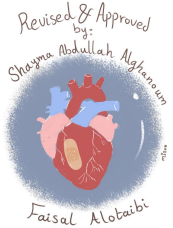
Immunology of Tuberculosis

Color index
Red: Important
Grey: Extra information
Green: Notes
Slide reference



IMMUNOLOGY
TEAM 439

Objectives

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

As this lecture is found to be phrased in a confusing way, the team has chosen to paraphrase the slides. Rest assured that everything will be covered and a slide reference is added at the top of each page.

Immune defense of respiratory system

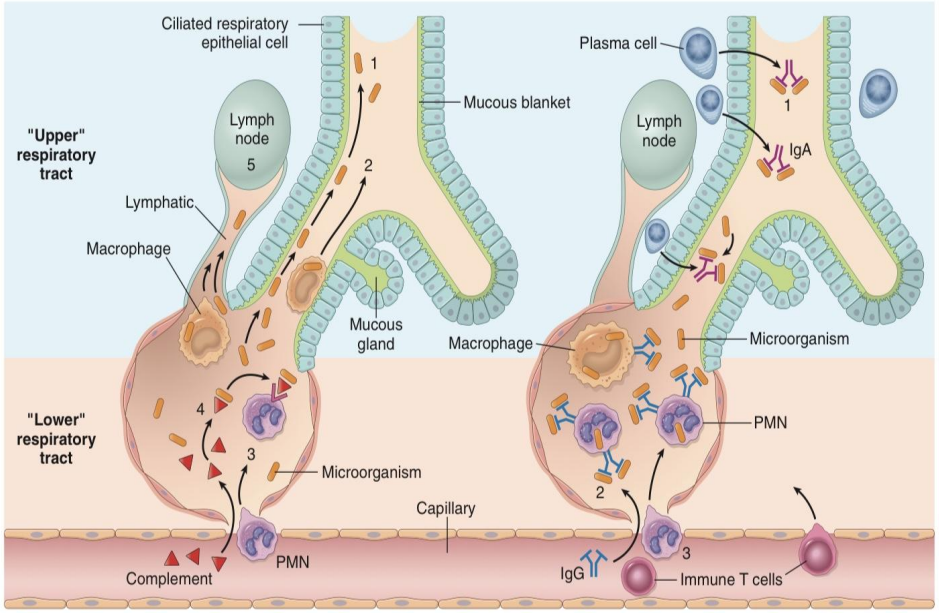


Fig. 13.28 Lung defense mechanisms. (A) Innate defenses against infection: *1*, In the normal lung, removal of microbial organisms depends on entrapment in the mucous blanket and removal by means of the mucociliary elevator; 2, Phagocytosis by alveolar macrophages can kill and degrade organisms and remove them from the air spaces by migrating onto the mucociliary elevator; or *3*, phagocytosis and killing by neutrophils recruited by macrophage factors; *4*, Complement may enter the alveoli and be activated by the alternative pathway to produce the opsonin C3b, which enhances phagocytosis; *5*, Organisms, including those ingested by phagocytes, may reach the draining lymph nodes to initiate immune responses. (B) Additional mechanisms operate after development of adaptive immunity: *1*, Secreted IgA can block attachment of the microorganism to epithelium in the upper-respiratory tract; 2, In the lower-respiratory tract, serum antibodies (IgM, IgG) are present in the alveolar lining fluid and activate complement more efficiently by the classic pathway, yielding C3b *(not shown)*; In addition, IgG is an opsonin; *3*, The accumulation of immune T cells is important for controlling infections by viruses and other intracellular microorganisms. *PMN*, neutrophil.

Infection occurs when the host defenses (such as innate & adaptive immunity) are lowered along with entry of a pathogen (in this case mycobacterium tb).

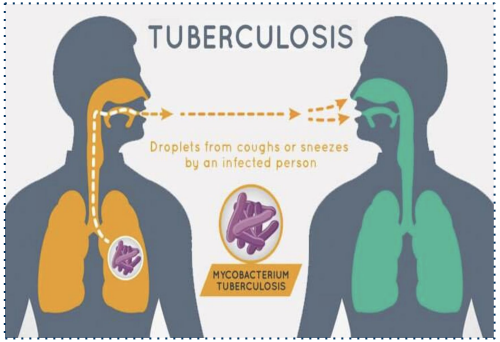
From Robbins:
The importance of immune defenses in preventing infection is emphasized by patients with inherited or acquired **defects in innate immunity** (including neutrophils and complement defects) **or adaptive immunity** (such as humoral immunodeficiency), all of which *lead to an increased incidence of infections.*

*Defects in Th1- cell-mediated immunity lead mainly to increased infections with **intracellular microbes** such as atypical mycobacteria. (Mycobacterium tuberculosis)

Introduction to Tuberculosis

- Mycobacterium tuberculosis is the second most common infectious cause of death in adults worldwide.
- It's a an intracellular microbe (replicates inside macrophage) where human host serves as the natural reservoir for M. Tuberculosis.
- The clinical development of the disease depends on the *effectiveness* of the host's innate and adaptive immune response to the infection. If the immune response is functioning well, the clinical disease has *little to no chance* of developing.
- Human immunodeficiency virus (HIV) increases the incidence of the disease. (Will be explained later)
- TB is transmitted through aerosols (airborne transmission) by coughing or sneezing and acquired mainly through inhalation.

Transmission: by sneezing/coughing from infectious person
Acquired: inhalation of organism



Recall: TB causes delayed-type (type 4) hypersensitivity reaction. Explained in foundation.

Overview of TB

Immunology

Tuberculosis is able to withstand the body's immune response ***after*** being phagocytosed by macrophages by several ways, including:

Virulence factors (Enables the bacteria to spread by evading host defense)	**Host factors** (An **intrinsic** factor which influences an individual's response to a causative agent)
The lipid-rich **waxy outer coat** blocks phagocyte enzymes and make the bacteria withstand drying and survive for long periods in air and house dust.	Resistance to reactive oxygen intermediates (ROIs)
Catalase-peroxidase resists the host cell oxidative response.	Inhibition of 1. phagosome-lysosome fusion 2. phagosome acidification
Glycolipid Lipoarabinomannan (LAM) induces cytokines, resists host oxidative stress and interfere with antigen presentation to CD4 T cells by MHC class II.	Escape from the phagosomal compartment into the cytoplasmic space.

Possible outcomes of inhalation of M. Tuberculosis (Infection)

1. Immediate clearance of the organism
2. *Immediate onset* of the disease (Primary Disease)
3. Latent infection
   by limiting it's spread so there is a balance between infection and immunity
4. Reactivation
   Onset of disease after many years

Primary disease

(Approximately 10% of infected individuals will develop the disease)

1. **Inhalation**: The bacteria enters the body via inhalation

2. **Phagocytosis**: The alveolar macrophages phagocytose the bacteria, but cannot kill it. (Failure of defense system)

3. **Recruitment**: The infected macrophages send out a distress (produce cytokines & chemokines that attract other phagocytic cells.

4. The newly recruited macrophages surround the bacteria, this eventually forms a nodular granuloma called a **tubercle**. This whole structure is known as a **Ghon's focus**.

5. If the replication isn't controlled, infection will spread to the draining lymph nodes (lymphadenopathy) in the hilum, forming a **Ghon's complex.**
   - **-Ghon focus:** lung lesion tubercle alone.
   - **-Ghon complex:** combination of lung lesion tubercule (Ghon focus) and lymphadenopathy

6. In some cases, the tubercles become fibrotic and heal, forming a **Ranke's complex**. This type of fibrosis never goes away. **Ranke Complex** : is an old tubercle (Ghon complex) that has **healed** and become fibrotic or calcified and persist as such for a lifetime.

In majority of cases, the old tuberculous lesion get calcified, so even if you just saw calcification in the lungs or hilar nodules you can say this is an old healed tuberculosis. Presence of early cavitations in the X-ray scan will highly indicates a previous TB infection.

Primary disease

(Approximately 10% of infected individuals will develop the disease)

What will happen after 3 weeks of infection?

First 3 weeks: m.tb replicated within macrophage without being "checked", no immune response
> 3 weeks: cmi tries to stop the replication

The mycobacterium continues to proliferate until an effective cell-mediated immune (CMI) response develops (usually *two to six weeks* after infection).

Which cells produce IFN-γ?
1. **Cytotoxic t cells (CD8)**
2. **T helper (Th1) (CD4)**

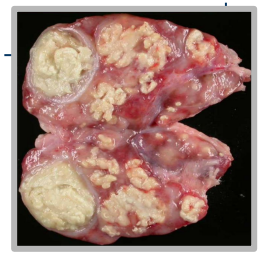
M.Tuberculosis peptides are presented to **Th1 (CD4)** lymphocytes which **release**:

- **Interferon-γ**
  - Enhances the ability of macrophage to kill phagocytosed bacilli
  - Further activation Of macrophage
- Tumor Necrosis Factor (**TNF**)
  - Induces local inflammation and further activation of macrophages

What happens if CMI **fails** to develop an effective response?
There will be progressive tissue destruction of the lung created by:

1. Reactive oxygen
2. Tumor necrosis factor (TNF)-alpha
3. Nitrogen intermediates
4. Contents of cytotoxic cells (granzymes, perforin)

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



Latent TB

a situation where the immune response is trying to contain m.tb and m.tb is trying to express itself by establishing infection. Patient is "potentially infected" but asymptomatic. Why? m.tb is not growing.

Pathogenesis:

1

Presentation of antigens by APCs in the lymph nodes (t-lymphocytes).
Type 4 hypersensitivity.

2

Activation of cd4+ (**Th1**) lymphocytes. This phase coincides (تتزامن) with ***high rate*** *of replication of bacilli.*

3

Low induction of cd8. Cd8+ recognize the antigen and **produce IFN-γ**, leading to macrophage activation. (They are the main source of IFN-gamma).

4

Induction of **high** number of cd8+. Increased production of **IFN-γ** and cytotoxic activity. This phase coincides (تتزامن) with *bacterial growth stabilization.*

5

Bacterial load remains constant and infection is kept in a dormant (latent) state.

The immune response and Anti-mycobacterium tuberculosis drugs are directed towards the **growing bacilli**, therefore making the non-replicating bacilli in latent TB somewhat invisible to the body (resistant).*

*بمعنى انه الجهاز المناعي والادوية المخصصة لهذا المرض يكونوا موجهين لل micro organisms اللي **تتكاثر** لكن هذه البكتيريا في ال latent infection **ما تتكاثر** زائد انها تكون **مختبئة** داخل ال macrophages لذلك صعب على الجهاز المناعي انه يسوي detection لها وكذلك نفس الشي ينطبق على الادوية، صحيح انه المريض قاعد ياخذ الدواء لكن ال dose **يوصل بصعوبه** للبكتيريا اللي تكون مختبئة وما تتكاثر.
Treatment is necessary though to avoid developing active tb.

Other types of TB

Chronic TB disease

Characterized by repeated episodes of healing by fibrotic changes around the lesions and tissue breakdown. 20% of untreated patients could develop chronic disease or recover. Unfortunately, 80% of untreated patients die.

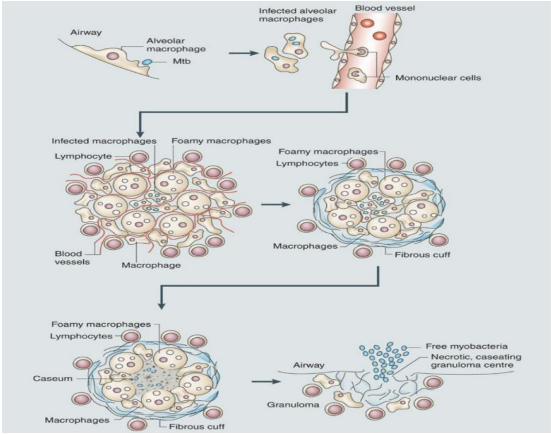
Miliary TB disease (expanded TB)

It's a disseminated disease with lesions resembling millet seeds. Develops when m.tuberculosis spreads throughout the lung and to other organs though hematogenous lymphatic spread**. Its most common presentation is **meningeal TB**.

**hematogenous lymphatic spread:
هو انه البكتيريات توصل لل blood vessels وتخترقها
وتصير تمشي مع الدم لكل انحاء الجسم it is like giving
an injection filled with bacteria .

Eventually, the caseating lesions start to erode, spreading to the airways; at this point the host becomes infectious to others*. **Only active tb is contagious.**

*معناه انه لما توصل الlesions الى ال lung airways يصير هذا
الشخص ناشر للمرض لانه مع كل نفس فيه بكتيريا تطلع.



Reactivation Disease

Reactivation occurs when cell mediated immunity is affected

- Reactivating of TB results from the proliferation of the dormant bacteria which was suspended in the primary infection and this occurs in 5-10% of the cases that has no other medical problems.

Reactivation of a latent TB is less severe than directly developing TB (progressive primary tb). Progressive primary tb means that the person is unable to fight the infection or even contain it as in latent tb, therefore his immunity is weaker and the disease would be much more severe as in reactivated tb.

- The disease process in reactivation TB tends to be:

1. **Localized** (in contrast to primary disease)
2. **Little** regional lymph node involvement and **less** caseation**.**
3. The lesion typically occurs at the **lung apices**
4. **Disseminated disease is unusual** (Spreading to other areas is rare/unusual)

- **Immunosuppression** is clearly associated with reactivation TB.
- Associated conditions that could lead to reactivation include:

HIV infection and AIDS

Malignant lymphoma

Diminution in CMI associated with age

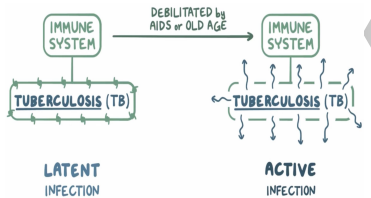
Diabetes mellitus

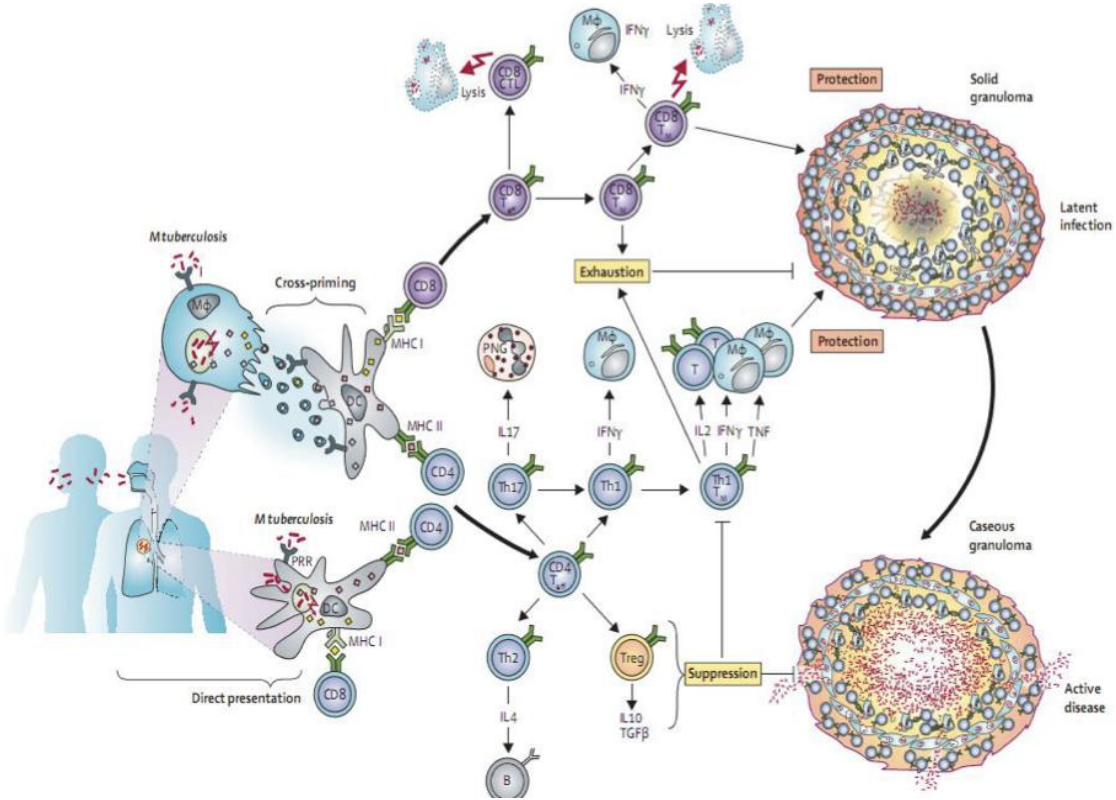
Inhibitor of TNF-alpha and its receptor

End-stage renal disease

Corticosteroid use

HIV kills CD4 which is responsible for producing IFN-γ so it results in decreasing its numbers and causing Tb. IFN-γ function is getting rid of TB outside of the macrophages





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

Granulomas form when the immune system attempts to wall off substances it perceives as foreign, but is unable to eliminate them.

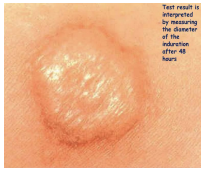
TB tests (Diagnosis)

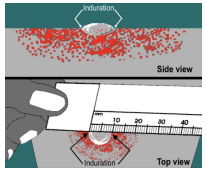
Tuberculin test or (Mantoux)

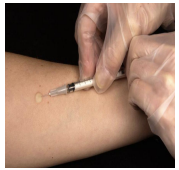
- It's a delayed hypersensitivity skin test where PPD (purified protein derivative) is injected intradermally.
- It's a nonspecific test for M. Tuberculosis because it can't differentiate between a patient vaccinated with BCG and an infected patient.
- Correct interpretation of the result is *unreliable* in immunocompromised states affecting CMI.

Immunocompromised (ex. w/ HIV) patients get a negative result which is untrue (false-negative), as they do not possess enough t-cells to react with the ppd = induration is not much.

- The results are out after 48-72 hours because it's a delayed type hypersensitivity. The result is characterized by redness, swelling and the induration should be measured.







IFN-γ release assay (IGRA)

- The test measures *interferon-gamma released into blood from T cells* when they are activated by M. tuberculosis antigens in vitro.

Steps: Take the patients blood in vitro> extract mononuclear blood cells> add antigen of M.tuberculosis> measure the release of IFN-γ

- The antigens added are a) ESAT-6: early secretory antigenic target 6 b) CFP-10: culture filtrate protein which are specific for M. Tuberculosis. This enables them to differentiate between who has a **latent infection and who is vaccinated with BCG** because these proteins are absent in vaccine strain BCG, or M. bovis.

ESAT-6 and CFP-10 are found in the bacteria. So if the bacteria was already in the blood and the antigen was injected, the **IFN levels would increase**.

Mycobacterium bovis (M. bovis) is a slow-growing aerobic bacterium and the causative agent of tuberculosis in cattle (known as bovine TB).

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

The **main difference** is that IGRA is more specific for M.tuberculosis it can differentiate between an infected and a vaccinated patient, but the tuberculin test (Mantoux) can't.

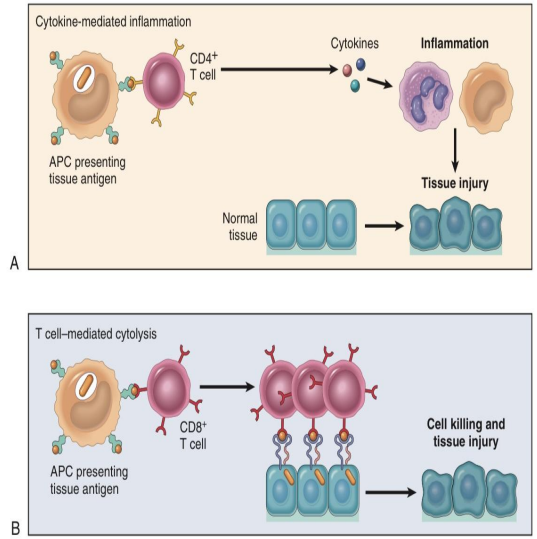


Fig. 5.16 Mechanisms of T-cell–mediated (type IV) hypersensitivity reactions. (A) CD4+ T_H1 cells (and sometimes CD8+ T cells, *not shown*) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leading to tissue injury. CD4+ T_H17 cells contribute to inflammation by recruiting neutrophils (and, to a lesser extent, monocytes). (B) In some diseases, CD8+ cytotoxic T lymphocytes (CTLs) directly kill tissue cells expressing intracellular antigens (shown as orange bars inside cells). *APC*, Antigen-presenting cell.

Take home messages

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 immunocompromised

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

Helpful sources

- TB (osmosis)
- TB (medicosis perfectionalis)
- Overview of TB
- Tuberculin test
- Immunology of tb

اذا دخلت المايكوبكتيريا

١)تكون المناعه عاليه جدا اول مايدخل الجسم مايسمح له يسوي انفكشن ويموت

(**Immediate clearance**)

٢)ممكن المناعه تكون عاليه لكن قدرت تتلاعب المايكوبكتيريا وتتجاوز مناعه الجسم رغم الظروف مثل الي انذكرت في الڤيرولنس اند هوست فاكترز وبتتبع خطوات الباثوجينيسس اللي ذكرناها لكن بالنهايه بيروح المرض اي جسمك بيقدر يسيطر على الموضوع وبتموت البكتيريا زي لما يجيك انفلونزا ويمكن تبان عليك اعراض تعب بس جسمك بالنهايه قدر يقاومه بعد فتره

(**Primary tb disease**)

٣) بيدخل البكتيريا مثل اللي بنقطه ٢ والجسم بيحاول يقاوم بس مايقدر والشي الوحيد اللي قادر يسويه هو انه "to contain it" and stop replication

(**Latent tb disease**)

٤) يصير نفس خطوه ثلاثه لكن في اي لحظه اذا مناعتك صارت ضعيفه بسبة اي شيء او احد من الاشياء المذكوره بيرجع يتحفز ويصير "ري-اكتڤيشن

(**Reactivated/Secondary tb disease**)

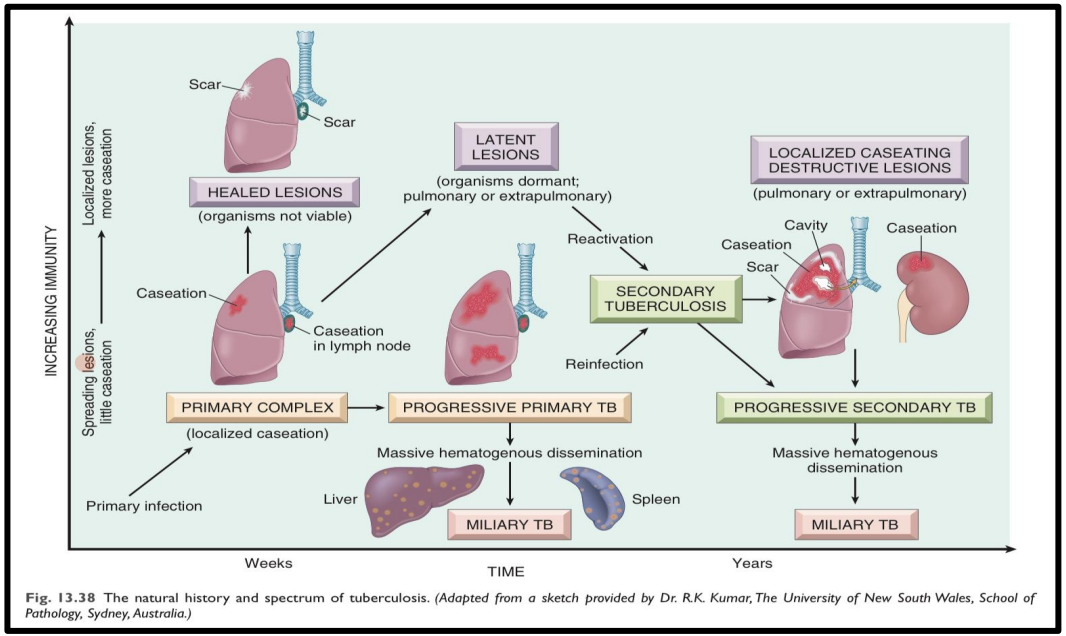
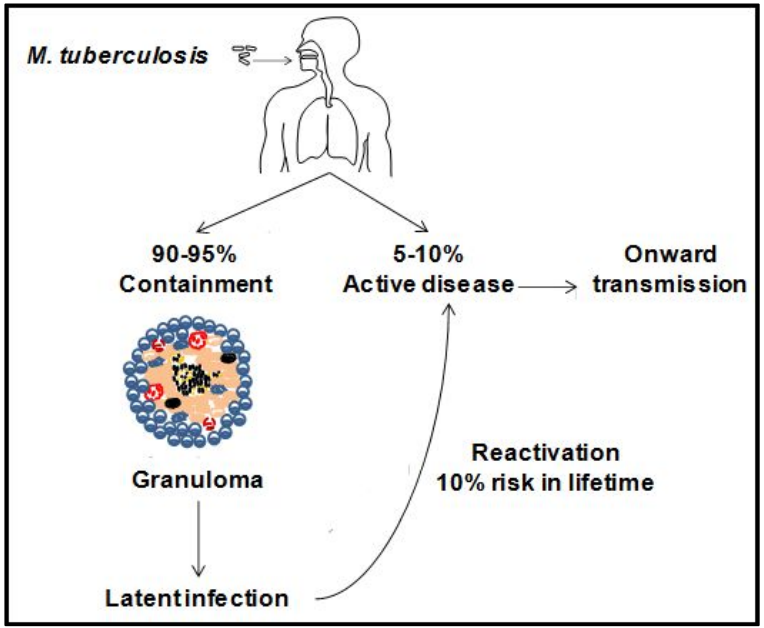


Fig. 13.38 The natural history and spectrum of tuberculosis. *(Adapted from a sketch provided by Dr. R.K. Kumar, The University of New South Wales, School of Pathology, Sydney, Australia.)*



Tuberculosis

Primary

Approximately 10% of infected individuals develop the disease (tb).

Contains ghon's complex(ghon's focus + enlarged lymph nodes)

Lymphadenopathy

It may contribute in the development of caseating necrosis

Has ranke complex (fibrotic or calcified tubercle)

Miliary

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

Looks like millet seeds

Most common:
TB meningitis

Chronic

80% of the patients die if not treated

The remaining develop chronic disease or recover

repeated episodes of healing by fibrotic changes around the lesions and tissue breakdown.

Complete spontaneous eradication of the bacilli is rare

Latent

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

non-replicating bacilli will be **less obvious** to the protective cellular response.

TB drugs aren't effective in latent TB

Reactivation

occurs to approximately **5 to 10 %** of cases with latent disease.

Less caseation than primary

Immuno-suppression is associated with reactivation of TB

Localized

Occurs on Lung apices

Disseminated disease is unusual

Quiz

Q1) Most common presentation of extrapulmonary tuberculosis:							
A	Pott's disease	B	Meningitis TB	C	Lymphadenitis TB	D	Intestinal TB
Q2) Which of the following tests is used to differentiate latent tb to BCG vaccines?							
A	Mantoux	B	Tuberculin	C	IGRA	D	PCR
Q3) Which of the following is secreted by Th1 (Cd4+)?							
A	IFN-γ	B	TNF	C	IL-2	D	A & B
Q4) Miliary Tb is said to be?							
A	A dormant type	B	A disseminated type	C	Localized in periphery of lungs	D	-
Q5) What type of hypersensitivity is mediated in TB?							
A	Type Ⅰ	B	Type Ⅱ	C	Type Ⅲ	D	Type Ⅳ

Q1) B Q2) C Q3) D Q4) B Q5) D

Special thanks to Shayma AlGhanoum + Team438

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