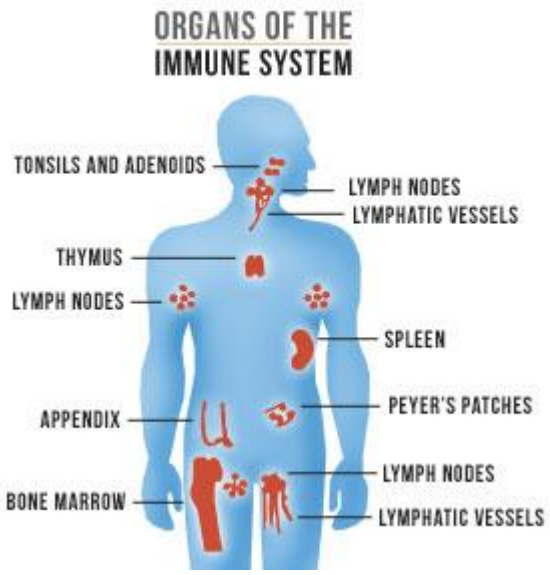
Immunology of tuberculosis

Respiratory block

Second lecture



Brought to you by:

Muath Alsabih
Walled Muhammad
Bayan Al-Amr

- **Objectives:**

- To know how M. tuberculosis infection is contracted and its initial encounter with the immune system.
- To understand delayed type of hypersensitivity reaction against M. tuberculosis
- To be familiar with the possible outcomes of the infection with M. tuberculosis in immuno-competent and immuno-compromised hosts.
- To understand the basis of tuberculin test and its importance in gauging immunity against M. tuberculosis

- **Tuberculosis:** Is an example of an infection in which protective immunity & pathologic hypersensitivity coexist, and the lesions are caused mainly by the host response
- TB undergoes **hypersensitivity type IV (Cell mediated)**

- **Introduction**
- Mycobacterium tuberculosis is the second most common infectious cause of death in adults worldwide.
- The human host serves is the natural reservoir for M. tuberculosis.
- The disease incidence is magnified by the concurrent epidemic of human immunodeficiency virus (HIV) infection

- **Mode of transmission:**
- Infection is acquired by **inhalation of M.tuberculosis** in aerosols and dust (airborne transmission)
- Infected people cough up large numbers of mycobacteria
- The organisms waxy outer coat can withstand (resist) drying and survive for long periods in air and house dust around **6-8 hours.**
- **Virulence factors of M.tuberculosis bacteria:**

1. Waxy coat blocks phagocyte (**lysosomal**)enzymes of macrophages.
2. Catalase-peroxidase, which resists the host cell oxidative response and that will help the bacteria to survive.
3. Lipoarabinomannan (LAM) a glycolipid (Secreted from Mycobacterium Tuberculosis):

   Can induce cytokines and resist host oxidative stress
   Interfere with antigen presentation by MHC class II molecules for priming CD4 T cells.

   Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage.

   Remember that CD4 and CD8 are T-lymphocytes:
   CD4: helper cells (Th1-Th2)
   CD8:Cytotoxic cells

- ***Immunology*:**

- **The majority of individuals in the general population who become infected with M. tuberculosis never develop clinical disease**

- **This demonstrates that the innate and adaptive immune response of the host in controlling TB infection is effective.**

  It is harder to develop TB if you..

  - **Get BCG vaccine.**
  - **Have strong innate immunity. (non-specific immunity)**
  - **Have strong adaptive immunity. (specific immunity includes lymphocytes an antibodies)**

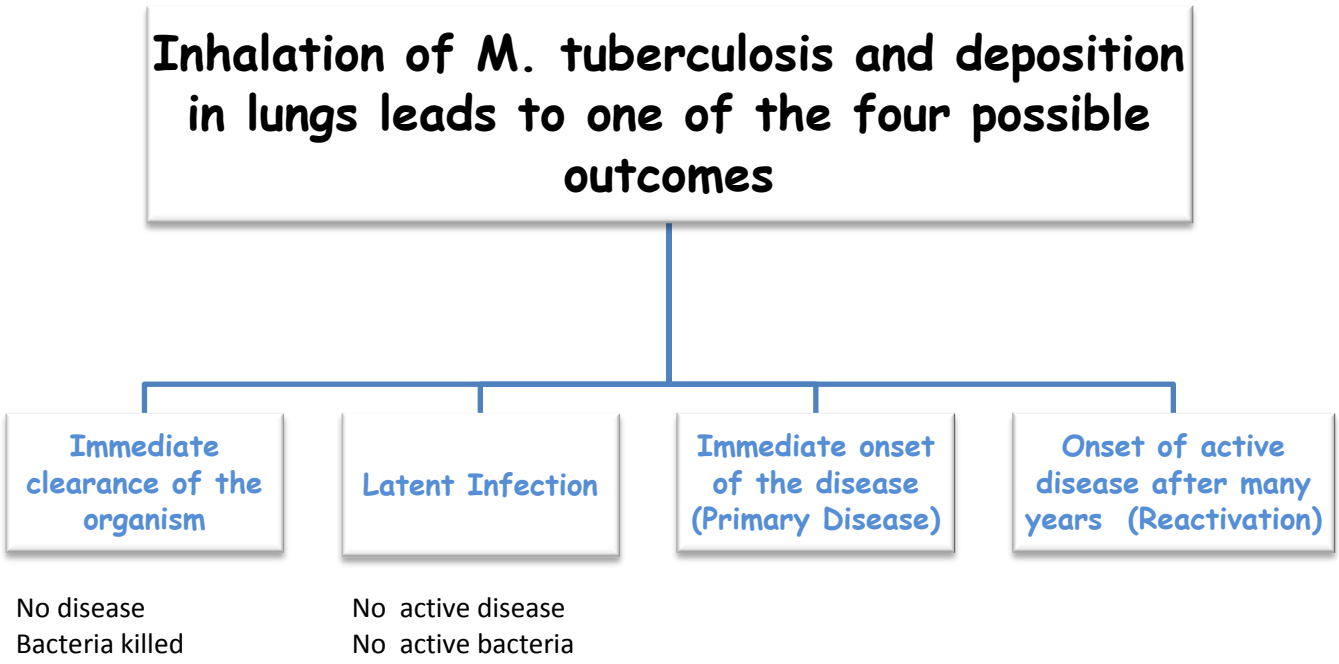
- **Host factors:**

  Innate immunity:

  The tubercle bacillus ultimately gets taken up by macrophages and has evolved several strategies to evade early intracellular killing mechanisms. These include:

  - **Resistance to reactive oxygen intermediates (ROIs)**
  - **Inhibition of phagosome-lysosome fusion**
  - **Inhibition of phagosome acidification (high PH)**
  - **Escape from the phagosomal compartment into the cytoplasmic space**

- ***Natural history infection*** **:**



First Fate: he got infected, but his immunity was stronger than M.Tuberculosis.

Second Fate: he got infected, but no active disease at this stage , the bacteria won't replicate in this case.

Third Fate: he got infected and developed the disease.

Fourth Fate: The bacteria that was inside the body and in an inactive form, now it will become active; due to different reasons associated with low immunity like (HIV ,diabetes..etc.)

Primary disease

(Approximately 10% of infected individuals)

- The tubercle bacilli establish infection in the lungs after they are carried in droplets to reach the alveolar space.
- If the **innate defense system** of the host fails to eliminate the infection, the **bacilli proliferate** inside alveolar macrophages and eventually kill the cells.
- The infected macrophages produce cytokines and chemokines that attract other phagocytic cells, which eventually form a nodular granulomatous structure called the **tubercle**.
- If the bacterial replication **is not controlled, the tubercle enlarges** and the bacilli enter local draining lymph nodes.
- **This leads to lymphadenopathy**, a characteristic manifestation of primary TB.
- The lesion produced by the expansion of the tubercle into the lung parenchyma and lymph node involvement is called the **Ghon complex.**

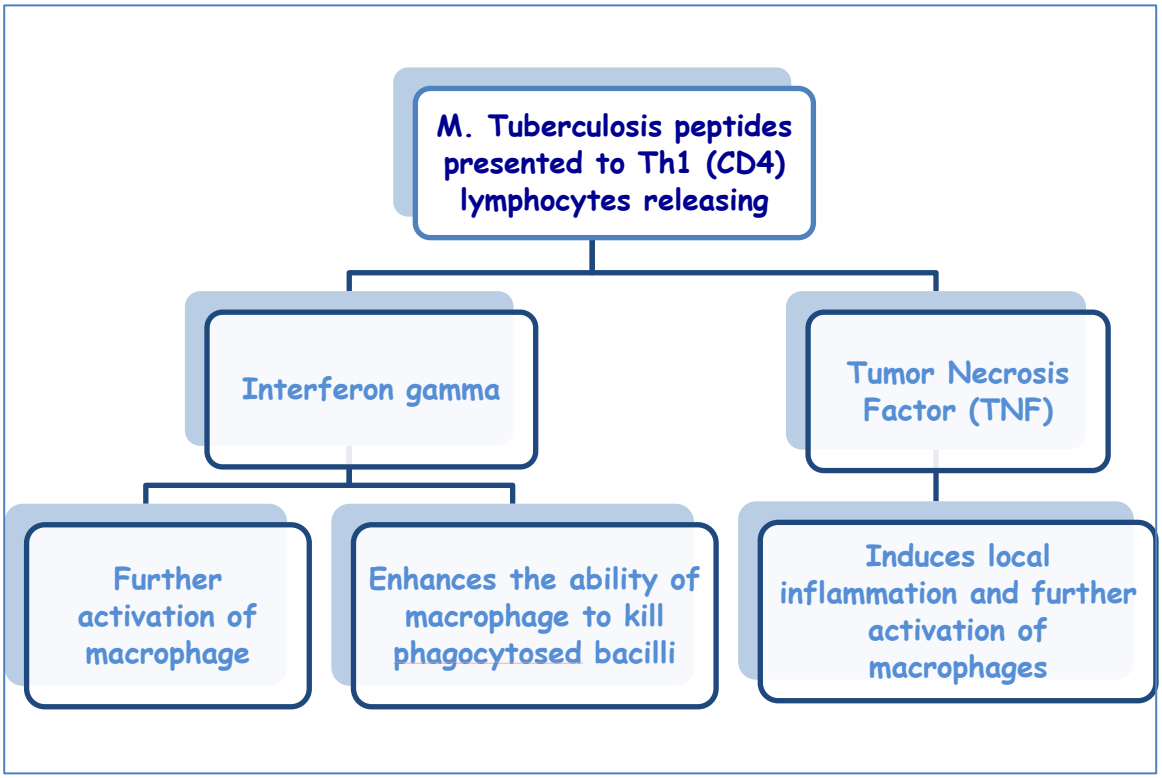
Ghon's Complex: Lesion in lung----produced by M.TUberculosis---- associated with enlargement, granuloma and involvement of Lymph nodes.

Summary: Inhale M.Tuberculosis > reach alveolar space > engulfed by alveolar macrophage > can't kill the bacteria > bacteria replicates > cytokines are released by macrophages > attract other macrophage > tubercle > enters lymph nodes>lymphadenopathy. (GHON COMPLEX)

- ***Ghon's and Ranke complex*:**
- The lung lesions (tubercles –small granulomas (Ghon's focus) and the enlarged lymph nodes constitutes **Ghon's complex**
- Tubercles may heal become **fibrotic or calcified and persist** as such for a lifetime (**Ranke Complex**)

Ranke complex = fibrosis and calcification of tubercle = late stage Ghon's complex

- **Weeks after infection:**

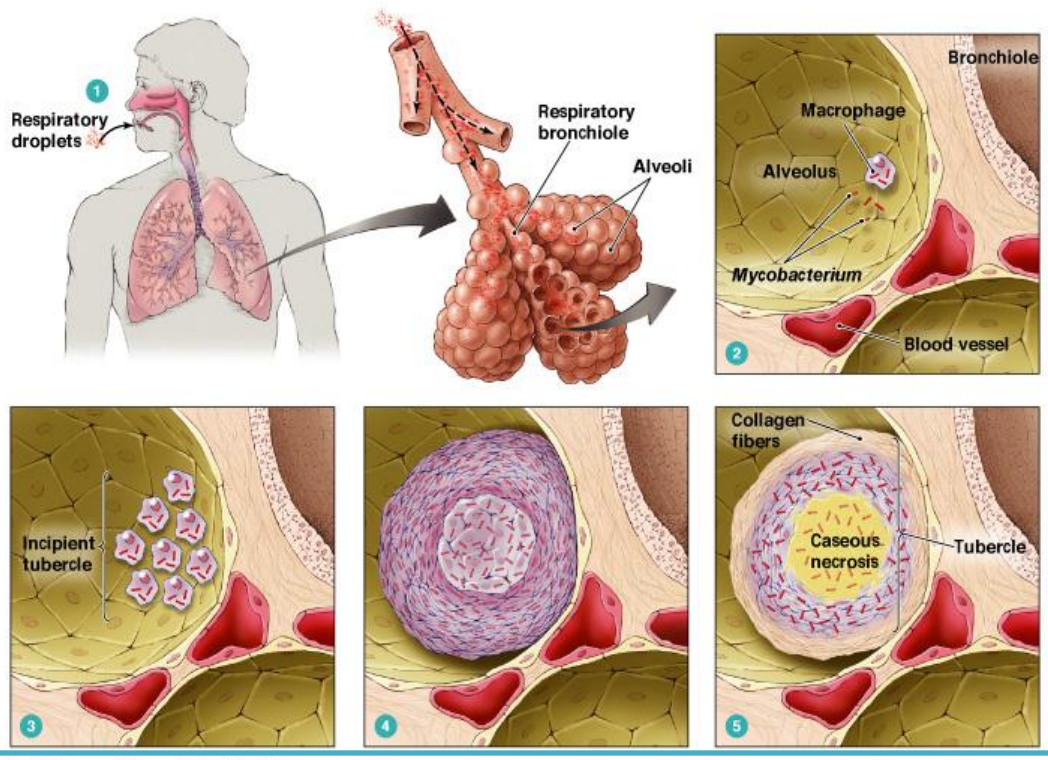


IFN-gamma: Also known as macrophage activating factor.

TNF: Helps in forming a focus.

Primary disease

- The bacilli continue to proliferate until an effective cell-mediated immune (CMI) response develops, usually two to six weeks after infection.
- Failure by the host to mount an effective CMI response and tissue repair leads to progressive destruction of the lung by:
  - Tumor necrosis factor (TNF)-alpha,
  - Reactive oxygen
  - Nitrogen intermediates
  - Contents of cytotoxic cells (CD8) (granzymes, perforin)
- All of the above may contribute to the development of caseating necrosis that characterizes a tuberculous lesion

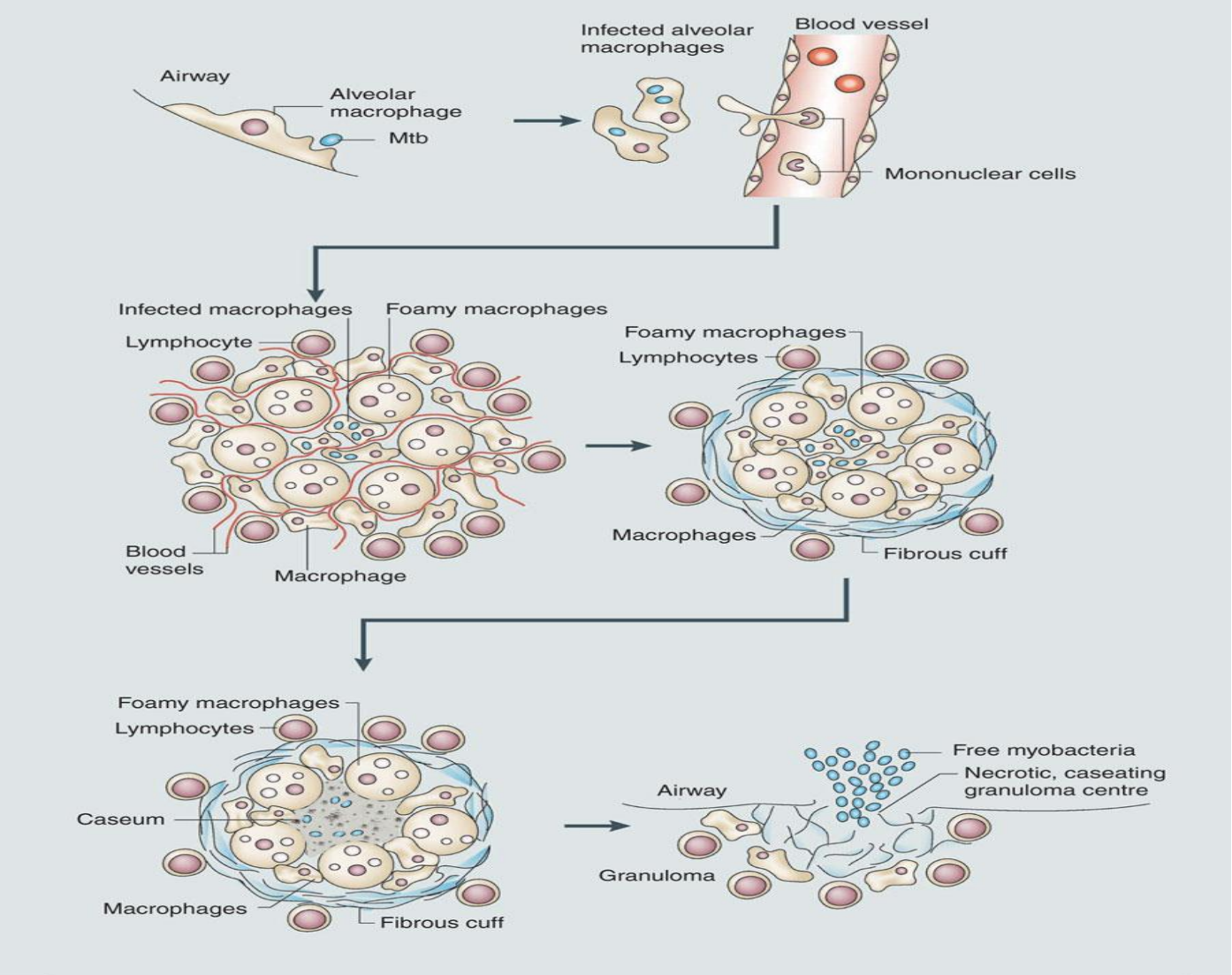


(a) Primary tuberculosis infection

1- Inhalation of M.Tubeculosis, then it Moves until it reaches alveolar space.
2- M.Tuberculosis and Macrophage reaction.
3-Cytokines are released and it will attract other macrophages to help in digesting M.Tuberculosis.
4- Bacteria is surrounded by other inflammatory cells, trying to contain the disease by forming a granuloma.
5- At late stages, there is formation of caseous necrosis and it will be surrounded by fiber collagen (fibrosis).

Outcomes

- **1- Bacilli can spread mechanically by erosion of the caseating lesions into the lung airways; at this point the host becomes infectious to others**



After formation of granuloma, if this granuloma opened (notice that a patient with TB will have more than one granuloma) we will have free mycobacteria in the airways of the lung. There mycobacteria will work as irritants and that will stimulate the irritant receptors. After stimulation of the receptors patient will cough mycobacteria outside. At this level the disease will be contagious (Open TB).

Outcomes

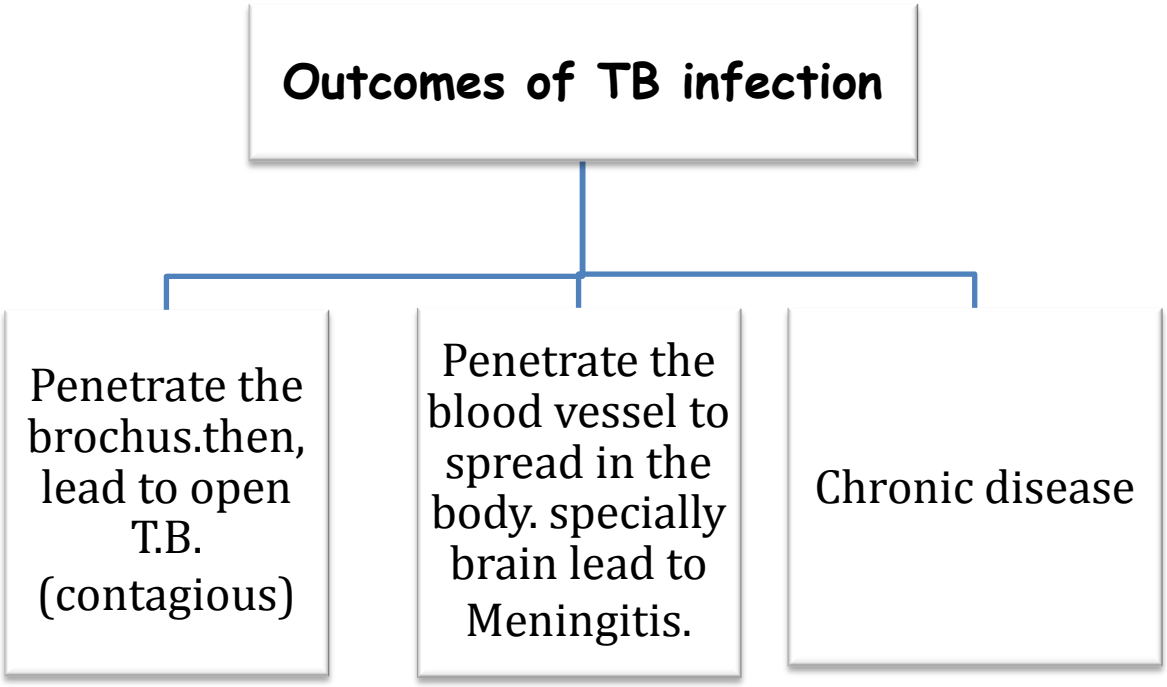
- ## 2-Miliary TB:

- Unchecked bacterial growth may lead to **hematogenous spread** of bacilli to produce disseminated TB.
- Disseminated disease with lesions resembling millet seeds has been termed miliary TB.
- **Most common presentation – TB meningitis.**

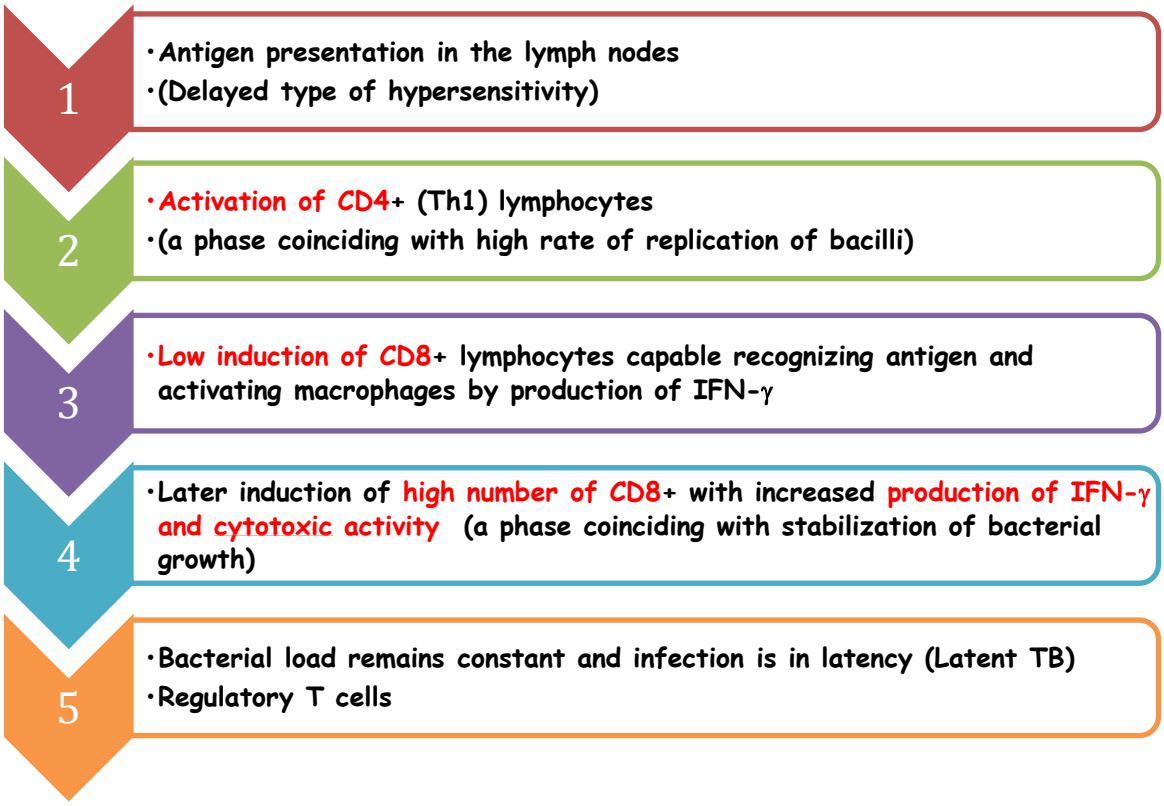
Tuberculin test is negative in a case of TB meningitis

- ## 3-Chronic disease:

- In the **absence of treatment,** death occurs in 80 percent of cases.
- The remaining patients develop **chronic disease or recover**.
- Chronic disease is characterized by repeated episodes of healing by fibrotic changes around the lesions and tissue breakdown.
- Complete spontaneous eradication of the bacilli is **rare.**


Outcomes of TB infection
Penetrate the brochus.then, lead to open T.B. (contagious)
Penetrate the blood vessel to spread in the body. specially brain lead to Meningitis.
Chronic disease

Latent Tuberculosis



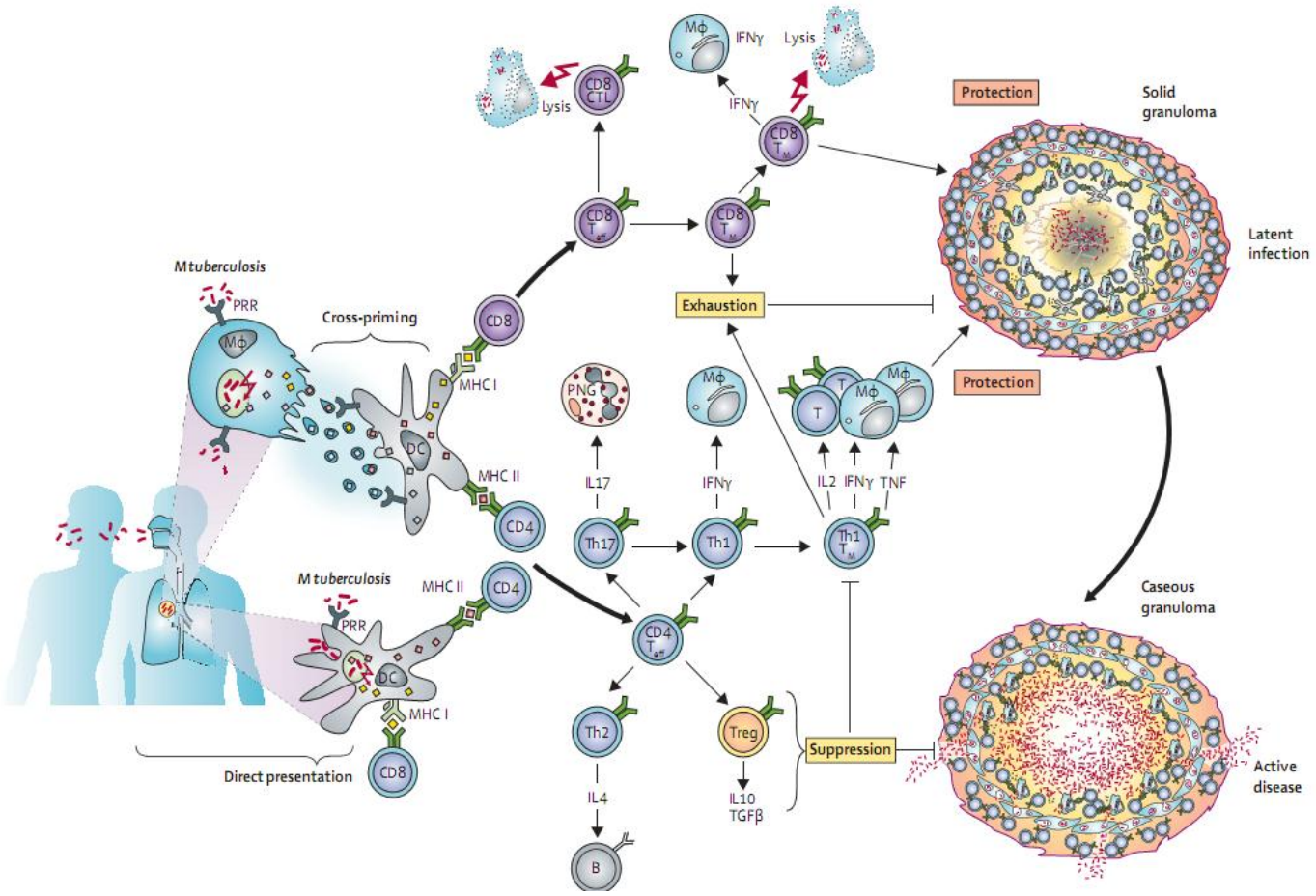
First cell to encounter with MTB is macrophages BUT immunity to tubercular infection is primarily mediated by TH1 cells, which stimulate macrophages to kill bacteria.

- This period of latency is sustained predominantly by a population of **non-replicating bacilli** rather than a population of growing bacilli.
- It is believed that the immune response is mainly directed towards **antigens secreted by growing bacilli.**
- Therefore non-replicating bacilli will be **less** obvious to the protective cellular response.
- This state correlates directly with an innate **resistance to anti-Mtb** drugs, most of which target processes active in replicating organisms.

Reactivation disease

1. Reactivation TB results from **proliferation of a previously dormant bacteria** seeded at the time of the primary infection.
2. Among individuals with latent infection and no underlying medical problems, reactivation disease occurs in approximately **5 to 10 percent** of cases.
3. The disease process in reactivation TB tends to be:
    - **Localized** (in contrast to primary disease)
    - **Little** regional lymph node involvement and **less caseation**.
    - The lesion typically occurs at the **lung apices**
    - **Disseminated disease is unusual**
4. **Immuno-suppression** is clearly associated with reactivation TB.
5. Associated conditions include:
6. **HIV infection and AIDS**
    - End-stage renal disease
    - Diabetes mellitus
    - Malignant lymphoma
    - Corticosteroid use
    - **Inhibitors of TNF-alpha and its receptor**
    - Diminution in cell mediated immunity associated with age

*Reactivation of latent lesions due to relapse of immune system.



PRR : Pattern Recognition Receptors.

Cross priming: denotes the ability of certain antigen-presenting cells to take up, process and present extracellular antigens with MHC class I molecules to CD8 T cells (cytotoxic T cells).

Large numbers of CD8 means containing the disease by forming solid granuloma.

CD4 activates Treg (regulatory T cells) inflammation will be suppressed by secreting IL-10 and TGF that will activate the disease.

Notice that a small amount of antibodies will form.

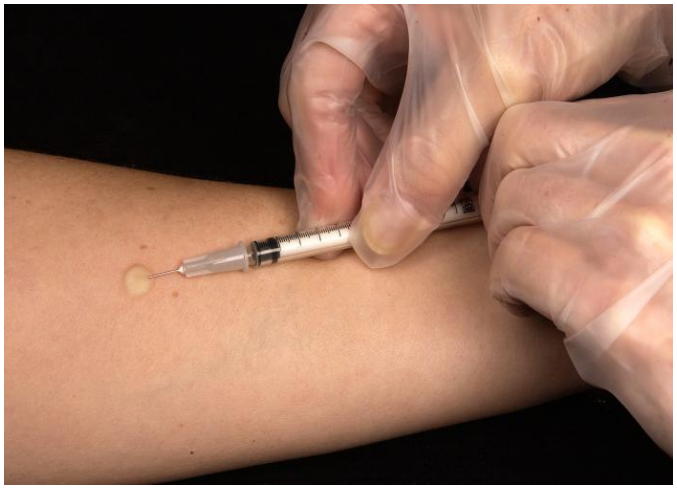
The role of the granuloma as a host protective factor needs a revision in thinking as it may also play a role in protecting the tubercle bacilli for its long-term survival in the host

Test for immunity against TB

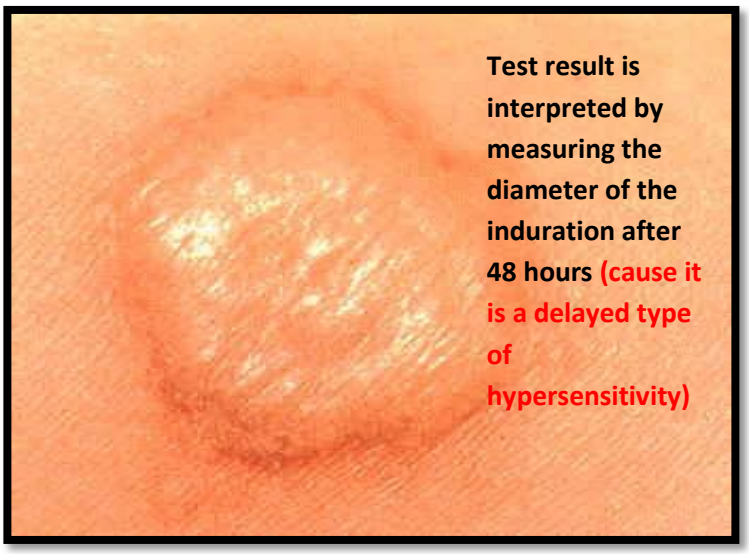
Delayed hypersensitivity skin test: Tuberculin test or (Mantoux)

Intradermal injection of PPD

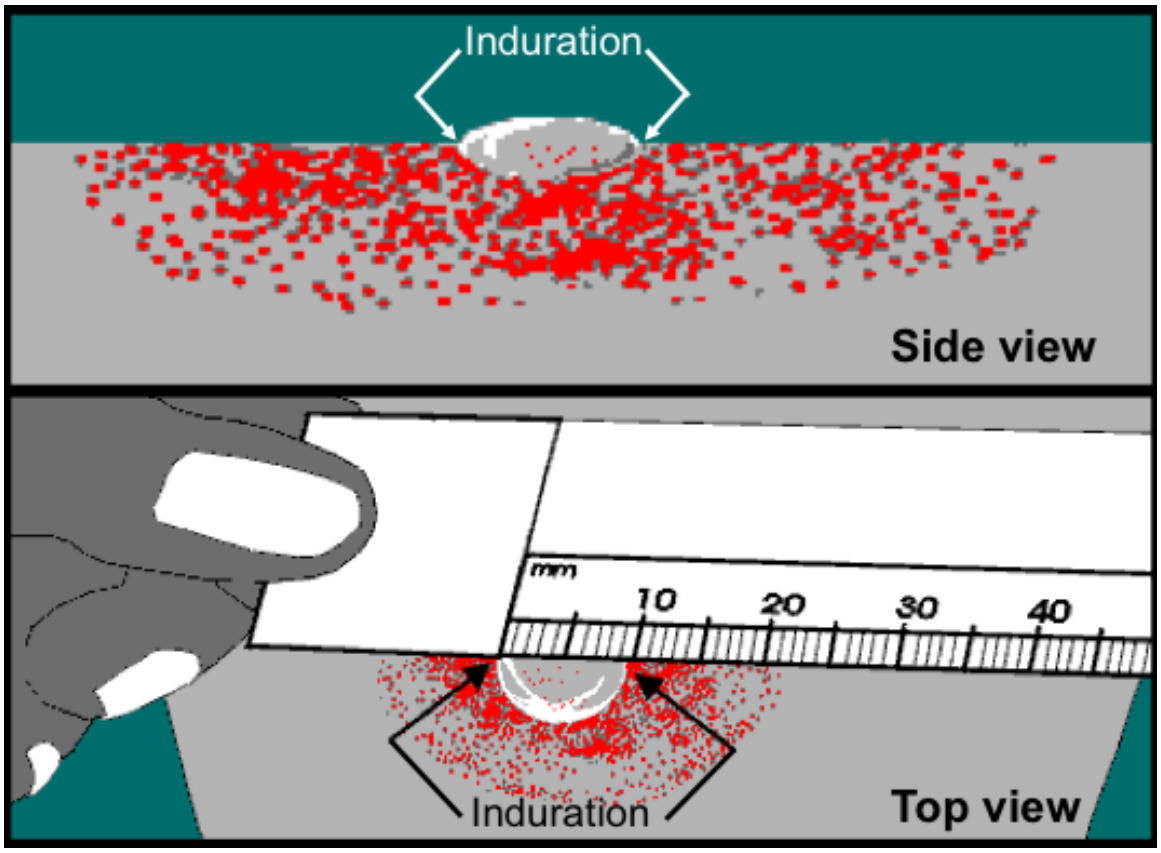
(purified protein derivative)



Correct interpretation of the result is unreliable in immuno-compromised states affecting CMI



Test result is interpreted by measuring the diameter of the induration after 48 hours (cause it is a delayed type of hypersensitivity)



Positive:

>10 mm= active disease.

<10mm= T.B. vaccine.(immunity is found) OR latent TB.

Negative = immuno-compromised.

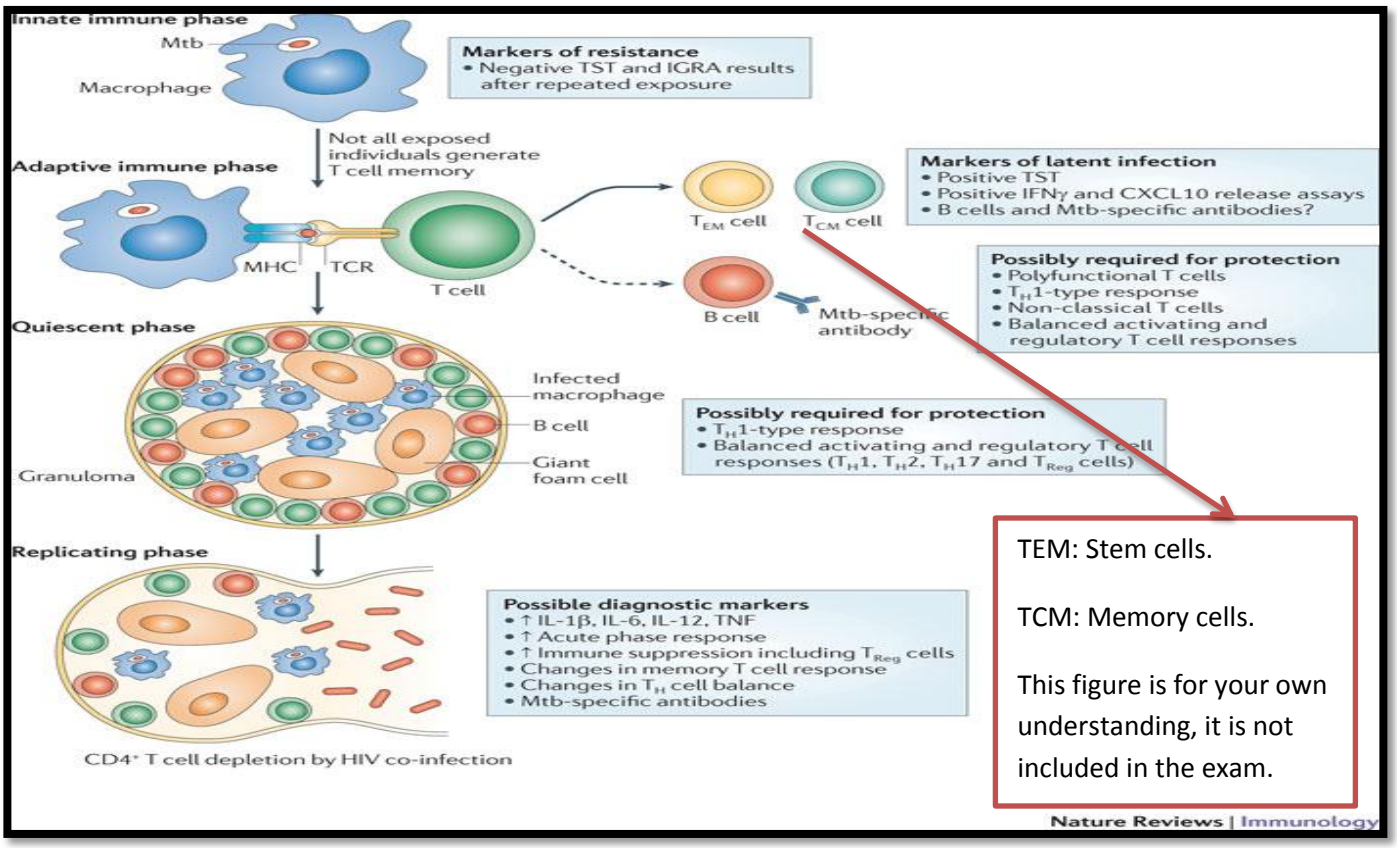
Delayed-type hypersensitivity (DTH) response

- The DTH response **does not correlate with protection against TB**, since numerous BCG vaccination trials have demonstrated that disease can occur in those who mount a DTH response.
- As a result, the protective T cell response must be distinguished from the T cell response associated with DTH.
- An in vitro **interferon-gamma release assay** has been developed.
- The assay is an **alternative** to the tuberculin skin test (TST) for detection of latent M. tuberculosis infection in human hosts.

IFN-γ release assay

- The test **measures** interferon-gamma released into blood from T cells when they are activated by M. tuberculosis antigens in vitro.
- The tests use antigens specific to M. tuberculosis including **the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein (CFP-10).**
- **These proteins are absent in vaccine strain BCG, or M. bovis.**
- **This enables the test to differentiate those latently infected with M. tuberculosis from those vaccinated with BCG.**

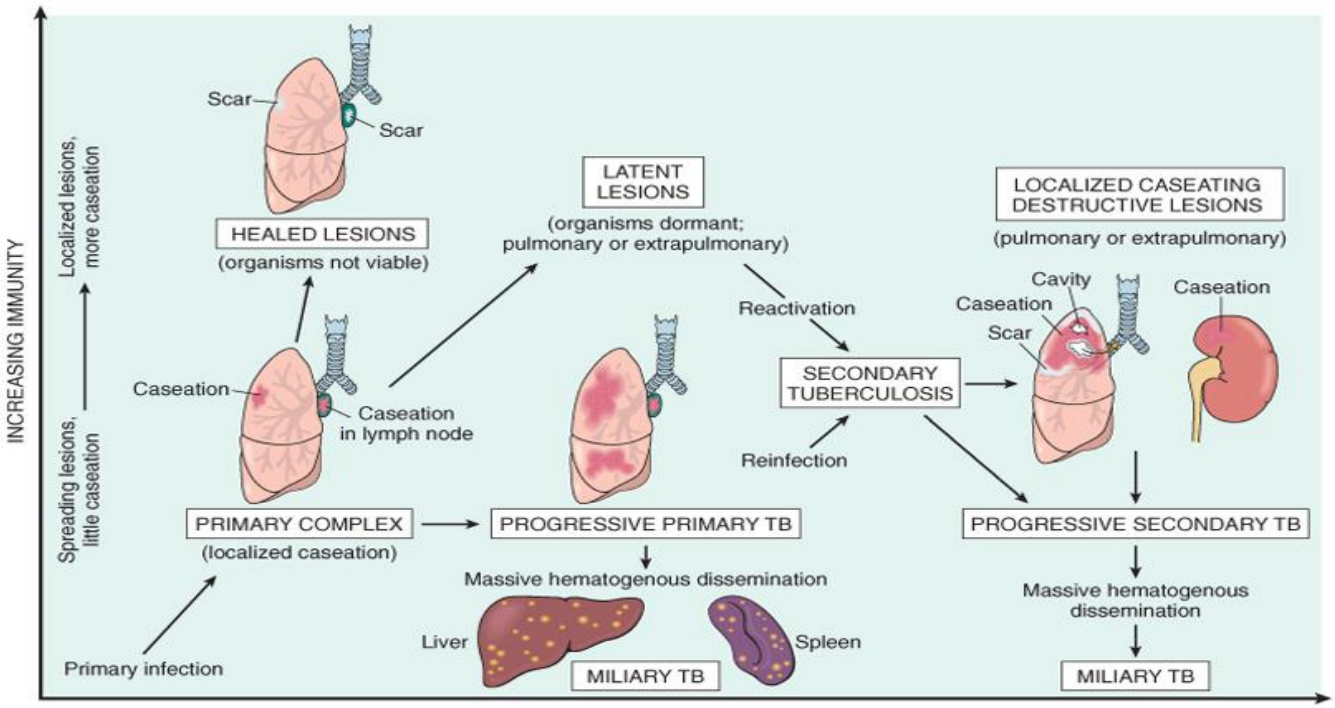
Even with BCG vaccine you are NOT immunized against these 2 antigens (ESAT-6) and (CFP-10).



TEM: Stem cells.

TCM: Memory cells.

This figure is for your own understanding, it is not included in the exam.



This Figure was taken from Robbins basic pathology book, it is not included in the slides but it can be very helpful.

Take home message

- **After exposure to M. tuberculosis immune handling of the infection determines the final outcome.**
- **Relatively small proportion of individuals develop primary disease**
- **Reactivation of tuberculosis can occur in patients who are immuno-compromised**
- **Tuberculin test should be interpreted with caution as it may be difficult to differentiate between DTH against M. tuberculosis and latent disease.**