Immunology of Tuberculosis

Immunology Unit
Department of Pathology

Reference
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Chapter 15 Pages 508
Chapter 17 pages 564-565

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 (TB)

Is an example of an infection in which protective immunity & pathologic hypersensitivity coexist, and the lesions are caused mainly by the host response

Introduction

- Mycobacterium tuberculosis is the second most common infectious cause of death in adults worldwide.
- The human host serves as 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.

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.

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

Inhalation of M. tuberculosis and deposition in lungs leads to one of the four possible outcomes

- Immediate clearance of the organism
- Latent Infection
- Immediate onset of the disease (Primary Disease)
- Onset of active disease after many years (Reactivation)

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.

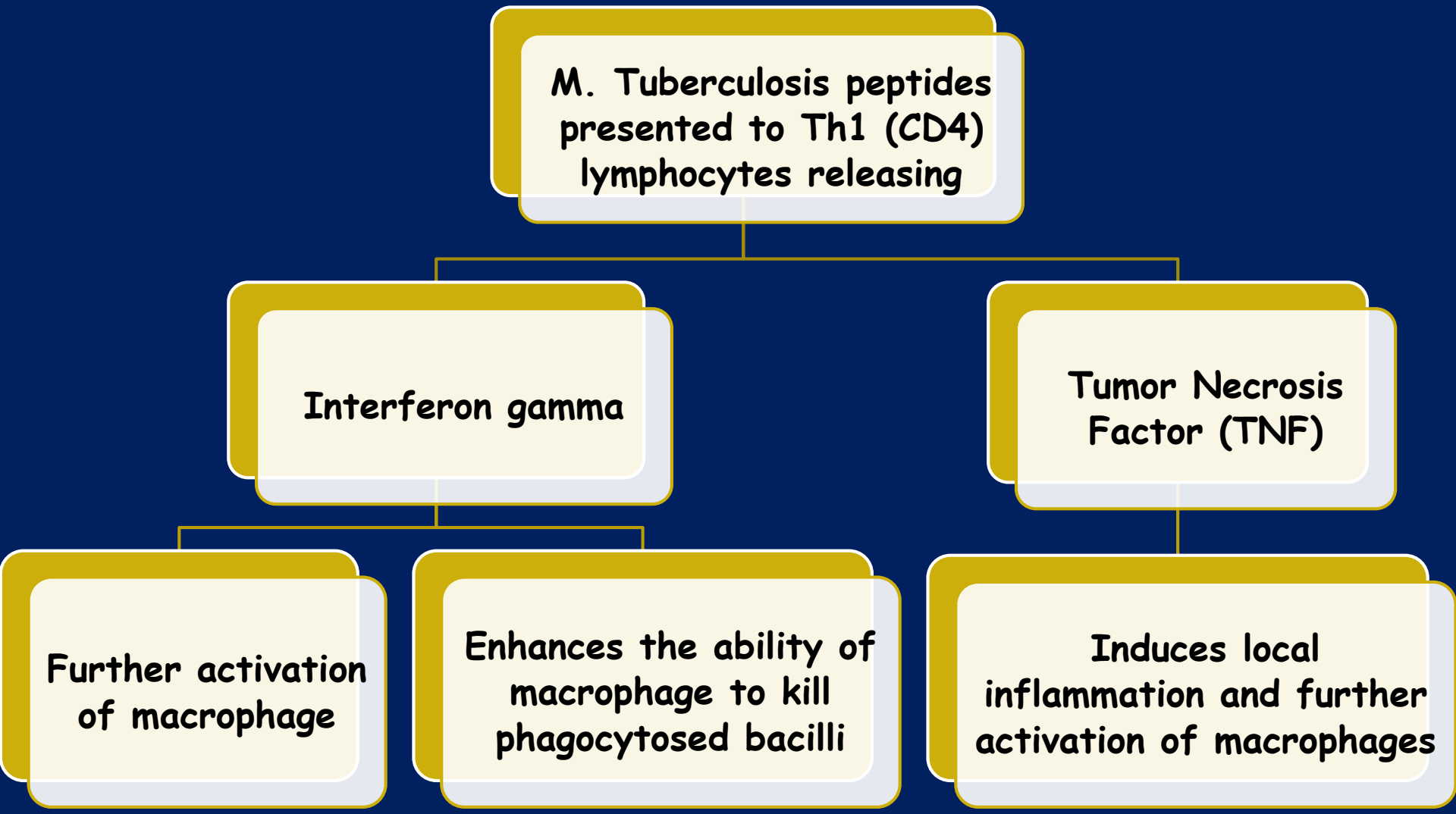
Primary disease

- 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

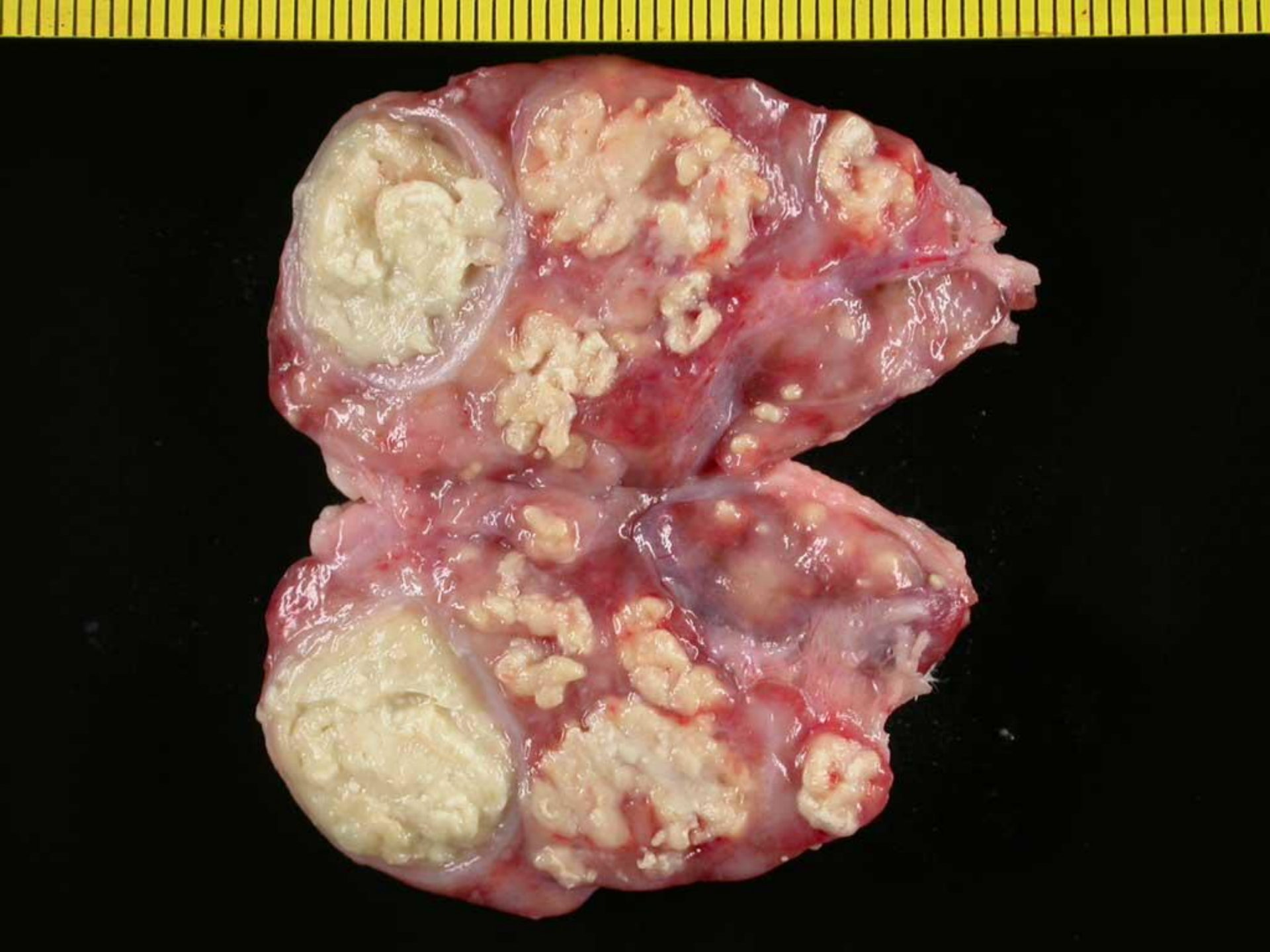
- The lung lesions (tubercles –small granulomas (Ghon's focus) and the enlarged lymph nodes constitutes Ghon's complex
- Tubercles may heal become fibrotic or calcified and persist as such for a lifetime (Ranke Complex)

Weeks after infection



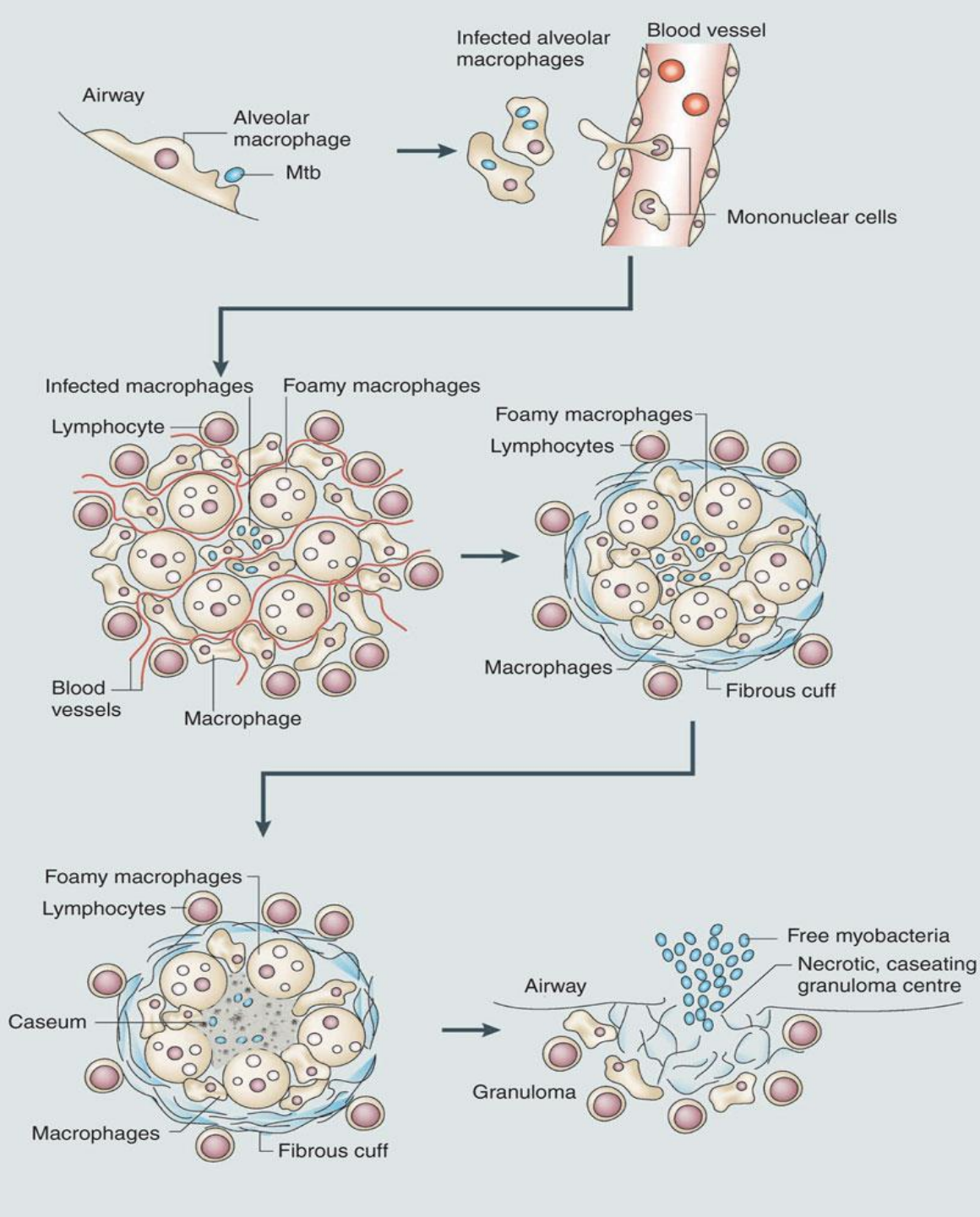
Primary disease

- 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 tuberculous lesion



Outcomes

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

- 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

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.

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 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 TB

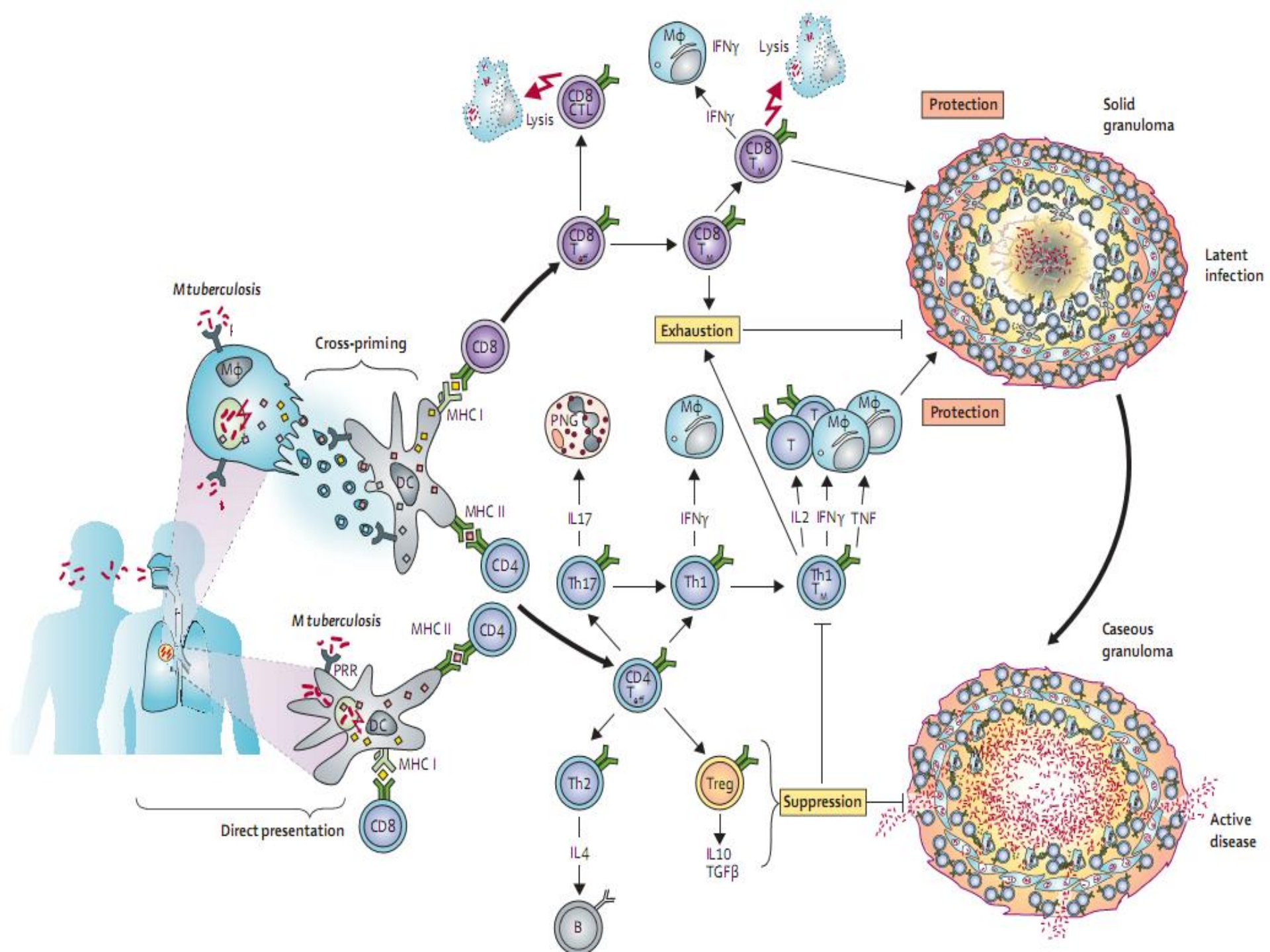
- This period of latency is sustained predominantly by a population of non-replicating bacilli rather than a population of growing bacilli.
- It is believed that the immune response is mainly directed towards antigens secreted by growing bacilli.
- Therefore non-replicating bacilli will be less obvious 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 and no underlying medical problems, 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

Reactivation disease

- Immuno-suppression is clearly associated with reactivation TB.
- Associated conditions include:
  - 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


Mϕ
IFNγ
Lysis
CD8 CTL
Lysis
IFNγ
CD8 T_M
Protection
Solid granuloma
CD8 T_{eff}
CD8 T_M
Latent infection
M tuberculosis
Cross-priming
CD8
Exhaustion
Mϕ
MHC I
DC
PNG
Mϕ
T
T
Mϕ
Protection
MHC II
IL17
IFNγ
IL2
IFNγ
TNF
CD4
Th17
Th1
Th1 T_M
M tuberculosis
MHC II
CD4
PRR
DC
CD4 T_{eff}
Caseous granuloma
MHC I
Th2
Treg
Suppression
Direct presentation
CD8
IL4
IL10
TGFβ
Active disease
B

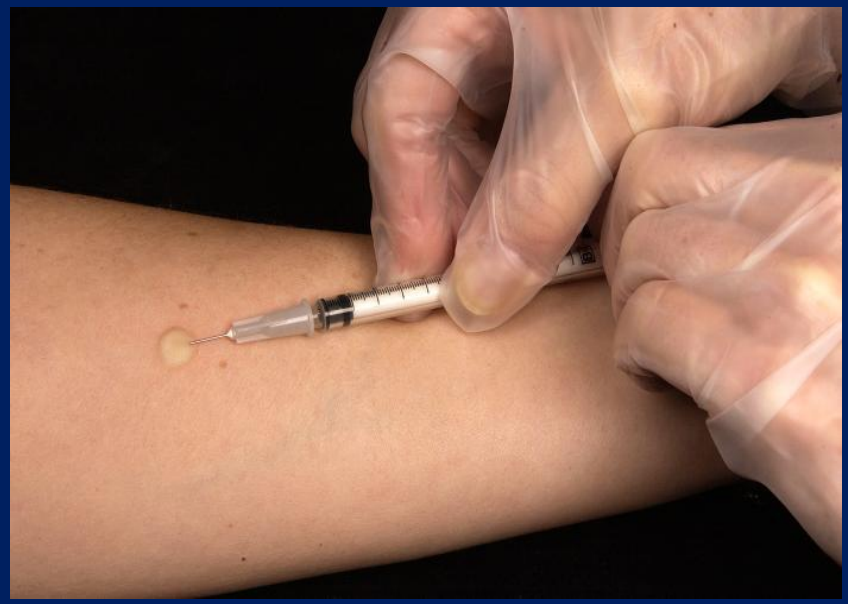
The role of the granuloma as a host protective factor needs a revision in thinking as it may also play a role in protecting the tubercle bacilli for its long-term survival in the host

Test for immunity against TB

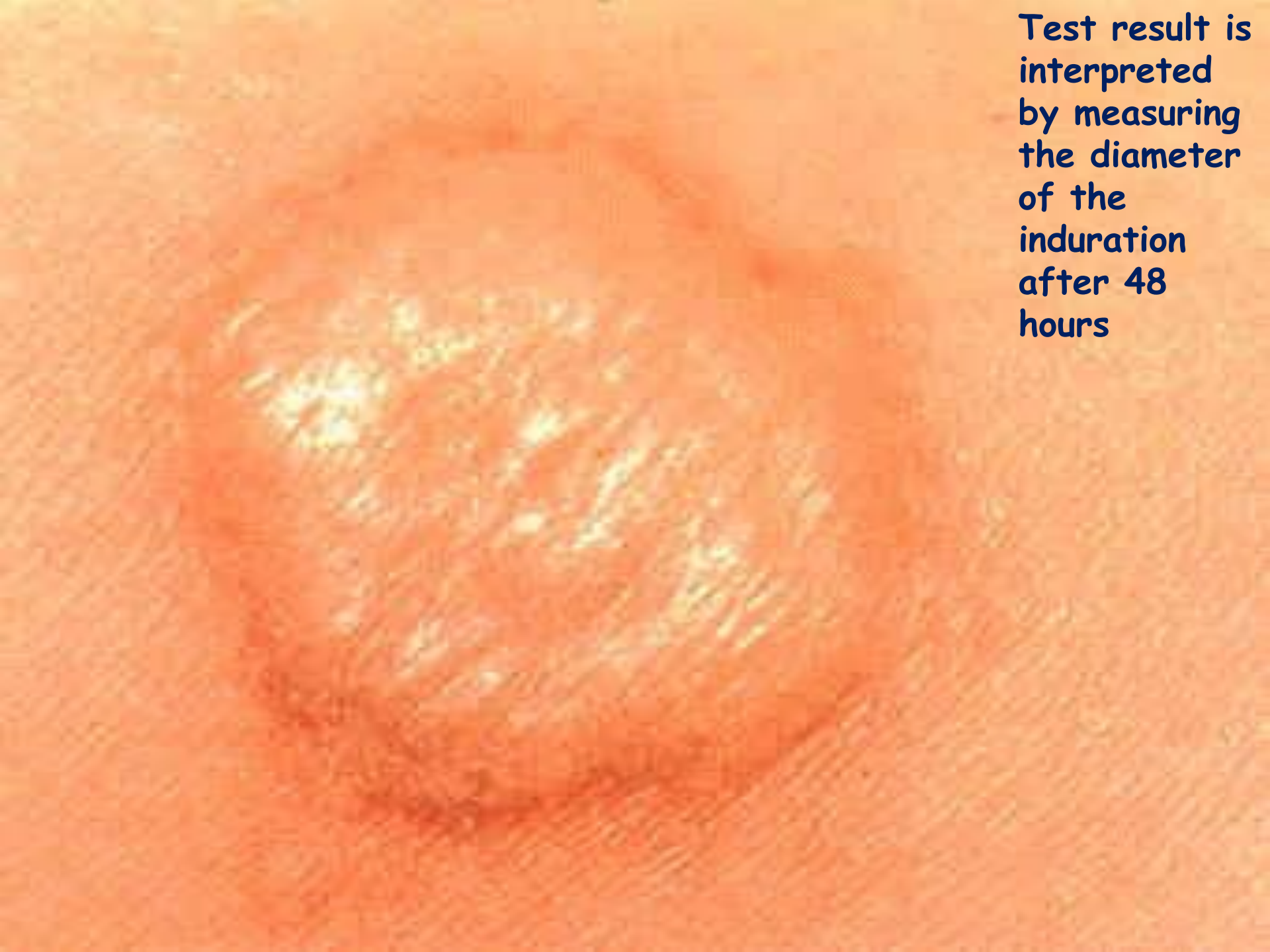
Delayed hypersensitivity skin test

Tuberculin test or (Mantoux)

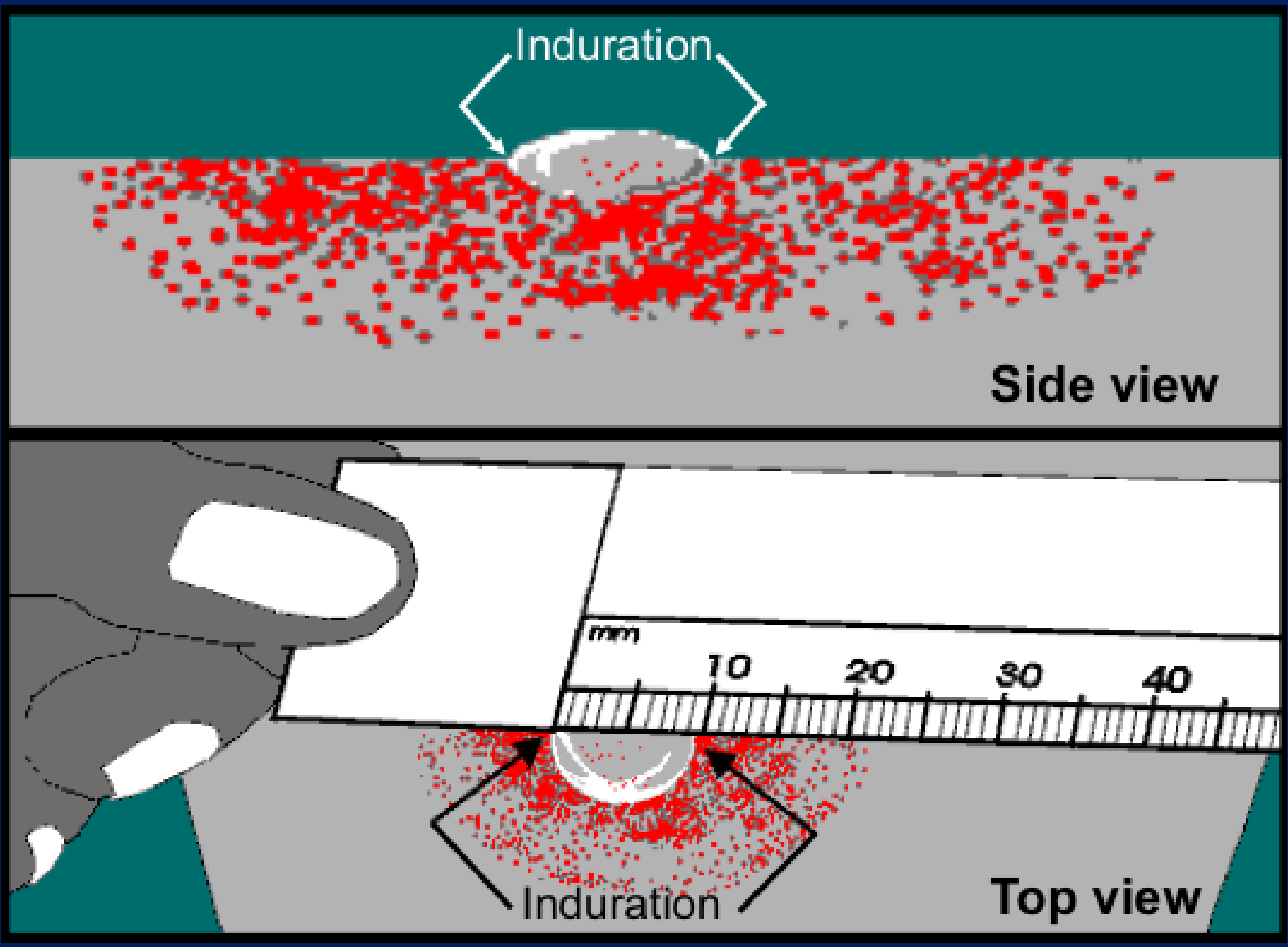
Intradermal injection of PPD (purified protein derivative)



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


Induration
Side view
mm
10
20
30
40
Induration
Top view

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.

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.

Thank you