Manage TB
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Lecture - 04
Pathogenesis of Tuberculosis
Session 01

Welcome to the session on the Pathogenesis of Tuberculosis I am Subash Babu scientific director of the India ISO program and we are going to be discussing pathogenesis of tuberculosis because of it is important importance in understanding natural history as well as the progression of TB infection and disease.

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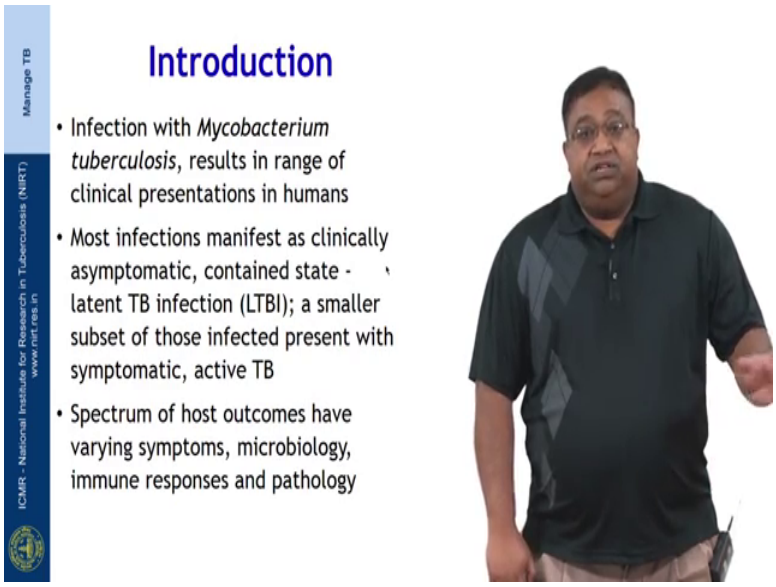

Infection with Mycobacterium tuberculosis, typically results in a range of clinical manifestations in humans. Most infections manifest as clinically asymptomatic contains state called latent TB infection or LTBI. It is only in a smaller subset of infected people that present with symptomatic active TB.

Thus, there is a spectrum of host outcomes with varying symptoms, microbiology, immune responses and pathology within this binary state.

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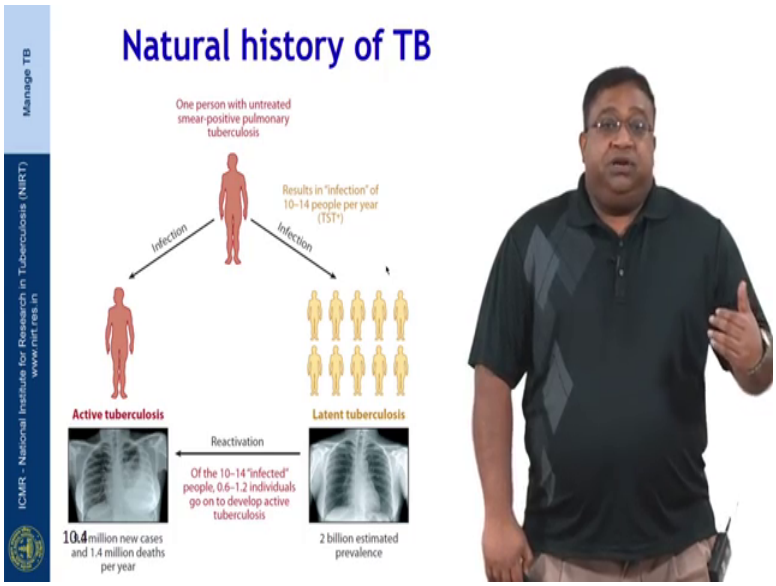

So, when we look at the natural history of TB; transmission typically begins with an untreated smear positive pulmonary TB case this individual can infect up to 10 to 14 individuals per year these individuals typically are able to contain the infection and belong to the latent tuberculosis group they are thought to comprise about 2 billion people worldwide.

Only about 5 to 10 percent of a latent TB individuals go on to subsequently undergo reactivation or progression from latent infection to active disease and these are the ones who want to develop symptomatic active tuberculosis. And it is estimated that there are about 10.4 million new cases of active tuberculosis each year with the conformant and death rate of about 1.4 million per year.

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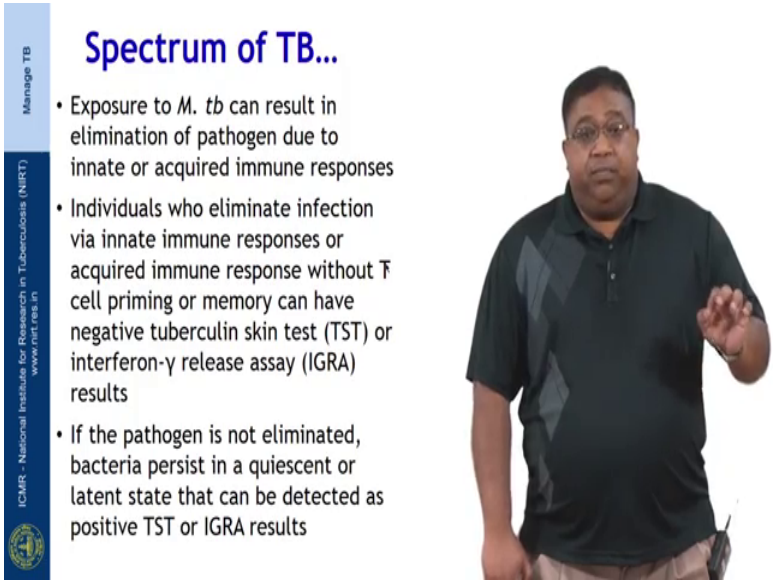

So, in examining the spectrum of tuberculosis; exposure to a TB can result in elimination of pathogen due to innate or acquired immune responses, individuals who eliminated faction either via innate immune responses or by acquired immune responses without T cell priming or memory usually have negative tuberculin skin test or negative interferon gamma release assay also known as IGRA.

If the pathogen is not eliminated, bacteria persist in a quiescent or latent state that can be detected as a positive TST or a positive IGRA.

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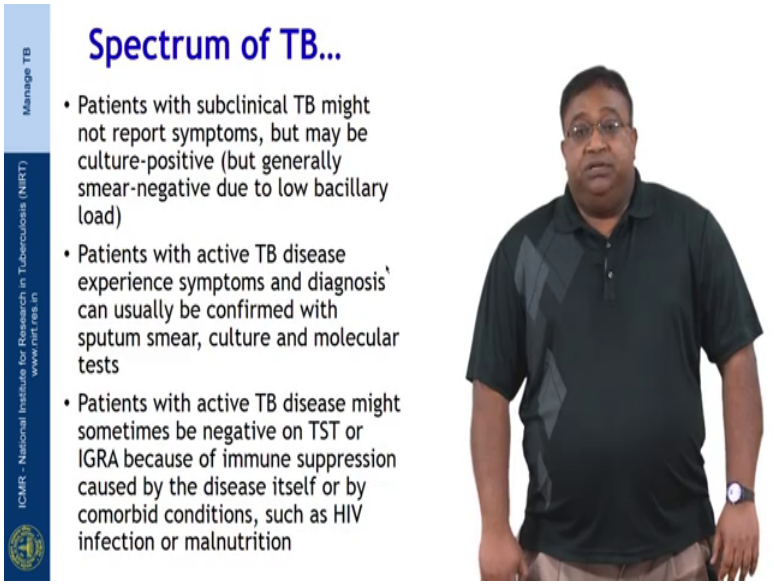

Patients with subclinical TB might not report symptoms, but may be culture positive, but generally ours we are negative due to low bacillary loads patients with active TB disease experience symptoms and diagnosis can usually be confirmed with sputum smear culture and molecular tests. Patients with active TB might sometimes be negative on TST or IGRA because of immune suppression caused by the disease itself or by co morbid conditions such as HIV infection or malnutrition.

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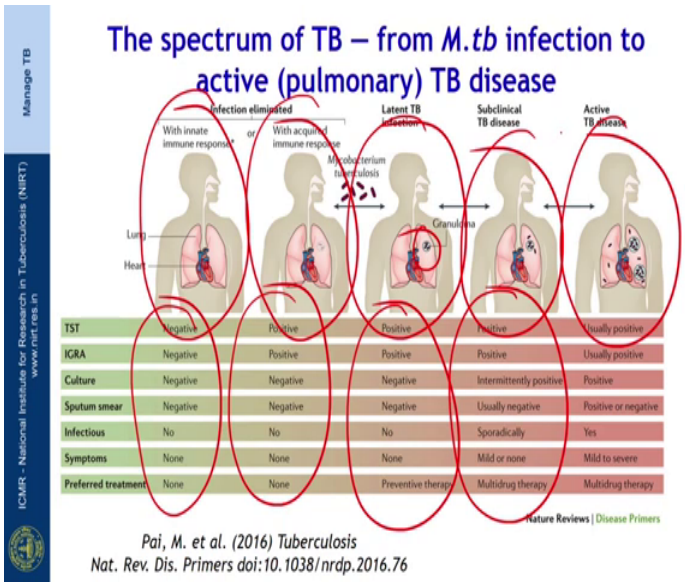

So, the spectrum of TB from M TB infection to disease is basically summarized here on the slide; infection can be eliminated with an innate immune response which typically results in a negative TST, negative IGRA, negative culture and sputum smear these people are not infectious do not have any symptoms and do not require any treatment.

If infection is eliminated with an acquired immune response you have a positive TST, positive IGRA, negative culture and sputum smear they are not infectious, do not have any symptoms and do not require any treatment as well. When the infection actually is not contagious not eliminated you go on to develop latent TB where in the bacilli are contained within the granuloma and these people typically have a positive TST, positive IGRA, negative culture and sputum smear are not infectious, are not symptomatic and do not may or may not require preventive therapy.

The next stage of progression is the subclinical disease; wherein the TST and IGRA are positive the culture can be intermittently positive, sputum smear is usually negative these

people are sporadically infectious, they do have mild or no symptoms and do require multi drug therapy and finally, in terms of the full blown active TB disease the usually manifests as TST or IGRA positive have positive culture, positive or negative sputum smear are definitely infectious, have mild to severe symptoms and absolutely require multi drug therapy.

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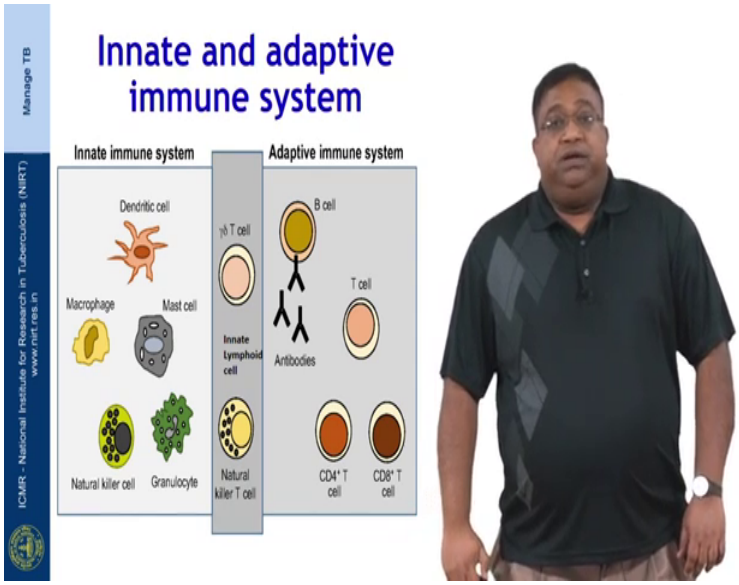

We will now take a step back and look at the basic principles behind the innate and adaptive immune system. In order to better understand the relationship with TB infection and disease.

As most of you already know; the innate immune system is comprised of different cell types including the dendritic cell, the macrophage, the natural killer cell granulocyte such as eosinophils, neutrophils and basophils as well as mast cells. The adaptive immune system is basically composed of a 2 beta cell types the B cells which produce antibodies and form the main component of humoral immunity and the T cells which come in two flavors CD 4 positive T cells and CD 8 positive T cells and which basically comprise the main component of the cell mediated immune response.

In addition there are other cell types such as the gamma delta T cell, the innate lymphoid cell and the natural killer T cell which play a bridge role between the innate and adaptive immune systems.

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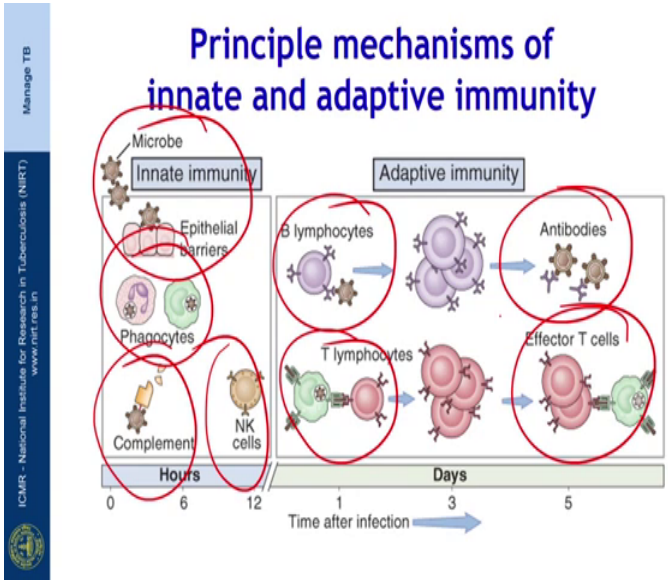

Looking at the principal mechanisms that underline innate and adaptive immunity innate; immunity is typically comprised of epithelial barriers which help in preventing entry by host entry of microbes into the host; phagocytes are one of the bridge of competence of the innate immune response, because of their ability to engulf and destroy pathogens.

The complement system is another major component of the unit immunity due to it is propensity to entry to seek out and destroy infecting organisms and finally, natural killer cells as the name suggests can kill infected cells and also form an important component of the innate immune response.

In terms of adaptive immunity; B lymphocytes upon encounter with antigen can expand and differentiate and lead to plasma cells which then produce antibodies which are the hallmark of the humeral immune response; while T lymphocytes upon encounter with antigen can expand and differentiate and from effector T cells which then mediate; the cell mediated immune response.

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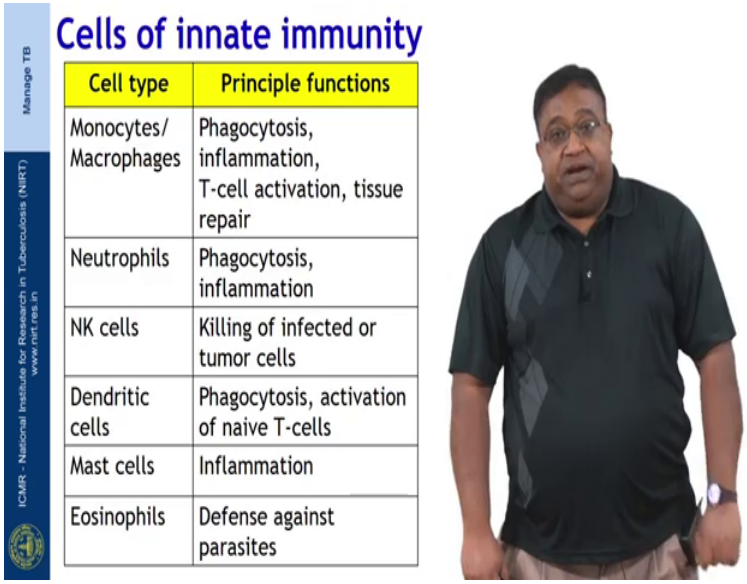

So, this slide basically summarizes the principal functions of the cells of the innate immune response monocytes and macrophages are typically involved in phagocytosis. T cell activation, inflammation as well as tissue repair. Neutrophils are involved in phagocytosis and inflammation.

Natural killer cells are important in killing of infected or tumor cells. Dendritic cells are involved in the activation of naive T cells as well as in phagocytosis. Mast cells are important for inflammation, while eosinophils are considered important for defense against parasites.

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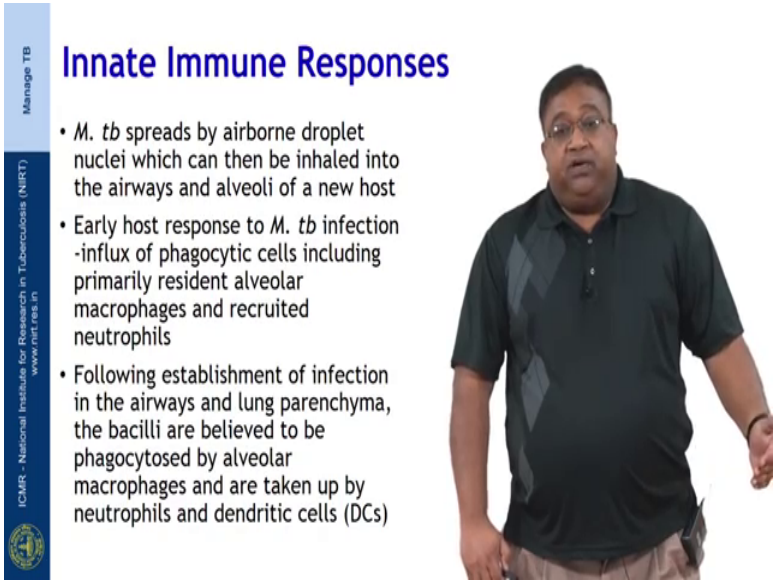

So, in terms of the innate immune responses in TB infection mycobacterium tuberculosis spreads by airborne droplet nuclei; which can then be inhaled into the airways and alveoli of a new host.

The early host response to infection is a typical influx of phagocytic cells including; primary resident alveolar macrophages and recruited neutrophils. Following establishment of infection in the airways and the lung parenchyma the bacilli are believed to be phagocytosed, by alveolar macrophages and are subsequently taken up by neutrophils and dendritic cells.

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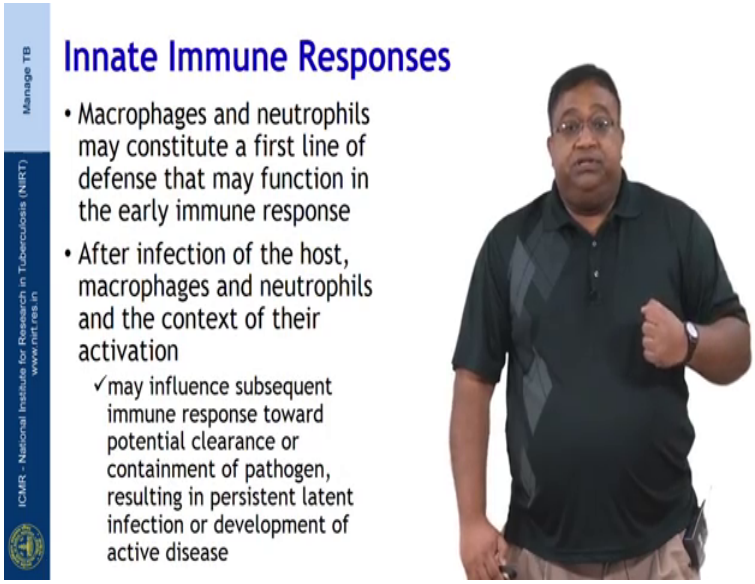

Macrophages and neutrophils as I mentioned constitute the first line of defense that function in the early immune response. After infection of the host these macrophages and neutrophils and the context of their activation can influence subsequent immune responses towards either potential clearance or containment of pathogen; which results in a persistent latent infection or the inability to contain the pathogen which results the development of active disease.

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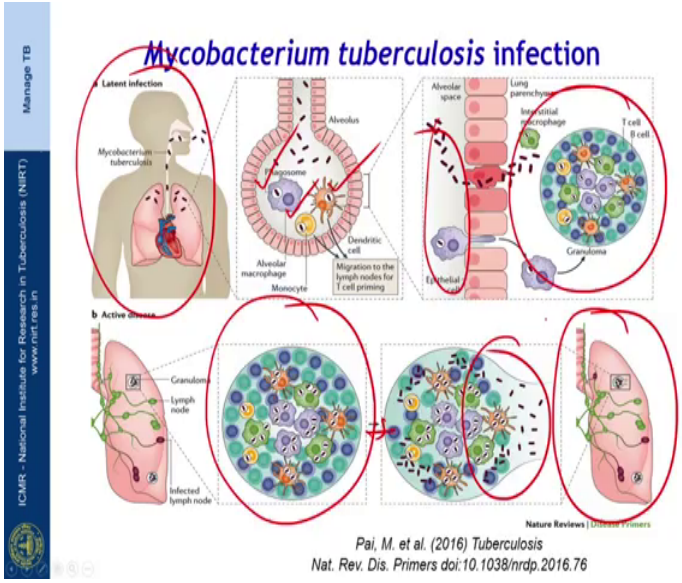

So, this interaction between the innate and immune response and MTB is summarized on this slide wherein if we look at latent infection; the upon entry of the bacilli into the lungs you have the influx of alveolar macrophages, monocytes and dendritic cells, you have the subsequent flux of a variety of other cell types, this basically results in the formation of a solid granuloma.

In terms of active disease this ability to form the solid granuloma fails, you have necrotic cell death within the granulomatous lesion as well as extrusion of both intracellular and extracellular bacilli; which then subsequently spreads to the other parts of the lung as well as for the reigning lymph nodes.

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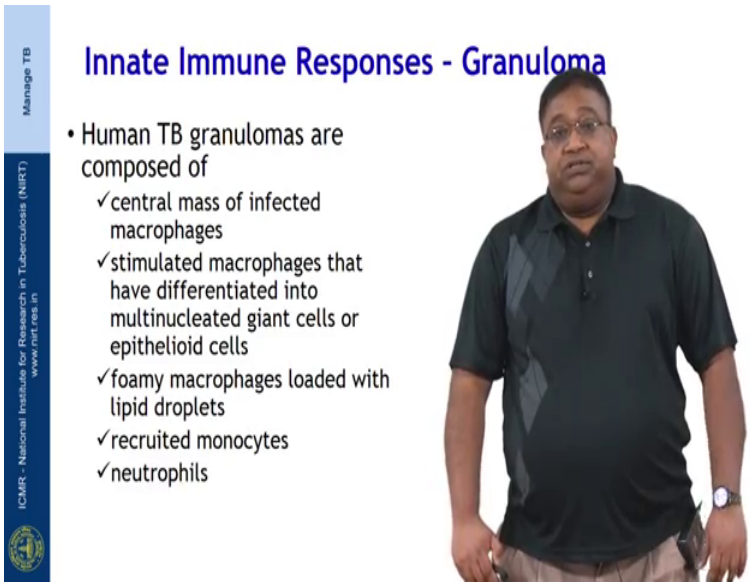

So, this brings us to the granulomatous reaction and the importance of the granuloma in TB infection and disease. Human TB granulomatous are the classic hallmarks of TB infection and disease and are composed of a central mass of infected macrophages, stimulated macrophages that have differentiated into multinucleated giant cells or epithelioid cells. Foamy macrophages loaded with lipid droplets, recruited monocytes and neutrophils.

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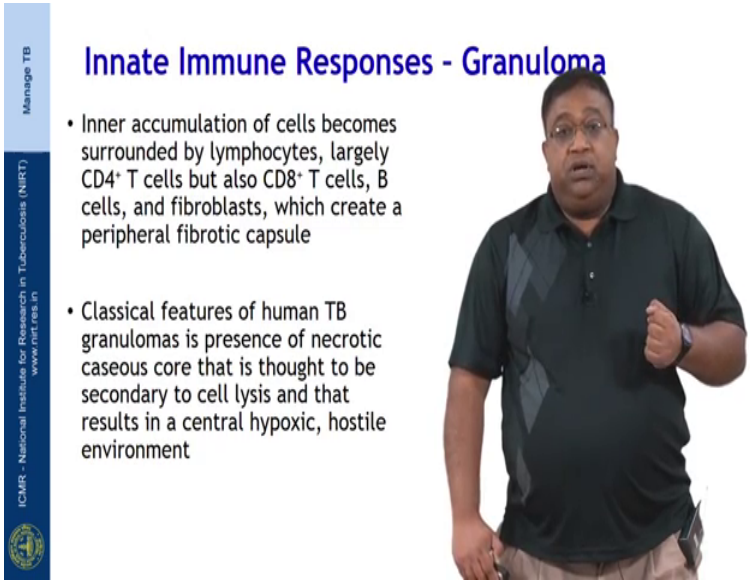

For surrounding this inner accumulation of cells our lymphocytes largely CD 4 positive T cells, but also CD 8 positive T cells, B cells and fibroblasts which create a peripheral fibrotic capsule and one of the classical features of human TB granulomas is the presence of a necrotic caseous core; that is thought to be secondary to cell lysis and that results in a central hypoxic hostile environment.

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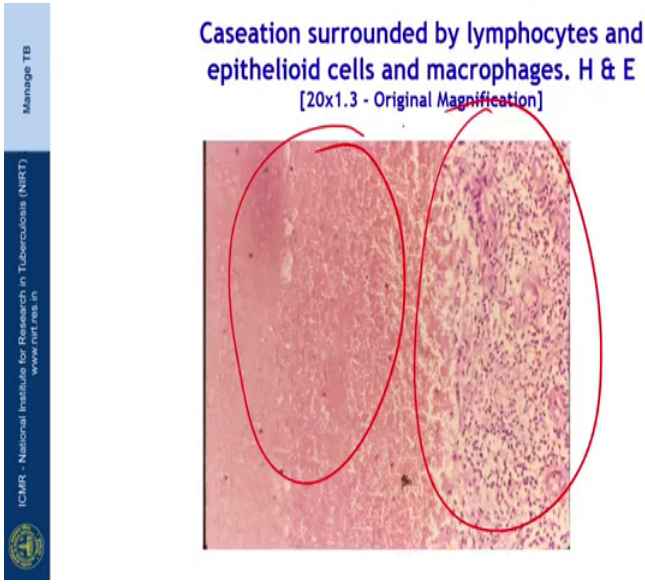

Shown here is a histological picture of a typical case shading granuloma and what we see here in pink is the central caseating core surrounded by the purple staining lymphocytes epithelioid cells and macrophages.

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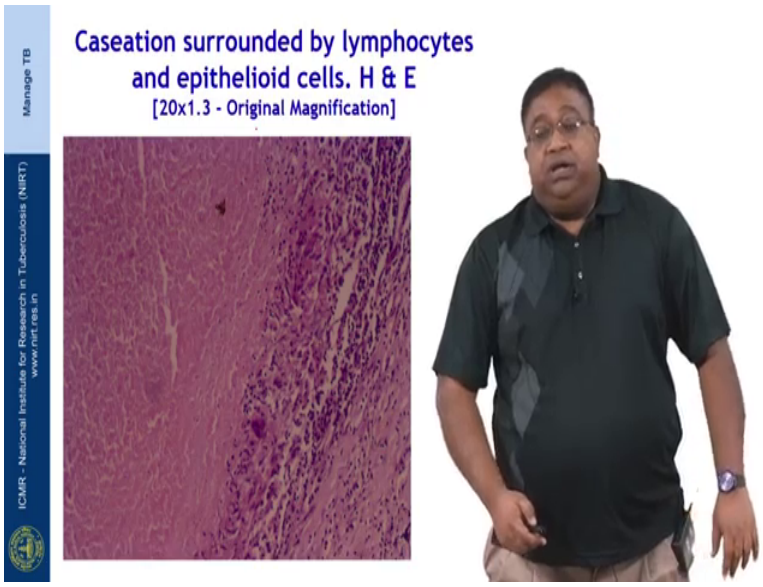

It is also shown here as a different histological picture of a caseating granuloma and again you can very clearly see the caseous central core surrounded by lymphocytes and epithelioid cells.

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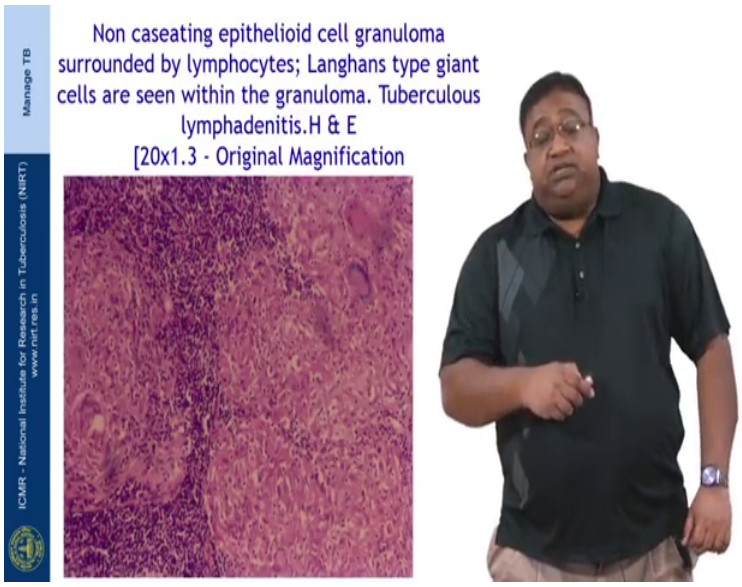

In contrast if we look at a non-caseating granuloma you see that there is actually a central solid core; which is composed of different cells including macrophages and lymphocytes and this is again surrounded by different cell types such as the epithelial cells langhans type giant cells etcetera.

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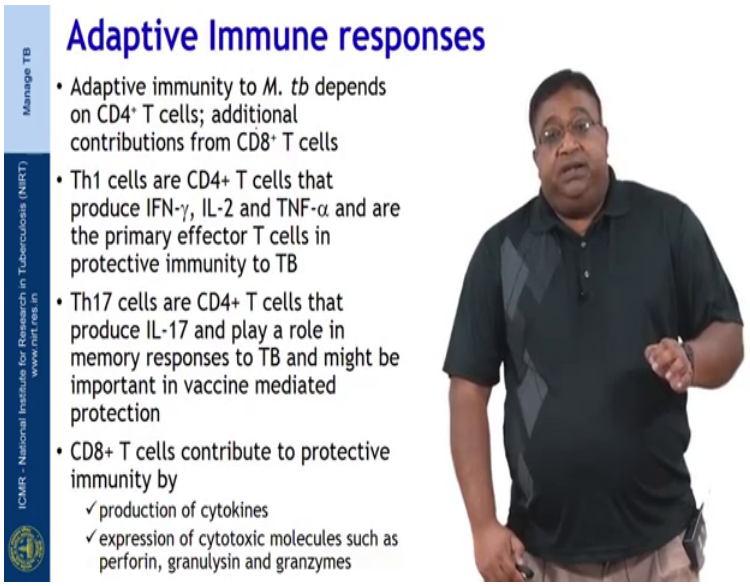

So, with that we now move on to the component of adaptive immune responses and their interaction with TB infection and disease. As I mentioned before adaptive immunity to TB depends on CD 4 positive T cells with additional contributions from CD 8 positive T cells Th 1 cells or CD 4 positive T cells that produce a different gamma IL 2 and TNF alpha and are the primary effector cells in protective immunity to TB.

Th 17th cells are CD 4 positive T cells that produce IL 17 and play a role in memory responses to TB and might be important in vaccine mediated protection and CD 8 T cells also contribute to protective immunity by production of cytokines expression of cytotoxic molecules such as perforin, granulysin and granzymes; which enable the CD 8 T cells equalize infective cells.

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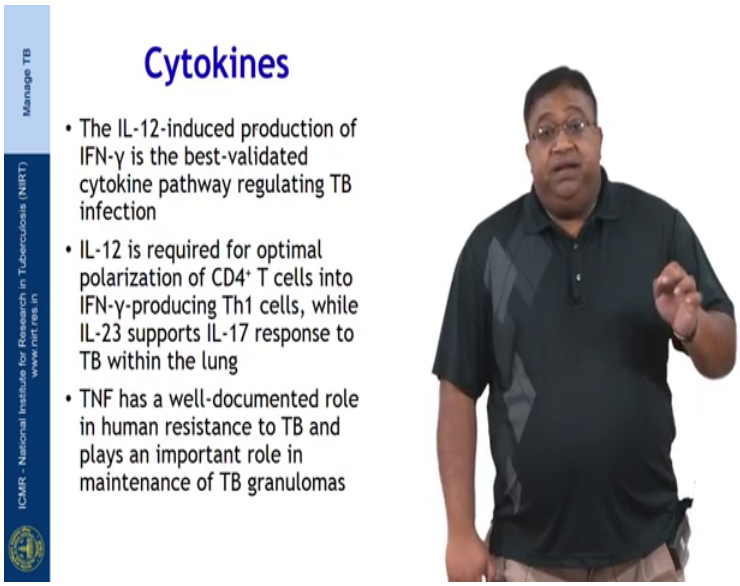

So, moving on to the role of cytokines in either protective or susceptible immune responses to TB we know that the IL o IL 12 induce production of interferon gamma is the best validated cytokine pathway regulating TB infection.

IL 12 is required for the optimal polarization of CD 4 T cells into interferon gamma producing Th 1 cells while IL 23 supports the IL 17 response to TB within the lung. TNF has a well documented role in human resistance to TB and plays an important role in the maintenance of TB granulomas.

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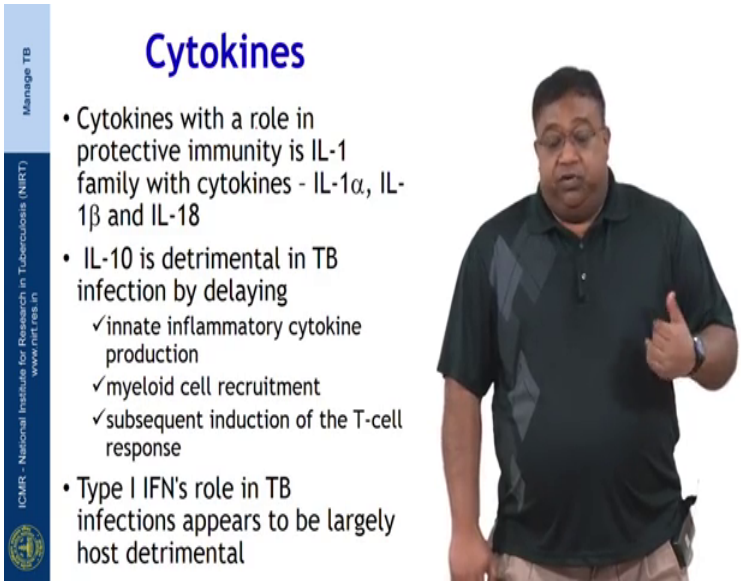

In terms of the other cytokines that also play a role in TB infection; I have one family of cytokines IL 1 alpha IL 1 beta and IL 18 are associated with protective immune responses, while IL 10 is thought to play a detrimental role in TB infection.

It does this by crossing a delay in the innate inflammatory cytokine production; in the process of myeloid cell recruitment and also in the subsequent induction of the T cell response finally, type 1 interferon similar to IL 10 are also taught to play a role that is hosted to mental by down modulating protective immune responses in TB.

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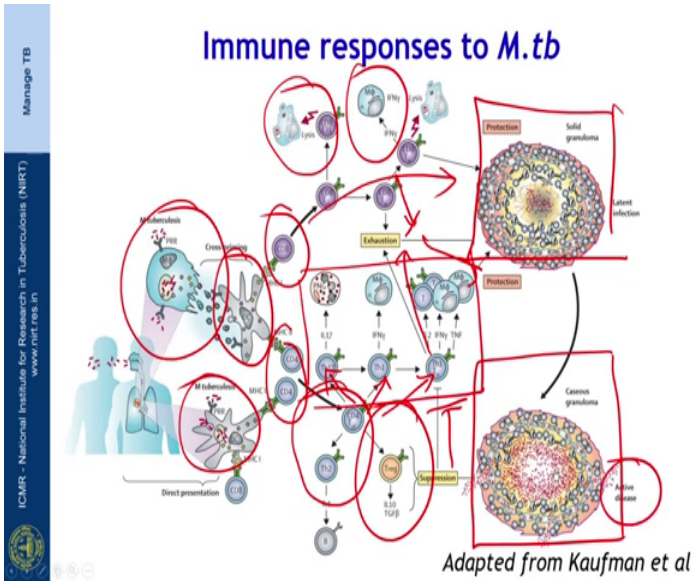

So, my final slide basically summarizes the global interaction of the immune response to TB infection and disease. Mycobacterium tuberculosis infected cells typically interact first with dendritic cells; which are the important initiators of innate or adaptive immune responses; these dendritic cells then activate both CD 4 as well as CD 8 positive T cells in terms of the CD 4 T cell arm of the immune responses we know that the CD 4 T cells differentiate into Th 1 cells into Th 17 cells as well as into multifunctional Th 1 cells.

So, all these components of the CD 4 T cell arm as well as the ability of CD 8 T cells to produce cytokines or to lyse target cells all basically result in a protective immune response with the formation of a solid granuloma and the establishment of latent infection. In contrast when any of the arms of these immune responses break down and I am just giving you example of a few for example, the induction of a Th 2 response or the induction of a regulatory T cell response either of which can suppress these immune

protective responses or if the Th 1 and CD 8 T cells undergo exhaustion; which can also suppress the protective responses you end up with the caseous granuloma and active disease. So, with this we come to the conclusion of the first session on the pathogenesis of tuberculosis.

Thank you very much.