Essentials In Immunology
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Lecture No. # 34
Host response mechanisms during infectious diseases – part 1

In the past few lectures what we have been looking at is different aspects of the immune response. So, in today's lecture what I will be focusing on is to try and get it where all these things come together, which is in terms of one of the main aims of having the immune systems is that, it responds to different types of pathogens, and few types of tumors. But how does it all come together? Now, in the past few lectures, we have been looking at different aspects of this.

Over here in the next todays, and the next one will be trying and see, how the immune system is integrate in generating this response and therefore, coming to title of this lecture it is 'Host Response Mechanisms during Infectious Diseases' and we will be covering some infectious diseases, but the two main ones that, will be focusing on are the micro bacterial tuberculosis and H I V, because I feel these two represent two ends, one is bacterial disease and the other is a viral disease, ok.

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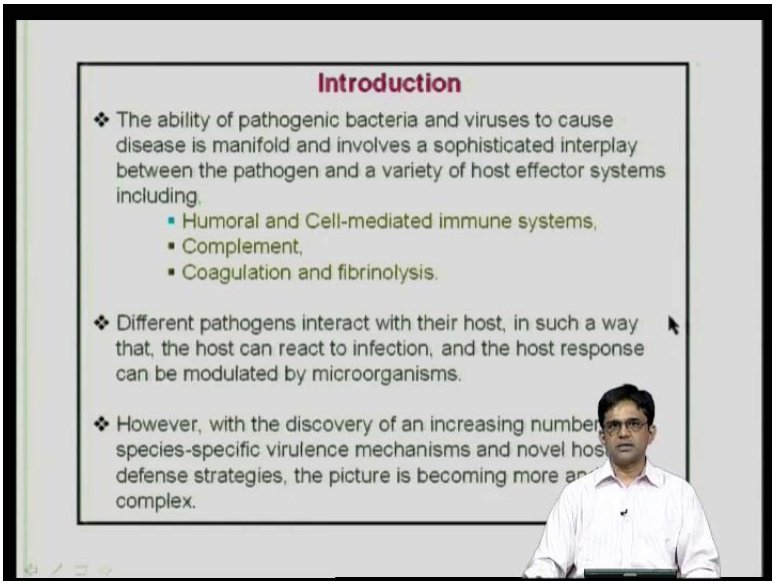

So before that, we will just discuss some general concepts. Now, what has been happening and I am sure you understand this. That you know the way a pathogen causes diseases, there are different types of it and this involves, you know different interpolates of both the pathogen and the host. So, what is happening is there is the constant fight between the pathogen and the host, and trying to see who will overcome you know each other. So, and there are different responses over here, one is you have the humoral and cell mediated immune response, which is something that I am sure you are all aware that several of the lectures have covered over here. Then, you have the complement system and you have also what is important is a coagulation and the fibrin and the clot formation. So, these are all important aspects of it.

Now, what is happening is over the years, we are trying, we are, we are able to understand better the different strategies, that microbes have used in order to severset, in order to subvert the host. Similarly, host mechanisms in that are involved in various responses during infection are also coming to light. So, that is what these lectures are therefore.

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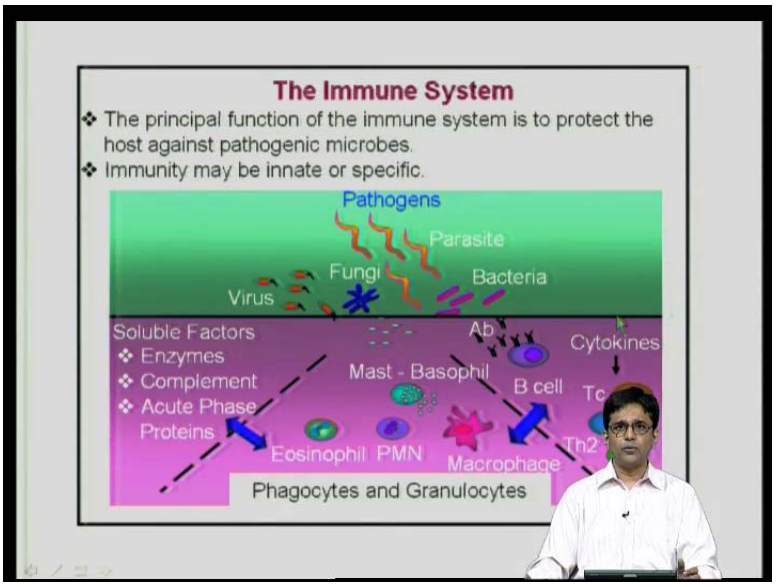

So, this one tells us about the different pathogens that are there, you have viruses, you have bacteria, you have fungi, you have parasite and so on. They are now in coming in touch with the host, and they are trying to see if some of these, if they would able to replicate and use host as a better means to replicate. So, in order to do that, they would

have to, in fact, they would have to grow within, find out mechanisms by which can they can infect the host, increase the cell numbers and disseminate their progeny. So, that is the most important aspect and the host, of course, you know cannot be quiet to this, and it will naturally respond. And these are something that you have talked about. You have different soluble factors. You have enzymes, a compliment, the acute phase proteins that made in the Liver and you have different kinds of cells that are important. You have the neutrophils, the eosinophil, the basophil, the macrophages, and then you also have the cells of the adaptive immune response which is your B cells and T cells, and where you have cytotoxic T cells, the different types of helper cells makes cytokines, and you know they try and get a better host response.

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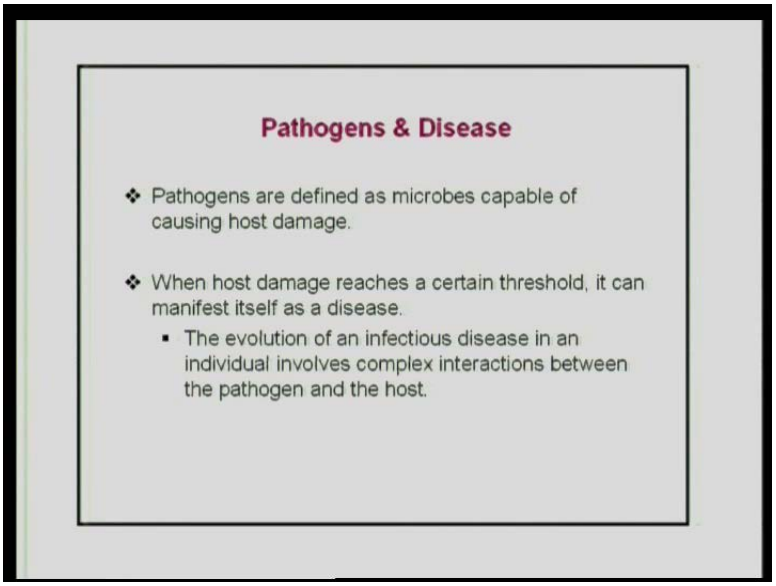

Now, pathogens are defined as microbes that are capable of causing host damage. When host damage is reached, you know it beyond a certain point, it manifest itself as a disease. And therefore, the evolution of an infectious disease in an individual is a complex interplay between the pathogen and the host.

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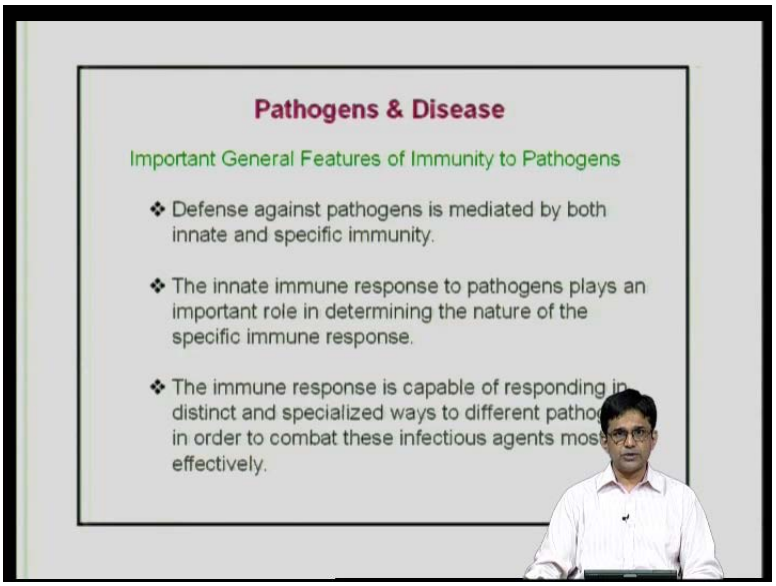

And what are the some of the important general features of immunity to pathogens? One is that the host response is mediated by both the innate and the adaptive for the specific immunity. The innate immune response plays an important role in determining the nature of the specific response because the initial response is really the key. So, if you have a good initial response and the innate system is able to manage it, then they respond, perhaps no need to you know get a adaptive response coming. However, often you know because of the replication time or the quick replication of pathogens, they are able to subvert this process and therefore, you need both innate and adaptive to come in and play. Adaptive is also important, not only generating specific response, but also in generating a memory response which may come into play years later after the first time the pathogen did the host. And there are of course, different distinct and specialized cells, as well as molecules, that are involved in this, and this is something that we will be discussing.

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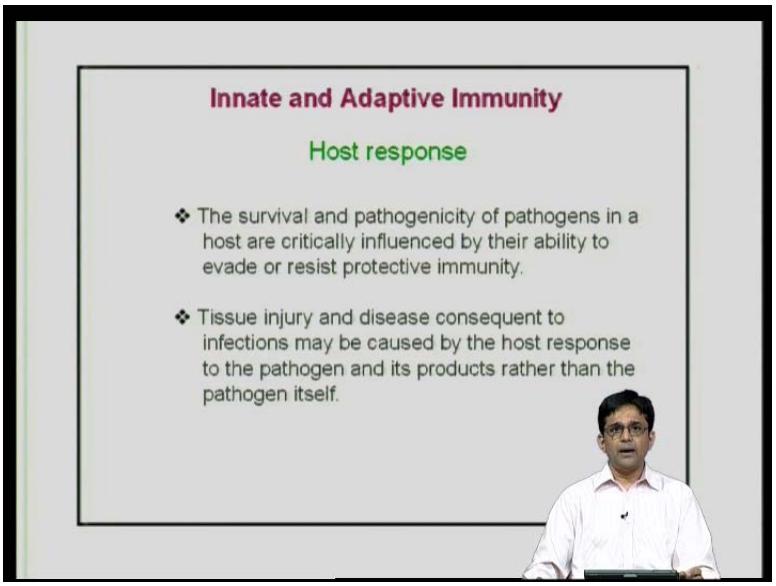

Now, the other important aspects is a, is a not only the host response important, but sometimes what happens is that the host response to a pathogen in such a way that it hurts itself. This is the very important aspect, and which is often not so well appreciated, because often the onus is put entirely on the pathogen, that the pathogen is causing response. But sometimes, you know there is pathogen infection. The host tries to take care of it, and sometimes it generates an exaggerated response, and this is which causes organ damage and hurts the host itself. So, upon infection host sometime respond, and the response sometimes is a little far greater than what is required, and it causes damage to the host itself.

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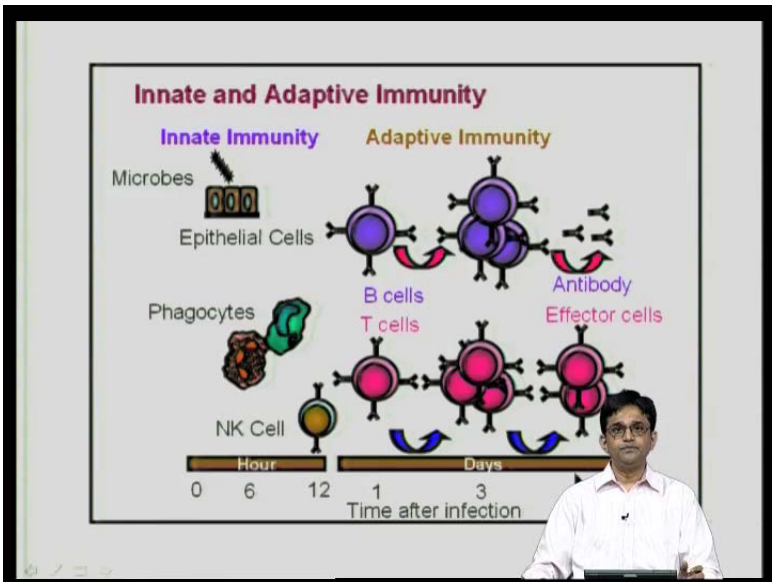

This is an important aspect, often you know in a crosses on a (()) is often result of that. So, this slide is sort of a tells us about the microbes and immune, some of the initial cells that come in contact with the epithelial cells, and some of the epithelial cells make antimicrobial peptides. Then, you have contact with phagocytes, the natural killer cells, and these happens early on, because they are part of the innate, immune response. Subsequently, and you can see that are days listed over here. You have specific responses, you have B cell and T cells, and then you have antibodies been produced. You have the effector T cell responses which produce cytokine, and which will respond against these pathogens.

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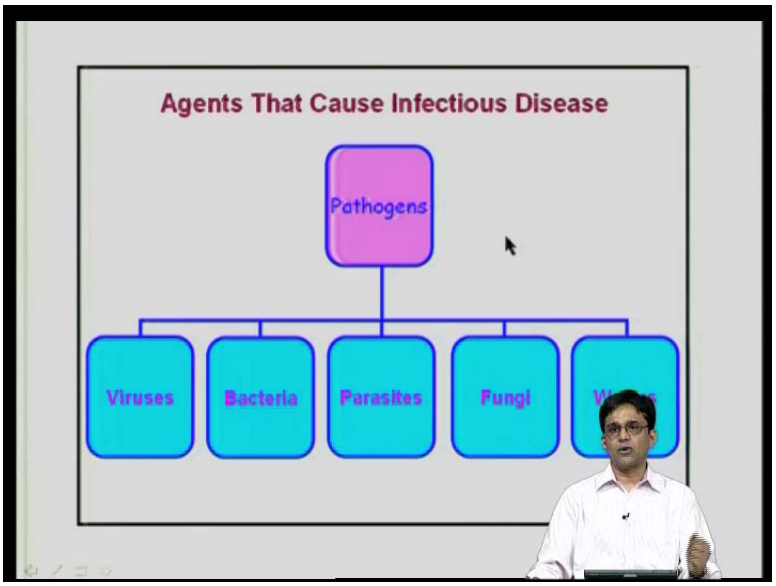

So, what are the different types of agents that cause infectious diseases? And this is something that I am sure you know, you are well versed with, you have viruses, you have bacteria, parasites, fungi, worms so on and so forth.

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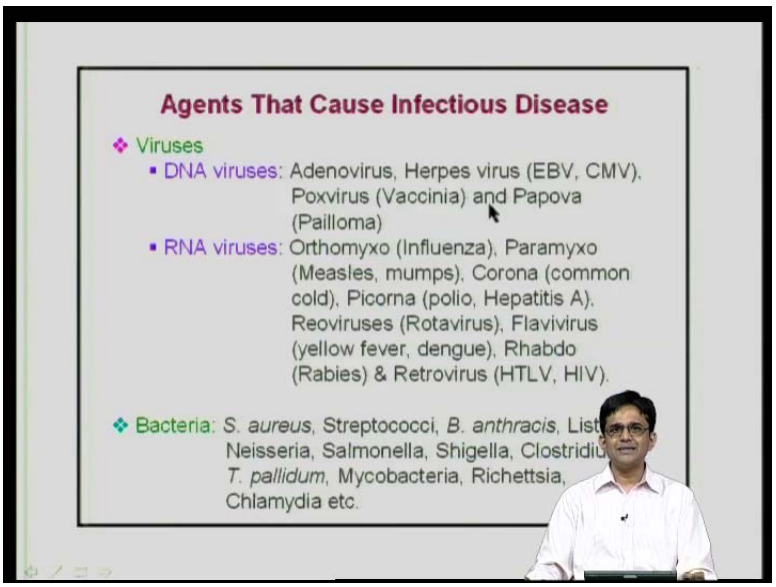

So, let us discuss little bit some of these. So, in the viruses there are two main kinds. You have the DNA viruses, the RNA viruses and some of the well known viruses, that I am sure you are sort of aware of are a you have the corona viruses which are responsible for your common cold. You have the flavi viruses which have responsible for dengue, then

Japanese encephalitis virus, then you have the retrovirus, the most famous of them being the HIV.

There are also several bacterial diseases that I am sure you are familiar with. You know treponema palladium, which is important for is in case of syphilis. Then, you have a salmonella tippy which is important in case of typhoid. It is a gram negative organism that causes typhoid which and is taken in by the gastro internal roll, and it disseminates from the gut into the different parts the body. And then, you have mycobacterial tuberculosis. Mycobacteria is taken up in terms of aureus, is ingested by the lung and it forms nodules or kinema in lung, and it generates equiped cell mediated host response.

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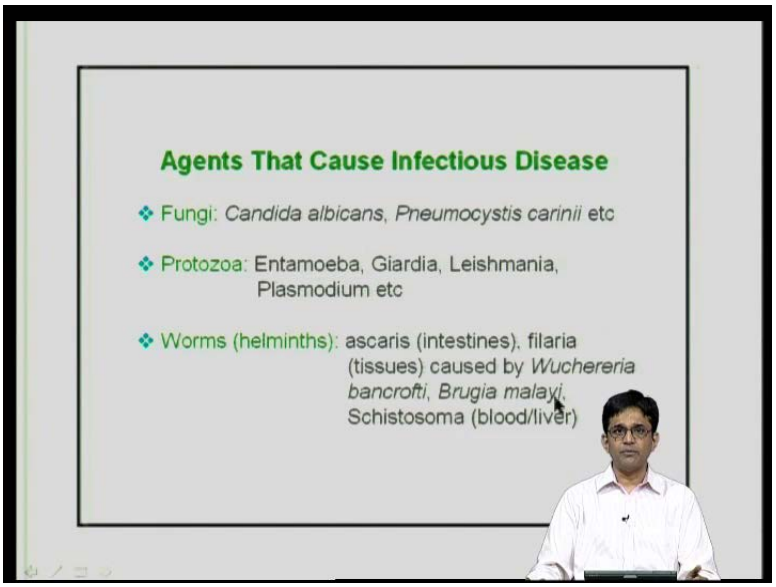

I am sure these are some, these are one sort of malayi. Then you have the fungi diseases. candida albicans is a primary response, often candida albicans, for examples often effects of this fungi diseases, often effects immune, suppress individuals or people where whose immunity has is a little bit lower for example, aged individual. Then, you have the protozoa, you have giardia, leishmania plasmodium, which plasberm so on which causes malaria and you have the worms, worm infections. You have filariasis which is often goes by the name of elephant foot and again, there again, you know it is host response that causes reaction to these worms.

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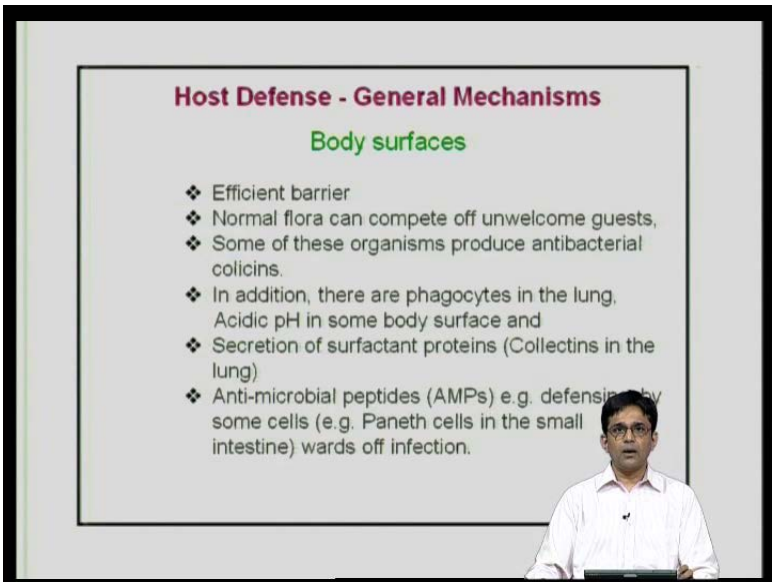

In general, in terms of host responses, the first barrier that the pathogen has to deal with is the body surfaces, and over here you have a nature barrier, plus our body has lot of commensals. And so, therefore, this pathogen has to compete with the commensals that are already present in there in order to get an infection going. And also some of these, some of the bacteria that are present in gut flora or in our body surfaces, these produce antibacterial colicins which you know, which would target other bacteria.

Now, in case for the lung for example, you have phagocytes in the lung, and you know and there is the acidic pH on some of our body surfaces. So, these would certainly hurt the organisms that plan on trying to pathogenesis the host. Then, there are other mechanisms for example, our T s contain lysozyme which specifically target cell valve of bacteria. Then, you have also secretion of surfactant proteins, for example, collectins in the lung and these are surfactant. So, they would sort of you know, they would act as soap and so, they would sort of dissolve the cell valve and membrane of different pathogens.

One important strategy of course, is, the production of anti microbial peptide. In fact, the production of anti microbial peptide is a very important aspect and this is often done by cells known as paneth cells in the small intestine. And you have a lot of cells in there, lot of microbes in there, and anti microbial peptide is a very important part of that mechanism.

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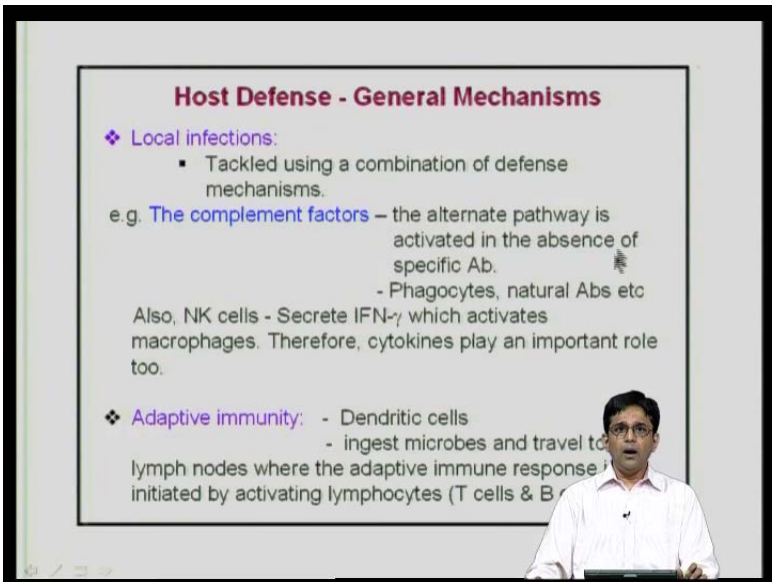

Then, the other ones are the ones that you know, you have sort of heard, and have been discussing these lectures. The complement for example, is a very important. Now over here you can have specific immunity. In some cases, the alternate pathway of complement is activated in the absence of specific antibody, because some of the microbial molecules that are present on microbes surfaces activate or turn on the alternate pathway, and so that would result in activation the complement and lyses of this. You also have natural killer cells they secrete important cytokines like in different gamma which activates macrophages and again, this is important. Then, you have the adaptive immunity which of course, would be looking little bit later. You have dendritic cells, these would ingest these microbes travel to lymph nodes where it would initiate specific immune responses B, and as well as T cell immune responses against these invading pathogens.

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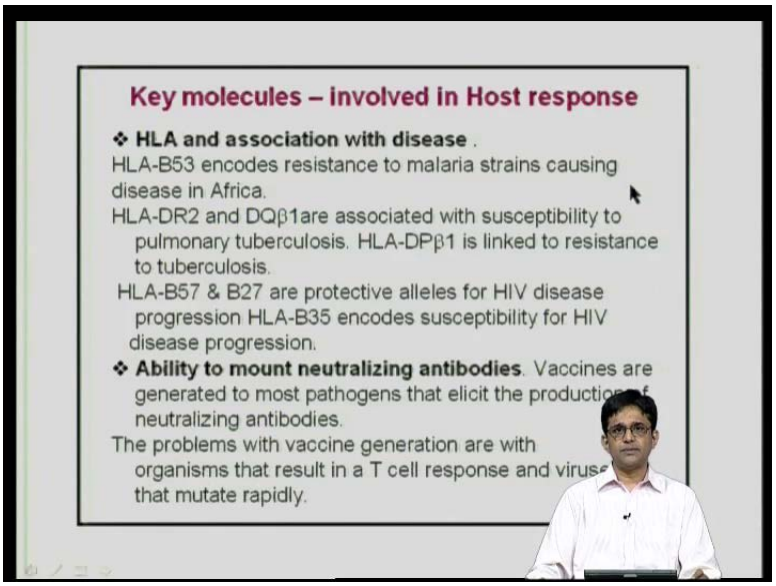

What are some of the key molecules that are involved in the host response? One of the first ones is MHC and M H C has been very well discussed. But certainly you know MHC is very important, because what they do is the present peptide or pathogen specific peptides onto your T cells. And so, they have been association of between diseases and that particular M H C. So, for example, this particular allele HLA- B 53 encodes resistance to malaria strains in Africa. Then, you have the HLA- DR2 and DQbeta 1 which is associated with the pulmonary tuberculosis. In case of HIV, again HLA- B57 and B27 are protective alleles whereas, B35 encodes susceptibility for HIV disease progression.

So, these are cause and effect relationship that have been studied. You know especially in populations where they look at cohorts and they find which population or which individuals are susceptible or resistant and can there be a correlation with the MHC. Perhaps, one of the most important features of the ability to get rid of pathogens is the ability of the host generate neutralizing antibodies. This is the most fundamental feature. In fact, the vaccines that, we have today are once that elicit, good robust neutralizing antibody.

What do you mean by neutralizing? That means the antibodies that are produced they neutralize the microbes. That means, they neutralize the bioactivity and actions, so that, these microbes are no longer able to replicate. So, the antibodies can be against particular

toxins or they can be against whole viruses. For example, small poxes are good example. So, the ability of small pox vaccine to eradicate small pox is because it induced potent neutralizing antibodies, as such that the small pox could not recover, and has not been able to come back because this small pox vaccine strategy had been so successful. So, one of the big goals of having a good vaccine is or one of the aims is that it elicits good neutralizing antibodies. This runs into problems of course with organisms that generate a T cell response and not that much B cell response. So, HIV for example, one of the big problems has been is to generate good and sustained anti HIV neutralizing antibody virus. And especially when organism is small and multiplies rapidly, then it becomes a problem, because it often fool proof the host. Because you can generate a particular antibody response, but by the time is generated the organism has changed and muted into a different form. So, then of course, it becomes problem. But overall, one of the big success of vaccines have been or the once that have been successful are the once that have been able to elicit good robust, neutralizing antibody response.

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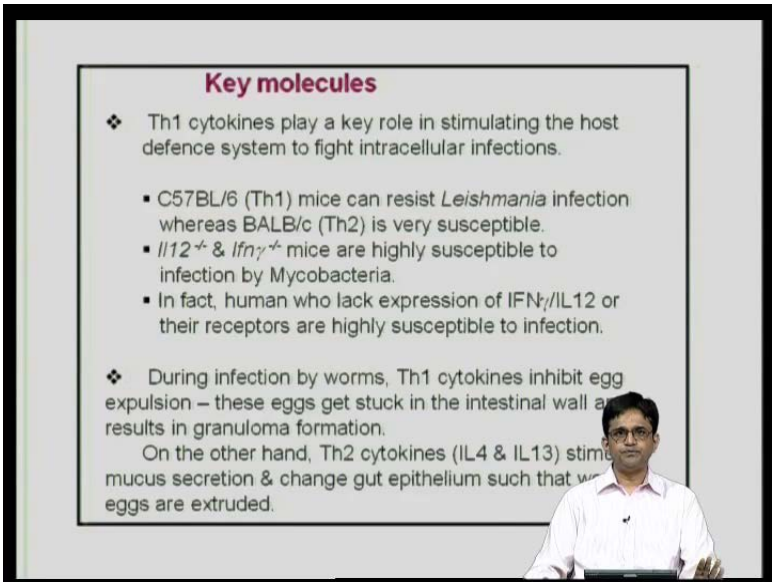

The other factors that are involved are the cytokines or the cytokines patterns. So for example TH1, TH2 responses. So, in case of leishmania infections for example, black six C57 black 6 which is primarily TH1 producing and produces high amount of T H 1 cytokines and are able to resist leishmania whereas, blab C are more susceptible because it tend to be T H 2.

Now, ability to produce certain inflammatory cytokines are also important because into Il12 mice that lacks Il12 or that do not produce interferon gamma are highly susceptible to infection with mycobacteria. So, it tells us the importance about Il 12 and interferon gamma in determinacy in susceptibility to mycobacterial infections. And this is not only true in mice, it also true in humans because those who lack expression of these are highly susceptible to infection, and we will be discussing this little bit, even when you come to vaccine. Because if you give a live vaccine to patients who lack these molecules, they come down with disease. So, that is again a problem, but it tells you about important rolls of interferon gamma I l12 in determining susceptibility.

Now, this TH1, TH2 profile as has been discussed in previous class has other important affects also. So, for example, when we have worm infection for example, the worm produces eggs so that they can disseminate. So, it goes on in the fesses and so it disseminate. Now what TH1 cytokines do is that they inhibit egg expulsion. So, they form granulomas over here which causes you know more hosted related problems and eggs get started and they result in granuloma formation. It causes problem. The TH2 on the other hand, if the host is more TH2 type, then they would they would stimulate mucus secretion they would be change in gut epithelium, so that the eggs would be extruded. So, would not you know realize that this person has a major problem because you know the eggs are extruded, the host responses is somewhat different. So, what this is telling us that the type of cytokines that are produced are important in determining what is the response to these different organisms. And the worms are the very good example of this.

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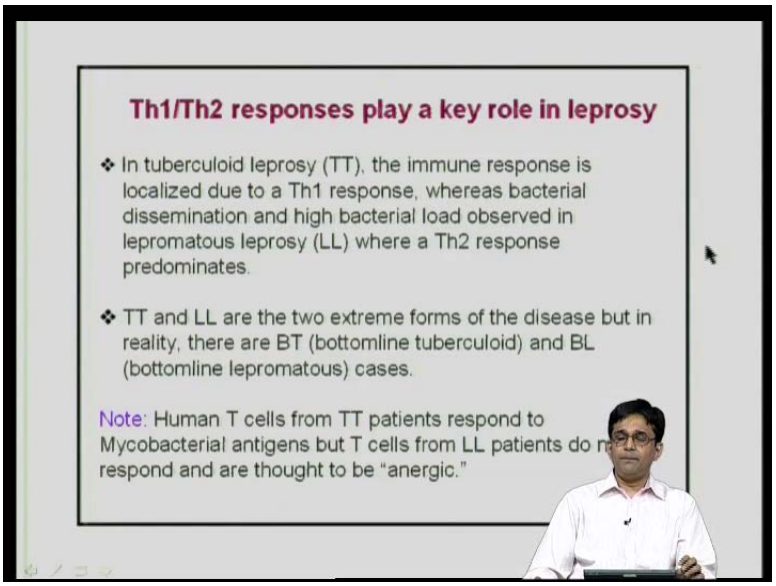

The other place where you see very small differences between TH1 and TH2 responses are in case of leprosy. So, in case of leprosy there are two ends of the pool. One is the tuberculoid form where the immune response is primarily TH1, and the diseases contain in terms of tuberculoid and the other lepromatous form the disease disseminated. Now, what has been seen is that patients who are primarily in tuberculoid form are shown T H 1 response, where as those who are show a lepromatous form are mainly TH2.

Now, this of course, TT and LL that are discussed are two extreme forms of the disease. But you know usually they are the once are in between. So, you have bottom line tuberculoid, and bottom line lepromatous, and this these are in between cases. So, you probably have a mix. But at the two ends are the polar once, where you have the TH1 TH2 and that have been shown very nicely in several studies.

Now, human T cells from TT patients in fact, respond to micro bacterial antigen the T cells from the lepromatous once are thought to be energy. And so the human T cells are able to respond, and generate this T H 1 and whereas, the once from the lepromatous LL once are not good, in fact, thought are poor responders to these antigens.

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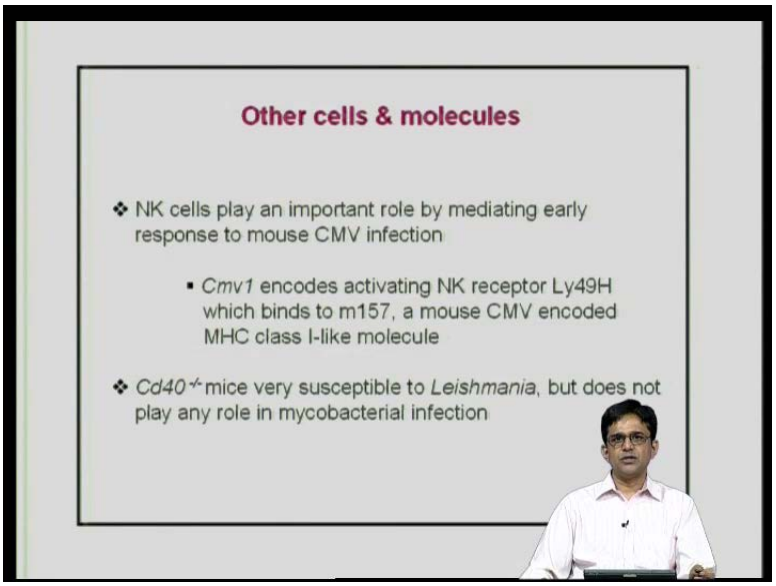

The other cells that play an important role are natural killer cells and here, natural killer cells are important because in some cases they are important in response to viral infections, and this came out when with the discovery of Cmv1. Cmv1 was a locus which was encoding resistance to particular virus, and people were not clear as to what the mechanisms work. Subsequent study showed, the Cmv1 encodes NK receptor, or is activating NK type of receptor Ly49 H which binds to CMV or mouse cytomegalic virus, virus and it generates a some sort of response. So, what this showed was that inter relationship of in cases NK receptors of host encoded NK receptors in determining susceptibility to viral infections.

Now, all molecules are not the same. Some molecules can have some sort of role in some diseases, but not the other and that is shown in case of Cd40. Cd40 mice are higher, are very susceptible to leishmania which means Cd40 plays an important role in determining resistance to leishmania. But there does not seem to be any role with micro victim, perhaps there are other molecules that are important and play a role in this case.

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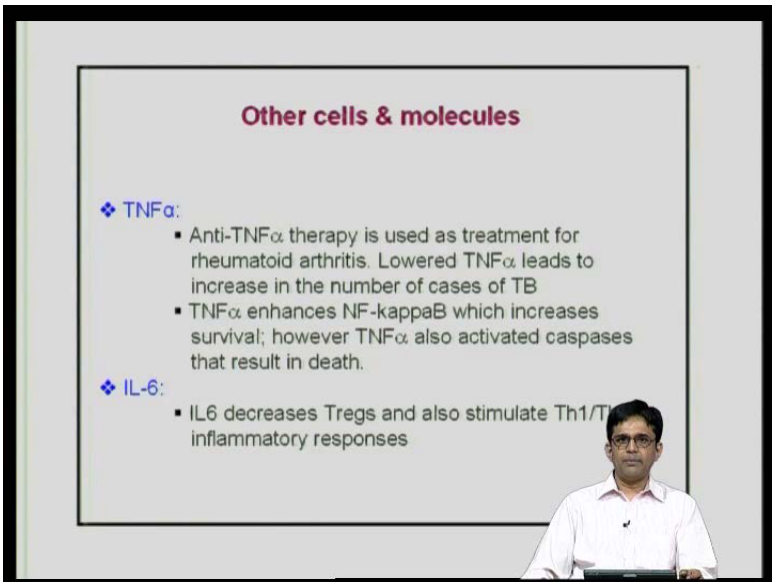

Now, TNF alpha is tumor necrosis factor, alpha is clearly an important player in immune responses, and what has been shown in case of rheumatoid arthritis is that you is anti TNF treatment is given and what anti T N F treatment does is ameliorate the disease symptoms of this auto immune disease. Now ever since anti TNF treatment has been going on in the clinic, what people have found is that, with rise in the use of anti TNF, there is concomitant rise in the case of TB. So, it clearly shows the role of TNF alpha in determining resistance to micro bacterial diseases. So, previously, so the moment anti TNF was given, it helps you against rheumatoid arthritis. But what it also does is that it makes most of susceptible TB. So, you know if you are, if you have been exposing and in previous cases you had NF key an alpha that was sort of taking care of this. Now the absence of that now there is the cases of susceptibility rises and you have more cases coming on TB.

Now, also T N F alpha, tumor necrosis factors is it enhances necrosis. It enhances N F kappa B which increases it also activates caspases and results in death. It also plays some sort of role in terms of organ damage. Now inter look in six is other cytokine which is an important and what has been shown is and this part was covered in, when we discussed that you T rag part or regulatory T cell, with the role of regulatory T cells is to suppress immune responses. Now, if immune response are constantly suppressed how do you generate immune response and pathogen comes in. So, once pathogen comes in, one of the way it does through the T l r is of regulate production of IL6.

Now, what IL6 will do is that it reduces the activity of the T regs. So, the T regs function is suppressed and you have more antipathogen response that can be initiated. So, clearly IL 6 plays an important role in this especially initiating the TH1 and the T H17, T H mediated responses.

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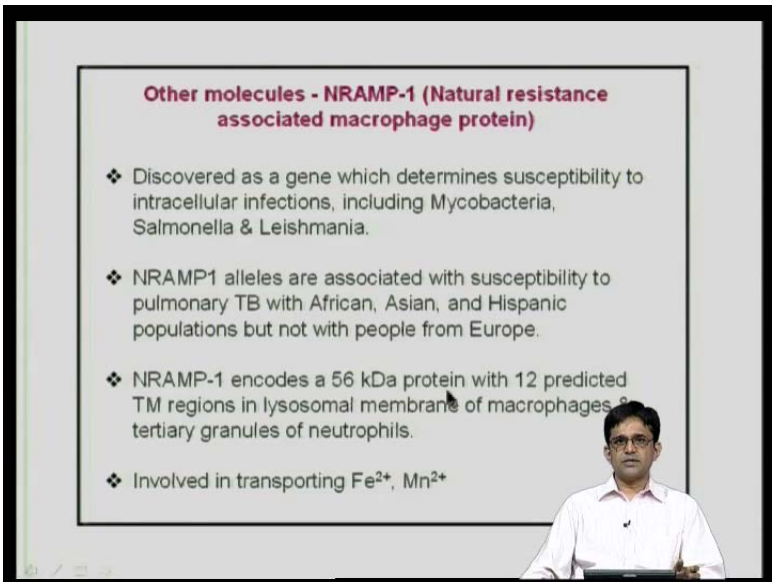

Ok, one important molecule which is important in terms of which plays important roles in infection diseases is nramp, especially intracellular bacterial diseases against salmonella, against mycobacterium and what was found is and let me just give a little bit of a story. When a new world was discovered, new world being the Americas, you had the European population that went in, and to and was taking over land and the people. Now endogenous people which is the American Indians, they were not exposed to these that the diseases that the Europeans also brought along with them, especially micro bacterial diseases. And you know large populations of them succumbed to these infections and it was, it was really in fact, a tragic scenario, because you know you had several people who had never been exposed to this. So, their host they had zero host immunity against and they succumbed greatly.

Now, during this process what people try to find is, what are some genes that are involved in coding resistance. And using the similar studies, people came up both in human as well as in mice on molecule known as NRAMP, and so that is the name of this. NRAMP is a natural resistance associated macrophage protein, and it determines

susceptibility to intracellular infections as mentioned. So, what NRAMP is? It associates with the intracellular, it is present intracellularly, and it is important in transporting metal ions, especially ion maganese and so on. So, it's about a 56 kDa protein, and it's called a transfer rate, the predicted 12 transform rate predicted regions and associates with lysosomal membrane.

Remember, these parts are important because often intracellular bacteria, they harbor in certain vesicles, which these vesicles are similar to lysosomal, but they actually do not fuse with lysosomal, because when the fuse, then the bacteria would be ingested. So, they are similar and so, it is interesting that NRAMP is found in these sort of vesicles.

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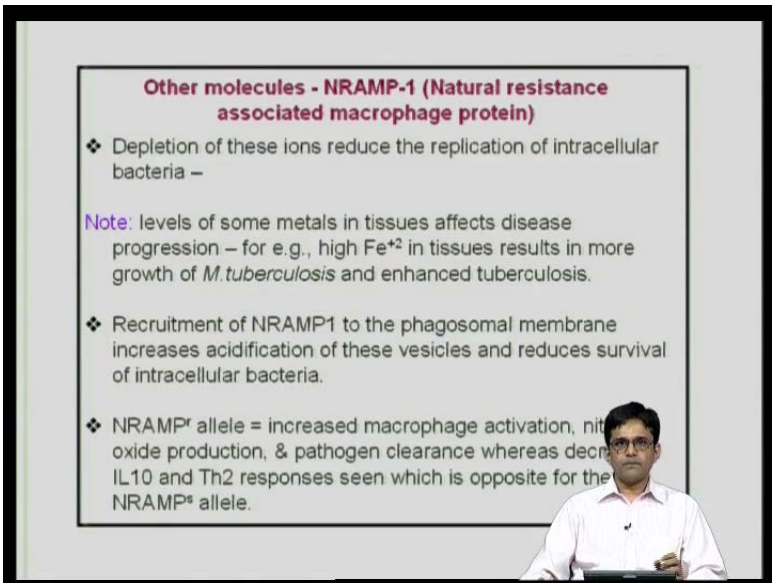

Now, why are these ions are like iron and manganese important in terms of intracellular application. So, it turns out that for bacterial replication they need design. So, for example, in case of m tuberculosis if the more ions you give, the more bacterial growth, because its ion is required for for for replication, and there are different forms of NRAMP. So, you have different alleles of NRAMP. So, you have NRAMP R allele which is resistance allele and this increases macrophage activation, nitric oxide production and pathogen clearance. Whereas, you have the NRAMP susceptible allele which is opposite and so it induces primarily TH2 responses which sort of suppress this. So, clearly NRAMP plays an important role, because especially depending on the allele that is there it is important in determining susceptibility to infection diseases

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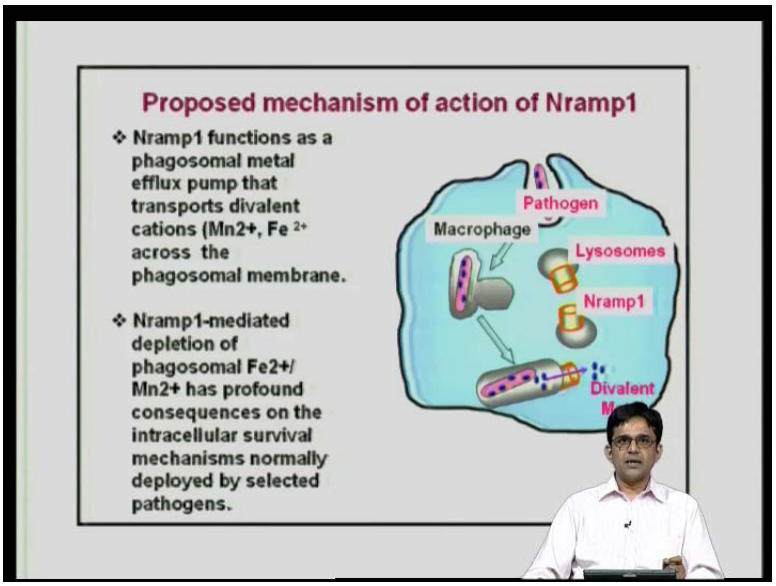

And that is what is sort of shown over here, you have pathogens over here, and that is what I was saying that the pathogens try and hide away from the lysosomes, and NRAMP is there, and NRAMP is probably important and transporting this ions, and in determining susceptibility.

So, if you have NRAMP R, then you have a heightened post production against the pathogen, whereas, if your NRAMP S, so you know the pathogen has a better chance or better ability to grow and replicate in within the host. So, very important and NRAMP is the very nice study in this case. And therefore, it is therefore important for students to understand the role of NRAMP in determining susceptibility to intracellular pathogens.

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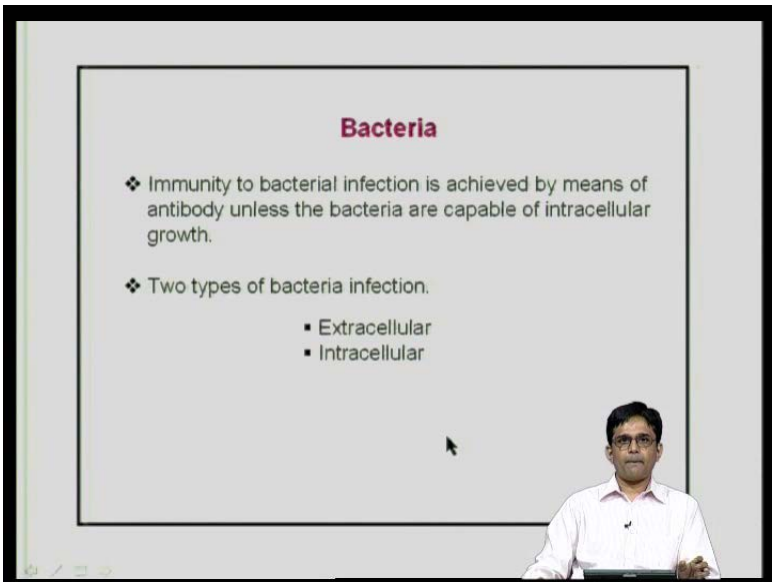

So, we will now discuss some aspects in terms of bacteria. So, immunity to bacteria is there is often you know due to antibody production, and this is true especially in case of extracellular bacteria. In case of intracellular bacteria, it gets a little complicated because bacteria is residing within a cell, and within a cell how do you get rid of that is much more complicated than extracellular bacteria which is you know in essence most straight forward in that sense. So, if a high generate a good antibody response to it, you should be able to manage it.

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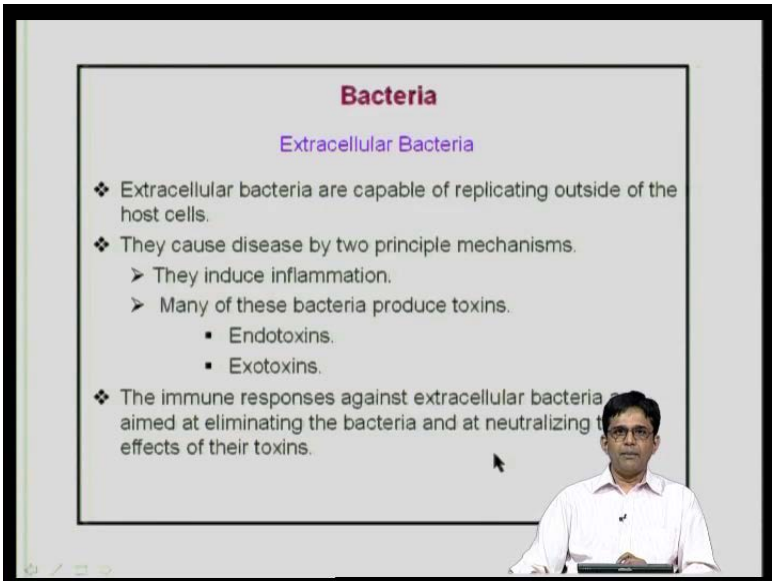

So, extracellular bacteria are called extracellular because they replicate outside of the host cells, and they induce a disease by different mechanisms. One of which is they generate inflammation, it produce toxins, the Endotoxins. Exotoxins are again, Endotoxins are associated within themselves, Exotoxins are release outside. And so again a good way to deal with these Exotoxins bacteria is to generate neutralizing antibody as well as mentioned.

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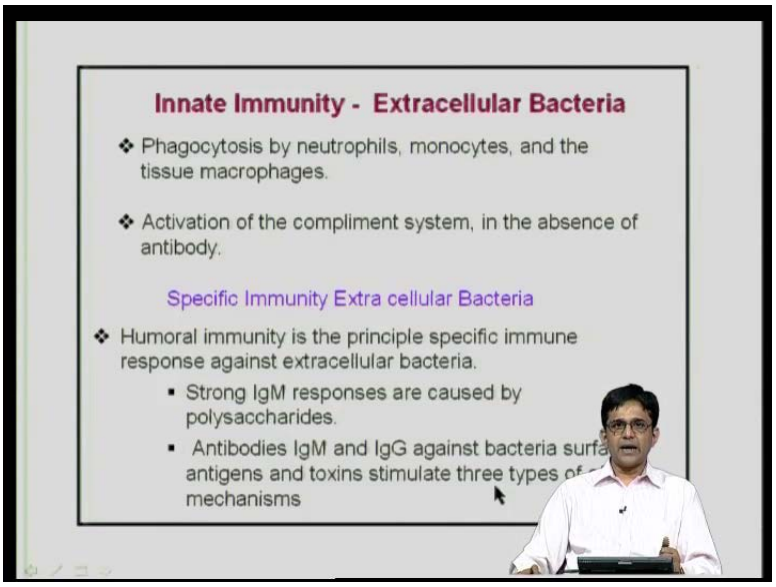

Now one of the apart from the neutralizing antibody response which will take some time you have phagocytosis by neutrophils monocytes, and tissue macrophages which would be part of the innate response and which will take care of that.

Now, the activation of the compliment system is again important. Now, the humoral immune response which is we said the antibody mediated response of the neutralizing antibody response was an important one. What has been seen is that, the strong IgM response caused by polysaccharides, and then antibodies IgM and IgG, these stimulate different types of mechanisms by which these antibodies are generated, and they play an important role.

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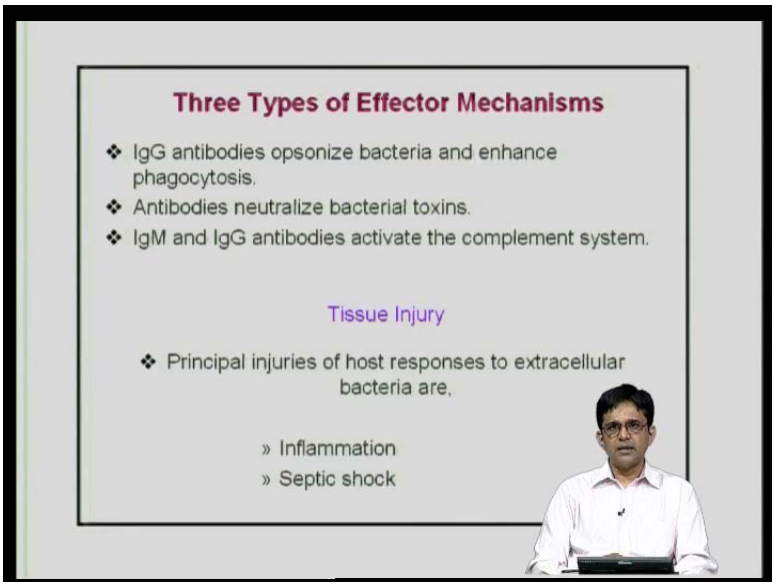

Now, there are different types of effectors mechanisms. The IgG antibodies opsonize bacteria. So, these would bind to bacteria. They would opsonize it and would enhance phagocytosis. So, macrophages and nuetrople there would be able to ingest this much better. Antibodies may neutralize bacterial toxins that would be most straight forward way, and IgM and IgG can activate the compliment system.

Now, one of the host responses of bacteria are again if you have too much of it, it results in information septic shock. This again septic shock was something that was discussed in great detail, in my class on innate immunity, and I would urge students to look that, because that is really an important part. Because especially in hospital infections, you know a large majority of hospital cases were, you go in with the particular case history, but you know you have some disease that is often due to septic shock. Often also hospital cases are associated with infections, with the drug resistance with bacteria. So, septic shock is something that is important, student need to look this up and this, and I will not discuss it over here, because it been discussed in the class on innate immunity.

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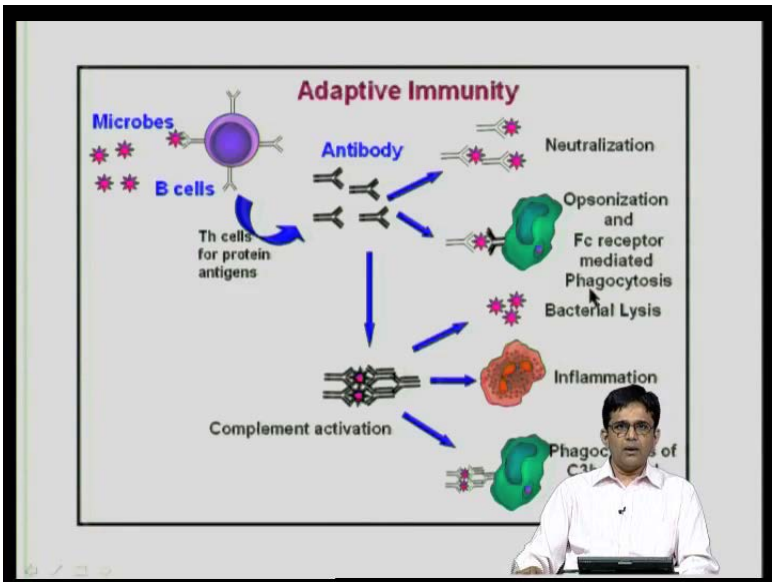

So, this sort of gives us a little bit of view. You have microbes and you have B cells and antibody response. You have, and you have neutralizing neutralization of your toxins of the microbial toxins opsonization, and FC mediated phagocytosis. So, the sort of taken up, you have the bacterial lysis because activation of the complement system, you have inflammation and then, phagocytosis of complemented coded bacteria.

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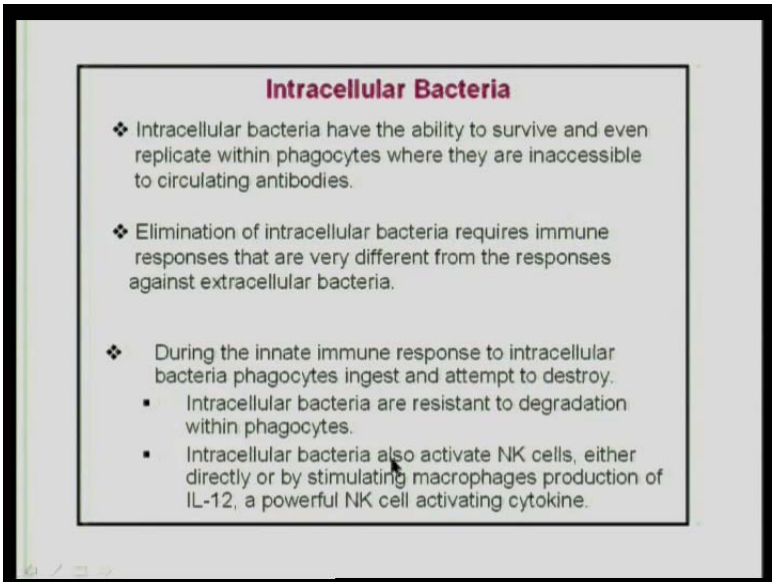

Now, as previously mentioned intracellular bacteria is a little bit more problematic. Primarily, because they have the ability to survive and replicate within phagocytes,

where they are inaccessible to circulating antibodies, so, this is a little bit of problem. And so elimination of intracellular bacteria requires immune response, that are very different from that for accessible bacteria, because in that sense accessible bacteria are most straight forward.

So, what has been seen, are intracellular bacteria they grow within phagocytes, and so they are able to resist lysis, within the phagocytic machinery which is what I said. They do not fuse with lysosomes, they stay alive and replicate vesicles other than that these are also activate. So, IL 12 for example, they activate natural killer cells. The natural killer cells can stimulate by production of the cytokines and flu like for example, IL12.

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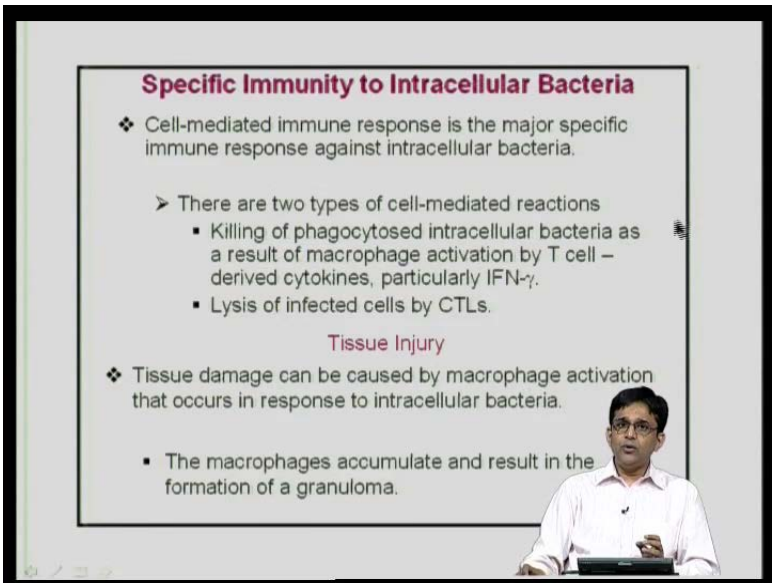

Now, the way to get rid of a intracellular bacteria, there are two main types. One is you have production of cytokines, like interferon gamma which would activate the macrophages or phagocytes. And they would then the heightened activation would result in increased production of reactive oxygen, and at the mediate increased production of cytokines, and that would sort of take care of the bacteria. The other way is to have lyses of infected cells with cytotoxic T lymphocyte. So, in which case, you would generate T cell response and its part of the T cell response would take care of these bacteria.

In often in infection intracellular bacteria, you have tissue damage, and the macrophages you know often accumulate over here, because they are trying to contain the disease and

this results in granuloma formation. This is something, which we will study a little bit in greater detail when we discuss macro tuberculosis infections.

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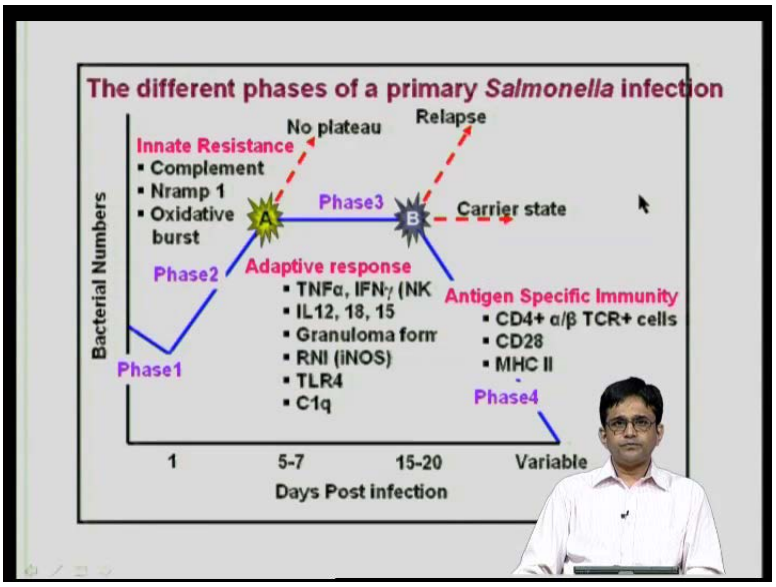

Ok, so, let me just briefly discuss one intracellular mycobacterium infection before we go on to mycobacterium tuberculosis. Now, this is the case of salmonella. In case of salmonella typhae, salmonella typhae is gram negative bacteria, which is ingested by through the oral route and so it enters the gastrointestinal system and from there it is disseminated systematically to the body. That means, from the intestines, the bacteria enter the body through the intestines. So, they are able to colonize through the intestine route and what it results in. It results in fever, it results in a manifestation known as typhoid. So, what are the host responses over here, and this slide sort of tells you about the different phases in case of salmonella infection.

So, you have, this is initial phase and then you have the phase two which is the peak phase, and then by phase three they have sort of you know, they have been contained that cause a host as sort of taken charge, and as contained. Now once it iss come here, they can be a relapse enter into carrier state, or you have the antigen specific immunity coming down, as a result of which it comes down. So, that is what shown over here.

So, in fact, as it has been shown as phase three, but in case, sometimes it can even go up. If the response in the host is not good, but what are the host response and in again it shown kinetically. So, you can see them. So, the first response is obviously, the innate

resistance. So, you have NRAMP which is important, oxidative burst complement sort of which are important in the first phase. Then, you have the adaptive responses, and here you have the interferon gamma IL12 granuloma formation, the production of nitrogen intermediate, the complement so on.

Then subsequently at later point you have antigen specific immunity. So, for example, you have the C d, you have the T cell response, you have the C d 28 which is the co stimulatory receptor class 2 response and so, that is what is shown over here. So, you can see the initial one is the innate and the later one is the antigen specific response, and right over here, you have sort of adoptive form way. You have interferon gamma, the T L R and the complement that sort of play an important role over here.

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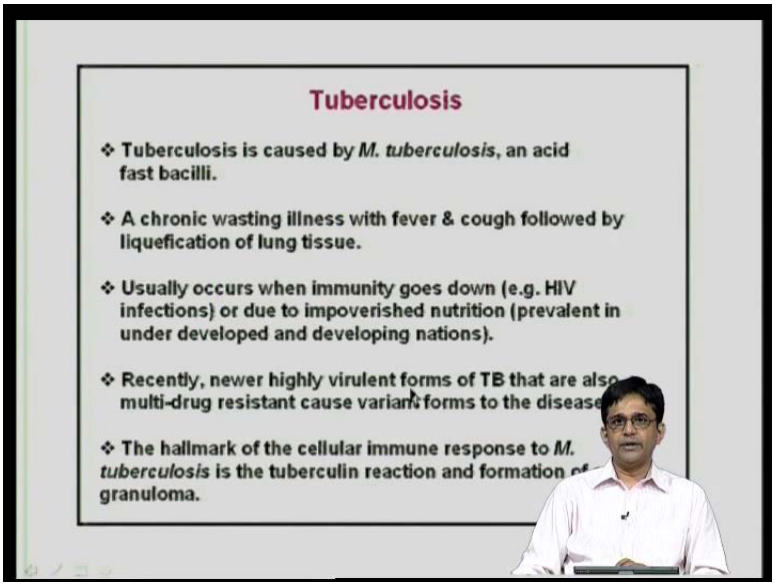

But in terms of bacterial diseases, the one that we will be studying in certain greater detail is tuberculosis. Now tuberculosis as you are well aware is caused by micro victim tuberculosis is an acid fast bacilli. What do you mean by acid fast bacilli? So, an acid fast one that is resistant to counter staining with acid alcohol, and why is it resistant to count staining, is because the mycolic acid that is present gives this ability. Most of the bacteria are very, can be easily decolorized and stain with the counter counter stain, but not micro bacteria, and that is because of its mycolic cell valve nature, and hence it is called an acid fast. So, students who are not aware it of it, should look up and try and understand this

acid fast staining procedure which is an important. So, it is a wasting illness, it is with fever, cough and you know, the lung, tissue gets affected.

In the older days what people would do is to ask people with TB to go to a hill station, and lead, you know a calm and stressful, stress free lives. You know try and recover from the disease, because I think stress does not help host response. In fact, it hurts it. So, may be a calmer lifestyle helps the host in sort of recovering from back from TB. Now T B also occurs when immunity goes down. So, for again with increase in the HIV cases, you know what has been found. One of the common manifestation has been, have been TB, usually even once that do not cause these problems are under normal circumstances, when host is just about is ok and there is if host immunity is lower, then you have these cases that show up.

One of the problems in recent times has been that there are virulent forms of newer virulent forms of TB. So, for example, micro victim tuberculosis strain w, which cause various forms to the disease, and the organism has also changed over, and I mean, so it can form the traditional form of TB, but it also infects other organs, it has trying to it, has newer manifestation of the disease.

So, tuberculosis is a, is disease that one has to be very careful and about. Now one of the… that there are two main hallmarks about TB. One is the tuberculin reaction which is something we will discuss, and second is formation of granuloma.

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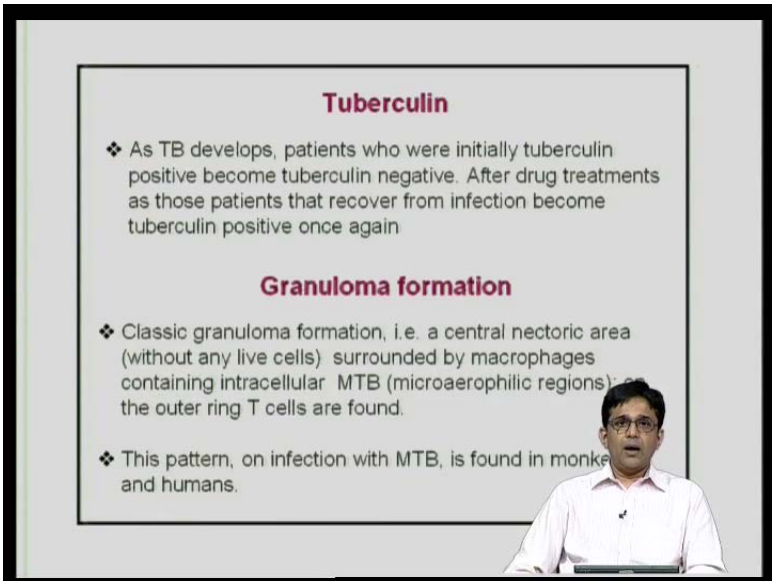

Now, in case of tuberculin, now tuberculin is actually the secreted antigens secreted protein of m tuberculosis. So, if these are injected within are, within the skin, then you the host there is very quick response by the host against it, because it what you are doing is generating a delay type hyper sensible response, and this can be measured, and this is known as tuberculin reaction. So, those people who have been exposed to tuberculosis often generate a good tuberculin reaction, and what is interesting is seen that, people who were tuberculin positive initially, subsequently develop TB they become tuberculin negative. They become tuberculin negative, because their host immunity has gone down and the bacteria has sort of over sort of won with. Once antibiotics are given or anti tubercular treatment is given the dots and so on, and as there immunity against TB increases, you see the tuberculin reaction coming back order.

So, it is a very very interesting scenario, and it is something that the student should be aware of. Tuberculin is a very important aspect of study here. The other is granuloma formation. Now what is granuloma? So, you see the organism infects if primarily in the lungs and there it forms the granuloma. So, what granuloma is because the host is trying to contain the disease. What it does? It forms initially macrophages, try an ingested the macrophage area is often surrounded by T cells. So, right in the middle we have a necrotic patch and this is because you have dead bacteria, dead cells over here. So, following the central necrotic patch around surrounding once of the macrophages which are secreting interferon gamma, and try to contain these disease and on the outer ring, you have your lymphocyte over here. So, the granuloma is particularly interesting and it can be seen very clearly and so, this is clearly seen in case of monkeys and in humans.

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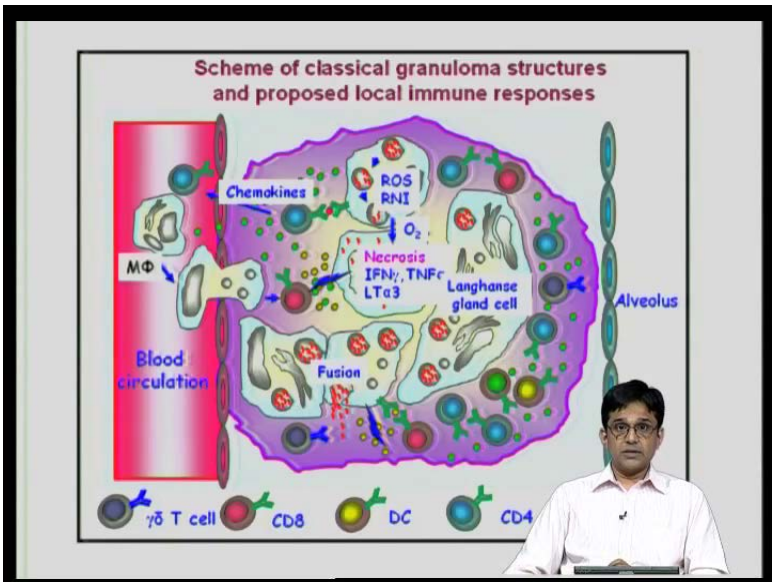

And so, this sort of figure is to give you an example of that. So, this is the central necrotic part, where you see a lot of necrosis and clearing, and have the macrophages and cells around over here. And then you have the lymphocytes, which I have shown over here, at the outer periphery are the once where the lymphocytes are, and especially your T cells which are sort of responding to the gamma, and they are also trying to fill the macrophages and the T cells from this, and that give rise to what is the granuloma formation.

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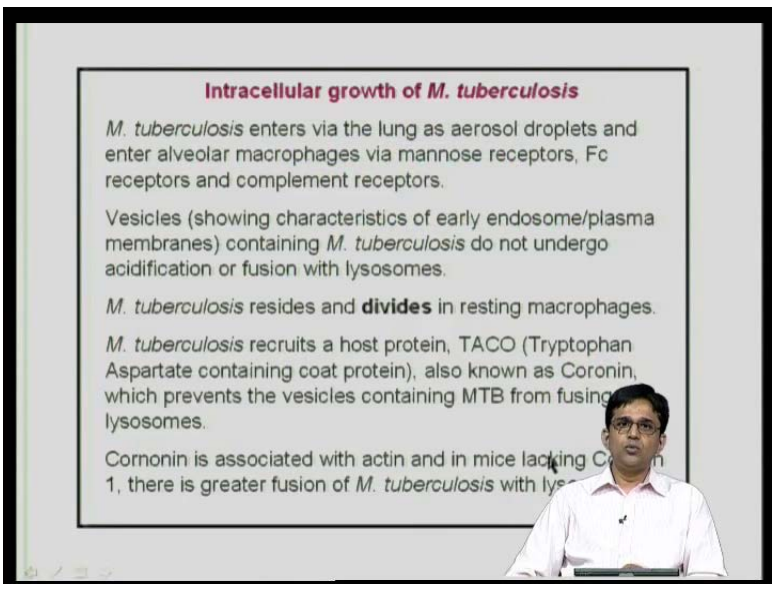

Now, in terms of intracellular growth of M tuberculosis as was mentioned M. tuberculosis enters via the lung and terms of aerosol sort of inhale it and so, they enter alveolar macrophages via mannose receptors F C receptors complement receptors. So, they that is how it enters. Now what is shown is the vesicles they they they stay with vesicles and these vesicles do not fuse with lysosomes. So, in case if they were to fuse then, the M. tuberculosis would be sort of digested by lisosomal enzymes.

However, so it is in interest on the bacteria on M. tuberculosis over here not to fuse with lysosomes. So, M tuberculosis resides and divides in resting macrophages not in activated macrophages, but in resting macrophages. Now, how does it do that? What it does is M tuberculosis recruits a host protein known as coronin, previously it was known as taco tryptophan aspartate containing coat protein, and which prevents these vesicles from containing MTB from fusing. So, what micro bacteria has done is it has become very smart. So, it recruits host protein. So, that you know and which enables it not to fuse with lysosomes and that again is very much in interest of the bacteria. Now coronin is associated with actin, and in mice lacking coronin there is a greater fusion of M tuberculosis with lysosomes, and which is an important part and which makes them important part. So, this is the very interesting now I talked about, you know m tuberculosis and different host responses. One was the n ramp. You know n ramp is important in determining host susceptibility, different intracellular infection, coronin is very important one, because in terms of determining you know in the way the bacteria has got hold of host protein, and try to figure out of how to escape this fusion.

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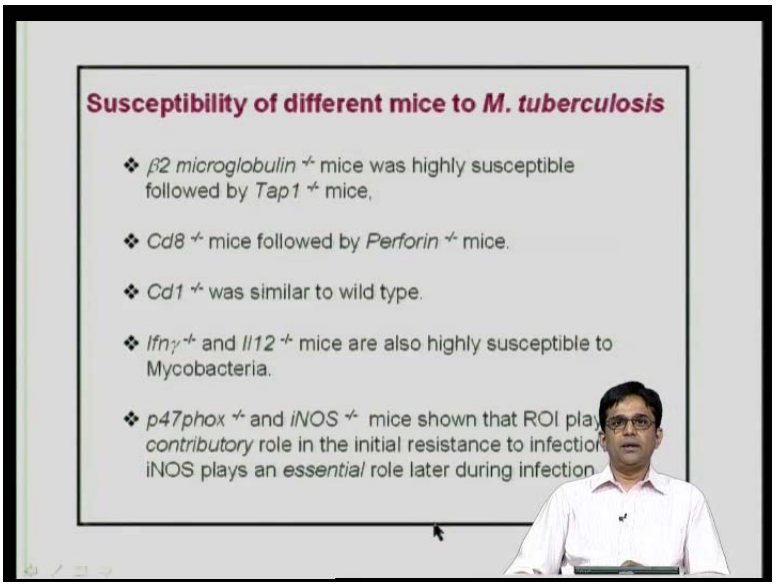

Now, what about some other host responses? Now what has been and this is something that has been discussed previously is the interferon gamma and IL12 are important in determining susceptibility micro bacteria. This we have covered previously, and because these molecules are important, in that sense. Now, we also talked about the p47 phlox which is a component of the nadpH oxidize and NOS2 which is an important and production of nitric oxide syntheses which will results in production of nitric oxide. So, what has been shown is that reactive oxygen into be this play and contributory role, but NOS2 plays and essential role in the later part of the infection.

Now, some years back a very interesting experiment was done. Different knockout mice were tested for the ability to check for susceptibility to micro bacteria. What was shown is the beta 2 knockout mice are highly susceptible, followed by the tap 1 knock out. Now beta 2 macroglobulin as you will, as you can understand is a component of the M H C class 1. It is important in that sense and tap 1 is transport associated. So, both these two were highly susceptible telling which tells us that better to macroglobulin tap 1 play a important role. What was interesting is the C d 8 mice were then, they followed then by C d 8 and then subsequently by perforin.

Now, perforin is an important in terms of killing. But you can see that the perforin is not playing a very important role, or certainly or put it other way, beta 2 macroglobulin is playing a more important role then perforin. Now then C d 1 was similar to wild type.

Now C d 1 is M H C class 1 like molecule which it belongs to the non classical M H C which which which is an important in presenting lipid molecules to your T cells. Then, especially a type of T cell known as be natural T cells, or the N K T cells. Now N K T cells it is a quite obvious from here that the N K T cells are not playing much of role, but beta 2 macroglobulin is playing the most important, and what is important to see that beta 2 was more important then the C d 8.

Now, remember in the beta 2 knock out, there are no C d 8t. So, clearly beta 2 has role other than just the strictly the C d 8 apart. So, this was the very important part, and you can see the killing in terms of perforin were not playing an important role. So, this I thought was an very important aspect. It tells you about the complexity of the immune response. And how, if you change one parameter, you know there are other parameter that also get changed and which is an important in determining the overall response of the host towards the microorganisms. A very a interesting study by Barry blame's groove which was published in p n a s and I would suggest students to take a look at that, to try and understand this aspect, a little bit in greater detail.

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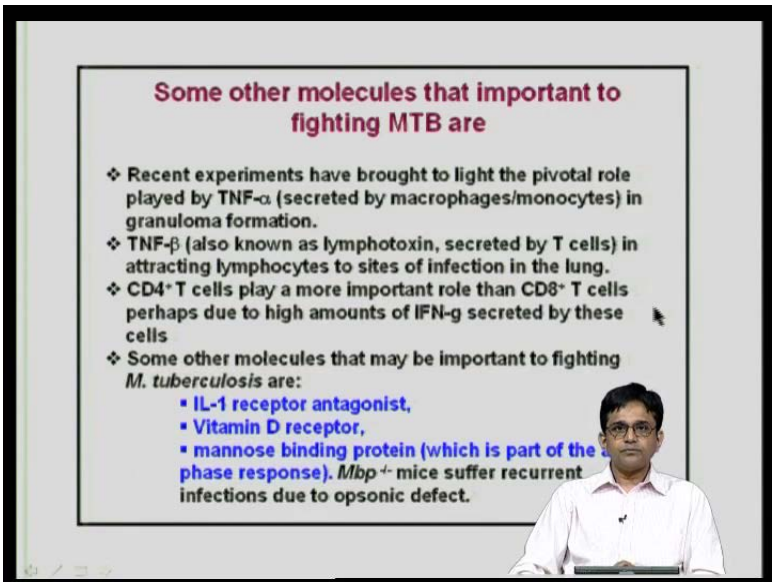

Now, they are having been other molecules that, are also important in playing role in T B infection. So, T N F a is clearly important. Now, we have talked about the anti T N F for (()) back and how with the use of T N F for rheumatoid arthritis there is in rise in TB cases. Now a another molecules which is a lymphotoxin is also important, because its

important in recruiting lymphocytes to the sites of infection in the lung. C d f 4 plays a very important role because of the production of in different gamma.

Now, there are other molecules. So, Il1 receptor antagonist is important, vitamin D three vitamin D receptor. In fact, there are some study which show that if you take in a lot of vitamin D it helps you with better immunity against a tuberculosis, and then mannose binding protein Mbp. Mbp is an important in terms of opsonisation. Again an important part that was covered in our lectures on innate immunity. Please take a look at it, and its Mbp plays a role against m infection with in tuberculosis.

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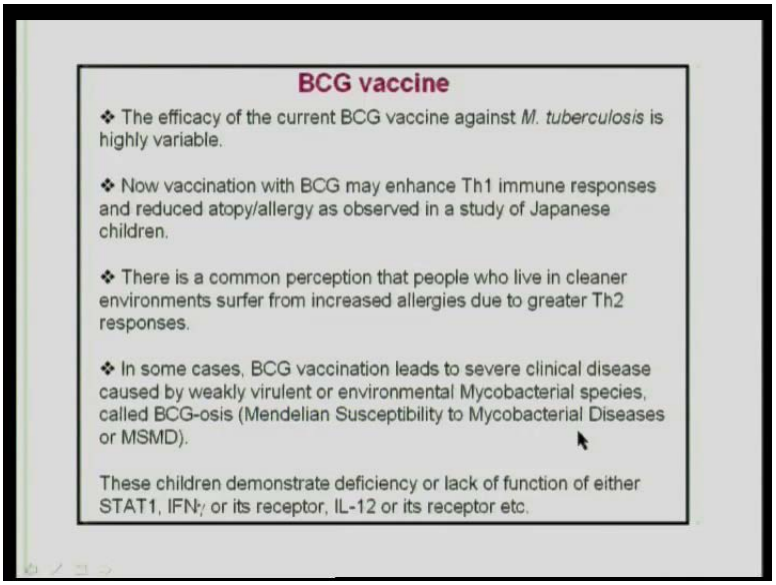

Let's talk a little bit about BCG vaccination. The moment you know BCG is good pediatric vaccine against M tuberculosis. So that means, that when kids are born they often the first vaccine that they get is BCG. What BCG does is that, it protects young kids with vaccination. However, the efficacy of BCG vaccine with respect to adults is controversial. There are different, there are two aspects that I would like to cover in this slide One is while B C G is an important and clearly good pediatric vaccine. It enhances TH1 immune responses and this enhance TH1 responses has been shown. It would reduce cases of allergy in Japanese, in study of Japanese children. Why is that? Because there is common perception that people who live in cleaner environments suffer more from allergies because they primarily more TH2 like.

So, there is lot of secretion and lot of allergy because they primarily are TH2 and so, if you give BCG vaccination you are trying to modulate immune response more to T H1. So, I think that makes an important that sort of that changes their immune response parameters and so it becomes little bit different. The other case is that some kids who are giving BCG vaccination, they come down with the disease, and that is because if they do, they lack of proper immune system in terms of functional stat 1 which is an important on a interferon responses, interferon gamma with receptor I L 12 or its receptor.

In fact, all these three stat 1 I F N, I L 12 are play a very important role in host resistant through infections, and so if you do not have it, so kids do not have it are highly susceptible to the B C G vaccination in that sense.

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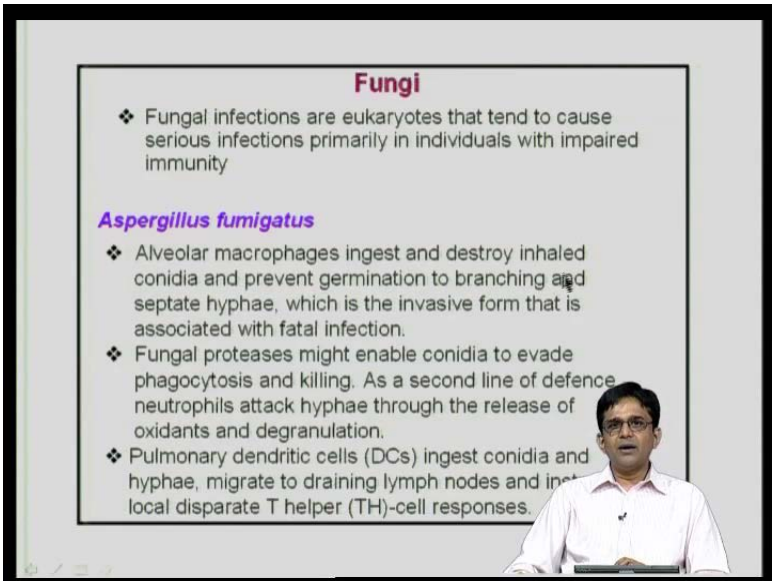

We will cover the fungus, the fungal infections in little bit, because in the next class I will be covering mainly viruses and parasitic diseases. So, over here fungal infections are those previously mentioned. They are primarily caused in individuals where they are either immune suppress because of treatment, or due to age, because of their immune system has been compromised. In case of aspergillums, these are sports are sort of ingested the conidia are ingested, and these sort of attack the host cells, and try and germinate. One of the main reasons, one of the main mechanism by which this is host response does is that, you have you have neutrophils are the once that are supposed to

attack the hyphen, and sort of kill these, this sort of infection. You also have dendritic cells which in the conidia hyphen and they try and maintain this infection.

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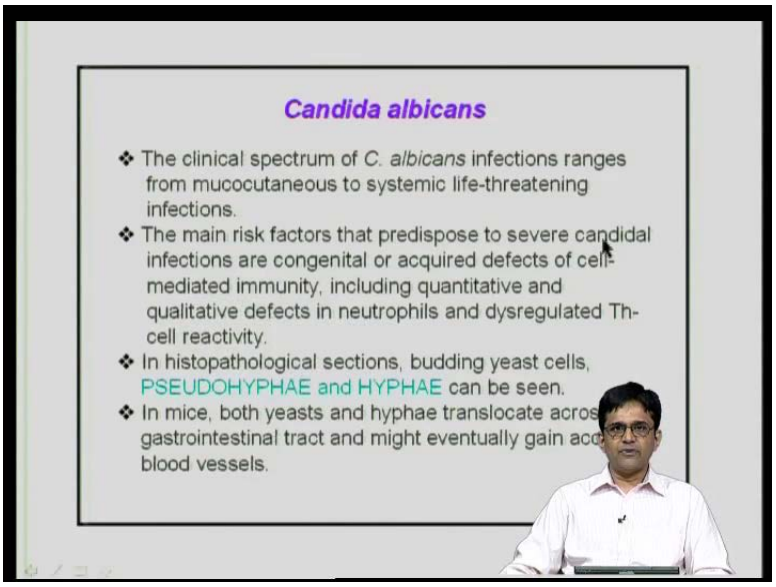

However the infection that is perhaps that is well studied or is the one caused by Candida Albicans. And it you have Mucocutaneous which means a localize probably its skin related or presented in the year to a systemic, and systemic, if it systemic become systemic then of course, it is a life threatening infection. So, and again what you have is immune response involving Neutrophils, and you have a T Hyphae cells which play an important role. Often what happens is that what is seen in this yeast cell, candida Albicans can switch from a yeast state to a pseudohyphae state. You can see this in mice. In fact, both yeasts and hyphae translocate across gastrointestinal tract and may gain access to blood vessel.

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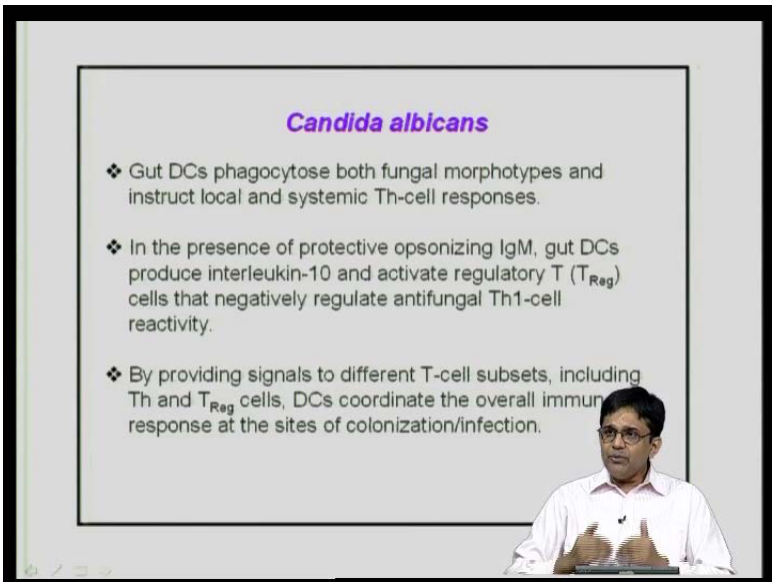

Now, type of responses that are seen again you have opsonizing I G M responses you have gut Dendritic cells and you have T cells that play an important role with the cytokines that they produce.

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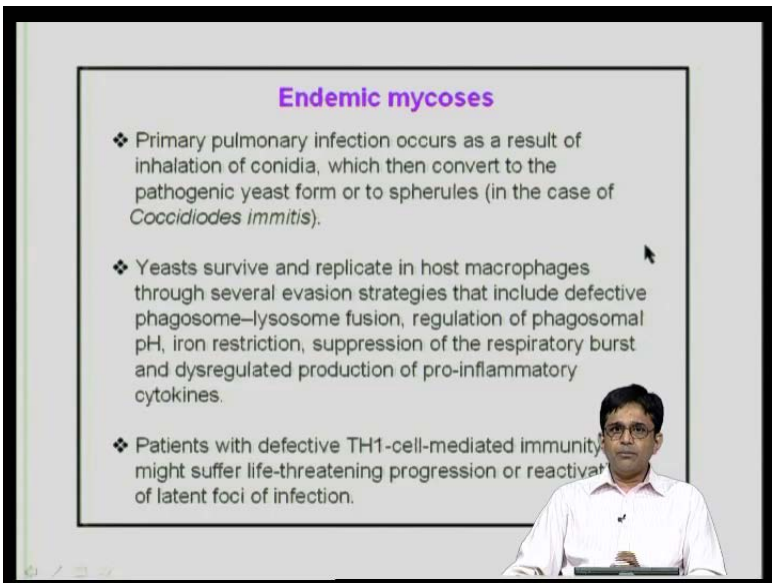

One of the important ways by which this happens is, you generate a good response using your Neutrophils and macrophages and you have a good T cell response primarily using your T H 1 T H 2 responses that are in place. So, Neutrophils as I said play an important role. Phagocytose fungi for intracellular killing and they are present in macrophages.

Macrophages also generate cytokines boost up the host difference and so, you have cytokines that have been produced and that would do it. So, what I will do over here is to briefly summarize the talk today.

So, initially what we have done we have to covered different agents that cause disease. You have viral, bacterial, fungal and so on, and some of the viral ones you know. Some of the recent ones that are important to cause cold, H I V is I think that will be discussed. This class we discussed some aspects of salmonella and primarily micro bacterial diseases. What are the general mechanisms involved in the host response? General mechanisms involved in the body surfaces, you have dendritic cells, you have the T H 1, T H 2 responses, and the T H 17 responses. Now in some cases T H 17 plays a very important role especially in case of fungal infections has been seen lately.

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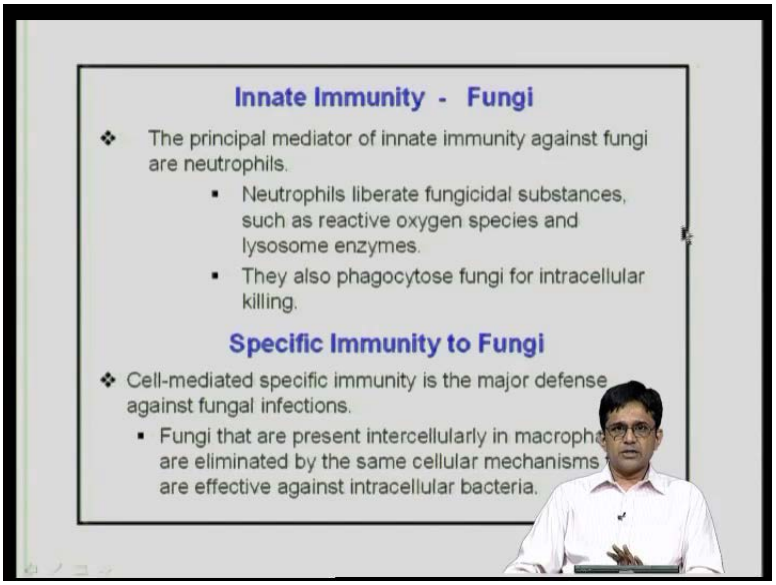

In fact, as we probably know and has been discussed is that they there is interferon, and I l 17 are sort of inversely to related to each other, and so even in the absence of lower amounts of interferon gamma, you have very good T H 17 responses. There are some aspects that I would like to emphasize, one is the use of, immune modulatory roles. So, you know due to rheumatoid arthritis people start giving anti T N F, but this while it has helped rheumatoid arthritis, it has resulted in increase in cases of T B.

So, you can see how you know tickling one aspects of the immune system affects some other. So, it is a very, it is a is an dynamic flux, and if you change one parameter you

know several other things get changed. The other was the use of B C G vaccination and ectopic. So, use of BCG vaccination increases or increases our T H 1 response and therefore, and consequently reduces a2 p or ability to be develop allergic reactions. The other fascinating story is that NRAMP. Especially the role of NRAMP which is involved in transporting ion, manganese, and its ability to determine susceptibility to intracellular infections, depending on the allele that is expressed. The NRAMP r which encodes for resistance or NRAMP s, and I really think NRAMP is a really a fascinated story. We also discussed a micro bacterial infections, the granuloma formation, tuberculin, very important aspects for students. You must pay close attention to these. What is tuberculin? What is granuloma? How are these, sort of related to each other? Remember tuberculin, you know as a person develops T B, they become from tuberculin positive they become tuberculin negative. As they start recovering, they regain tuberculin reactivity. So, very important aspect.

We also discussed the role of cronin, during micro bacterial infections. Remember the micro bacterial enter from the lung and they play an important role. Finally, we discussed some aspects of fungal infections. Fungal infections as was mentioned they occur mainly in immune suppressed individuals, and candid albcans important aspects. The main roles are with neutrophils and macrophages, you should be sort of would tend to take care. Then you have the role of the T H T hypo cytokine helping boost of immunity. So, over all what this lecture has to cover is given as general ideas about the host responses infectious diseases, and then, we study tuberculosis as paradigm for intracellular infection. In the next class what will be discussing are mainly viral diseases, we will be discussing a little bit in depth about HIV, and we will discuss other diseases, more importantly will be discussing emerging diseases. Thank you.