MEDICINE
KING SAUD UNIVERSITY

Revised by
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Respiratory Block

Lecture Two

Immunology of Tuberculosis

IMMUNOLOGY
436's TEAMWORK

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 immunocompromised hosts.
- To know the basis of interferon gamma release assay and its potential to detect latent tuberculosis.
- To understand the basis of tuberculin test and its importance in gauging immunity against M. tuberculosis

- **Important.**
- **Extra notes.**
- **Doctors' notes**

Tuberculosis (TB)

It's an example of an infection in which **protective** immunity & **pathologic** hypersensitivity coexist, and the lesions are caused mainly by the host response (immune cells response).

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 drying and survive for long periods in air and house dust.

Virulence factors:

- **Waxy coat** blocks phagocyte enzymes
- **Catalase-peroxidase**, which resists the host cell oxidative response
- **Lipoarabinomannan** (LAM) a **glycolipid**:

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

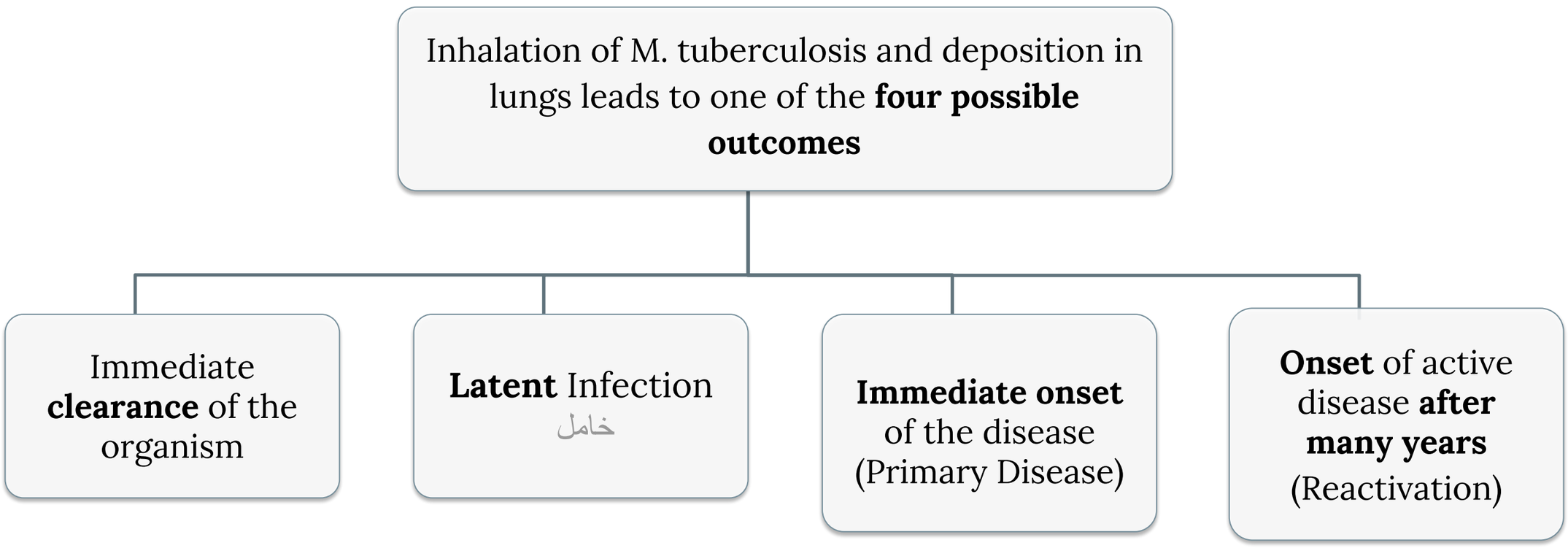
- The **majority** of individuals in the general population who become infected with M. tuberculosis **never develop** clinical disease
- This demonstrates that the **innate and adaptive immune response** of the host in controlling TB infection is effective.

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**.
    - Escape from the phagosomal compartment into the **cytoplasmic space**.

Natural History of Infection



Primary Disease Steps

(Approximately 10% of infected individuals):

1. The **tubercle bacilli establish** infection in the lungs after they are carried in droplets to reach the alveolar space.

2. If the innate defense system of the host fails to eliminate the infection, the **bacilli proliferate inside** alveolar **macrophages** and eventually kill the cells.

3. The infected **macrophages produce cytokines and chemokines** that attract other phagocytic cells, which eventually form a nodular granulomatous structure called the **tubercle**.

4. If the bacterial replication is not controlled, the tubercle enlarges and the bacilli **enter local draining lymph nodes**.

5. This leads to **lymphadenopathy**, a characteristic manifestation of primary TB.

6. The lesion produced by the expansion of the tubercle into the lung parenchyma and lymph node involvement is called the **Ghon complex**.

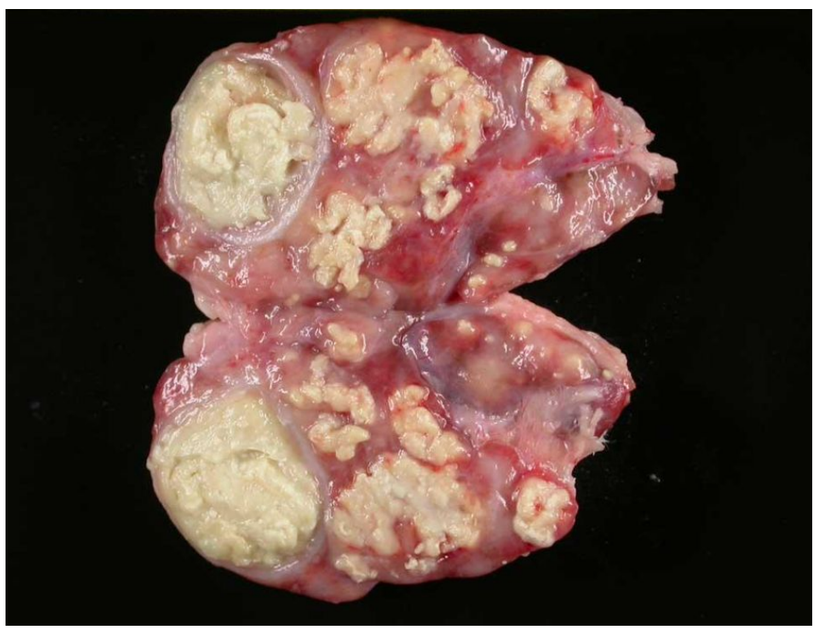
    Ghon's and Ranke complex:

    - 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)**.

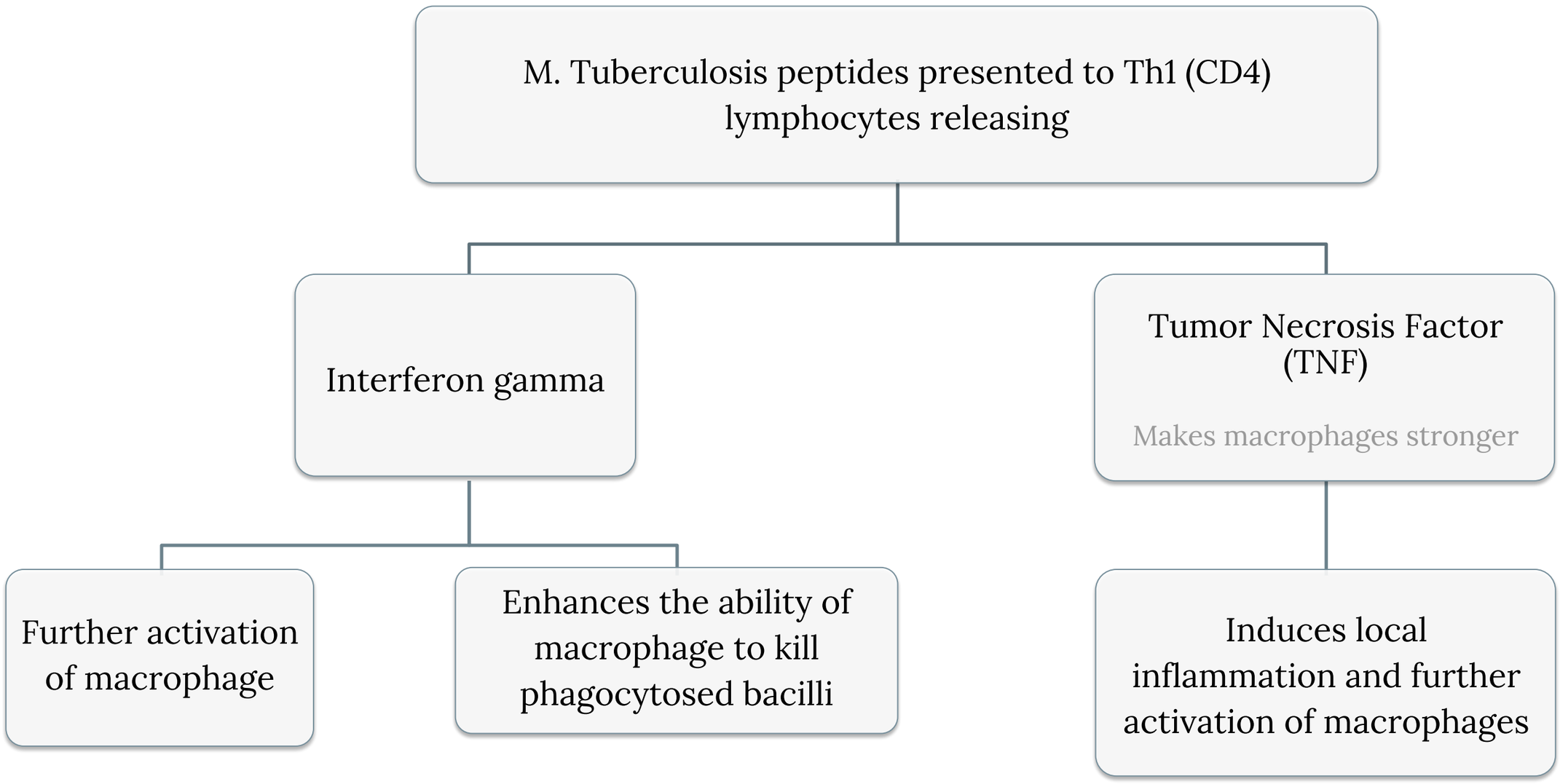
7. The bacilli continue to proliferate until an effective cell-mediated immune (CMI) response develops, usually **two to six weeks** after infection.

8. 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 (granzymes, perforin) .

9. All of the above may contribute to the development of **caseating necrosis** that characterizes a tuberculous lesion.

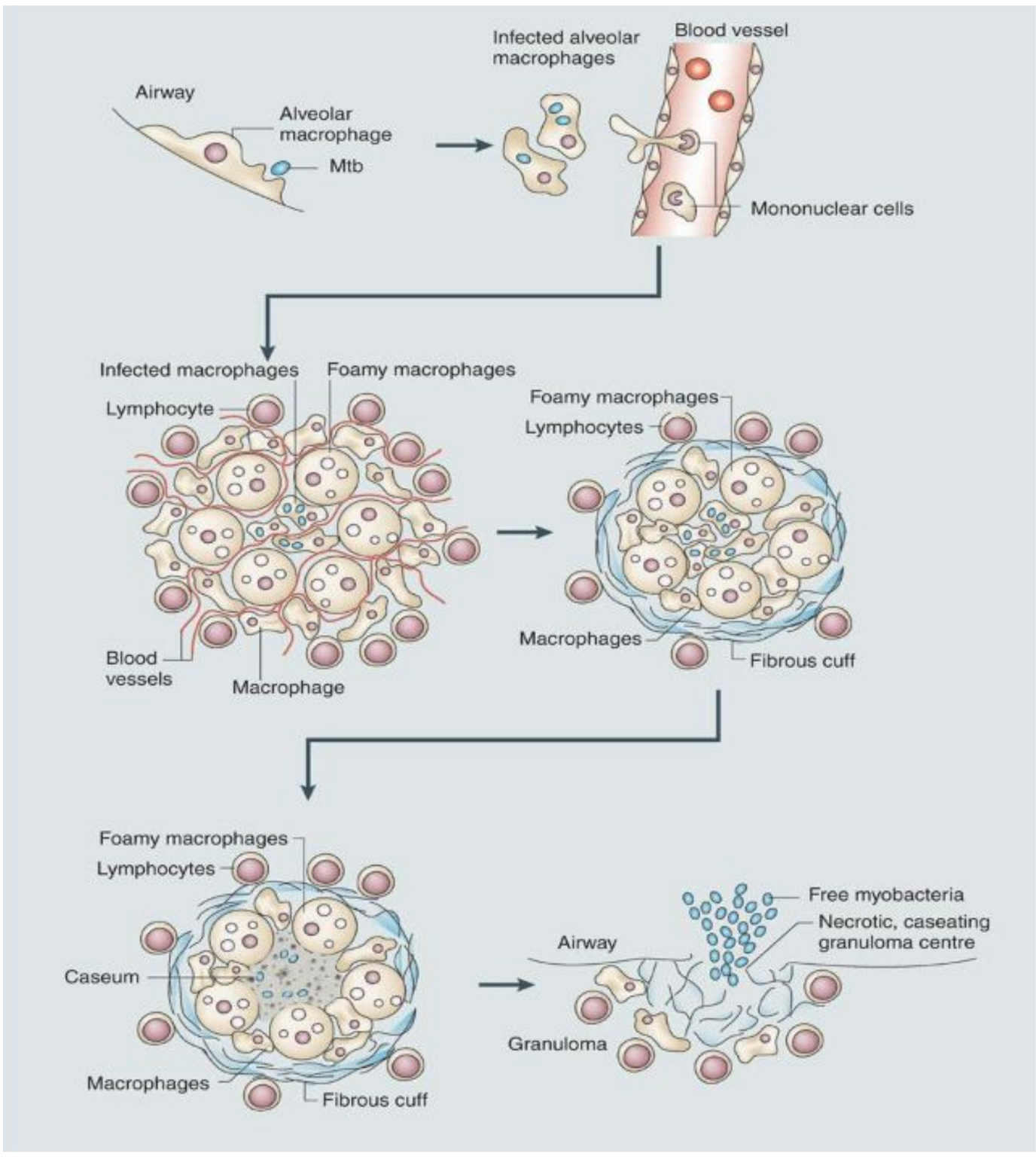


Weeks after infection



Outcomes:

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



Miliary and chronic TB

Unchecked bacterial growth may lead to **hematogenous spread** of bacilli to produce disseminated TB.

What is Disseminated TB?

Disseminated disease with lesions resembling millet seeds* has been termed **miliary TB**.
*على شكل بذور موزعة في مكان العدوى

- Most common presentation: **TB meningitis**.

Chronic TB:

- 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**.

Latent Tuberculosis Steps

1. • Antigen presentation in the lymph nodes
   • **(Delayed type of hypersensitivity)**
2. • Activation of CD4+ (Th1) lymphocytes
   • (a phase coinciding with high rate of replication of bacilli)
3. • Low induction of CD8+ lymphocytes capable of recognizing antigen and activating macrophages by production of IFN-γ
4. • Later induction of high number of CD8+ with increased production of IFN-γ and cytotoxic activity (a phase coinciding with stabilization of bacterial growth)
5. • Bacterial load remains constant and infection is in latency (Latent TB)

Latent Tuberculosis

Populated by **non-replicating bacilli** rather than a population of growing bacilli.

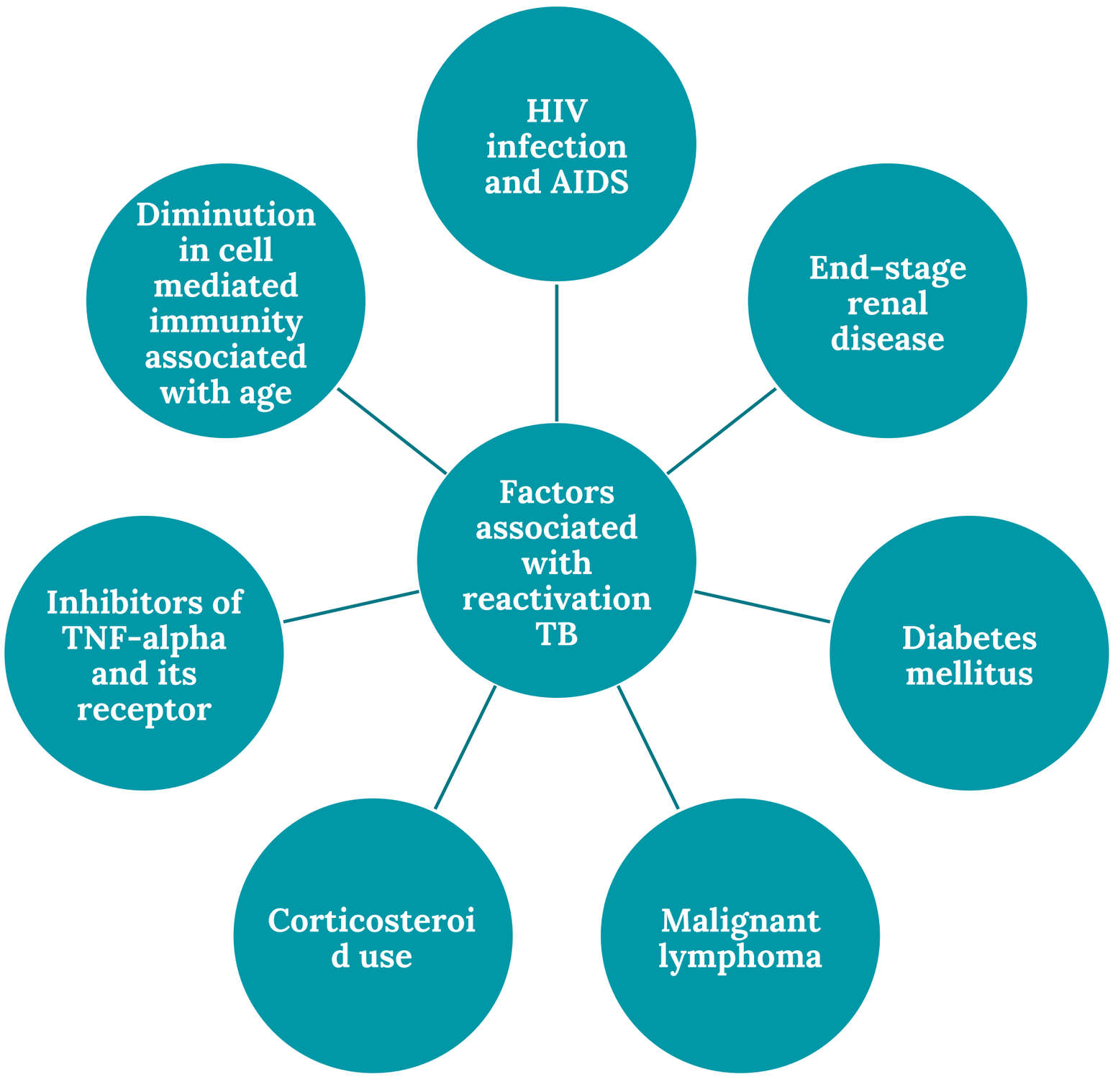
Why? because the immune response is mainly directed towards antigens secreted by **growing bacilli**. Therefore non-replicating bacilli will be **less obvious** to the protective cellular response. This state correlates (ترتبط) directly with an innate resistance to **anti-MTB drugs**. (TB drugs aren't effective in latent TB because the bacteria isn't proliferating while they act on the Bacteria's DNA)

Reactivation disease (2ry TB)

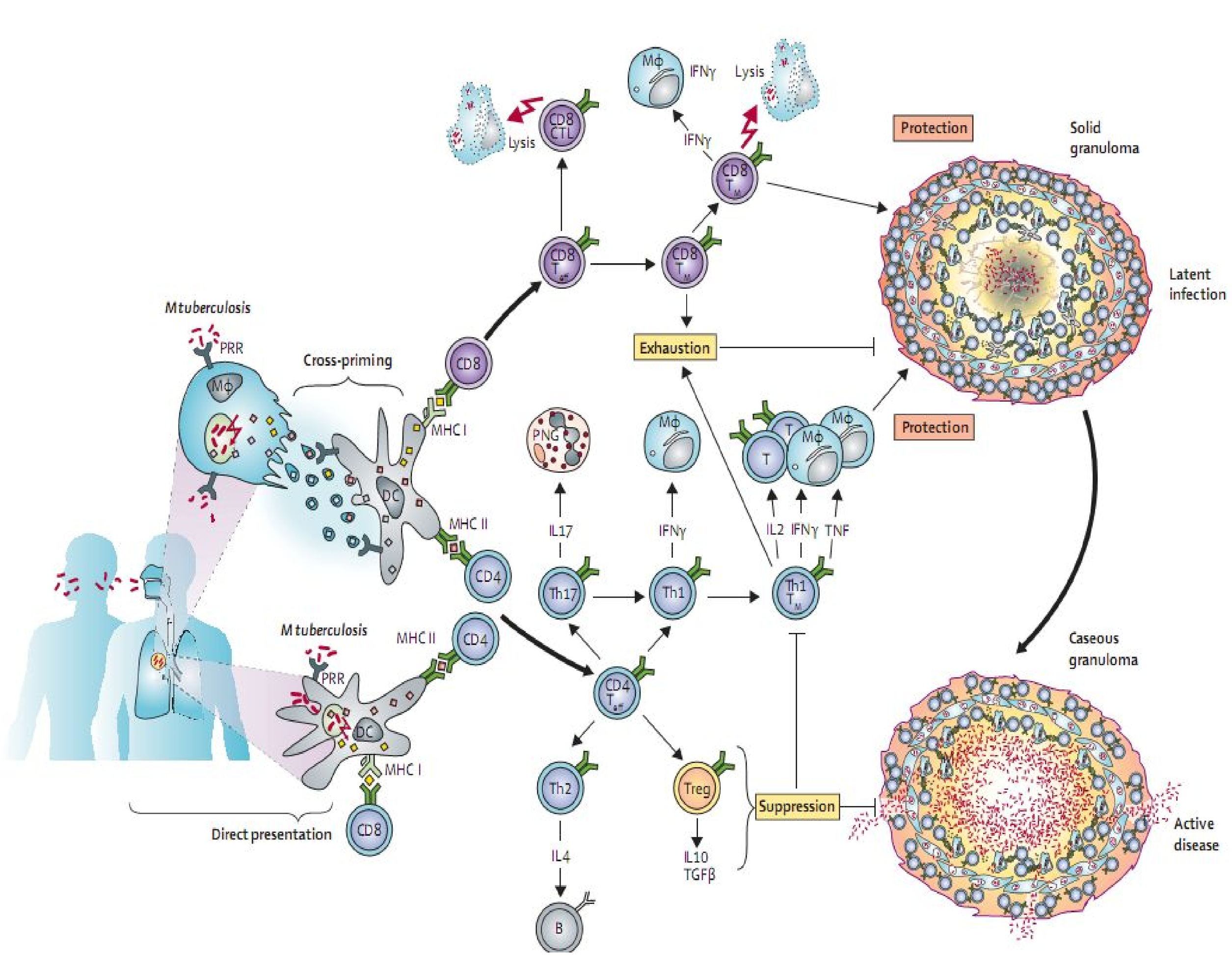
Reactivation TB results from **proliferation of a previously dormant bacteria** seeded at the time of the primary infection.
Among individuals with latent infection and no underlying medical problems, reactivation disease occurs in approximately **5% to 10%** of cases.
Immuno-suppression is clearly associated with reactivation TB.

Process in reactivation TB tends to be:

- **Localized** (in contrast to primary disease)
  - The lesion typically occurs at the lung apices
  - Since it's localized, little regional lymph node involvement and **less caseation.**
- **Disseminated** disease is unusual

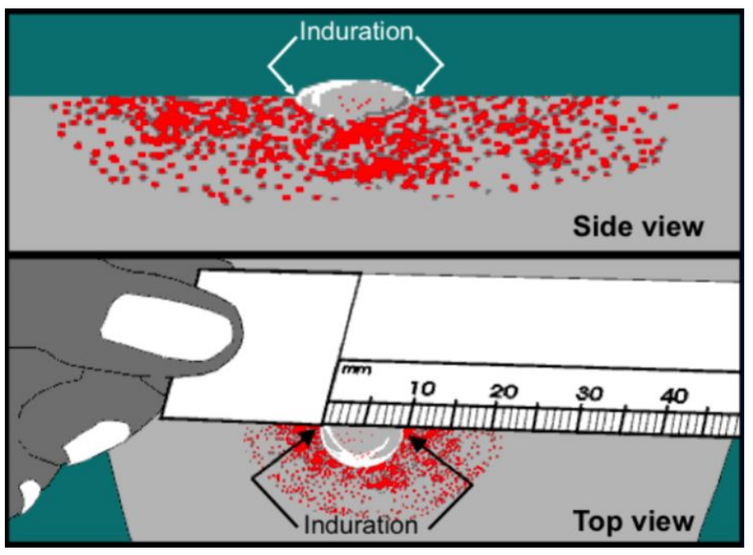


The role of the granuloma as a host protective factor needs a revision in thinking as it may also play a role in protecting the tubercle bacilli for its long-term survival in the host



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 (cell mediated immunity).
- Test result is interpreted by measuring the diameter of the induration after 48 hours.

Delayed-Type Hypersensitivity (DTH) Response:

(Type IV Hypersensitivity) remember types of hypersensitivity we took in foundation block?

- 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. (to help us differentiate between DTH and Latent TB)

IFN-γ release assay:

- The assay is an alternative to the tuberculin skin test (TST) for **detection of latent M. tuberculosis** infection in human hosts.
- 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.

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.

Useful videos:

https://youtu.be/yR51KVF4OX0

https://youtu.be/IGZLkRN76Dc

MCQs

1- The M. tuberculosis proliferate inside which of the following inflammatory cell:

A) neutrophil b) dendritic cell c) macrophage

2- Most important cytokine in TB that enhance further activation of macrophage:

A) IL-5 B) IF- GAMMA C) IF-ALPHA D) IL-13

3- Which type of immunity is not important in TB:

a) innate immunity b) cell mediated immunity c) humoral immunity

4- Type of hypersensitivity in TB:

A) I B) II C) III D) IV

5- Interfere with antigen presentation by MHC class II molecules for priming CD4 T cells:

A) Catalase-peroxidase b) Lipoarabinomannan c) ESAT-6 d) IF-gamma

6- Tubercles may heal and become fibrotic or calcified:

a) Ghon's complex b) latent TB c) Ranke Complex

7- which of the following will have negative Tuberculin test:

a) latent TB b) Ghon's complex c) BCG vaccine d) Miliary TB

1-C
2-B
3-C
4-D
5-B
6-C
7-D

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