LECTURE 2

IMMUNOLOGY OF TUBERCULOSIS

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.

INTRODUCTION

Definition: an infection in which protective immunity & pathologic hypersensitivity coexist, and the lesions are caused mainly by the host response.

Second most common infectious cause of death in adults worldwide.

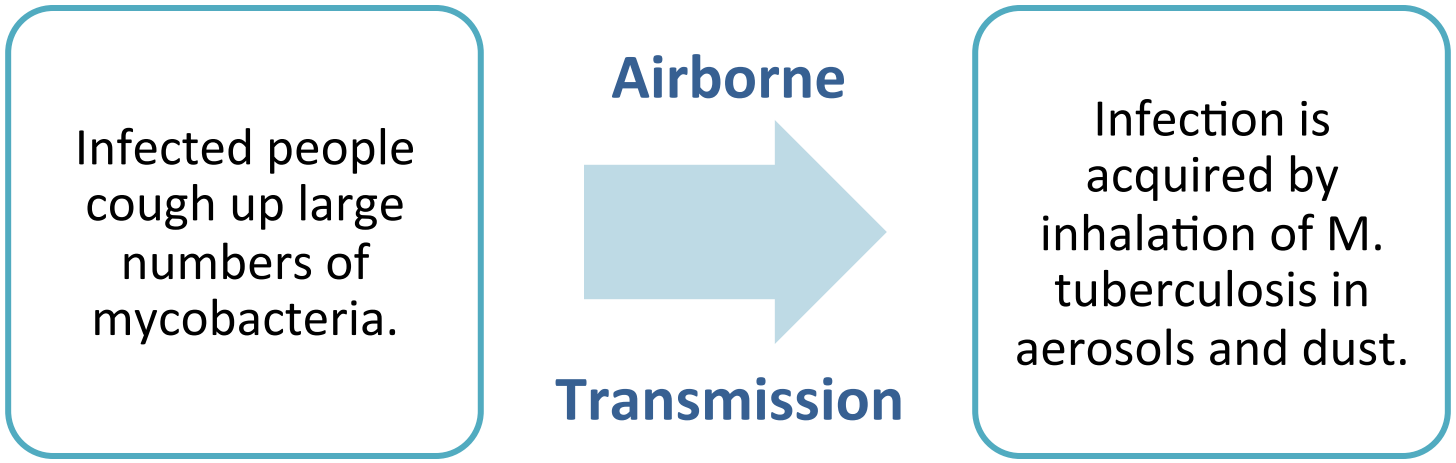
The human host serves as it's natural reservoir.

The disease incidence is magnified by the with cases (HIV) infection.

Note: *Reservoir* : a host for it to multiply in

MODE OF TRANSMISSION

How the transmission happens:



- **The organism's waxy outer coat:** can withstand drying and survive for long periods in air and house dust.

VIRULENCE FACTORS

What helps the infection grow:

Waxy Coat

- blocks *phagocyte enzymes*

Catalase-peroxidase

- resists the host cell *oxidative response*

Lipoarabinomannan (LAM)

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

IMMUNOLOGY

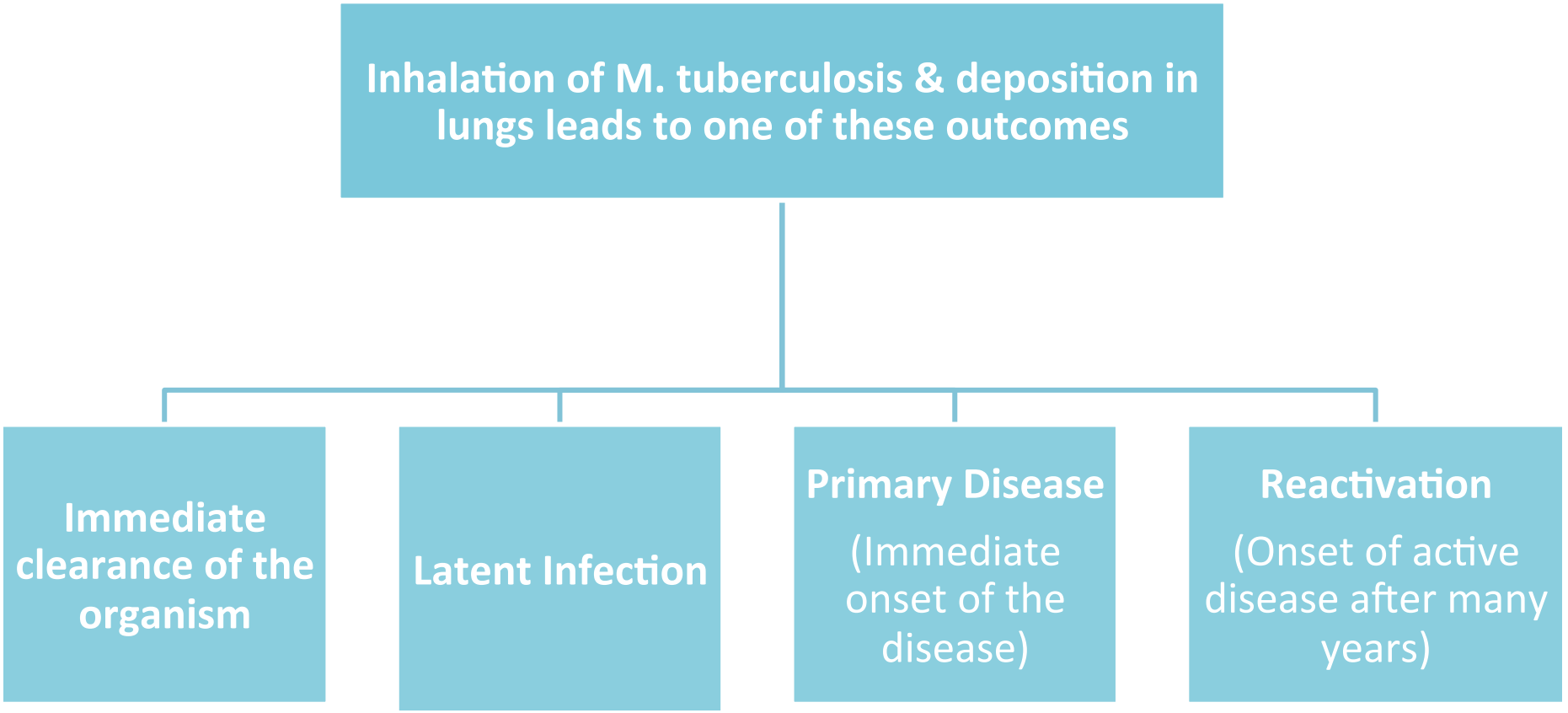
- The majority of infected individuals never develop clinical disease.
- This demonstrates that the innate and adaptive immune response of the host in controlling TB infection is effective.

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 phagosomal compartment into cytoplasmic space

NATURAL HISTORY OF INFECTION



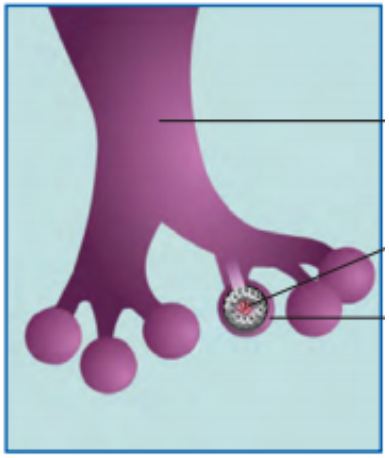
PRIMARY DISEASE

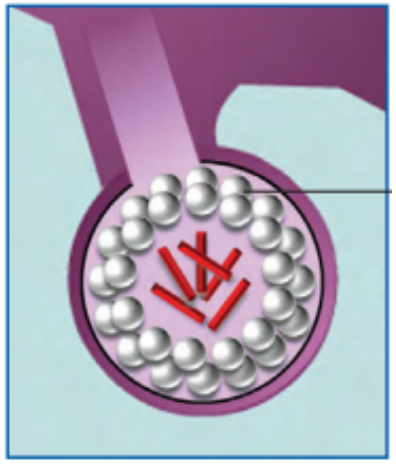
(10% OF INFECTED INDIVIDUALS)

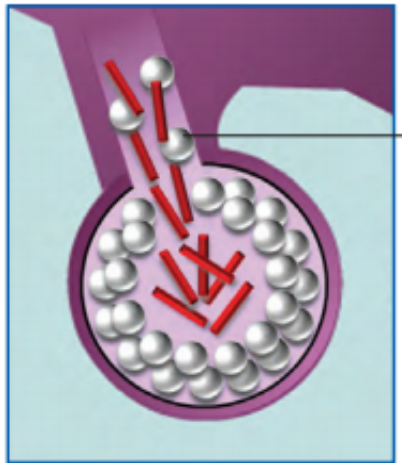
The tubercle bacilli establish infection in the lungs after they are carried in droplets to reach the alveolar space.

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.



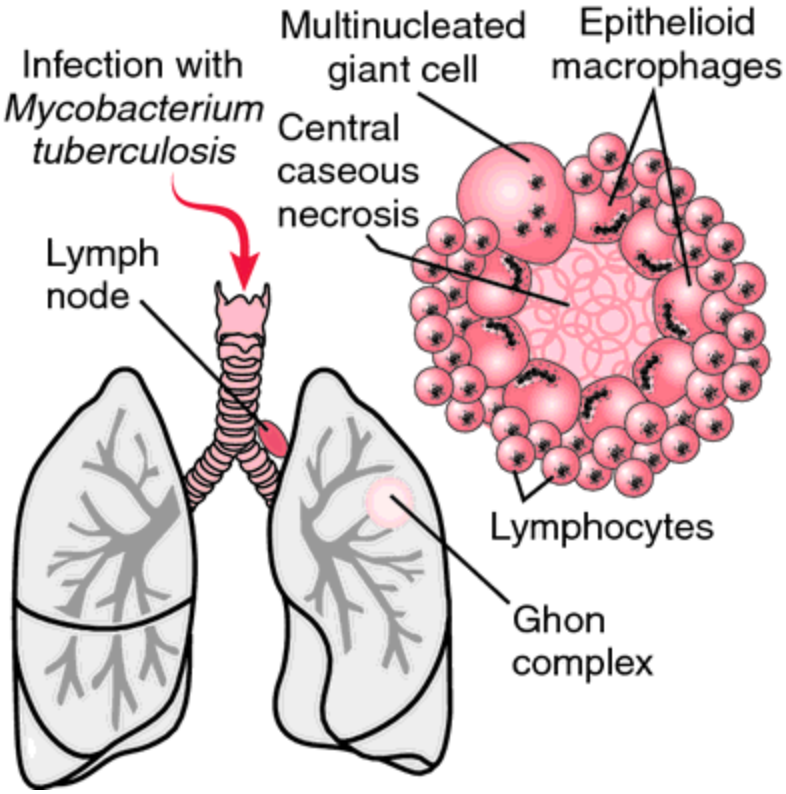




If the bacterial replication is not controlled, the tubercle enlarges and the bacilli enter local draining lymph nodes.

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 AND RANKE COMPLEX

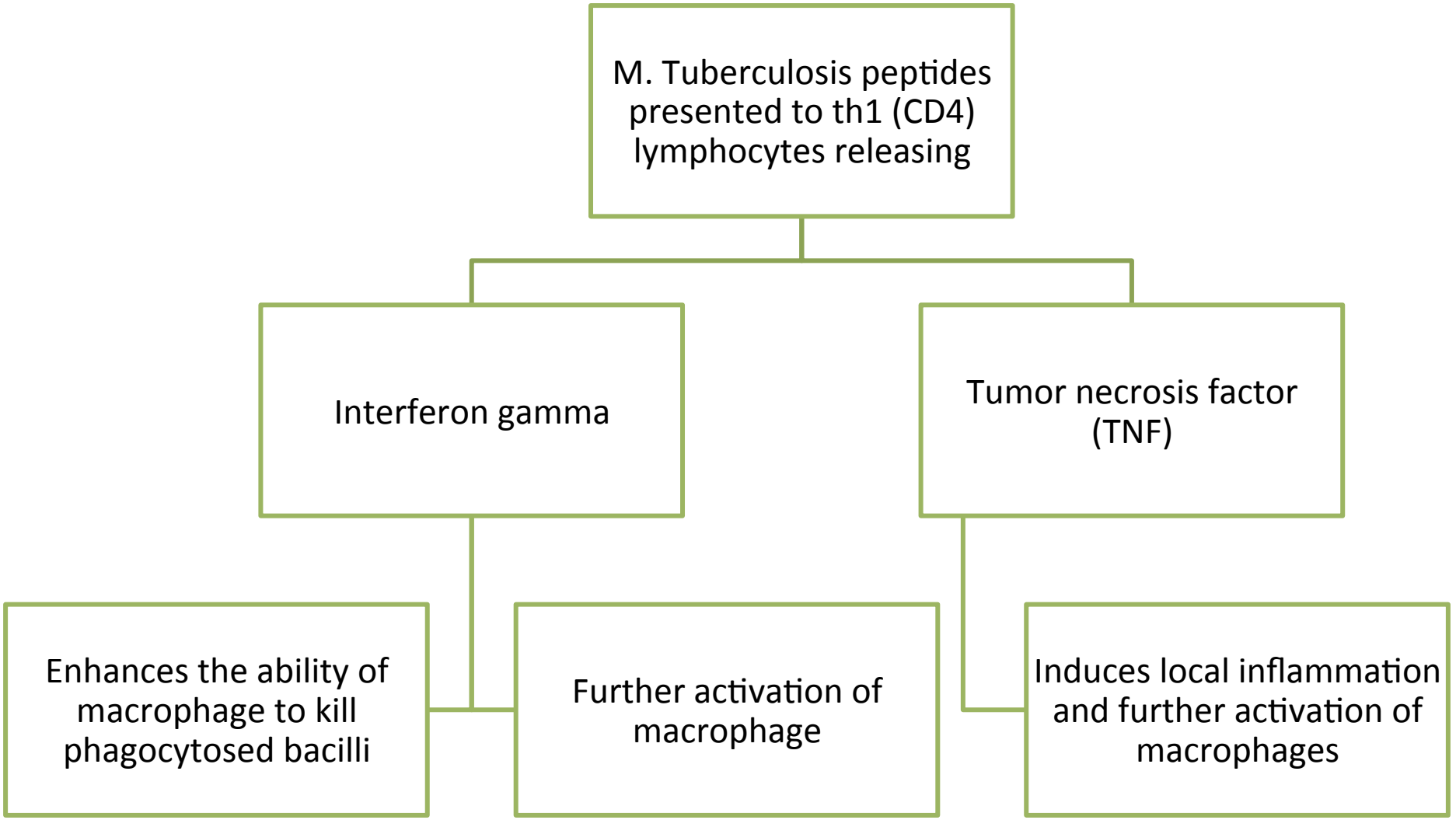
Ghon's

The lung lesions (tubercles –small granulomas (Ghon's focus) and the enlarged lymph nodes constitutes Ghon's complex.

Ranke's

Tubercles may heal become fibrotic or calcified and persist as such for a lifetime.

WEEKS AFTER INFECTION



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 (granzymes, perforin)
- All of the above may contribute to the development of caseating necrosis that characterizes a tuberculosis lesion.

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

Miliary TB	Chronic Disease
Unchecked bacterial growth may lead to hematogenous spread of bacilli to produce disseminated TB.	In the absence of treatment, death occurs in 80 percent of cases.
Disseminated disease with lesions resembling millet seeds has been termed miliary TB.	The remaining patients develop chronic disease or recover.
Most common presentation – TB meningitis.	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

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 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)

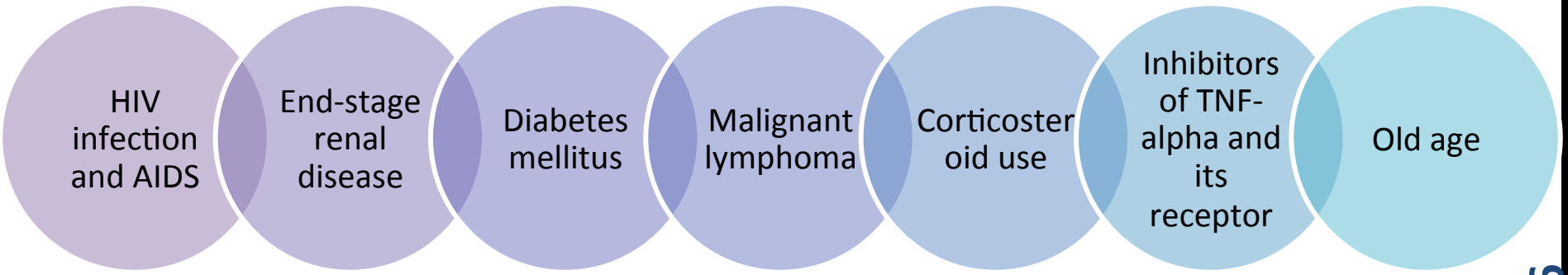
LATENT TB

- 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.

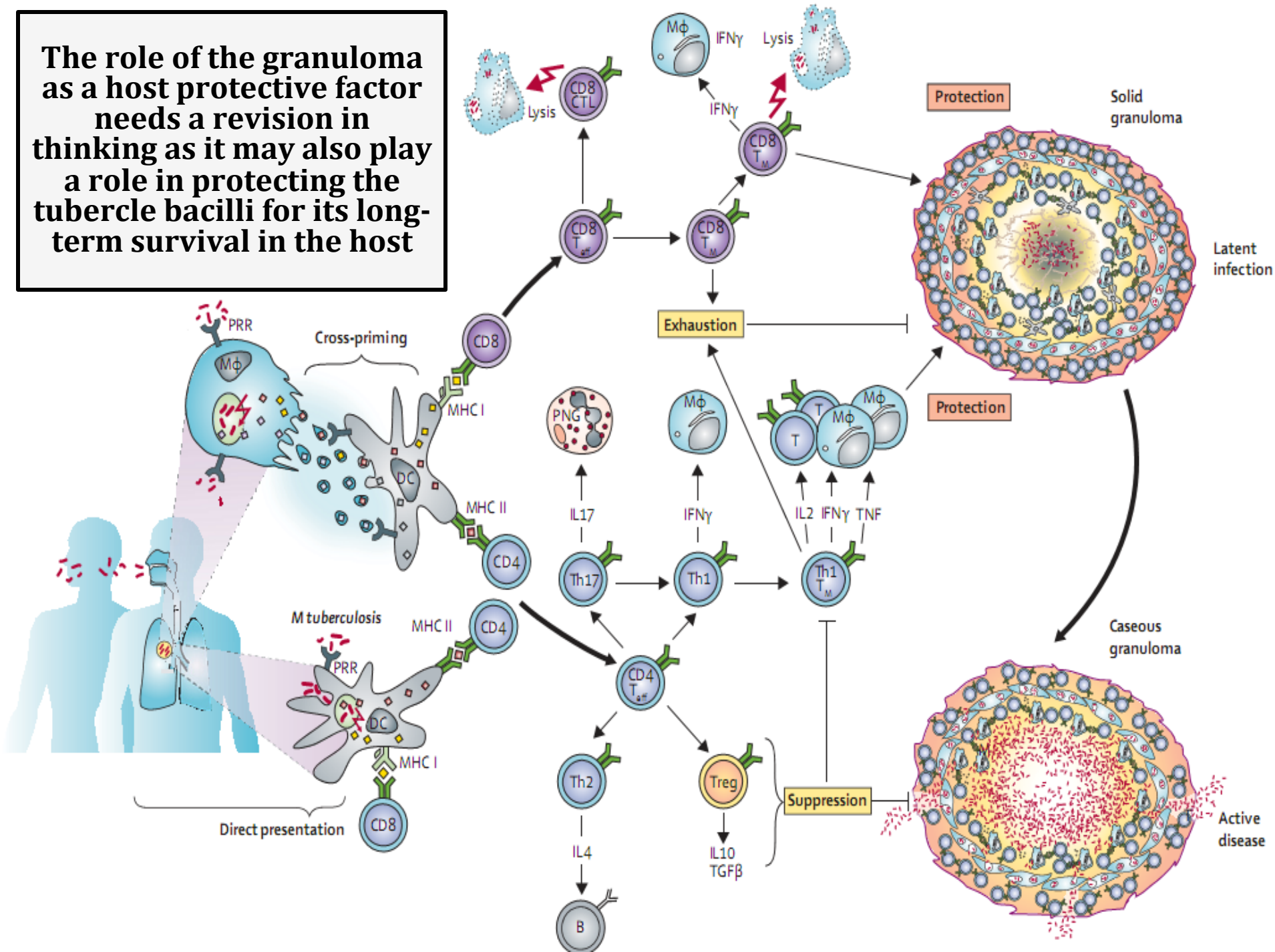
REACTIVATION DISEASE

- Reactivation TB results from proliferation of a previously dormant bacteria seeded at the time of the primary infection.
- Among individuals with latent infection reactivation disease occurs in approximately 5 to 10 percent of cases.
- 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

Immuno-suppression is clearly associated with reactivation TB.



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

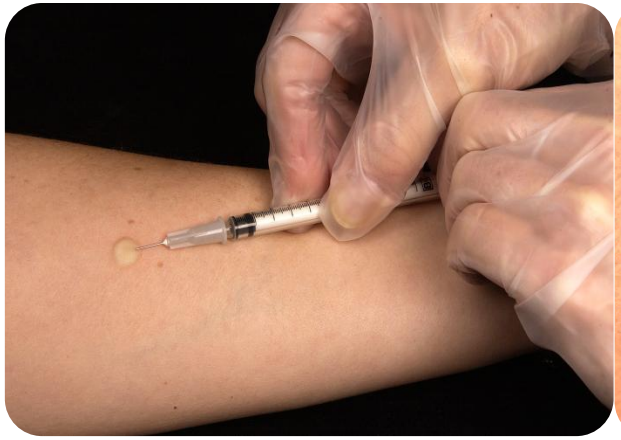


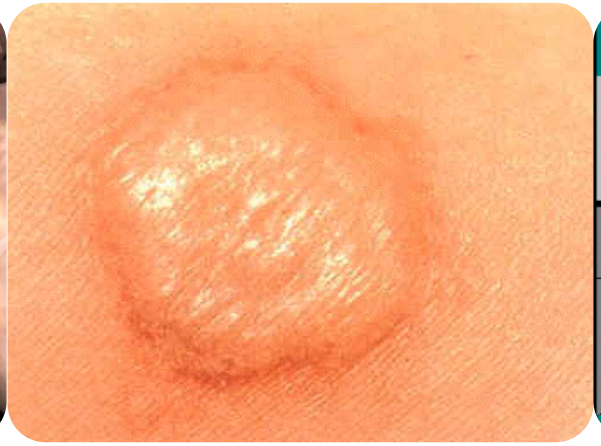
TEST FOR IMMUNITY AGAINST TB

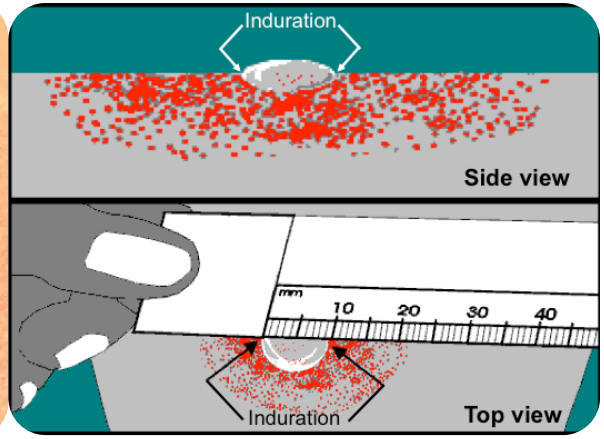
Delayed hypersensitivity skin test (Tuberculin test or Mantoux)

- Intradermal injection of PPD (purified protein derivative)
- Correct interpretation of the result is unreliable in immuno-compromised states affecting CMI

(e.g. not suitable for HIV patients)

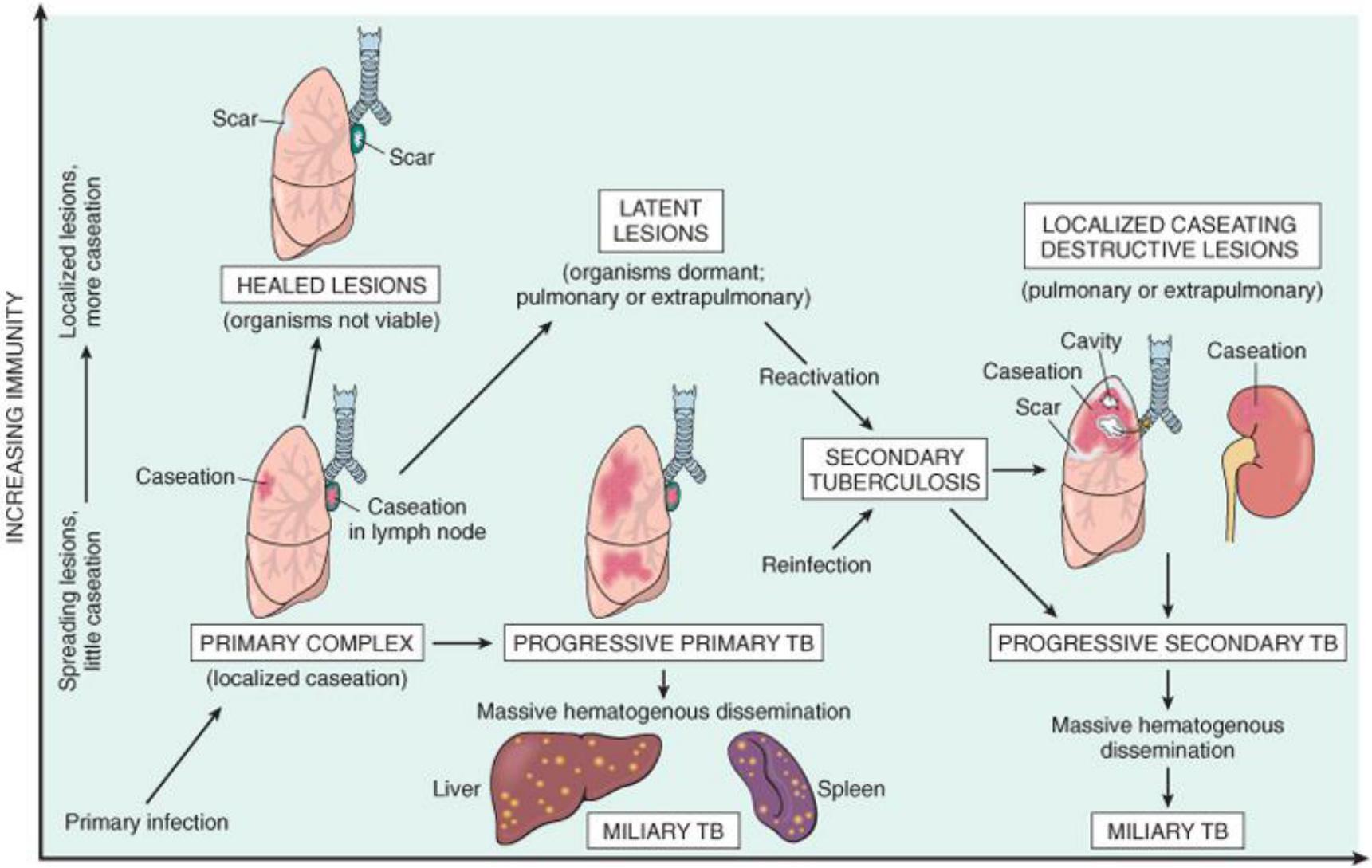






Delayed-type Hypersensitivity (DTH) Response	IFN-γ Release Assay
The DTH response does not correlate with protection against TB, since numerous BCG vaccination trials have demonstrated that disease can occur in those who mount a DTH response.	The test measures interferon-gamma released into blood from T cells when they are activated by M. tuberculosis antigens in vitro.
As a result, the protective T cell response must be distinguished from the T cell response associated with DTH.	The tests use antigens specific to M. tuberculosis including the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein (CFP-10).
An in vitro interferon-gamma release assay has been developed.	These proteins are absent in vaccine strain BCG, or M. bovis.
Assay is an alternative to the tuberculin skin test (TST) for detection of latent M. tuberculosis infection in human hosts.	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) & (CFP-10).



This figure will help you understand, it's taken from Robbin's Pathology

REMEMBER

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

MCQS

1- Primary TB affects approximately:

A- 5% B- 90% C- 10%

2- In the latent phase the IFN-g function is to:

A- Proliferate bacilli B- Activation of macrophages
C- Recruits Th1 cells

3- IFN-g release assay uses the following antigen:

A- (ESAT-6) & (ESAT-6) B- IGA C- IGE

4- Tuberculin test should be interpreted with caution as it may be difficult to differentiate between DTH against M. tuberculosis & latent

A- T B- F

1 C, 2 B, 3 A, 4 A