Host-Pathogen Interaction (Immunology)
Prof. Himanshu Kumar
Laboratory of Immunology and Infectious Disease Biology
Department of Biological Sciences
Indian Institute of Science Education and Research (IISER) – Bhopal

Lecture - 74
Bacterial Infection - Tuberculosis

Hi. So in previous session we have discussed all about the bacterial infection and we have learned the various kinds of immune responses developed against intracellular and extracellular bacteria. Then we have looked at how this bacteria is causing disease and where these disease causing factors or virulence factors are present in the bacterial genome. It could be in the form of extra chromosomal DNA, in the form of plasmids or it is located there is island.

There is some chunk of DNA of bacterial chromosome that contain these virulence factor. And all these virulence factors basically trigger by some environmental or external stimuli, the expression of these pathogenicity islands which is expressing the various virulence factor. We have learned about the various kinds of toxins that is exotoxin and endotoxin and we have looked at how this microbial pathogen basically triggered the disease when they are infecting the host.

So in continuation of this previous session, I will discuss one bacterial disease, this is a Mycobacterium tuberculosis which is a causative agent for the tuberculosis. So let us begin with the tuberculosis.

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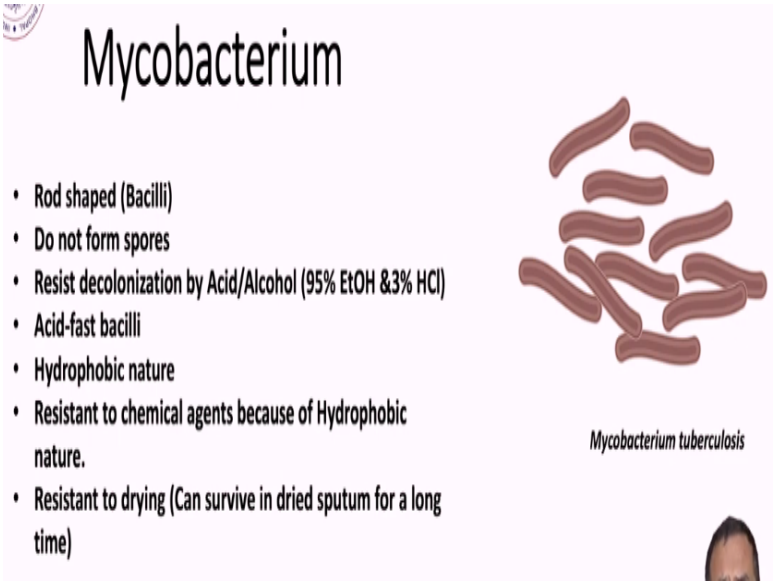

So tuberculosis is basically caused by Mycobacterium tuberculosis. I will give you some brief introduction about the mycobacteria as such. So Mycobacterium tuberculosis we call it as a bacilli. So they are basically rod shaped bacteria and here you can see there is a kind of a schematic of Mycobacterium tuberculosis. They do not form spores. There are some bacteria which makes spores. One very good example of bacteria which makes a spore is a Bacillus anthracis.

And due to this property, this Bacillus anthracis can be used as a biochemical weapon because it spores, you can understand spores are very resistant and tight and they can be easily transported without any special need, even in dried form one can transport it and that gives the property of a biochemical weapon. So this Mycobacterium is basically resistant to the decolourization by acid alcohol. So what is acid alcohol?

It is a simple mixture of 95 percent ethanol and it contains 3 percent hydrochloric acid. So even if you stain the Mycobacterium tuberculosis and if you wash it with this acid alcohol then it is a resistant to decolourizing by this mixture that is why we call it as an acid-fast bacilli. So this mycobacteria by ~~and~~ enlarge they are more hydrophobic in nature. They have a variety of lipid and lipid derivative or lipid and sugar derivatives over the wall.

We will take up this composition of wall in great detail in subsequent slide in this session. So they are hydrophobic in nature and due to this hydrophobic nature ~~of~~, due to this Mycobacterium tuberculosis this makes a very successful pathogen, we will discuss in

subsequent slide. So they are resistant to the chemical agent because of hydrophobic nature, so most of chemical agent are basically hydrophilic in property.

Like even if you see this acid alcohol mixture which is 95 percent ethanol and 3 percent HCl. So due to this hydrophobicity they cannot decolourize and due to this property they are resistant to even drying, this Mycobacterium tuberculosis can survive in dried sputum. So even the sputum is dried and generally Mycobacterium tuberculosis when the infection is too much then they are present in this sputum.

And this sputum if somebody spit it and if it is sun dried, still in that situation this Mycobacterium tuberculosis is alive. When they will get the appropriate host then again this can turn to virulent and then that can cause the disease.

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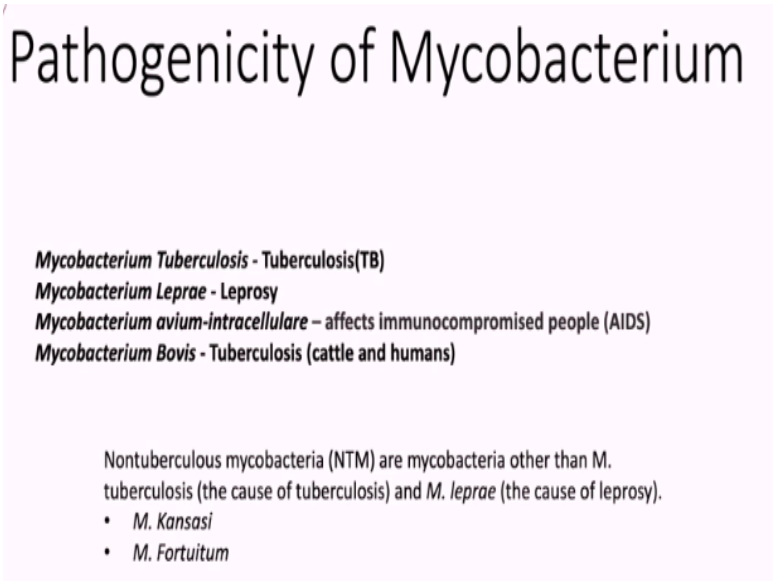

So this is a generalized property of Mycobacterium, particularly Mycobacterium tuberculosis and there are various mycobacteria. One is Mycobacterium tuberculosis which cause tuberculosis, Mycobacterium leprae which cause leprosy. There is Mycobacterium avium-intracellulare which basically affect immunocompromised individuals, so immunocompromised individual it could be an acquired immunodeficiency syndrome people who are infected with HIV or the individual who has a congenital immunodeficiency.

So this Mycobacterium avium can infect and that can cause the disease. Another is Mycobacterium bovis which is quite common, so this causes tuberculosis, but this tuberculosis is limited to the cattle and they do cause in some cases disease in human but again the point is

that basically this occurs in immunocompromised individuals. There is another group of mycobacteria which we call it as non-tuberculous mycobacteria NTM.

So, this NTM basically are bacteria other than Mycobacterium tuberculosis and M leprae, Mycobacterium leprae and basically they are present in soil in another form and in general they do not cause any disease. But sometimes they cause the disease because of depression of immunity by some or other way, some or other way means some individuals receive some transplant then their immunity is depressed or if the individual is infected with HIV.

So that can also cause the infection of this non-tuberculous mycobacteria infection. So generally, this NTM infects the soft tissues. It is not like a classical symptom of pulmonary tuberculosis, it is to be very important that this infection is very hard to detect, but they can respond with a normal anti-tuberculosis drug. But this nontuberculosis mycobacteria is not very common, it is a quite uncommon infection.

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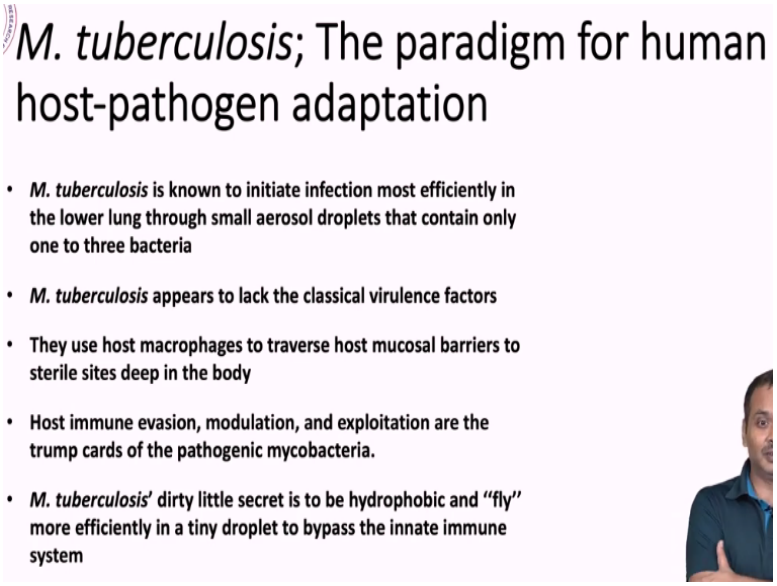

So Mycobacterium tuberculosis the paradigm for human host pathogen adaption. So this this Mycobacterium tuberculosis is a very smart pathogen, extremely smart, so they will not cause too severe disease immediately, but they will cause disease very slowly and calmly and eventually they will affect the host very badly, overall I want to say that. So Mycobacterium tuberculosis is known to initiate infection most efficiently in lower lung through a small aerosol droplet that contain only two or three bacteria.

So you can understand, only few bacteria is sufficient to cause the disease. And Mycobacterium tuberculosis appears to lack the classical virulence factor, so if you see very carefully if you see gram-positive bacteria, if you see gram-negative bacteria, so gram-positive bacteria or gram-negative bacteria they have some virulence factor and this virulence factor basically attract the attention of host immunity.

And then host immunity appropriately develop or clear or eliminate those infection through innate immune responses or adaptive immune responses, but Mycobacterium tuberculosis is not like that. They are just sitting silently in the macrophages and they slowly make their more copies and if they understand that host immunity is quite aggressive then they will even go in latent stage. They will not do too much activity.

So, in general they do not have a very specific virulence factor against which the host immunity will work and eliminate the infection. They do have but they do not provoke the host immunity very strongly that what I want to say. They use the host macrophages to transverse the host mucosal barriers to sterile site deep in the body. So basically they have a carrier, the carrier is the macrophage, the macrophage is host macrophage.

So through this carrier they can move here and there and they can cause the severe disease. So host immune evasion, modulation and exploitation are the trump card of this pathogenic mycobacteria. So Mycobacterium tuberculosis here there is a little thought, it is a dirty little secret of this Mycobacterium tuberculosis is to be hydrophobic and fly more efficiently in a tiny droplet to bypass the innate immune system.

So since it is hydrophobic they very easily mingle in the system and then their wall is extremely thick, it is a very resistant overall. So if you see very carefully all over the living world then you can see that there is one arthropod which is very successful which is appeared quite long back and still it is living very successfully and that arthropod is cockroach. So cockroaches are very efficient and very evolved.

If you do not give the food they will eat plastic, if you do not give oxygen they will start living without oxygen, so similarly Mycobacterium tuberculosis is also very successful pathogen and still they are causing a lot of disease.

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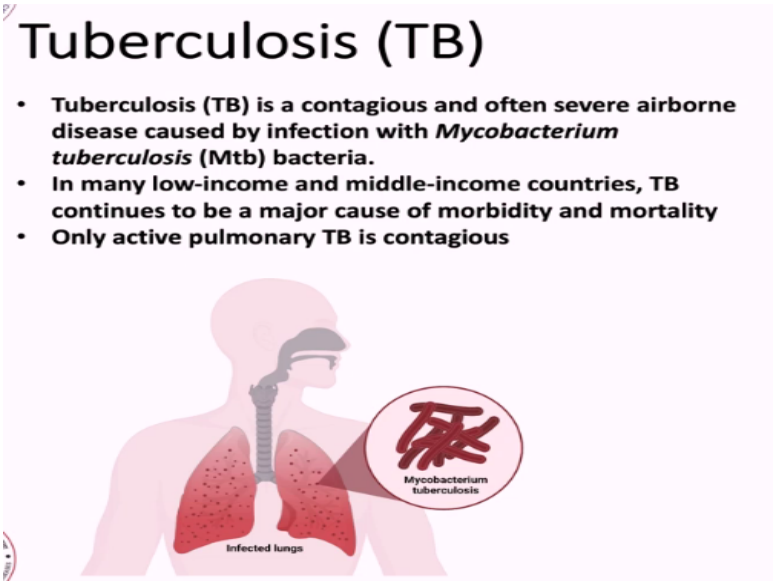

So how this infection is basically taking place? So tuberculosis is also denoted as TB. So tuberculosis is a contagious and often this is transported from one individual to another individual through this airborne droplet infection and this tuberculosis is, it is not always, it is a little dominant in low income or middle income countries that the number of cases is quite a lot in these countries.

And TB continued to be a major cause of morbidity and mortality, but this is not fully true. In a developed country also there is a reasonably good number of tuberculosis cases and over there is some drug resistant tuberculosis are also there, multiple drug resistant tuberculosis ~~classes~~ are also there. In subsequent session, I will talk about the drug and at that time I will discuss about the first line of drug, second line of drug and how to treat the multiple drug resistant tuberculosis.

So only active pulmonary tuberculosis is the contagious. Here just I want to say that most of Mycobacterium tuberculosis infect the lungs and that we call it as a pulmonary tuberculosis. There is another category of tuberculosis which we call it as extrapulmonary tuberculosis. So, basically this Mycobacterium tuberculosis infect the macrophages and these macrophages are mainly the first infection is mainly in the lungs through respiratory route.

But as you know that the macrophages are present all over our body, in bone there are macrophages, in connective tissues macrophages are there, in liver, in another almost all tissues have tissue specific macrophages. So, this Mycobacterium tuberculosis can infect those

macrophages and whatever infection caused by Mycobacterium tuberculosis other than lung we call it as extrapulmonary tuberculosis.

For example, the Mycobacterium tuberculosis is infecting the bone macrophages which you call it as osteoblast. So, if it is infecting them that will cause the bone tuberculosis and please note the pulmonary tuberculosis is reasonably very easy to manage, but extrapulmonary tuberculosis it is extremely difficult to manage, even the diagnosis is very difficult, finding that the bone has a tuberculosis it is extremely difficult. Generally, people confuse with bone cancer or other diseases, so the extrapulmonary tuberculosis is extremely difficult cases.

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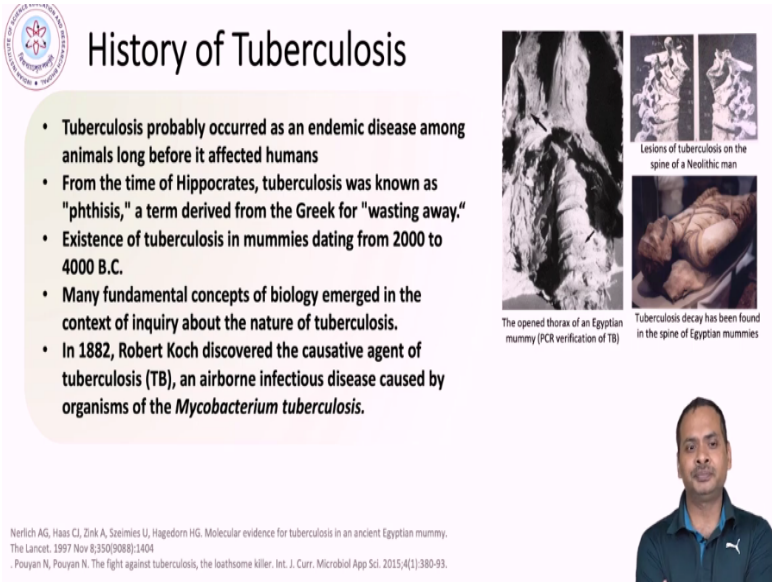

So now I just want to take to the history because I have discussed about the cockroach and I have discussed how mycobacteria is very successful and we have all evidences. So tuberculosis probably occur as an endemic disease among animal long before it affected human and from the time of Hippocrates tuberculosis was known as a phthisis. It is a term derived from Greek means wasting away.

Wasting away means the healthy individual started losing their weight and energy level and everything, so this we call it as a wasting condition, losing weight, getting more thin and like that, so this we call it as wasting away. So existence of a tuberculosis in mummies dating 2000 to 4000 BC, so it is already very well documented and reported that such old mummies they also has a tuberculosis.

As here you can see there is one Egyptian mummy and this mummy was having a tuberculosis which is verified by the PCR. Here you can see that lesion of a tuberculosis on the spine of a neolithic man, it is extremely old and here you can see that tuberculosis decay has been found in spine of Egyptian mummy. So this is very clearly demonstrated that this pathogen is present from quite early time.

So many fundamental concepts of biology emerged in the context of inquiry about the nature of tuberculosis. And basically, this tuberculosis was discovered by Robert Koch in 1882 as a causative agent of tuberculosis an airborne infectious disease caused by organism of Mycobacterium tuberculosis. And at that time this tuberculosis disease was known as white plague because it leaves the white lesion in the lung.

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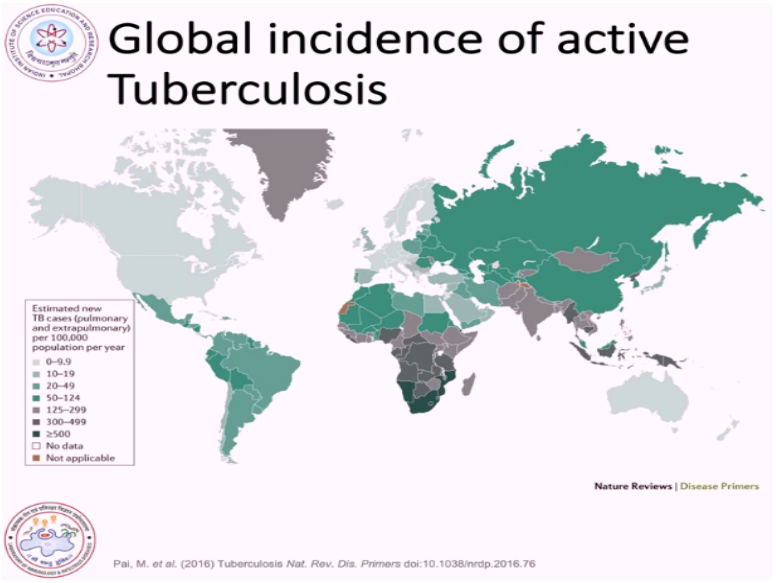

This is a global incidence of active tuberculosis. Here you can see that our country has in India there is a lot of tuberculosis cases and if you see carefully then you can find out that the number of tuberculosis cases not basically depend on the climatic condition. Here you can see that close to the north pole also there is a lot of tuberculosis cases, if you go to the south pole also there is a reasonably good number of tuberculosis cases and of course this Asia continent including India this has a lot of tuberculosis cases.

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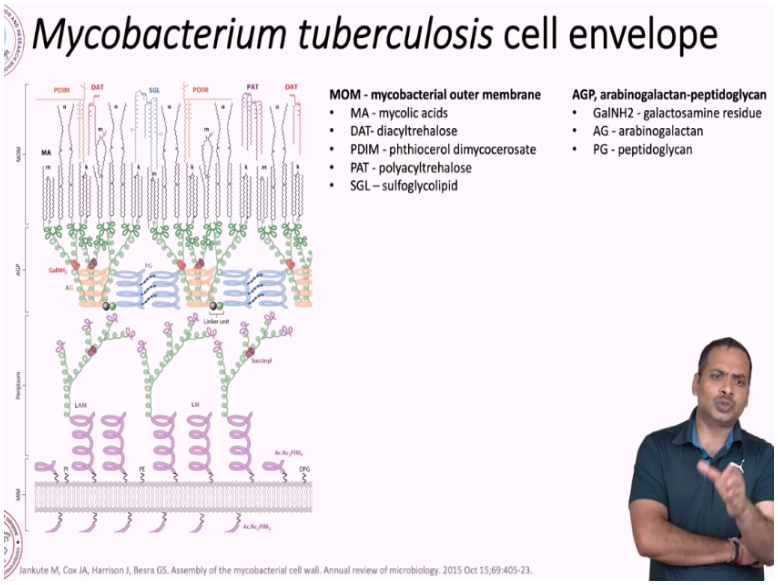

Now let us look at how this Mycobacterium tuberculosis the wall and the other things are there. So, this is a cell envelope of Mycobacterium tuberculosis where you can see that the cell wall is basically or envelope is basically divided into several distinct group. One is that mycobacterial outer membrane. So, this mycobacterial outer membrane basically resemble with gram-negative bacteria. So gram-negative bacteria do have an extracellular membrane and that contain the LPS.

So similarly, the Mycobacterium tuberculosis have mycobacterial outer membrane, here you can see that which contain mycolic acid. There is a diacyltrehalose, here you can see that there is a sugared derivative there. There is phthiocerol dimycocerosate, a this is a quite complex molecule. There is polyacyltrehalose and there is a sulfoglycolipid. So these are very complex molecule and if you see very carefully then you can find out that this is more lipid and lipid sugar derivatives and long chain carbon compounds are there.

Below this mycobacterial outer membrane there is AGP which stands for arabinogalactan peptidoglycan. So again, in case of gram-negative bacteria there is outer membrane and below that there is a thin peptidoglycan is there, so similarly something similar present in the Mycobacterium tuberculosis as well and this is basically AGP, arabinogalactan peptidoglycan which is consists of galactosamine residue, arabinogalactan and peptidoglycan and here you can see the image that it is quite complex.

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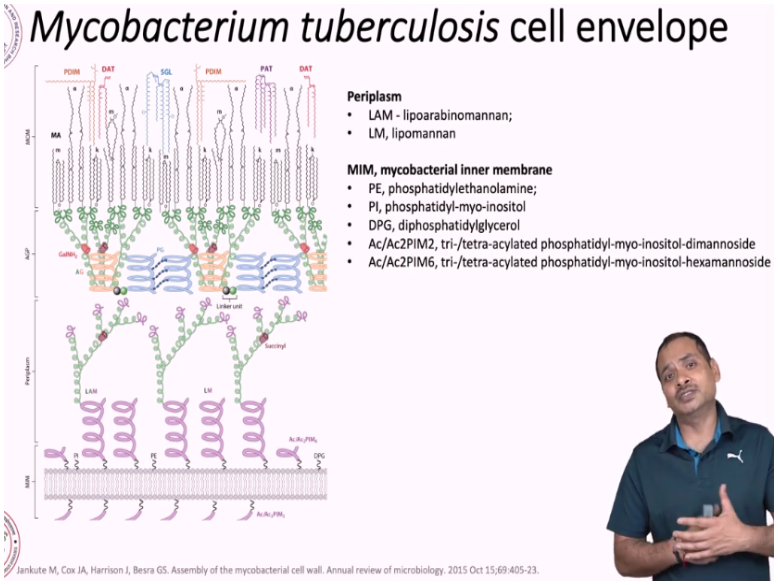

Below this AGP, there is a periplasm and this periplasm is again containing the complex lipid sugar molecules, here you can see that there is LAM lipoarabinomannan, there is LM this is lipomannan, so again this is a derivative of sugar and lipid. And below periplasm there is MIM, this is mycobacterial inner membrane and this consists of phosphatidylethanolamine and phosphatidyl-myo-inositol and DPG this is a diphosphatidylglycerol.

And there is a tri or tetra acyl phosphatidyl-myo-inositol-dimannoside and there is also tri and tetra acyl phosphatidyl-myo-inositol-hexamannoside, so understand this is a quite complex molecule which is made from sugar as well as lipid.

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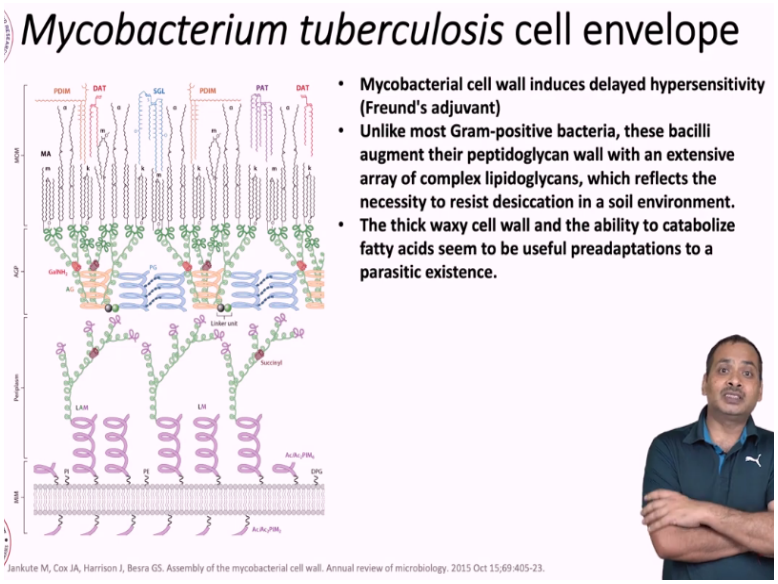

Now what is the function of this thick envelope? So mycobacterial cell wall induces delayed type of hypersensitivity. So if it is injected into the animal or human then it will induce the

delayed type of hypersensitivity and due to this property it is used as a complete Freund's ~~fluent~~ adjuvant. So if you remember the complete Freund's ~~fluent~~ adjuvant is basically consists of heat killed dried Mycobacterium tuberculosis mixed in the mineral oil.

So mineral oil is basically an oil kind of thing in that there is dried powder of Mycobacterium tuberculosis we add and this component basically induces the delayed type of hypersensitivity. So delayed type of hypersensitivity will enhance the immune response. So whatever antigen is present in this Freund's ~~fluent~~ adjunct then there will be a slow release and then there will be a delayed type of a hypersensitivity reaction.

So unlike most gram-positive bacteria, these bacilli augment their peptidoglycan wall with extensive array of complex lipoglycan which reflect the necessity to resist desiccation in soil environment. I have told you in previous slide that this bacteria will survive even it is sun dried why because of this property. The thick waxy cell wall has ability to catabolize fatty acid, so this has a lot of fatty acid, seems to be useful preadaptation to a parasitic existence.

So with this, I will stop the first session about the Mycobacterium tuberculosis. In next session I will discuss about the pathology and test and then subsequently I will discuss about the anti-tuberculosis ~~colossus~~ drugs. Thank you.