Essentials in Immunology
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Module No. # 08
Lecture No. # 15
Hypersensitivity types II, III, IV and Autoimmunity

So, today, I am going to start on hypersensitivity once again. In fact, this is the continuation of the earlier class.

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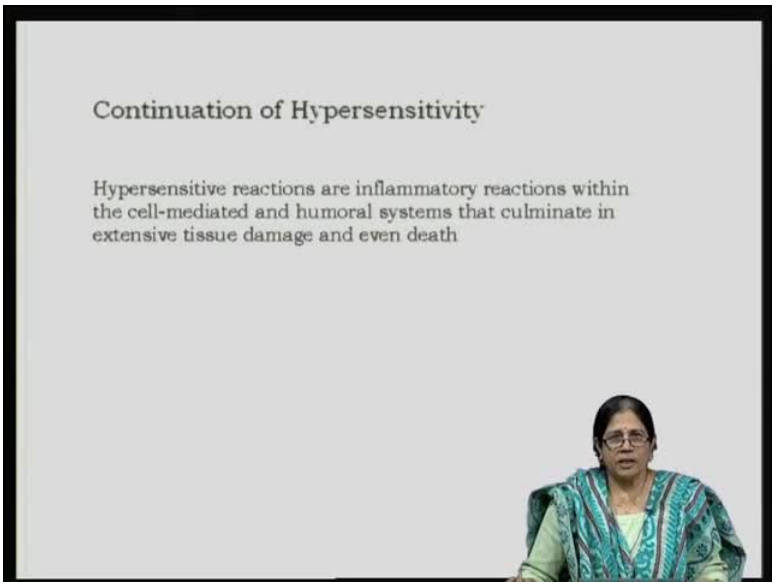

Just to recapitulate your memory, hypersensitive reactions are inflammatory reactions within the cell-mediated and humoral systems that culminate in extensive tissue damage and even death. Just to reiterate the same thing, under normal circumstances, when we are invaded with pathogen, then our immune system both cell-mediated as well as humoral immune system are able to mount an immune response by way of localized inflammatory reaction. Now, this helps in obliterating the pathogen. However, in certain instances, there can be a heightened immune response, which can culminate in extensive damage to the surrounding cells; this could also be systemic. The inflammation can be so much that death can ensue.

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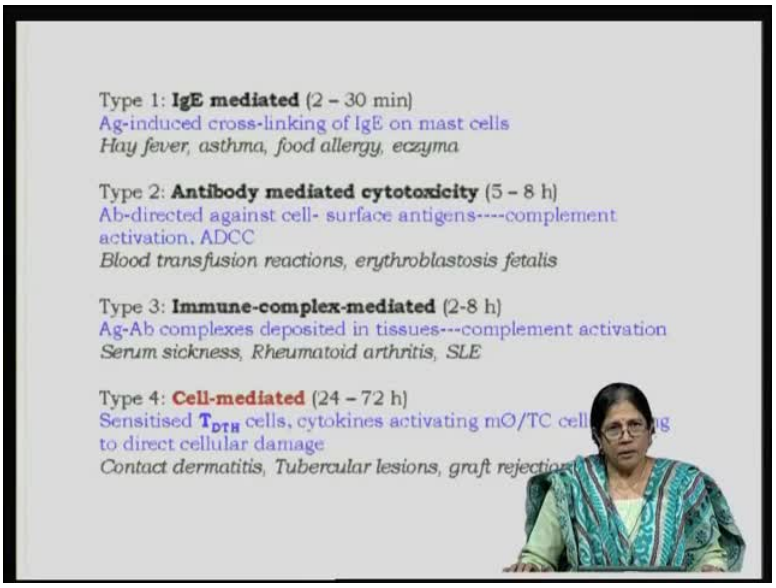

Hypersensitive reactions as I have discussed last week can be understood under four different categories: type 1 to type 4. Type 1, 2 and 3 are antibody-mediated, whereas type 4 is because of T cells. Of the type 1, 2 and 3 which are anti-body mediated, the first one - type 1, which I have covered in much detail, is mediated through IgE. Type 1, 2 and 3 reactions happen or occur shortly after the exposure to the antigen. It could be 2 to 30 minutes, as in case of type 1 or 2 to 8 hours as could be with type 2 and 3. Type 4 hypersensitivity however, which again, I will say is cell-mediated, takes 2 to 4 days.

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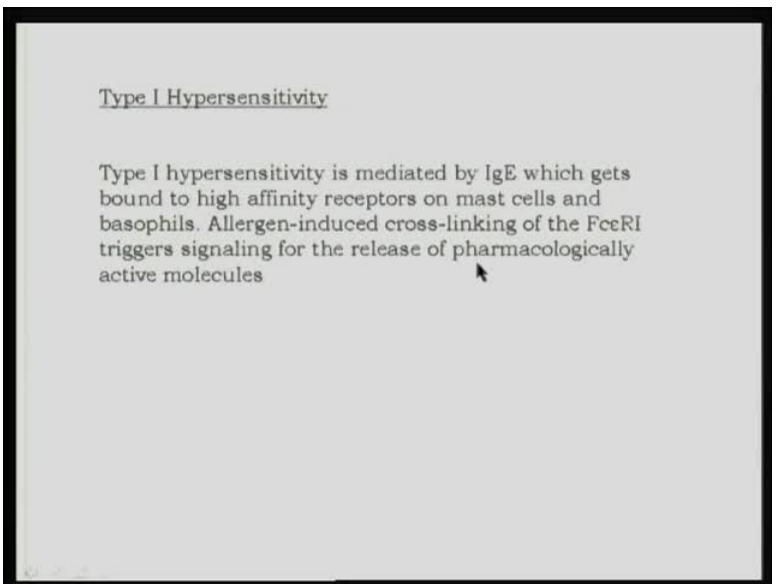

Now I have already discussed like I said about type 1, but I will just go over the summary of what I spoke last time. Type 1 hypersensitivity is mediated by IgE which gets bound to high affinity receptors on mast cells and basophils. Subsequently, when the allergen presents itself again in the body, then allergen induces crosslinking of the Fc receptors specific for IgE, which happens through the IgE which gets docked onto Fc eta R1, which triggers signaling for the release of pharmacologically active molecules such as histamine, serotonin and subsequently, bradykinins, leukotrienes etcetera.

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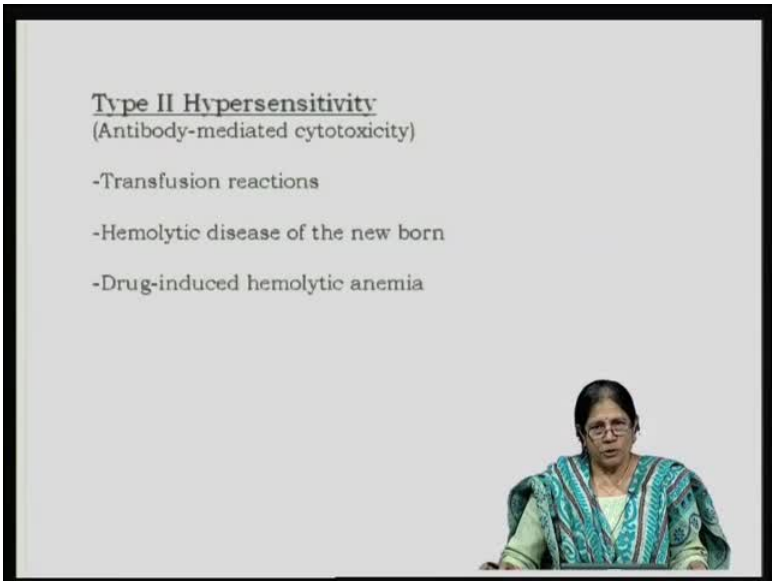

So, now, having talked about type 1 hypersensitivity, and if you might remember that the signaling process itself is quite elaborate, is dependent on ITAMS, that is immunoreceptor tyrosine-based activation motifs and therefore, phosphorylation of several molecules in the mast cells and basophils, all of which, in fact, go to releasing first preformed granules from the cytoplasm and subsequently, by way of allowing calcium to get into the cell, there are other activation processes, which now makes the cell synthesize molecules like bradykinins and leukotriene, which then gets exocytosed. So, the primary response is milder than the secondary response in case of type 1 hypersensitivity, when mast cells start getting degranulated.

Now, let us come to type 2 hypersensitivity. Now, I had already mentioned that type 2 hypersensitivity is also antibody mediated, but this is not through IgE. So, let us look at what happens in type 2 hypersensitivity. Now, this is antibody-mediated cytotoxicity and

the examples one can give are transfusion reactions, hemolytic disease of the new-born, drug-induced hemolytic anemia. Now, in all three cases of course, these are responses which happen only under conditions, where for example, in the first case, there is a transfusion reaction.

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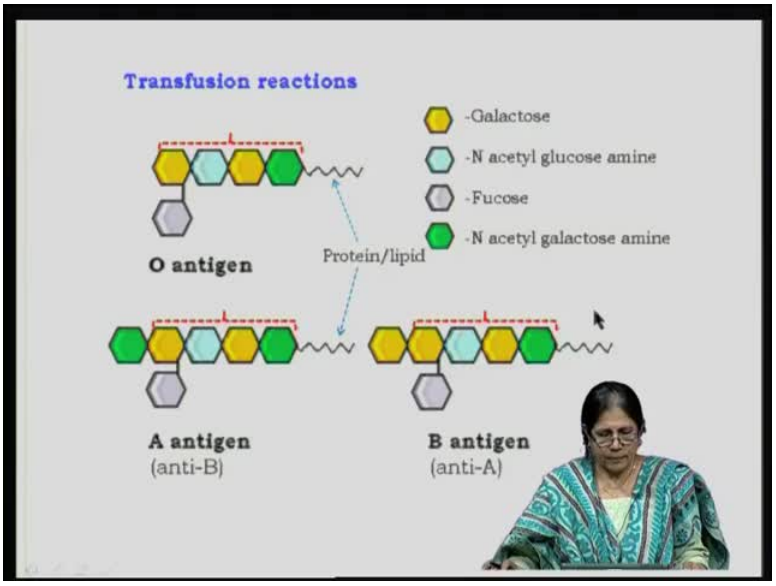

Now, one cannot talk about transfusion reactions until one talks about the antigens, which are present on red blood cells. Only then can one understand how these transfusion reactions can lead to cell-mediated cytotoxicity. I have 3 pictures here, one which represents. Now, I am sure all of you know that by the method of classification of Landsteiner, which is now commonly used for typing blood groups in individuals, all of us can either be of type O, type A or type B. I am sure it is common knowledge now that individuals, who are type O do not have any antigens, either A or B on this on the RBC surface. People who have A type blood have the A antigen and also, have in the circulation anti-B - that means antibodies, naturally occurring antibodies to antigen B. Similarly, individuals who are B, who are typed as B have the B antigen and have in their blood stream antibodies to A.

Now, O group people would have antibodies both to A and B and there is a fourth class which of course, is not mentioned here, which would be A plus B. So, there are individuals who have both A as well as B antigens and therefore, would not have any

antibodies, either to A or B. This therefore, allows people with O group blood to donate blood to either A, B or AB, and AB individuals who can receive blood.

Now, of course, the presence of antigen, since I have drawn this maybe, I should just discuss. There is a stem cell factor. First a protein or a lipid on which there are additions of sugars and the sugars, the 4 chains that you see here, all of them are present on all the blood groups. You can see the 4 hexagons that are present on all O, A, B and of course, it would also be AB. Therefore, now, the sugars N acetyl galactose amine – green, galactose followed by N acetyl glucose amine followed by galactose. Now, these four and the last one is bound to fucose. Therefore, these five sugars in sequence are present on all the blood group red blood cells. Now, the addition of another a terminal N acetyl galactose amine determines that person to be having A antigen and the termination of the and the chain with galactose determines the person to be of B antigen.

Now, how is it that there are naturally occurring antibodies. Now, this is a question which is quite simple, but this is some answer to which very often people are not able to come up with. Now, initially of course, there are no naturally occurring antibodies in newborns. Now, soon after birth, one starts to get colonized with bacteria which are common cells. They are beneficial to us. Many of these bacterial antigens or sugars are similar to A and B and therefore, once they colonize and if the sugars are of A type or B type, they would start to evoke an immune response. Sugars, as you might remember from my previous lectures, sugars are weak and immunogens and therefore, they only evoke response, which is restricted to the IgM.

Now, why would an A antigen person have anti-B. That is simple. You have also learnt about clonal deletion of self-reactive antigens, self-antigens sorry, which would mean that an individual in the bone marrow would have B cells that are making that have the capacity to make anti-A and anti-B, but those B cells in A individuals, those B cells that have receptors for A, anti-A, I mean making antibodies to A would get automatically deleted because in the bone marrow, these immature B cells, which have only IgM receptors not IgD as yet, would get exposed to self-antigen and get undergo apoptosis and therefore, cleared. Same would happen in case of B individuals. Now, in case of O antigen individuals, there would be neither A or B and therefore, they have antibodies to both A and B and of course, therefore, then plainly and simply follows that individuals with AB group antigens would have no antibodies to either A or B. So, if one has to use

serum from individuals, one would be using serum from AB individuals because they would have neither A nor B antibodies and if cells are to be donated, then one would take cells from O blood group people.

Now what happens in Now, let us come back to this transfusion reactions. What would happen? Now, I told you that there are naturally occurring antibodies in A individuals to B antibody, I mean to B antigens. So, A individual, suppose, an individual with A group gets by mistake now, is given blood of B type, then the naturally occurring IgM antibodies to B would start agglutinating and this would of course, bring about antigen-antibody interactions, small agglutinates, red blood cells would get lysed because IgM antibodies are excellent for fixing complement. There would be complement, the classical pathway of complement-mediated lysis would get initiated and red blood cells would get lysed. There would be hemoglobin in the circulation, which of course, can get thrown out of the system, but if there is too much, some of it can break down before the hemoglobin is cleared, would break down to bilirubin; bilirubin can be toxic, if it crosses the blood-brain barrier. Now, bilirubin is lipid soluble and therefore, can cross the blood-brain barrier and deposition of it in the brain can cause problems.

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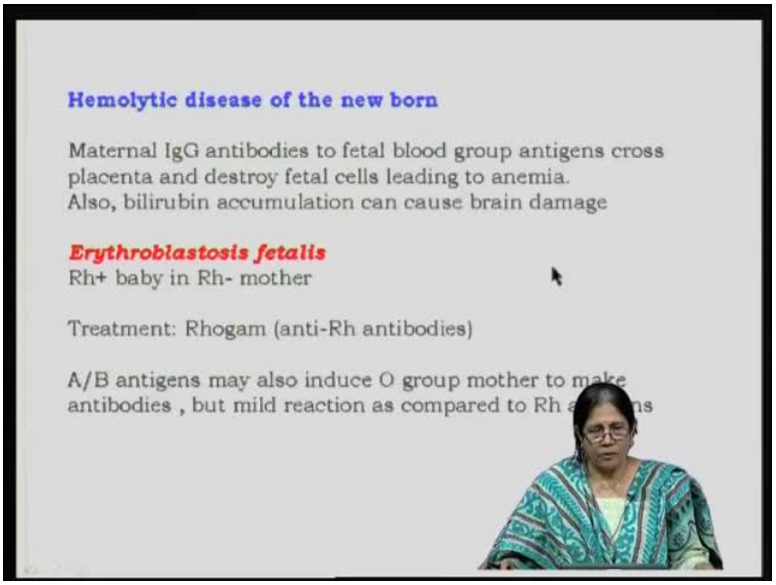

Now, in adults of course, this does not happen and transfusion reactions can be taken care of, are usually not fatal and can be taken care of as soon as the transfusion reactions can be seen, by way of the person would suffer chills and fever because of too many red

blood cells getting lysed in circulation and also, the split products being formed which will also give rise to something similar to type 1 hypersensitivity, but as soon as the blood infusion or transfusion is stopped, this reaction will also stop. However, there are other conditions - hemolytic conditions, which could be fatal as it happens in the newborn.

Now, hemolytic disease of the newborn is a second that I would be discussing. Under this type 2 hypersensitivity, hemolytic disease of the newborn, the one that immediately comes to one's mind would be because of Rh factor. now Rh factor Rh is an antigen, which is present on RBCs. Asian population, especially Indians, 70 percent of us are Rh positive, whereas in the west, there is a larger population that is Rh negative. Now, Rh being a protein antigen, it evokes a types evokes an immune response by way of switching IgM type of response to IgG. If you might remember, while IgM cannot cross the placenta, cross the placenta cannot therefore, go into the foetus. IgG has specific receptors on the placenta or tropoblast cells because of which IgG can cross. Because of class-switching, you might remember, there is also affinity maturation. So, whereas IgM antibodies might have low affinity for Rh, once the IgM antibodies switch to IgG, they would also be automatic higher affinity antibodies. So, these IgG can cross the placenta and cause damage.

Now, let us see what would happen in case of this erythroblastosis fetalis because this is presented when Rh negative mother has an Rh positive baby. Now, the first child usually is safe because there is this blood barrier between the mother and the child and only IgG antibodies can go through and anyway the mother has not even made any antibodies to the Rh positive because of this barrier, the mother's immune system has not been exposed to the Rh factor. However, during birth when the cord disengages itself from the uterine walls, there is some amount of mixing of blood that takes place, some of the blood or foetal red blood cells, which are Rh positive now, enter the circulation of the mother and now induces an immune response, which would be IgM to begin with and would switch to IgG. So, the problem arises during the second child, when the mother is pregnant with a second baby. Now, when if class switching has taken place and if IgG type of antibodies are made, then these would cross the placenta, enter the foetus and now, with a very efficient mechanism, which is determined through complement fixation, red blood cells get lysed. Now, this can happen in the foetus itself. This can lead

of course, to anemia and therefore, ultimately, if the reactivity is extremely severe, then it would lead to death of the foetus.

Rh factor also, there are actually four different antigens and I will not talk about them. This That the factor d, you know this might ring a bell. That factor d in fact, is the strongest of them all and if one has an allele, which is capital D, capital D, then antibodies that are made to this would definitely evoke a much stronger hypersensitive reaction than if it was small d, small d, both of which would be recessive. So, there are questions of course, people ask, there are cases where the mother is Rh negative, but yet, and all the babies are, where they could be as many as three, and all the babies are Rh positive. How come there has been no problem? This only would be because of the allele of the stronger versus weaker type of Rh factors.

Is there any treatment for this kind of case? Of course, yes. Now, the moment Of course, it is much simpler. One knows what blood group one belongs to and a mother who is Rh negative and if she is harbouring an Rh I mean if her husband is, the woman's husband is Rh positive and if they find that the foetus is Rh positive, then soon after the birth of the first child, the mother is given, within 48 hours, the mother is given anti Rh antibodies called rhogam and these antibodies lyse any foetal cells that are in the mother's circulation and that these antibodies would be very efficient in doing that and thereby now, the mother's B cells would not evoke an immune response at all, even before they become memory cells. Therefore, now the mother can, after this treatment of course, the mother can safely have the second child.

Now, if one is talking about these Rh antibodies, which are crossing the placenta, then there is a possibility that you can also have antibodies to the A, B group individuals. Let us say, for example, the mother is of the blood group B she harbours a A group baby. Now under normal We have these naturally occurring antibodies, which are IgM, which would be naturally occurring because of, I told you, triggering of the immune system of the person by way of bacterial antigens. Now, those would be only IgM type, but it has been seen that when foetal red blood cells go to the mother, then this kind of an immune response can of course, will always be IgM to begin with, but can also switch to IgG. Fortunately, the immune response generated, even if it is IgG type to A, B, it is mild and this mild reaction as compared to Rh factor, which is a much stronger immunogen antibodies to either A or B, even if they are IgG type, do not cause much harm and you

might have heard that there are babies born soon after birth, they have jaundice and that jaundice can be taken care of very easily and it is not fatal at all, but nevertheless, like you to remember that even A, B antigens can evoke a response similar, but much weaker than Rh factor.

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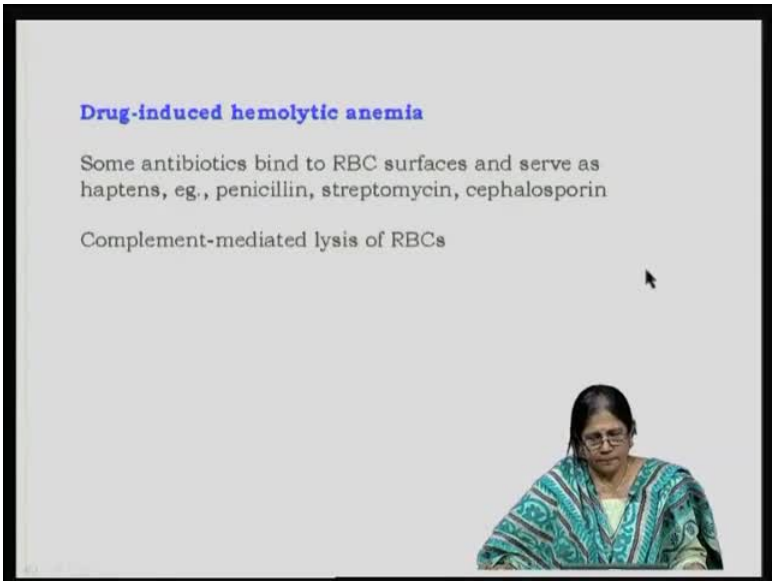

Third type of type 2 hypersensitivity would be drug-induced hemolytic anemia in another context of hypersensitivity. I did say that some antibiotics and small molecules bind to red blood cell surfaces. These serve as haptens. Penicillin, streptomycin, cephalosporin - these are very small molecules. On their own, they cannot evoke an immune response. However, when they bind to, you know some people's red blood cells are somehow more active with respect to conjugation. They conjugate penicillin, streptomycin, cephalosporin, these small molecules and then thereby making these small molecules haptens - immunogenic; these can evoke an immune response; there would be antibodies and therefore, whenever a person has taken, is under treatment with these antibiotics and has made antibodies to these, upon previous exposure would now suffer from complement-mediated lysis of RBCs. Now, as soon as this is realized, then of course, that particular antibiotic can be withdrawn and this usually has never proved to be very fatal.

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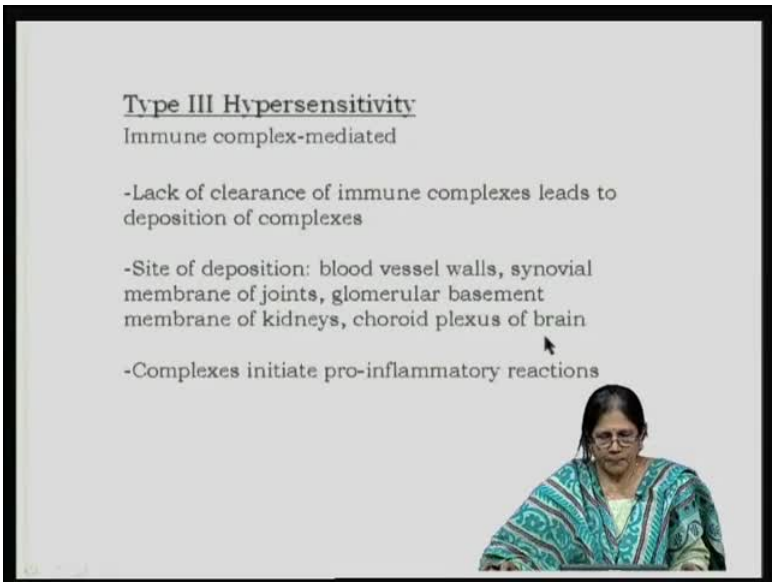

So, we have seen type 1, type 2 hypersensitivity, both of which are driven by antibodies. Now, we look at type 3 hypersensitivity, which is also caused by antibodies. Let us look at that. Type 3 hypersensitivity, though caused by antibodies, this is after I mean if immune complexes are developed. Now, why should immune complexes cause any hypersensitivity?

We do know that viruses, bacteria, any particulate antigens are very effectively thrown out of the system and negated by because I mean by the body because of the formation of immune complexes. A pathogen enters the body and antibody is made to this these particles, antibodies especially IgM and also of course, IgG can bring about crosslinking of these antigens, small complexes to large complexes are made very effectively, picked up by phagocytes and then deled from the system. So, why should there be hypersensitivity?

Now, this can only happen in unusual cases. For example, when there are antibodies present in the person and now, a large amount of antigen is injected. Let us look at what happens then. If you have too much of You know there has to efficient and an optimum antigen antibody interaction which will give rise to large complexes. If you have too much of antigen, then much smaller complexes are formed and if they are too many in number, then phagocyte sites are not adequate to clear the immune complexes from the system. So, what happens? They cannot be cleared. So, they get deposited mostly along

blood vessel walls, synovial membrane of joints, glomerular basement membrane of kidneys, choroid plexus of brain.

So, what if these complexes get deposited? What happens then? What ensues is that these complexes are nothing, but antigen-antibody interaction and if you remember complement-mediated lysis, complement activation then binding of the antibody to an antigen, if it is the antibodies are of IgM or IgG type, then there is accessibility of the C1q binding site on the Fc region of antibodies. Now, of course, in circulation, there are these complement components are in circulation. They get bound; the C1q gets bound to the Fc region or the region Fc the second region, the constant domain of IgG and third of IgM and then you have the entire cascade, which we have already discussed. This brings about an inflammatory reaction in the way that split products are formed. You remember C3a, C5a and C4a; all these three have receptors on mast cells and basophils and neutrophils and now, these can activate the cells, mast cells to degranulate and cause type 1 hypersensitive like reaction.

Now, this is the inflammatory reaction. The other thing that can happen of course, when the complement pathway is triggered, all the 3 pathways we know culminate in the formation of the membrane attack complex or mac and exactly that is what happens. So, wherever there is site of deposition of these immune complexes, complement cascade has been initiated and the mac that are formed, that are generated can start attacking the sites, where the complexes are formed. So, blood vessels get destroyed; synovial membrane, the membranes get destroyed and glomerular basement membrane of kidneys also get destroyed. So, there is both inflammatory reaction as well as death of the tissue, where the complexes get deposited. So, this could also be a chronic inflammation which persists for long periods of time.

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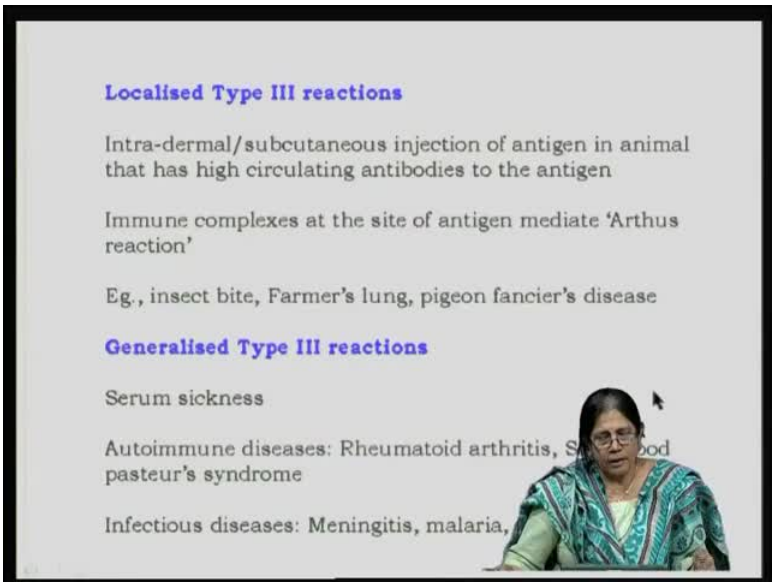

This type 3 reaction could either be localized type or generalized type. Let us look at the localized type. Now, for type 3 hypersensitive reaction to occur, there should be pre-formed antibodies circulation or in circulation to that particular immunogen. Intra-dermal You know if it is localized type, then it would be restricted to what I am going to describe is on the skin. So, intra-dermal or subcutaneous injection of an antigen in animal that has high circulating antibodies to the antigen would now have a reaction at that particular site and I will come to that in a little while.

I have a picture which will tell you exactly what happens, but there are immune because of the presence of high circulating antibodies and deposition of the antigen at one site like I said intra-dermal or subcutaneous, then there are immune complexes that are formed. This kind of reaction is called arthus reaction and the example of this condition is insect bite. Have you ever been bitten by an ant? Now, certain ants are able to evoke a small inflammation just around where the ant has bitten. Some of those that bite very, you know that the bites hurt and actually, do give much larger [wealds]. The other example is farmer's lung and pigeon fancier's disease. let us We will come to that a little later

Now, there can also be generalized type 3 reaction. this is localized; generalized – so, here of course, the antigen in this case, the antigen is on a particular patch of skin that is where let us say, an insect has bitten or in case of farmer's lung, actually the antigen has

gone and deposited in the alveoli. Generalized type reaction on the other hand is an example, where the entire there is a systemic disease. So, more than one particular site is involved; let us say serum sickness. Now, when would you think of serum sickness? What comes to my mind immediately is when a person has been bitten by let us say, a poisonous snake and the only antidote that is available right now in fact, is horse serum, which is given to people who are bitten. The horse serum has antibodies to the entire snake venom, so, would have of course, horse immunoglobulins. Now, there are antibodies.

now this process Of course, for the adequate protection from the venom, a large amount of antibody has to be given of the equine source and this would this evokes an immune response. There would be antibodies to the horse immunoglobulins and because there is large amount of antigen in this case of course, is the horse immunoglobulins and the other components of the horse serum like even the albumin, which is seen as a non-self and a very strong immune response is generated and this will of course, form small complexes. Now, because the serum is given and it is in circulation then of course, one can imagine that this would be systemic.

Autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, good pasture's syndrome - these also would evoke a generalized type 3 reaction and as well as in infectious diseases meningitis, malaria, hepatitis, you know there are antibodies that are made to these antigens to the pathogen and whenever this pathogen number increases, you would have antigen increase and there would be generalized type 3 reaction.

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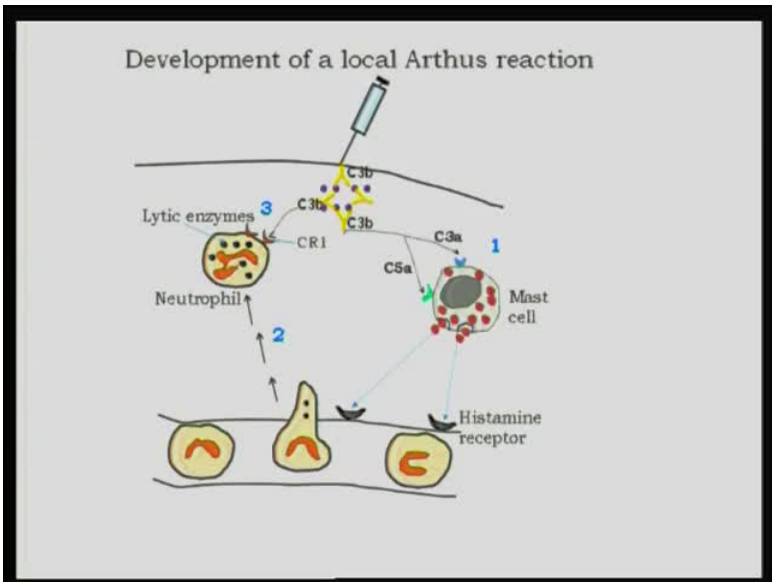

Now, you will be able to understand this type 3 reaction in the following way. Now, what I am going to describe to you is the localized one, where I mean, this is the arthus reaction, which can happen on the skin and this one denotes what happens, when an insect, now, of course, this shows a syringe, but an insect has bitten and the venom has gotten in. Now, there are already antibodies to that venom maybe, because of a prior exposure and has good amount of antibodies. Now, this is where the antigen enters. Now, what you can see as little dots are the antigen, which are very strong antigens of course.

Now, because of the presence of immunoglobulins, there is a complex that is formed. It continues to be present for some time in the skin, before the complex is cleared. Before that because of this antigen-antibody interaction, complement cascade gets triggered and you have deposition of C3b at that particular site, where antigen-antibody interaction has taken place. C3b has receptors CR1, Sorry. C3b binds to receptors CR1, which are present on neutrophils. So, neutrophils, when they come to that site, and start now they get activated upon the CR1 receptor binding to C3b and the neutrophils, which have large amounts of lytic enzymes, start pouring the enzymes.

There is another pathway here. When cascade complement cascade is triggered, then we have the split products which are formed; C3a, C4a and C5a. There are receptors for these split products of the complement cascade, complement components present on

mast cells; this is the mast cell and these are called anaphylatoxins because binding of these molecules to their cognate receptors induces signaling, which is similar to what happens when allergen binds to the IgE specific antibodies, which are docking onto Fc eta receptor 1.

Degranulation, therefore, takes place of the mast cells. Now, the histamine which is released and serotonin, they bind to histamine receptors, which are present. if you might remember, H1 and H2 receptors, which bind, which are present on blood cell sorry the blood vessel wall brings about now, an activation which is similar to hypersensitive type 1 reaction.

Now therefore, you have now, because of the presence of neutrophils, large number of them, which come to this site, this would definitely generate an inflammation at that site and this is called an arthus reaction; remember, this is because of neutrophils. Now, it is only not neutrophils, but in arthus reaction, you will see mostly neutrophils.

In case of the condition of farmer's lung, it has been seen that farmers who are constantly in contact with, when they are on their farm and they are in contact with let us say, birds. birds where the faeces of birds very often, when it is deposited Of course, birds, their faeces is deposited everywhere, but often these faeces can dry and become airborne and farmers get exposed to this. They inhale and these small particles now, get deposited in their alveoli and evoke a response, which is similar to this. So, these you can imagine that there is this inflammation in the lungs and accumulation of fluid; this could rather be debilitating, if not fatal.

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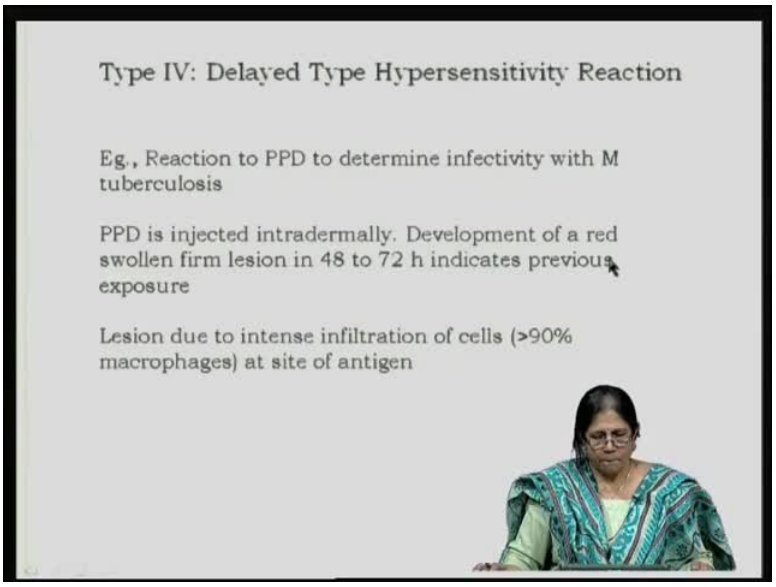

Let us come to the type 4 - delayed type hypersensitive reaction. Delayed type hypersensitive reaction as mentioned earlier, the name itself suggests that after exposure to the antigen, the reaction happens 48 to 72 hours later and this is mostly due to T cells. Let us see what happens in case of delayed type hypersensitive reaction.

The example of this is reaction to The example is when individuals this is a time-tested analysis or diagnostic test, which allows one to see whether one is infected with M tuberculosis. Now, this test involves the antigen from bacteria PPD (Purified Protein Derivative); it is an extract of the bacteria M tuberculosis and this is put onto skin; this is a skin test. Now, if one has antibodies to the T cells to micro bacteria and if the individual now is exposed to PPD, there is development of a red swollen firm lesion within 48 to 72 hours. So, this indicates a previous exposure in that individual to M tuberculosis. Now, what is this lesion due to? You know the hard lesion which is 48 to 72 hours. This lesion is due to intense infiltration of cells, 90 percent of which are macrophages at that particular site.

Now, one can see this delayed type hypersensitive reaction in people who in experimental animals and most of us probably have at some point of time generated antibodies to different antigens of interest and if you have done that, you would have used Commonly people use Freund's complete adjuvant as the sensitization adjuvant. Now, Freund's complete adjuvant has a part from mineral oil as well as the detergent,

which will allow an emulsification or a stable emulsion of the aqueous and the mineral oil, these two phases and also, has heat-killed micro bacteria. Now, this would of course, have PPD which allows, which would evoke this delayed type hypersensitive reaction or activation of T h 1 cells.

So, when we normally inject the emulsion subcutaneously or intro-dermally - subcutaneously, in mice and intra-dermally in rabbits and within 72 hours, if you go and see the area, where the antigen has been deposited, you will see a lesion. To begin with it looks like there is some puss, but soon after, it becomes a hard lesion and if you were to take a slice of this, a thin section of this through this lesion, there will be you will see that there is intense infiltration of cells, which are definitely different from the epithelia and these would be macrophages.

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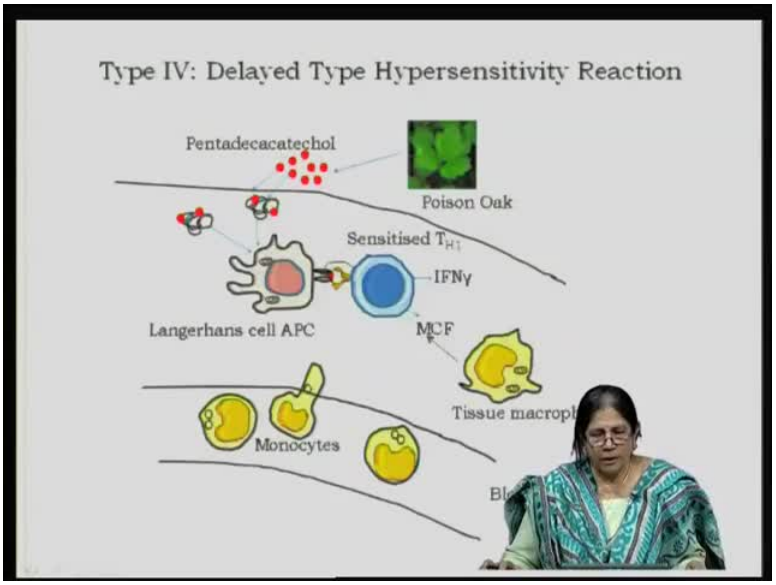

Now, here this particular slide tells you a little bit more in detail, with the actual reaction that takes place. Now, the example I had given you of course, is mycobacterium tuberculosis and all you know immunization experiments that one can when one neutralizes Freund's adjuvant or complete adjuvant, but let us look at another condition of delayed type hypersensitive reaction, where there are small molecules, which could be plant-derived. For example, or this could be even a cosmetic. Now, you might wonder that there are people who are allergic to hair dyes or you know certain cosmetics like

facial cream. That is because there are small molecules that are present and not all individuals, some individuals seem to react. How do they react to these?

As the example over here is poison oak, but this could be a small molecule. It could be turpentine; some people are hypersensitive to turpentine; it is also a small molecule just like this poison oak which the toxin part of which is pentadecacatechol. This is a small molecule on its own. It does not evoke any immune response, but when pentadecacatechol binds to proteins of the skin, now, this becomes a hapten and this is taken in by the protein as usually happens would be taken by the antigen presenting cells, which are present in the skin.

Langerhans cell, these are efficient antigen presenters. They would take the entire protein, the skin protein which is being modified now because of binding to pentadecacatechol and the molecule now is presented in the context of class 2 molecules – APCs; so, class 2 molecules and therefore, they present the antigen to T H cells, the helper cells. The T H 1 cells get sensitized by this and they start secreting gamma interferon as well as macrophage monocyte chemotactic factors. So, what the chemotactic factors do? They now send the message to or signal to blood monocytes to come to the site, where the sensitization has taken place. Therefore, now, there is a reaction, inflammatory reaction that takes place here.

Delayed type hypersensitive reactions can be treated by just withdrawing the source of the molecule. Now, in case of poison oak, one would of course, come across that only in a forest for example, and in case of people, who are sensitive to hair dyes for example, or turpentine. Then turpentine of course, is an occupational hazard. So, you just change your job or if you are if one is hypersensitive to hair dyes, then you stop using the hair dye or to any of these cosmetics. Now, of course, there are cosmetics available which say hyposensitized, which would mean that this cosmetics do not contain allergic substances.

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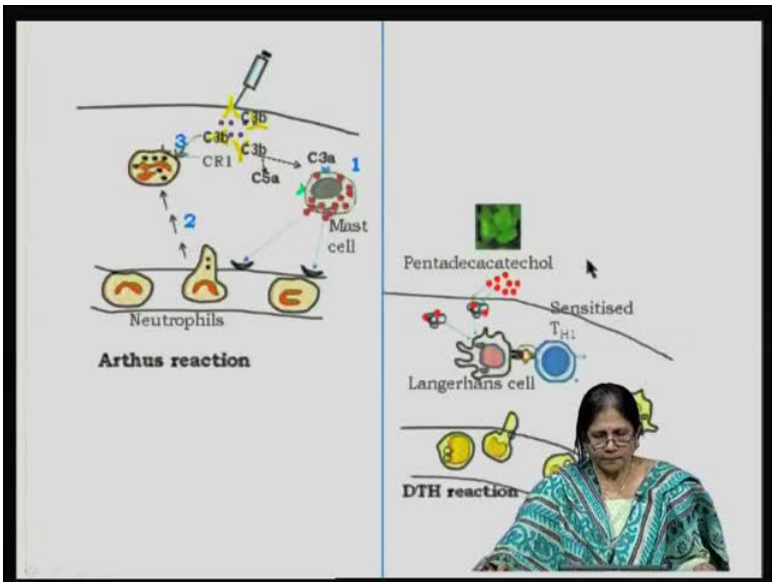

Now, the last two, the type 3 and type 4 - the localized type, the arthus reaction as well as the delayed type hypersensitive reaction look very similar. Now, both of them at the site, the localized one at the site of antigen deposition and similarly, at the site of antigen deposition, but I would just like to tell you the two differences: one is because of about at the site of antigen deposition, large number, more than 80 percent are neutrophils in case of arthus reaction, whereas in case of the delayed type hypersensitive reaction these are monocytes. Now, the type of cytokines that are secreted in these two instances would be different, whereas arthus reaction also engages mast cells for this inflammatory reaction; in case of delayed type hypersensitive reaction, it is totally by T H1 cells, delayed type hypersensitive cells.

Now, you have T H1 response also of course, in case of patients infected with and are diseased with lepromatous, leprosy or with tuberculosis lesions. The reactions would be very, very similar. What happens in those cases is that there would be cells which are infected like macrophages which are infected with bacteria. The T H cells, T H1 cells get sensitized, but they cannot do anything to the bacteria, which are sitting inside and thereby they are all the time being activated. They keep on making cytokines, which are deleterious, if they are too much of it locally.

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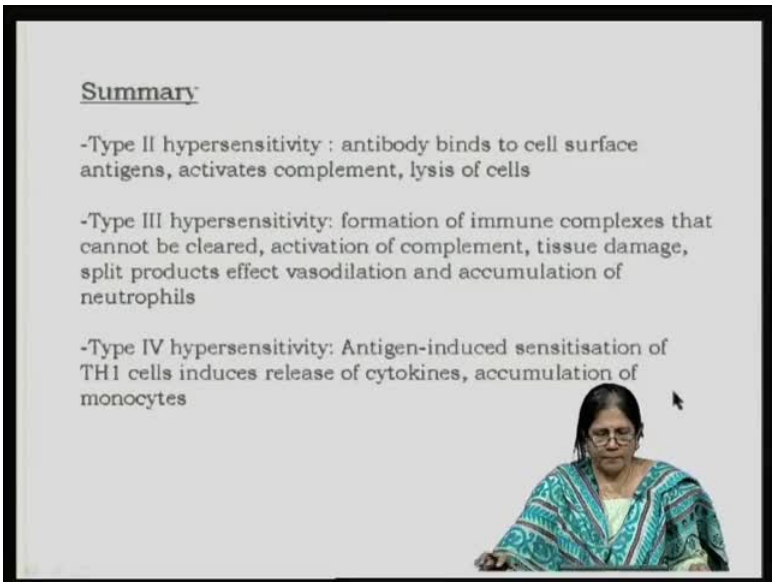

So, I just like to summarize this part of my talk. We have come to the end of hypersensitive reactions. Now, I have already talked about type 1 earlier. So, let us just summarize type 2, 3 and 4. So, type 2 hypersensitivity is I mean occurs, happens when antibodies bind to cell surface antigens, activate complement, which brings about lysis of cells. Now, type 2 hypersensitivity - would all of these would be like type 2 hypersensitivity. The example is transfusion reaction or erythroblastosis fetalis; there is toxicity to cells and thereby lysis and this is determined by antibodies.

In case of type 3 hypersensitivity, this formation of immune complexes; they are too many of them to get cleared. Therefore, the complexes get deposited in the body; they activate complement. The activation of complement which is now, it becomes almost a chronic kind of situation, where there is tissue damage; split products affect vasodilation and accumulation of neutrophils at that site. Type 4 hypersensitivity is antigen-induced sensitization of T H1 cells. This induces release of cytokines and accumulation of monocytes.

You would agree with me therefore, that none of these reactions would happen under normal circumstances. It would only be when in situations, where the hypersensitivity is evoked because of conditions which normally would not happen, in case of IgE. Normal conditions, normal individuals do not need too much IgE. Only a few people make too much IgE, which gets sequestered onto mast cells and basophils.

In type 2 hypersensitivity, it is only when by mistake one is given a blood group which is incompatible. Type 3 hypersensitivity is when you are bitten by a snake and you have to take the antidote to the venom and if you had to do that more than once, then you are surely going to get type 3 hypersensitivity. Type 4 hypersensitivity – well, examples what I have given you is turpentine or poison oak or cosmetics and these are also, whatever you say is artificial conditions. So, hypersensitive reactions are those pro-inflammatory, inflammatory reactions, which are able to induce and unwanted kind of an immune response and this could lead to tissue damage.

Now, let us switch gears. and come to You know let me introduce to you tolerance and autoimmunity. We talked about hypersensitivity, which is too much a bad kind of an immune response, which of course, deletes the pathogen, but also causes tissue damage to the hosts. So, let us come now from hypersensitivity to autoimmunity.

Autoimmunity, why should there be autoimmunity? We have always been talking about the immune system, which is capable of recognizing self from non-self and therefore, is able to mount an immune response only to delete that non-self.

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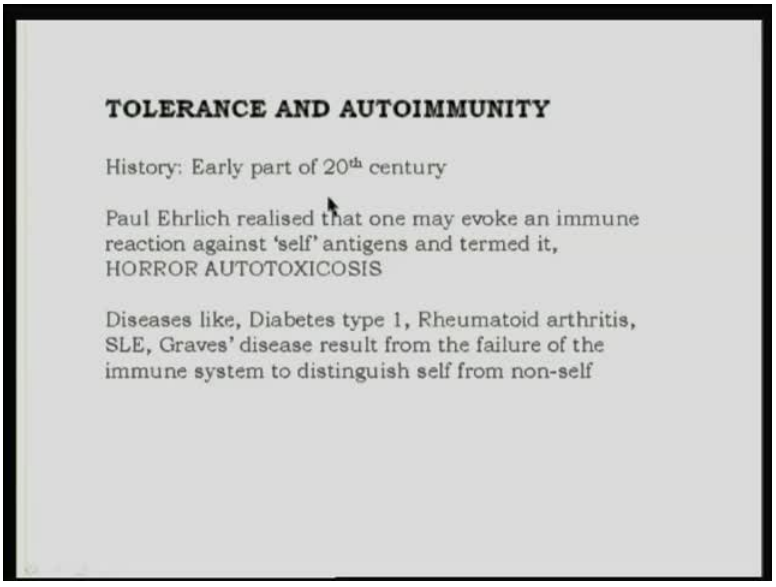

But it was early part of the 20th century that a scientist called Ehrlich realized that one may evoke an immune reaction against self-antigens and he called it horror autotoxicosis. A condition which is deleterious to one-self and the immune response is

generated to one-self. Now, which are what are the diseases which come under this category of autoimmunity? Diabetes type 1, rheumatoid arthritis, systemic lupus erythematosus, graves' disease all these result from the failure of the immune system to distinguish self from non-self.

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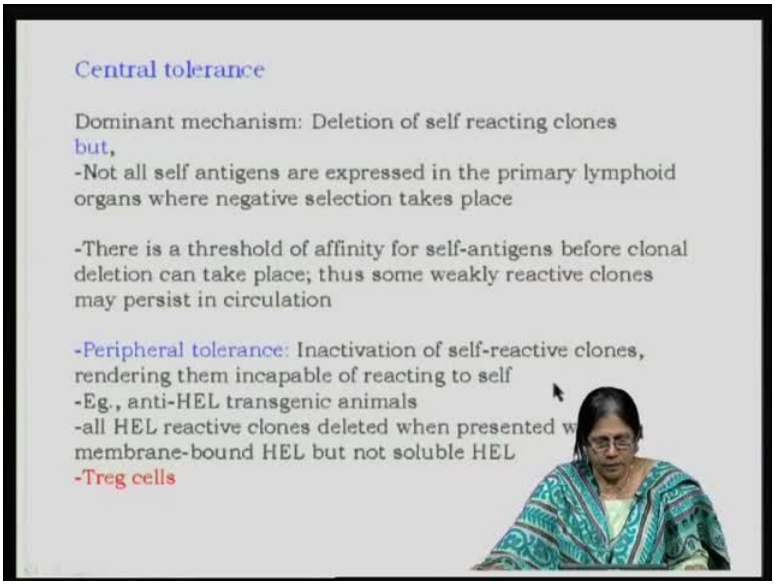

Now, why would we make or evoke an immune response to self? By now, you have of course, heard from me that self-reactive B cells are deleted in the bone marrow when those cells which have only IgM receptor on the cell surface are yet to also express IgD; when such cells, immature B cells are exposed to antigens, which have antigen under normal circumstances, it would be only self-antigens, then the cells undergo apoptosis and therefore, clonally deleted. So, this is in fact, a central tolerance. There is the central tolerance as well as peripheral tolerance because of which we react normally to non-self-antigens. Looking at self-tolerance, this is a dominant mechanism, which happens in the bone marrow, in case of B cells and thymus, the cord the medulla of the thymus in case of T cells.

Now, though deletion of self-reacting clones occurs, not all self-antigens are expressed in the primary lymphoid organs, where negative selection takes place. Now, of course, not all antigens are express expressed in the primary lymphoid organs, but the entire immune system is sort of a network and there would be migration of antigens through the circulation; bone marrow is of course, a part of the circulation. Therefore, a large number

of antigens are in fact exposed to cells or rather cells, immature cells are exposed to a large number of self-antigens, but not all self-antigens are expressed in the primary lymphoid organ, where negative selection takes place. So, those self-antigens, small number of self-antigen binding B cells would definitely escape and come into circulation.

Also, it has been seen that there is a threshold of affinity for self-antigens before clonal deletion can take place. Thus, some weakly reactive clones may persist in circulation. Fortunately, in spite of these small, I mean this population of cells, which are not destroyed come into circulation, fortunately, we have a peripheral tolerance, which actually inactivates self-reactive clones. Now, how does that happen? This can be given by one example.

People have made transgenic animals, which have anti-HEL. What is HEL? Hen egg lysozyme. Now, hen egg lysozyme has been a popular molecule with immunologists. This is a molecule which has 4 disulphide bonds and you know it has been studied very nicely with respect to B cell epitopes, with respect to continuous epitopes, discontinuous epitopes; for describing these type of epitopes, this molecule has been extremely useful

So, now, there is a transgenic mouse that has been made to anti-HEL. So, large number of B cells would have receptors for binding specifically to HEL. Now, in these animals it has been seen that when HEL, now the HEL, hen egg lysozyme would be an artificial system in case of mice, now the mouse has been made transgenic with respect to HEL. Normally, they would have a very small of each, I mean a receptor bearing B cells, to each antigens. Remember, we are supposed to evoke an immune response. We are capable of evoking immune response to something like a 100 million different antigens. Therefore, now, if you want to study a particular population, you would make transgenic animals. This particular mouse now, which is transgenic would have at least about let us say, 33 to 40 percent of the B cells, which react or have the receptor to react to HEL

Now they studied Afterwards, they studied now, how many of these HEL reactive clones get destroyed, when these B cells in the immature state are exposed to membrane-bound HEL versus soluble HEL. It was interesting that membrane bound HEL would all, that means another cell which is exposed, I mean, which is again this will be an artificial system of course, has HEL. So, the HEL is fixed onto the membrane of another cell.

Now, when HEL B cells are exposed to membrane-bound HEL, almost all the clones got deleted. You know, the viper process However, when such transgenic animals were exposed to soluble HEL, it was seen that quite a large population of self-reactive, now it would be self-reactive clones here because this is a transgenic animal self-reactive clones now come into circulation, but interestingly, in that circulation, when now transgenic animals were exposed to HEL, it did not induce clonal proliferation nor the anti-HEL bearing B cell receptor.

So therefore, we know that there is something known as peripheral tolerance and unless this tolerance is broken, self-reactive clones continue to be in circulation incapable of reacting to self and we will understand in the next lecture, how this barrier is broken. Another part of the peripheral tolerance which I am not going to deal with, but it is important this is going to be dealt with people who are who by professor Nandi or professor Manjunath, who deal with T regulatory cells.

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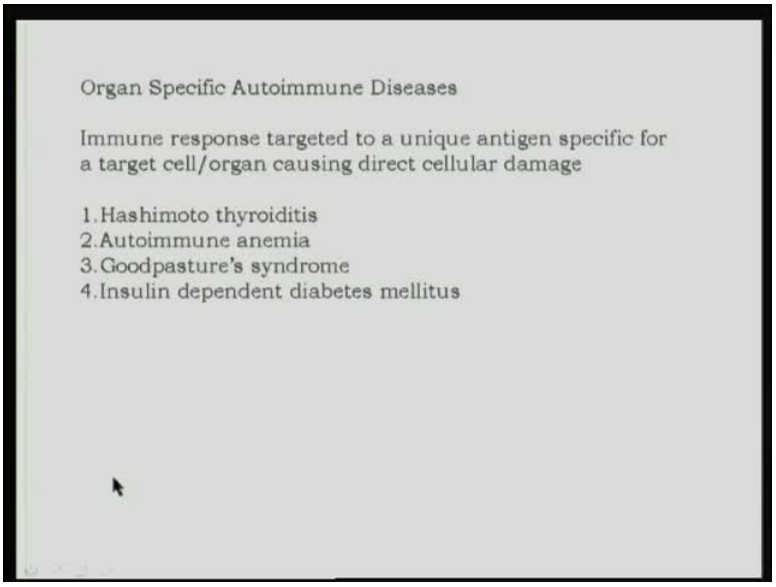

Now, I will just introduce to you these autoimmune diseases, and I will just the details of which you will continue in the next lecture, but now autoimmune diseases, we know now that there are autoimmune diseases. We are We can make antibodies or reactive T cells to different, either organs or self-molecules or we will come to those. Autoimmune diseases can be studied under organ specific autoimmune diseases versus systemic.

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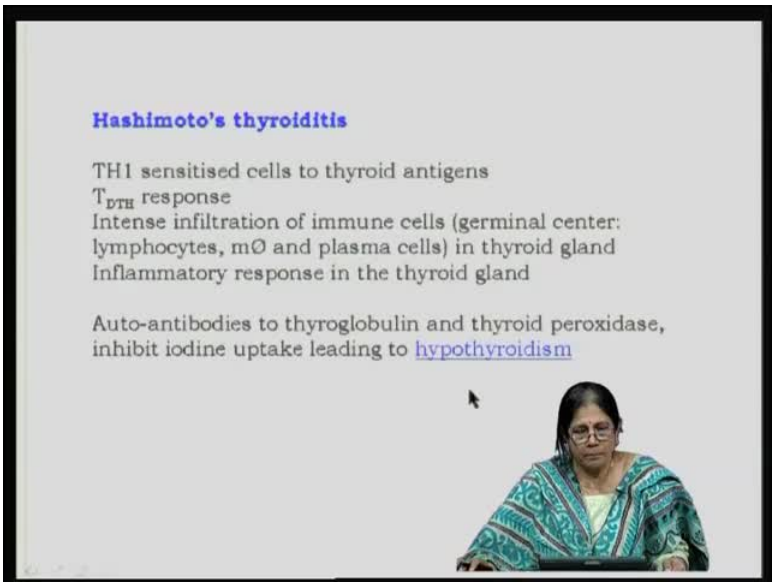

Organ specific immune diseases where these immune the immune response is targeted to a unique antigen, which is specific for a target cell or organ and therefore, the immune response causes direct cellular damage to that particular organ. The examples of these are hashimoto thyroiditis, autoimmune anaemia, good pasture's syndrome and insulin dependent diabetes mellitus. Now, of course, hashimoto thyroiditis would definitely involve, thyroid gland autoimmune anaemia would involve red blood cells, good pasture's syndrome involves kidney and insulin dependent diabetes mellitus of course, that the name suggests would involve beta cells. Now. I will stop here. Let us talk We will talk about organ specific autoimmune diseases in the next class and we will deal with what are these antigens.

Now, of course, we should remember with respect to organ specific immune diseases that of course, now, there would be small number of B cells, which have escaped deletion, just because let us say, in case of hashimoto's thyroiditis. Now, those cells wherein receptors for the very antigens which later on are involved in disease progression, now, these B cells have probably were allowed to come into circulation because they were not the immune the immune cells immature immune B cells were not exposed adequately to enough amount of the thyroid antigens. Therefore, these have come into circulation.

Again, under normal circumstances, there would be these cells would not even be exposed to the thyroid antigens again because thyroid antigen is localized. This can only happen in situations where let us say, there has been something like molecular mimicry, which we are going to talk about or there could be some kind of a damage because of which to the thyroid glands, let us say because of which a lot of cells are being destroyed and therefore, these antigens have come into circulation and just because there is large amount of the antigen that come into circulation, those quiescent self-reactive clones in the peripheral circulation now get exposed and start to get activated.

Insulin dependent diabetes mellitus is same thing. Why should one make antibodies or T cells reactive to beta cells? So, all this, we will be able to address in the next class and we will start off with description of all the four diseases hashimoto's, autoimmune anaemia, good pasture's syndrome, IDDM - insulin dependent diabetes mellitus and then go onto systemic autoimmune diseases. Also, next class, I will be talking about how what are the mechanisms of these autoimmune diseases, but before I end, I would like to also tell you there are reasons for which I am also going to explain in the in the next class, but there are reasons for which more women are prone to autoimmune diseases than men. So, obviously, steroid hormones must be playing a role.

Thank you.