid peroxidase.

Now, thyroid peroxidase is the enzyme, which is required for iodine uptake and therefore, if there are autoantibodies, they have, to the thyroid peroxidase, there would be inhibition of iodine uptake by the gland and this would result the condition, you know, the immune, the autoimmunity results or now causes hypothyroidism; hypo would mean lesser amount of thyroxin secreted by the gland.

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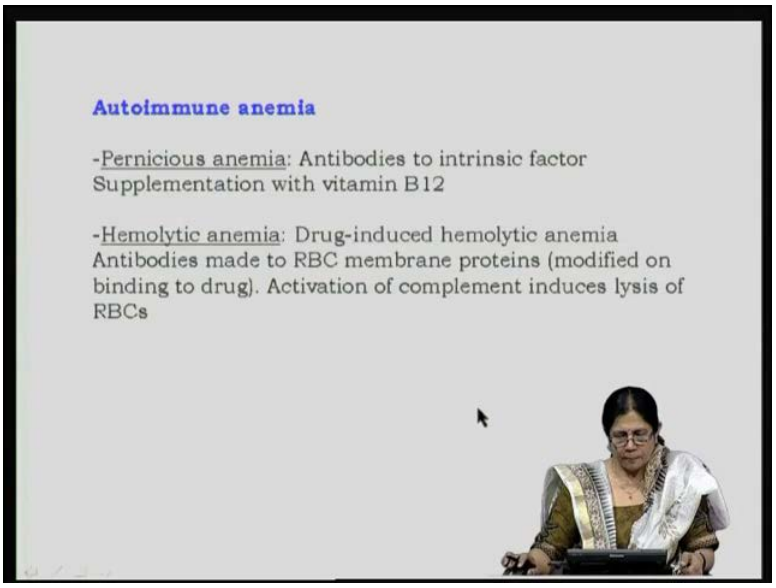

Now, the 2nd in this particular list of autoimmune diseases, which is organ specific, is autoimmune anemia. Autoimmune anemia again, can be due to several factors starting, let us start up with pernicious anemia, which is not very uncommon. Pernicious anemia is because of the antibodies to the intrinsic factor. Now, what, what is this intrinsic factor? It is a receptor, which is present on the parietal gastric cells and this allows the absorption of vitamin B12 from the, the, diet; so, antibodies bind to the intrinsic factor to not allow absorption of vitamin B12.

And therefore, now vitamin B12 is required for hematopoiesis and generation of red blood cells. Now, therefore, in this particular condition of pernicious anemia, there is lack of vitamin B12 and therefore, lack of hematopoiesis, adequate hematopoiesis and therefore, resulting in anemia. So, the, the treatment for this type of auto-anemia would be supplementation with vitamin B12. So, it is important therefore, that the anemia is diagnosed and found, that it is because of antibodies and therefore, the only way would be supplementation with vitamin B12 in the diet.

Hemolytic anemia - this can be, this can be caused because of antibodies that are made to modified red blood cell membrane proteins. Now, if you might remember my lecture on hypersensitivity, some individuals exhibit this property, (( )) cells, RBC's some time, so could be skin RBC's, in this of course we are talking about red blood cells. The membrane proteins have the capacity to bind to certain small molecules allowing now

these small molecules, which otherwise would not have, amino, been aminogenic to be immunogenic. Therefore, there would be antibodies to these modified membrane and antibodies, bound to the membrane now would attract complement cascade, trigger the complement to now make membrane attack complex, which would lyse, which lysis red blood cells and the anemia is caused because of constant lysis of red blood cells. Now, because this is drug induced hematologic anemia, the way to treat this would be to withdraw the drug. If there is no drug, there would be no drug, which is retained on the red blood cell membrane and therefore, there would be no, now for the cell lysis, because now red blood cell would not be modified.

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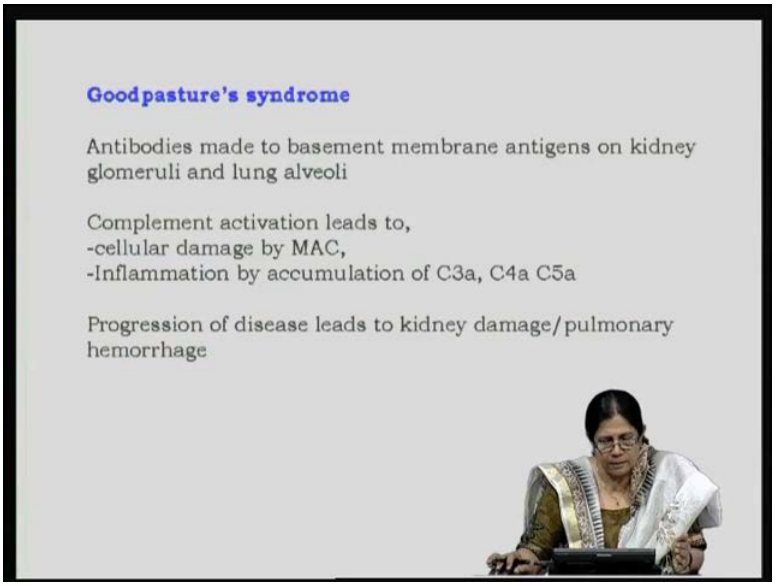

Goodpasture's syndrome - this is another autoimmune disease of, of an organ, a particular cell. Antibodies in this condition, antibodies are found to the basement membrane antigens, either on kidney glomeruli or lung alveoli. Again, in this particular case, though there are, now I mean, what does this condition, there are antibodies o.k., if the antibodies are not harmful does not matter, but what happens in this, in these cases, the antibodies, constant generation of antibodies to these membrane antigens would now result in antigen-antibody interaction on the membrane; this can effectively trigger the complement cascade. Just to recapitulate your memory with respect to this complement (( )) activation, you might remember, that complement activation leads to now activation of the complement components, the C starting with C1Q, then you have C4, C2, C3, C5. You might remember, that until the component C5, there is cleavage of an inactive form

of the component to an active form and the release of small components, as happens with C4, C3 and C5, that their, the cleavage of the proenzyme to an active enzyme and the release of the small factors C3a, C4a and C5a, this causes release of granules from mast cells because these binds to specific receptor on the mass cell and basophils.

So, therefore, this would now, you know, these are known as, also you might remember, anaphylatoxin because they are able to induce a hypersensitive type reaction, though slight milder, but they do evoke that response. Apart from that, apart from the information, that is caused because of these molecules, not only do they, they, anaphylatoxin with respect to release of prefilled granules, of, in mast cells, but they also are chemotactic factors.

So, therefore, they refer the complement where antigen-antibody interaction takes place. In this particular case, it would be the membrane antigen of kidney glomeruli and lung alveoli. At that site, there is attraction of several immune cells: neutrophils, macrophages, etcetera. Finally, there is also cellular damage caused by the formation of membrane attack complex. Now, the membrane attack complex is not very specific with respect to, you know, what it kills. All by standard cells, by standard cells would get killed wherever the MAC gets deposited, a membrane attack complex, and in this case, because the antigen-antibody interaction is taking place on the membrane cell, these cells get attacked and then these cells lyse because of MAC. The disease can be fatal because if not treated, progression of disease leads to kidney damage because we are talking about the glomeruli, as well as, if in the case of lung alveoli, then you have pulmonary hemorrhage, both the conditions being fatal.

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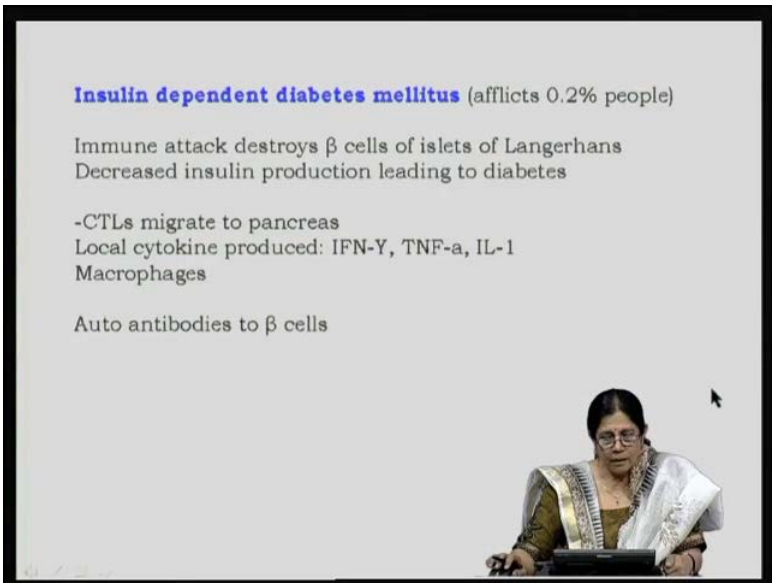

Let us come to now insulin dependent diabetes mellitus. Insulin dependent diabetes mellitus is also known as juvenile diabetes and if, it affects about 0.2 percent of people and it is juvenile, is called juvenile diabetes because we know, that it usually affects children. This happens because of immune attack destroying beta cells of islets of Langerhans. So, islets of Langerhans are the cells, which synthesize insulin, that because the beta cells themselves get destroyed. The amount of insulin, that is produced, is much lesser and this leads to diabetes.

This again can be mild versus severe; of course, in severe cases, there is almost no insulin production. What is this autoimmune disease because of apart from, because of now, what are the kind of cells, that are, seems to migrate to the pancreas? Starts off with large number of cytotoxic T cells or CTLs for short, because of, there is also local cytokine production, interferon-gamma, TNF-alpha, interleukin-1; interleukin-1, which is, which now activate macrophages. There are also, at a latter stage of this disease, autoantibodies to certain antigens on beta cells.

So, therefore, now, the inappropriate deposition of large number of immune cells to that site and activated cytotoxic T cells and antibodies to antigens of the beta cells now causes damage of beta cells, lowering number of beta cells and thereby lowering insulin production. These individuals have to be supplementation regime, supplementation with insulin.

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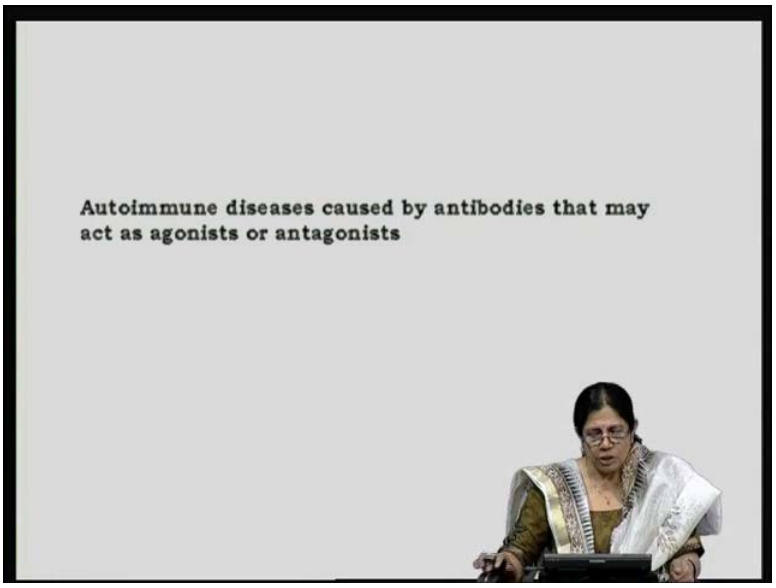

When we have talked about immune system, which are, which is directed to particular organ or a particular cell, we now come to autoimmune diseases, which are caused by antibodies that may act as agonists or antagonists. Let us look at what this means.

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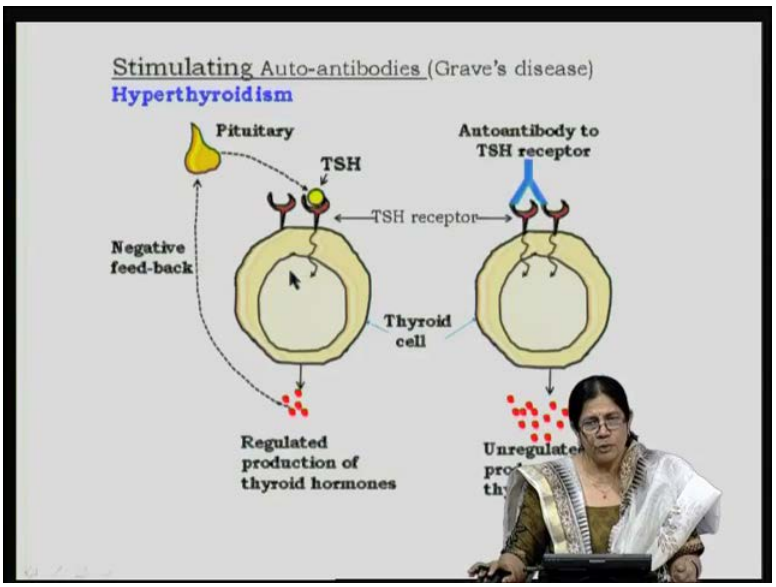

Agonist, which would mean, that in case it is a hormone or a lycan, these antibodies act synergistically to that hormone and increase. Whatever is the end or the result of this hormone action in this particular situation, in this case of an antibody being an agonist or

(( )) has an activity, which is the same as that of the hormone. The example is Grave's disease.

In this particular condition, there are stimulating autoantibodies to antigens on the thyroid cells. Let us look at what happens in this condition. There are antibodies to the thyroid stimulating hormone receptor; the TSH receptor is present on thyroid cells. Now, the TSH receptor receives thyroid stimulating hormone, which is synthesized and secreted by the pituitary. TSH binds to TSH receptor and this triggers the signaling process, which now leads to production of thyroid hormones. The thyroid hormones themselves can inhibit for the production of TSH.

So, there is an extremely, you know, many of these endocrine systems have a negative feedback. So, there is a loop. So, pituitary synthesizes TSH; TSH binds to its cognate receptor present on thyroid cells inducing signaling, which now results in the release of thyroid hormones by the thyroid cell; increase in this particular circulatory level of the hormones inhibits for the production of TSH . So, it is an extremely tightly regulated setup, a network between pituitary and thyroid cells in Grave's disease patients, there are antibodies to the TSH receptor.

So, what do these antibodies do? Now, I, am, must tell you, that not all antibodies are able to trigger. You might remember, when we studied signaling in B cells, you might remember, that the way signaling in B cell has been studied is by antibodies to the receptor, antigen receptor on B cells. If an antibody to an immunoglobulin molecule, this would bring about cross linking of receptors, 2 receptor with 1 antibody on the B cell triggering a signaling process, which was very similar to that seen when an antigen binds to the B cell receptor.

The same situation happens here. These individuals develop antibodies, that can cross link receptor and these antibodies cross link TSH receptor inducing a signaling, which is very similar to what happens when TSH hormone itself binds into the receptor. This would result therefore, in production of thyroid hormones.

Now, the production of thyroid hormone is now independent of the TSH binding to its receptor. Therefore, even though thyroid hormones, as happens in the normal case, would bind to the pituitary cells, the cells in the pituitary, which release TSH, the TSH may not anymore be made. But in this particular situation, production of thyroid

hormone is totally unregulated because the feedback loop, even though it is there and there is no further production of TSH, presence of antibodies themselves would keep on triggering in an unregulated fashion, the activation, the signaling and release of thyroid hormone.

So, Grave disease patients show symptoms of hyperthyroidism. So, we have just finished dealing with Hashimoto's thyroiditis, where there are, where there are antibodies to the [paroxities/paroxetine], which now inhibits thyroid hormone production by the thyroid gland. Now, in this same situation, I mean, in a situation where thyroid gland is involved, but here autoantibodies to the receptor, now induce a condition, which is opposite of Hashimoto's thyroiditis, it, now these patients show symptoms of hyperthyroidism.

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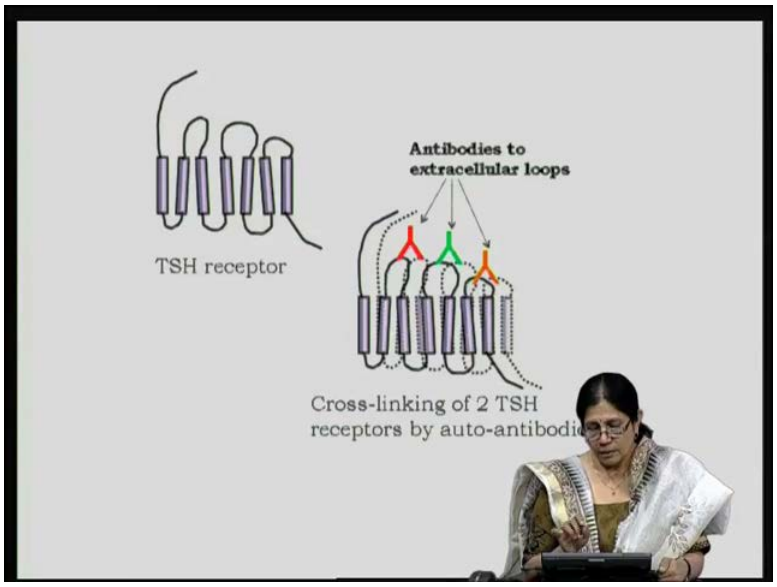

Just to recall little bit of in details with respect to the antibodies. Now, the TSH receptor belongs to the 7 transmembrane receptor family. When there are 2 such receptors, you know, as shown in the same picture here, associated with one with dotted lines - that is receptor number 2. There are antibodies in the (( )) seem to the extra cellular loops of the TSH receptor. Now, these loops are the ones, which extent in the, in the cell in the aqueous phase, you know, it is representment, they extend into the outside of the cell, where there is free access to the antibodies and you can see here, 2 receptors, you know, the loop 1 of both 2 receptors are being cross linked by antibody.

Now, the red antibody is different from the green antibody, which is to the 2nd extracellular loop and the 3rd, which is to the 3rd extracellular loop. Now, it has been seen, that there could be variation in the kind of triggering that happens, but all 3 are, antibodies to all 3 loops have the capacity to trigger signaling.

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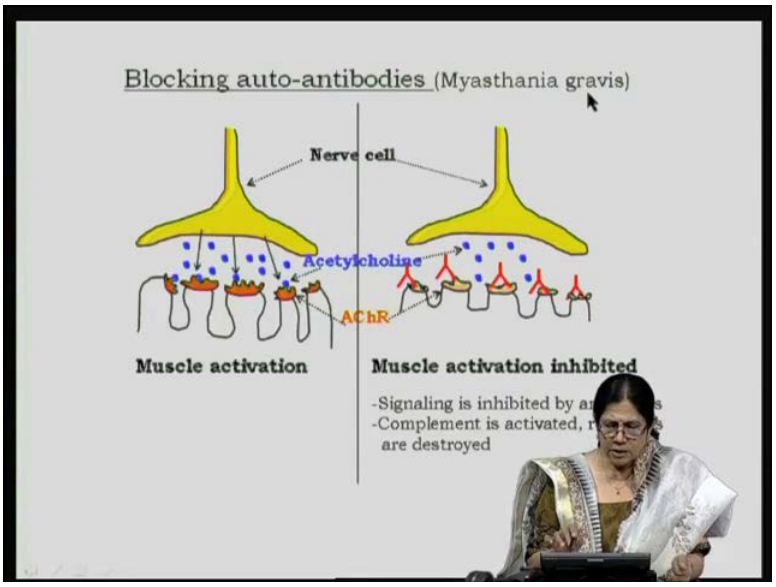

Let us come now to antibodies that are anti-callose. We have talked about the antibodies to TSH receptor, which act as agonists; we talk now about blocking antibodies, which inhibit a singling process. The example, that I would like to introduce here, I mean, talk about is Myasthania gravis, a condition where there is muscle in activation.

Now, what I have shown in the picture here is a nerve cell, which is in close proximity to the muscle plate, at this is the neuromuscle joint. When there is activation or an impulse of the nerve, there is secretion of acetylcholine, the acetylcholine molecules bind to the cognate receptors. Now, these are the, on the terminal ends of the muscle plates, there are these receptors to acetylcholine; this binding of acetylcholine to its receptor is what brings about muscle activation.

In case of Myasthania gravis patients, they develop antibodies to the acetylcholine receptors, which block the binding of the acetylcholine to the receptor. This results in loss of activation because there is no ligand receptor interaction since signaling is inhibited by antibodies. There will be no neuromuscular, I mean, there is no muscle activation. Also, with large number of molecules of antibodies bound to the

acetylcholine receptor, there is complement activation, as you know; IgM as well as IgG isotypes can activate the complement. And we just discussed a couple of minutes ago, that this activate is the complement, which can result in destruction of the acetylcholine receptor themselves by the membrane attack complex. So, receptors get destroyed and as you know, this disease if not treated or even treated, eventually leads to paralysis.

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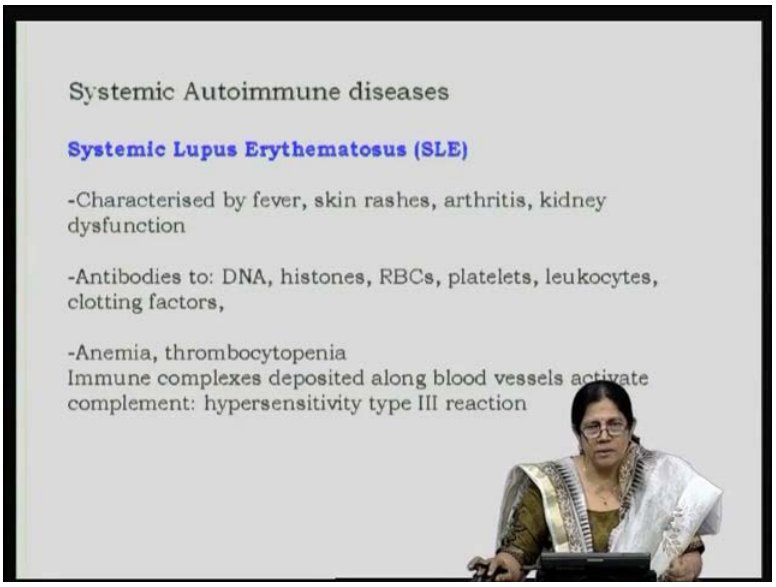

Now, we will come to systemic diseases, autoimmune, autoimmunity, which affects the entire system. The 1st one under this is a not so common, but known condition, called SLE - systemic lupus erythematosus. This is characterized by fever, well mild, but constant fever, skin rashes, arthritis, kidney dysfunction.

The name, you know, the loop, I mean, the name lupus, actually individuals with this condition are characterized by the butterfly kind of red patch on the face. These individual have antibodies to DNA, their own DNA of course, histones, red blood cells, platelets, leukocytes, clotting factors and the condition leads to anemia thrombocytopenia. Anemia, because red blood cells get destroyed by the same path, that I have been mentioning, that you have antigen-antibody interaction and activation of the complement, which would lyse the target cells. Thrombocytopenia, when the antibodies are to blood platelets, this depletion of platelets in the circulation. I have already said, that is because immune complexes, which are deposited along blood vessels activating the complement, not only is MAC or membrane attack complex found, which destroys

cells, but this is also hypersensitivity type 3 reaction because of immune complex, that are deposited all along blood vessels and that means, that is inflammatory.

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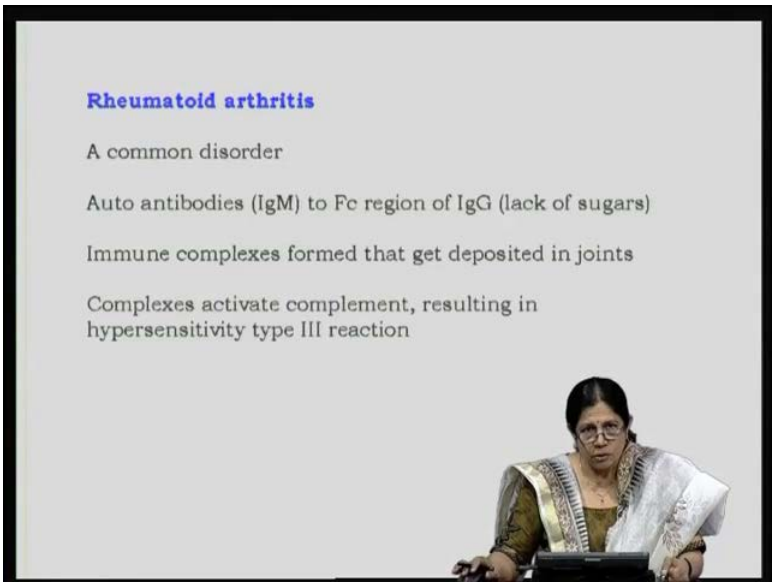

Now, we come to disease, which is more common than the ones that I have talked about so far. Rheumatoid arthritis - this is a disorder where individual develops auto antibodies of IgM class to IgG. I have already introduced briefly to this particular condition when I talked about the structure of immunoglobulins. Now, how is the structure of immunoglobulin associated with this, I will come to that, but the part on the FC region of, of the IgG is on the FC region. Now, that particular domain of IgG, mainly CH 2, which is glycosylated, this might ring a bell. I talked about the fact, that glycans and differences in glycan in certain individuals can bring about the establishment of, or availability of an epitope on the F C region, which otherwise would be hidden or covered by the glycans. So, you have now glycans, which are present on the CH, on the CH domain, in case of such individuals who have rheumatoid arthritis. In these individuals, there is lack of, you know, terminal, a lack of certain enzymes that add sugars and make this particular chain of glycans.

So, because of that, the region on the FC part of IgG gets exposed to immune cells and there are auto antibodies usually only of IgM type, which now complex with the IgG in circulation. So, there are small, small complexes, that are formed all the time. These would get deposited (( )) in blood vessels, but also in joints. Once again, as in previous

cases, these immune complexes activate complement resulting in hypersensitivity type 3 reaction.

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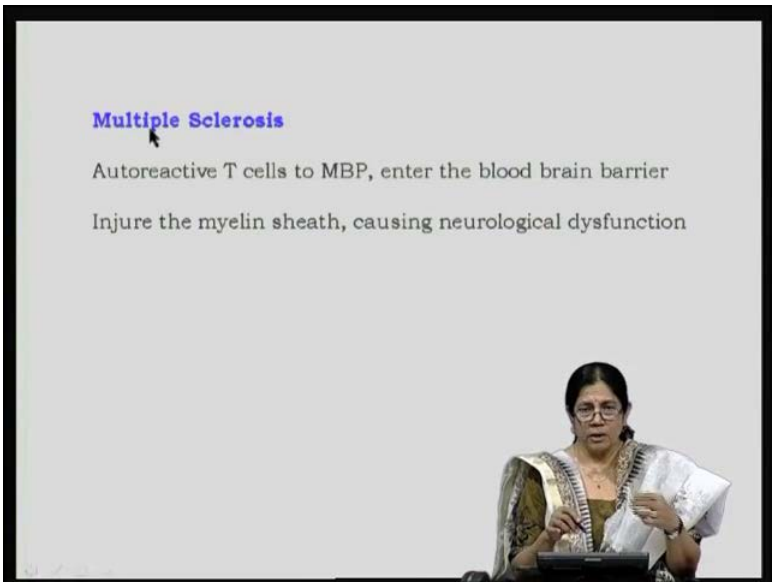

Now, I will come to, I will just introduce this particular condition because there will be, the lecture on T cell immune deficiencies will actually deal with this in more detail, but just to mention, multiple sclerosis is a condition where there are autoreactive T cells to the, the myelin basic protein, MBP is, you know, the, this MBP is present in the myelin sheath. As you all might know, that myelin sheath is what insulates the nerves, if, when there are, you know, normally T cells, like B cells do not cross the blood brain barrier, but activated T cells can.

So, when there are autoreactive T cells, they can enter the blood brain barrier and they injure the myelin sheath. This causes neurological dysfunction because once again the insulation is lost, like I said, this will be dealt with in details, this disease.

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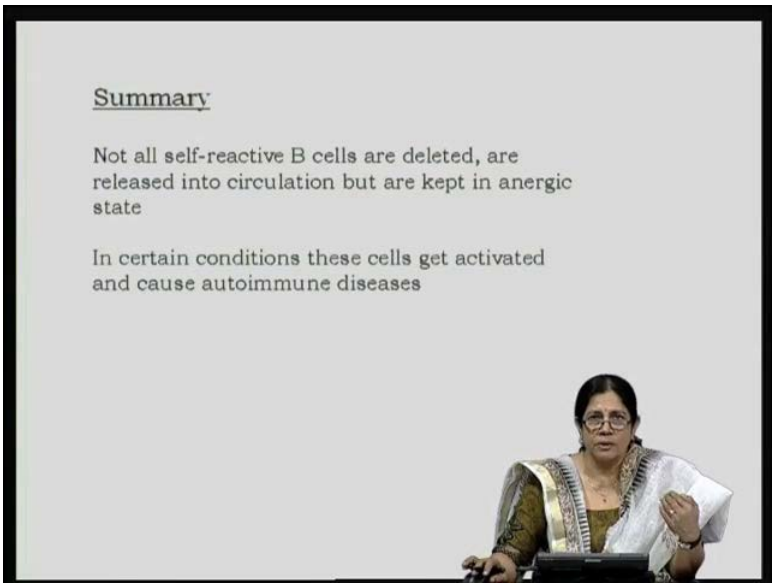

So, in summary, with regard to autoimmunity, not all self-reactive, I just like to reiterate, that though in the start of my course, especially when I talked about the development of these cells, I did mention, that in the bone marrow B cells, that I have developed to become from pro-B cell to mature B cell, there is a stage where they have only IgM receptor, antigen receptor, present on the cells.

Now, before they can acquire IgD type of receptors on the cell surface, these cells get undergo apoptosis, if either the receptors are cross linked, as is done experimentally, but in the situation, in the bone marrow, if they come across and bind to self-antigens, now at that time one can imagine, that there would be only self-antigens, which are circulating from the bone marrow to the periphery. In spite of this check, where auto reactive B cells should be deleted, it is known of course, that there are a small number of cells, B cells that carry receptors that have the capacity to react with self-antigens. These are released in circulation, but are kept in, in an energic state. However, in certain conditions and we will see what those conditions are, these very cells, which are quiescent get activated and cause autoimmune disease.

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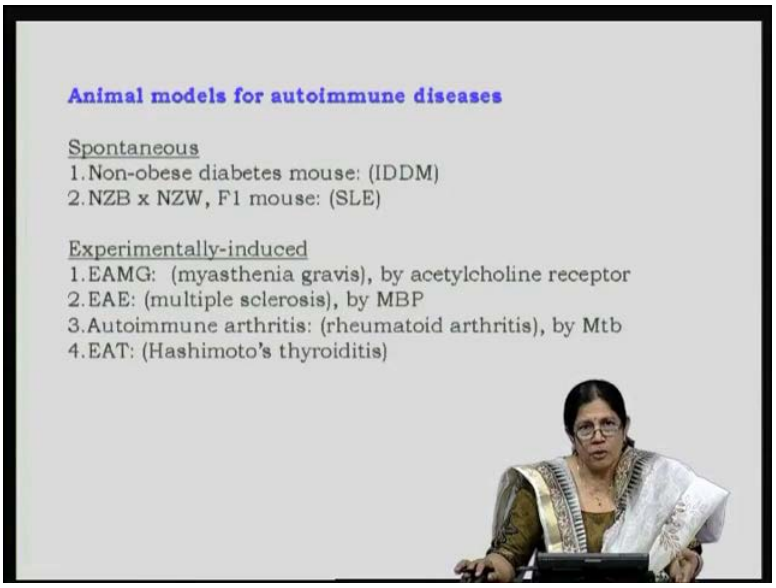

Are there any animal models to study autoimmune disease? Because of course, autoimmunity can be a condition, which can be of course, fatal; is also, this condition can be very chronic. To be able to understand, how this autoimmunity develops, one needs to have animal models and there are some experimentally induced conditions versus spontaneous.

Let us first talk about the spontaneous ones. Now, there is, there are strains of mice, the 1st being non-obese diabetic mouse. This mouse shows or develops insulin dependent diabetes mellitus; this develops spontaneously and is a very good animal model to understand IDDM. The 2nd is an Fl mouse, a cross between New Zealand B mice and New Zealand W mice; these mice develop spontaneously, the condition of systemic lupus erythematosus. So, these, these mice have autoantibodies to RBC's, platelets, DNA histones and conditions similar to what one sees in human.

Many mice models are available, where one can induce experimentally conditions of Myasthenia gravis, this can be in mice by injecting acetylcholine receptor so that antibodies to acetylcholine receptor developed. Now, experimentally, EAMG's experimental auto immune myasthenia gravis, when mice are injected with MBP or myelin basic protein. They developed experimental autoimmune encephalomyelitis, which is similar to the human multiple sclerosis. Similarly, injecting mice with mycobacterium tuberculosis bacteria induces in these mice something similar to

rheumatoid arthritis. They develop autoimmune arthritis also there, I mean, mice develop Hashimoto's thyroiditis.

So, there are these animal models, which have been established and they have helped understand autoimmune diseases.

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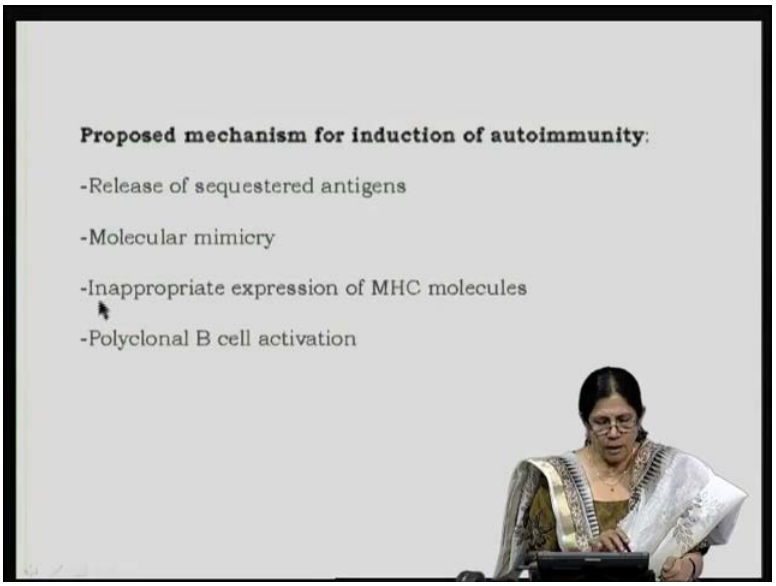

So, there have to be mechanisms, which induce autoimmunity because we know that fortunately, very few of us are afflicted with these conditions. The proposed mechanisms for induction of autoimmunity are release of sequestered antigen, molecular mimicry, which explains most of the autoimmune diseases, inappropriate expression of MHC molecules, polyclonal B cell activation.

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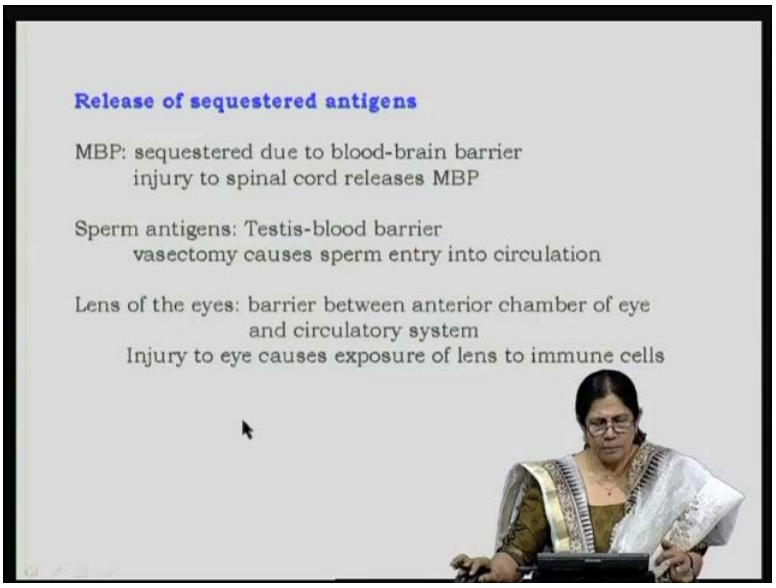

Let us start with release of sequestered antigens. The examples are myelin basic protein, sperm antigens or lens of the eyes.

Now, we go back again to self versus non-self. Now, in this particular situation of, like MBP, there is a blood brain barrier because of which MBP is totally sequestered in the, on the side of the neurological system and therefore, MBP is never allowed to enter the bone marrow, where negative selection takes place. Now, this is fine as long as there is no exposure of MBP to the immune system. This happens in case of injury to the spinal cord, which may release MBP into circulation and thereby, now T cells would get activated and subsequently also, B cells. And now activated T cells, like as I told you little while ago, activated T cell can cross the blood brain barrier and now start to cause damage.

So, MBP in normal circumstances would be a sequestered antigen, but this is broken because of injury sperm antigens. Again, there is a testes blood barrier, therefore sperms, which in fact, are the cells, which are made only after puberty, sperm antigens are again sequestered in the testes, but either injury to the testes or in case of vasectomy, there is sperm entry into circulation and these are of course, foreign to the circulatory system and therefore, antibodies are made. Some individuals who have been vasectomised, but would like to reverse the process, have been proven to be infertile because they develop antibodies to sperms.

Again, in the case of lens of the eyes, there are different proteins of, of the lens. Usually again, there is a barrier between the anterior chamber of eye and the circulatory system. Injury to, to the eye causes exposure of lens to immune cells and, there are, to the antibodies, which can actually attack the crystallines.

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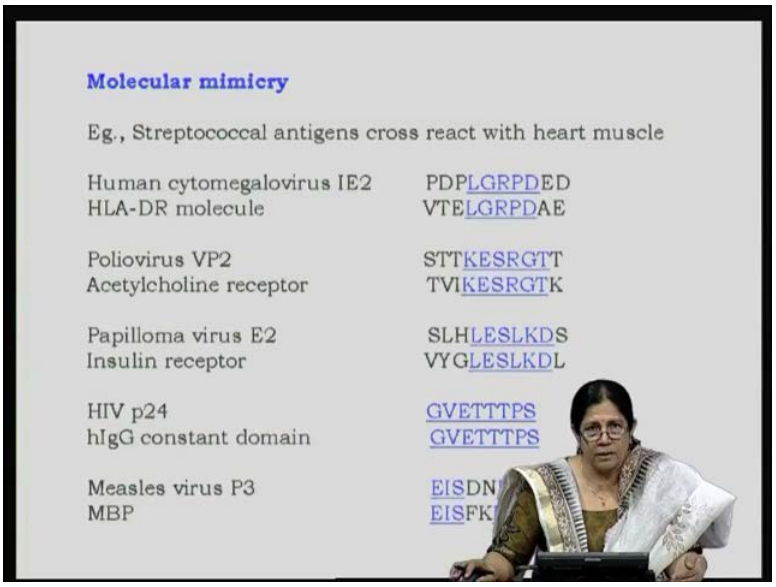

So, sequestered antigen is one, which is very, of course very easy to understand and this has been shown experimentally, that if one, now in the time of development, if, let us say animal is, a piece of the lens is now placed in the thymus, it is seen, that such animals to, would not develop autoimmune disease, alright to the crystallines or the proteins of the lens. So, therefore, sequestered antigens, that is, is understood very well, that anything that breaks the barrier, which keeps the sequestered antigen from being exposed to the circulatory system, may lead or would lead to activation of the immune cells to those sequestered antigens.

Second mechanism is molecular mimicry. There is much more data and that is what, I am, I have put on the slide here, but molecular mimicry is what explains most of the autoimmune conditions, where there are antigenic epitopes, that are antigens shear with bacterial proteins of bacterial or well, not just bacterial, also viral components. Example of molecular mimicry is, there are several examples, streptococcal antigens cross react with heart muscle.

Now, in certain conditions of heart failure, it has been shown, that those individuals, when it was realized, that those individual had had streptococcal infection prior to the heart attack, you know just recent, recent past, in the recent past. Now, people started to look at how streptococcal infections or whether there was any relationship between streptococcal antigens and the heart muscle, and found, that there are certain epitopes, which seem to be conserved in the true.

So, therefore, a prior exposure to the streptococcal antigens would evoke an immune response and because there are antibodies to these streptococcal antigens, they are, they can attack the heart muscle, which also carry the same epitope. Just to give you, how closely related these epitopes, may be, now here I have 6 different, 5 different pairs human cytomegalovirus IE2. A sequence of this particular protein in the cytomegalovirus shows almost, well 100 percent identity with respect to 5 of the amino acids with HLA-DR molecule. So, again, if there are antibodies, which if one generates antibodies to this particular region and then those very same antibodies can now bind HLA-DR.

Poliovirus VP2, you can see the similarity with 6 amino acids of the VP2 of poliovirus with an acetylcholine receptor. So, now, this becomes quite easy to understand. If one has been, affected one has been infected with poliovirus VP2, even without realizing, if one has made antibodies to this particular region, then that can bind to the acetylcholine receptors and could serve as blocking antibodies. Same is the situation with Papilloma virus E2, which has antigenic, determines similar to insulin receptor HIV protein p24. You can see 100 percent identity with the human IgG constant domain, measles virus P3 with MBP.

So, you can see, with the number of, now this also suggest, that fortunately again, these may not be immunogenic or not all individuals would make antibodies when infected with human cytomegalovirus or poliovirus or papilloma virus. These may not at, certainly not the immune dominant epitopes, either B or T cell epitopes, these are minor epitopes and only certain individuals by chance would make antibodies to these. Therefore, it is only, a certain individuals, that is, if one has made antibodies to certain regions or antigenic epitopes in the infecting organism, to the infecting organism, then there is a chance, that these antibodies would now cause auto immune disease.

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The 3rd one in appropriate expression of class 2 molecules – this, where explains the destruction of beta cells class 2 molecules. We have been discussing all along, class 2 molecules are expressed only on antigen presenting cells, which are B cells, which are dendritic cells and macrophages. Now, class 2 molecules are not expressed on any other cells, but can be expressed if there is local concentration of gamma-interferon. Now, presence of gamma-interferon; now presence of gamma interferon get activate the expression of class 2 molecules in cells, which normally would not have beta cells from health. Individuals express only MHC class 1 molecules because all nucleated cells express class 1 molecules, but it was observed, that from IDDM individuals, insulin dependent diabetes myelitis, individuals class 2 molecules also express on beta cells. Now, this gave an impetus to start to look at what would be the relevance.

So, similarly, now, thyroid acinar cells from Grave's disease individuals express class 2 molecules. Mitogens such as PHA, so is not only interferon-gamma, experimentally it has been seen, that even mitogens, such as phytohaemagglutinin, which activate T cells can induce expression of MHC molecules on non-antigen presenting cells, like epithelial cells.

Now, PHA of course, is a plant product. This is experimental, that it has been shown, that gamma-interferon can induce expression because the MHC molecule in the promoter region has a gamma-interferon binding site. So, think in terms of a viral infection and therefore, the earlier slide, which showed, let us say, infection with the papilloma virus, which induces antibodies, let us say, to this particular region. Then, the papilloma virus infection itself can bring about interferon-gamma production, which can result in inappropriate cells expressing class 2 molecules.

Now, class 2 molecule expression would make those cells non APC cells or antigen presenters. Therefore, now they would present the antigen to T cells, which are self and therefore, this activation of autoimmunity is triggered. Trauma or viral infection causes localized gamma-interferon secretion leading to class 2 expression on cells. This would now, especially in case of IDDM patient, it has been seen, that they are the beta cells, now start to express class 2 molecules and become antigen presenting cells. And these, now, induce the immune response to, to actually delete them form the pancreas.

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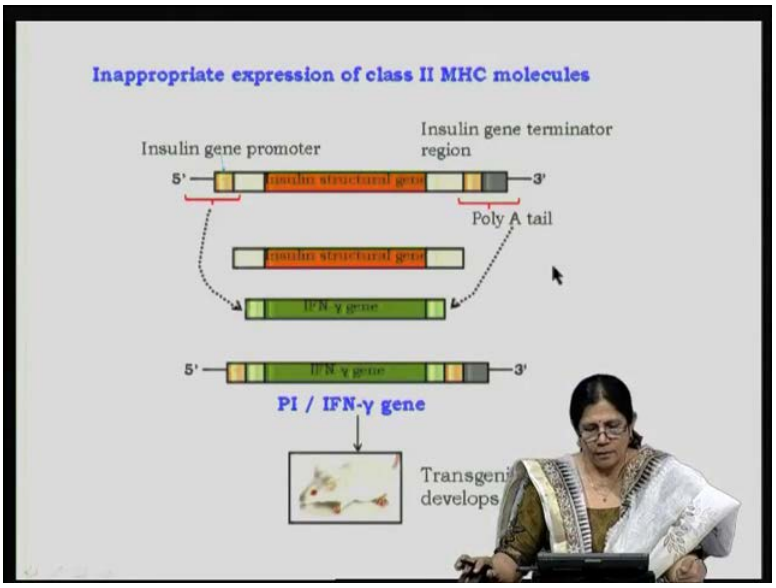

Inappropriate expression of class 2 molecules has been studied experimentally by making transgenic mice. What this experiment shows, that the insulin structural gene, insulin gene promoter is amplified, so as of course, the insulin gene terminator. Now, this is now put in frame with the, with the interferon-gamma gene insulin promoter. Now, if mice are made transgenic with this particular construct, then because of the presence of the insulin promoter, the gamma-interferon gene would, this entire gene would be now targeted to the pancreas. Because of this insulin gene promoter and this is where gamma-interferon is produced, such transgenic mice have been shown to develop diabetes by the, by the mechanism. They are just discussed, that gamma-interferon is produced localized in the pancreas, in the beta cells because of the presence of insulin gene promoter and the gamma-interferon now makes the pancreatic cells express class 2 molecules. These become antigen presenting cells and therefore, there is an immune, immune response evoked to the pancreatic cells destroying the pancreatic cells in these transgenic mice and resulting in development of diabetes.

So, this is the fine experiment, that was carried out to show, unequivoly, unequivocally, that gamma interferon production induces class 2 expression and of course, people are, in this paper, which describe its experiment, people have gone on to show the abnormal expression of class 2 molecules on cells, which are not antigen presenting cells.

So, any, so, this would support the autoimmunity theory of inappropriate expression, which is induced by viruses. Viral infection does lead to expression or accumulation of gamma-interferon, which in that local compartment would make non ACP cells express class 2 molecules and therefore, becoming antigen presenting cells.

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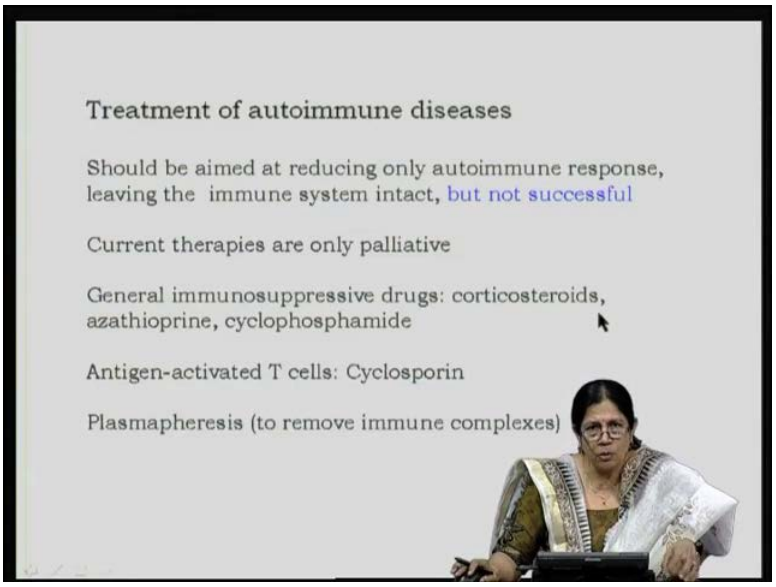

What are the treatments of autoimmune diseases? Obviously, the best treatment would be aimed at reducing only autoimmune responses, leaving the immune system intact; that is not successful, that is not even possible.

So, the current therapies are only palliative, that means, they only reduce the symptoms. This is done by using general immunosuppressive drugs, such as corticosteroids, which affect the interlocking 2 signaling azathioprine, cyclophosphamide, which inhibit proliferation of cells. So, this would be at the level of signaling and this would be at the level of proliferation. Cyclosporine is one, one drug, which is used on antigen activated T cells because cyclosporine, again it inhibits in a very specific manner, triggering the signaling of T cells. Finally, plasmapheresis can also be carried out as treatment, but all these are, you know, just palliative, just decrease the symptom. Plasmapheresis, you know, the plasma, it is put through a machine where immune complexes are depleted and therefore, this alleviation of symptoms, but patients need to undergo plasmapheresis from time to time.

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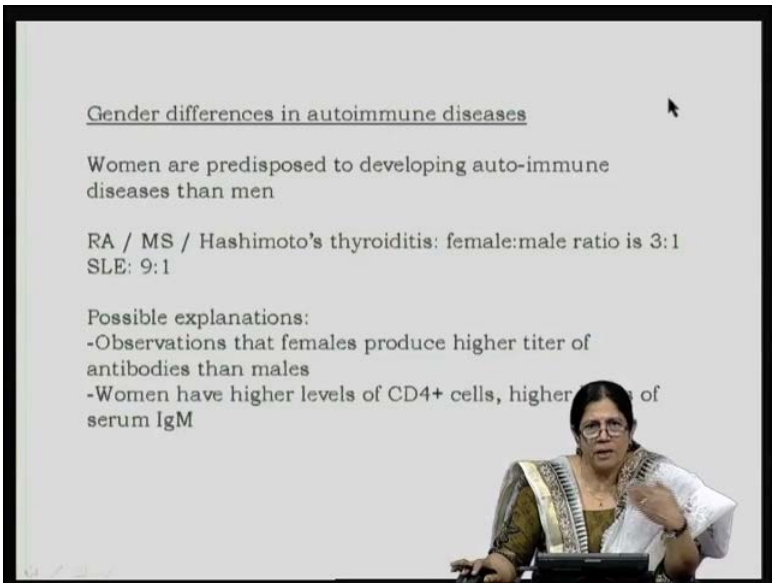

During the course of my lecture I did not mention gender bias with respect to autoimmunity, but it is known, that women are predisposed to developing autoimmune diseases than men. In fact, if the ratio of male to female or female to male is taken, observed in rheumatoid arthritis, multiple sclerosis and Hashimoto's thyroiditis, it is seen, that the ratio is 3 is to 1, 3 female to 1 male and in a system like SLE, is 9 is to 1, that is, ratio is extremely high. So, women are more prone to autoimmune diseases than men.

So, there are the possible explanations and also experimental evidences, experiments in mice, which show that females produce higher titers of antibodies than males, so that means, they are immunologically more proficient. Women have higher levels of CD 4T cells and also have higher levels of serum IgG than men. Now, these are of course, these are direct evidences, but gender bias can be reduced; obviously, therefore, gender bias is because of sex steroids.

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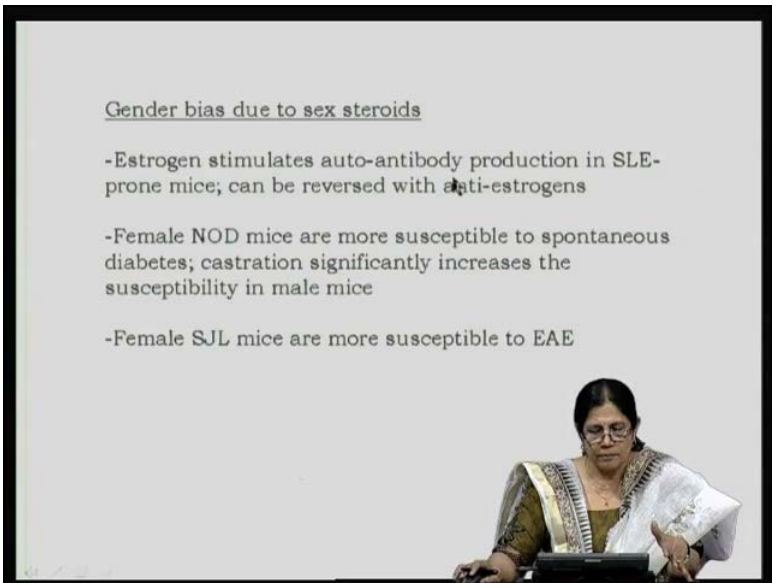

So, what does estrogen do? Estrogen stimulates auto antibody production in SLE mice, SLE prone mice and interestingly, this can be reversed with anti-estrogen. So, here is experimental evidence, that estrogen, the female hormone is directly correlated to auto antibody production and therefore, this is a gender bias. Now, interestingly, female non-obese diabetes mice are susceptible, more susceptible, sorry, to spontaneous diabetes. We already went through the non-obvious diabetes mice, which developed auto immune disease by developing IDDM, but female NOD mice are more susceptible. Also, castration of these female mice, significantly, sorry castration of male mice, which would mean, that testosterone is, I mean, acts opposite to estrogen. So, castration of male mice, male NOD mice, significantly increases the susceptibility in these. So, again, direct correlation of estrogen and auto immunity. Also, SJL mice, which are susceptible to developing EAE or experimental autoimmune encephalitis female mice, are much more susceptible then male.

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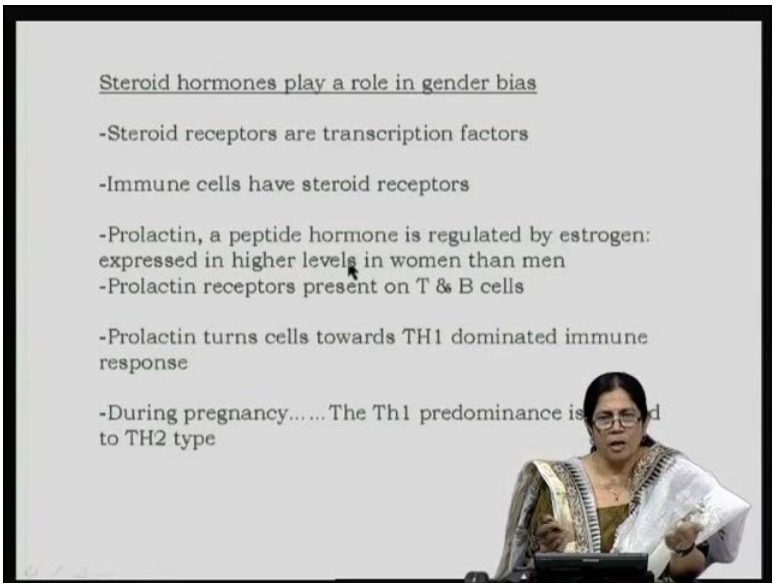

Steroid hormones play a role in gender bias. Steroid receptor are transcription factors, immune cells have steroid receptors. So, this is the way one can explain the gender bias. Also, now, prolactin, a peptide hormone, which is of course, a hormone of both males and females, but this is regulated by estrogen and, and therefore, expressed in higher levels in women than men. Again, T and B cells have prolactin receptors, not only steroid receptors, but also prolactin receptor.

Prolactin turns cells towards TH1 dominated immune response. So, once again, you can see that there would be a gender bias. Just like to inform you, that during pregnancy, the TH1 predominance is altered to a TH2 type.

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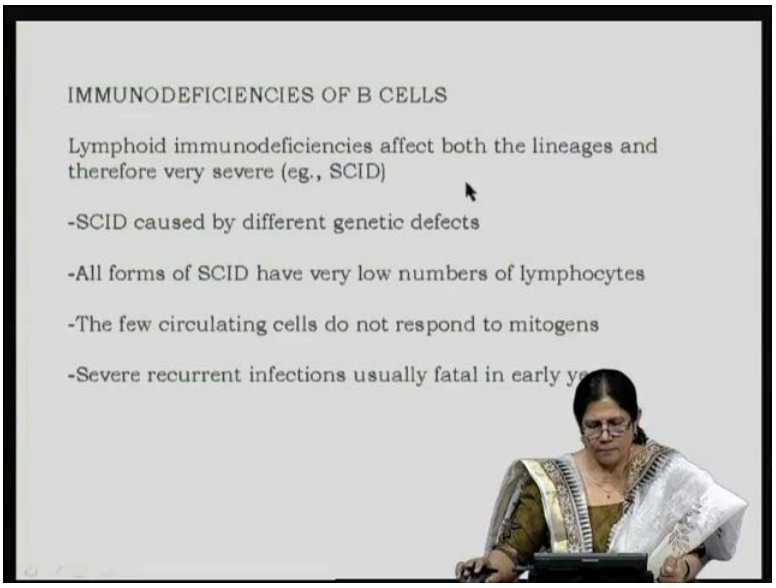

So, we now come to another aspect of immunological disorders. We talked about auto immunity, the reasons for auto immunity. Now, let us come to other immunological disorders and I will restrict myself to, B cells are immunodeficiencies. Immunodeficencies of B cells affect both the lineages of the lymphocytes. This causes severe combined immunodeficiencies. SCID can be caused by different genetic factors. In SCID, all forms of SCID have low numbers of lymphocytes, even, the low number of lymphocytes, even if they are present, they do not respond to mitogens. Mitogens are those proteins or molecules, that can be induced proliferation of T and or B cells and you know, the proliferation of T or B cells is a prerequisite activity before the cells differentiate to the effect of population.

So, in SCID, even if there are few number of lymphocytes, the few numbers themselves are not responders and because of lack of either number of cells or inadequacy of these cells, there is severe recurrent infections, which usually is fatal and in early years of life.

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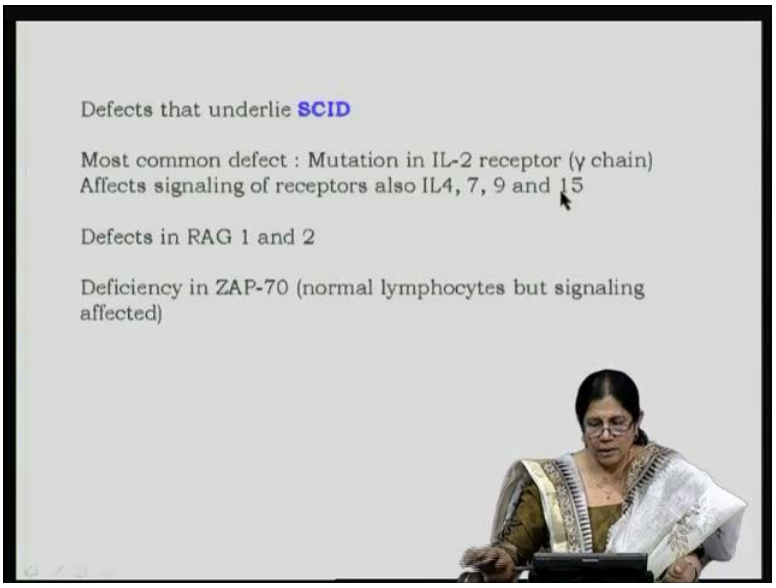

Defects, that underlies SCID - the most common one is mutation of the interleukin-2 receptors. The gamma chain, this affects signaling of receptors also for interleukin-4, 7, 9 and 15 because this is the common chain between all the receptors. The other defects, that underlie SCID is defects in RAG 1 and 2.

Now, in case of defects in RAG 1 and 2, you know, immediately, that this would not allow generation of T or B cells. In certain individuals there are normal lymphocytes, but signaling is affected totally. These do not have or have deficiency in a kinase, called ZAP-70 and therefore, there is inefficient signaling

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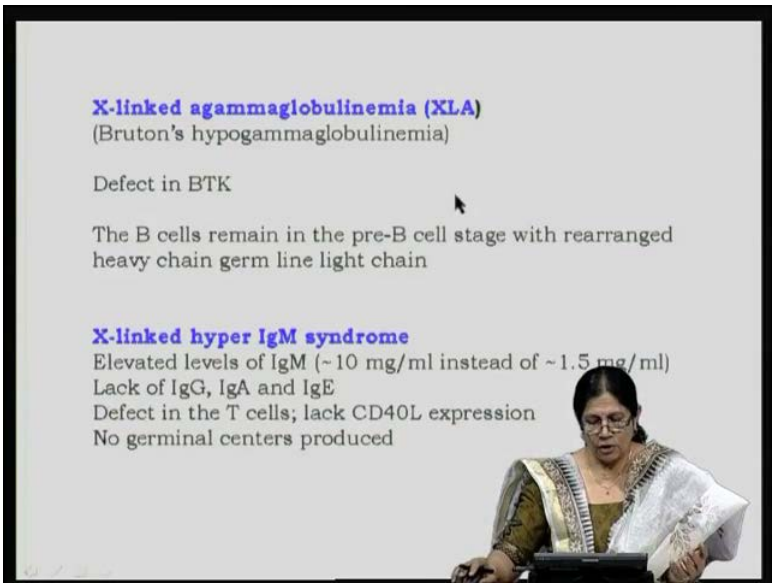

Now, there are 2 others, which I will go over quickly. X-linked agammaglobulinemia, Bruton's hypogammaglobulinemia, because there is defect in BTK, Bruton's tyrosine kinase. In these individuals, the B cells remain in the pre-B cell stage and there is no rearrangement of the heavy chain. In case of X-linked hyper IgM syndrome, these individuals have elevated level of IgM and lack totally IgG, IgA and IgE because these individuals lack CD40 ligand expression.

So, I will like to stop here and I will continue in my next lecture with the part of this immunodeficiencies and then go on to cancers, which can also be called immunodeficiency disease.

Thank you.