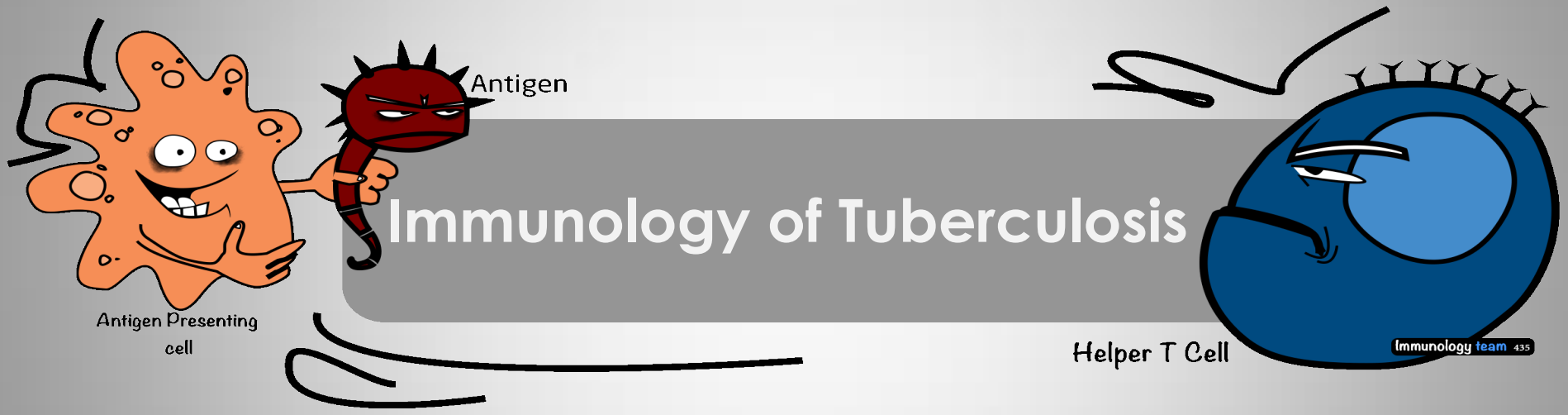


Immunology of Tuberculosis

Objectives :

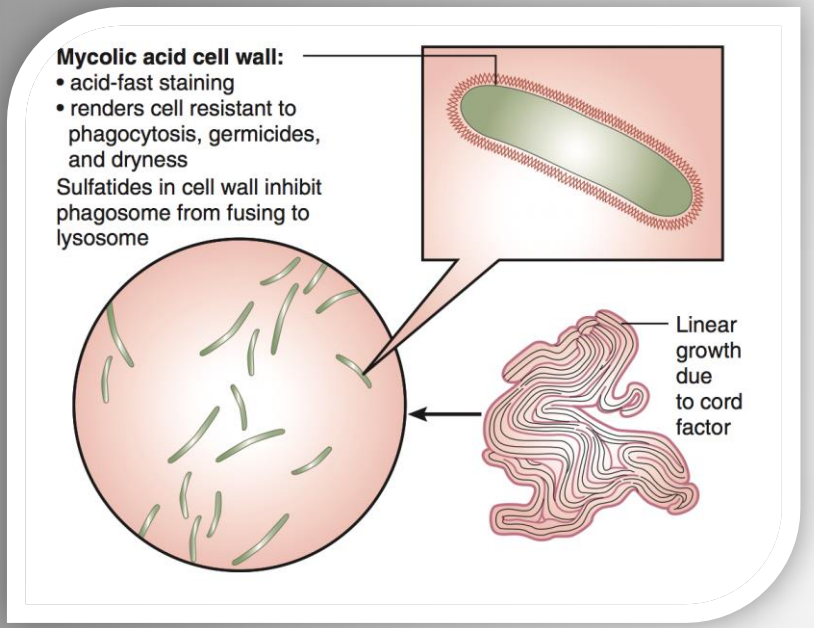
- To know how M. tuberculosis infection is contracted and its initial encounter with the immune system.

- 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



Acid fast bacteria

Thin rods,non-motile
Obligate aerobe

M.tuberculosis

M.leprae

The important mycobacteria in TB affecting human is M.TB

Clinical case:

A homeless man enters the hospital with wasting and **fever**. He has had a **chronic cough** for several months producing bloody sputum as well as **night sweats**. CXR reveals cavitation with air-fluid levels in the **apex** of his left lung.

*Extra slide

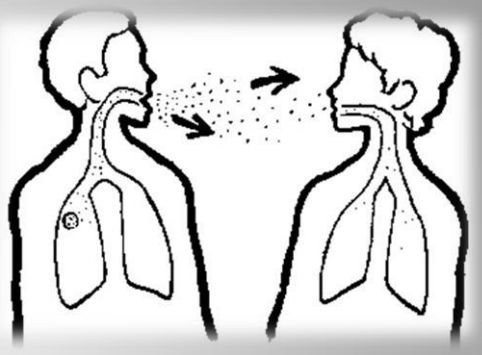
TB and mode of transmission

- 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.

-TB is an infection in which **protective immunity** and **pathologic hypersensitivity** coexist, and the lesions are caused mainly by the host response (immune system)

- The disease incidence is magnified by the concurrent epidemic of **human immunodeficiency virus (HIV)** infection.



Transmission

Infection is acquired by inhalation of *M. tuberculosis* in aerosols and dust (airborne transmission)

The organisms waxy outer coat can withstand drying and survive for long periods in air and house dust

تزداد احتمالية الاصابة بالسل عند الاشخاص اللي مناعتهم ضعيفة لان الجسم ما حيقدر يدافع عن نفسه وبالتالي البكتيريا ح تنتشر وحيحصل تدمير للرئة بشكل يفقدها وظيفتها او أي عضو آخر

Virulence factor

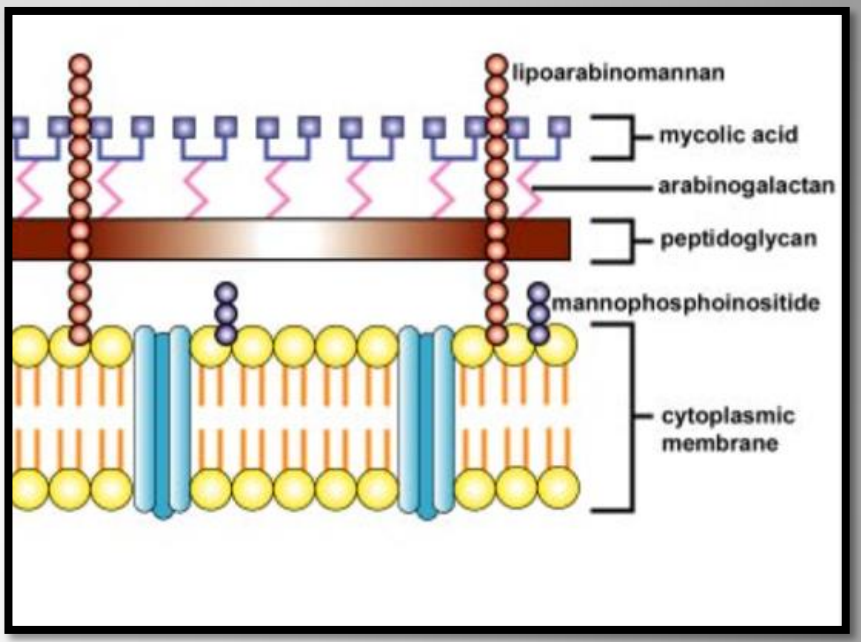
اللي يخلي M.tuberculosis خطيرة انه عندها virulence factor بهذه
العوامل تستطيع انها تعيش فالجو
لمدة طويلة وتستطيع انها تقاوم دفاع الجسم عن نفسه

1) Waxy coat blocks phagocyte enzymes

بسبب وجود طبقة سميكة من الدهون في (Acid Fast bacilli) تمنع هذا النوع من البكتيريا من ان يتم صبغه ب gram stain لذلك نستخدم صبغة خاصة

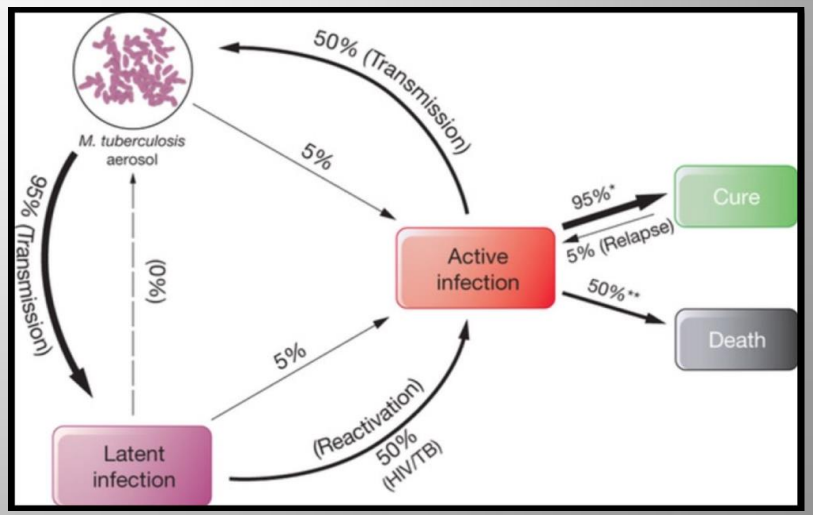
2) Catalase-peroxidase
which resists the host cell oxidative response

3) 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.

- 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

As if someone said "I was close to my grandpa who had TB and inhaled the M.tuberclosis what will happen to me?

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

- **Immediate clearance of the organism**
  مهما كانت قوة البكتيريا للجهاز المناعي القوة اللازمة للتخلص منها
- **Latent Infection**
  خاملة
- 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.

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.

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:

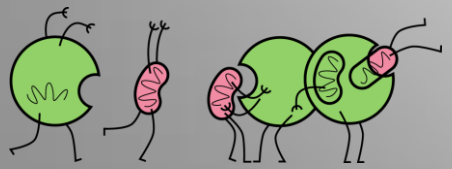
1- Tumor necrosis factor (TNF)-alpha,
2- Reactive oxygen
3-Nitrogen intermediates
4- Contents of cytotoxic cells (granzymes, perforin)

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

Ghon's and Ranke complex:

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

2- Tubercles may heal become fibrotic or calcified and persist as such for a lifetime (Ranke Complex)



Weeks after infection

M. Tuberculosis peptides presented to Th1 (CD4) lymphocytes releasing

Tumor Necrosis Factor (TNF)

Induces local inflammation and further activation of macrophages

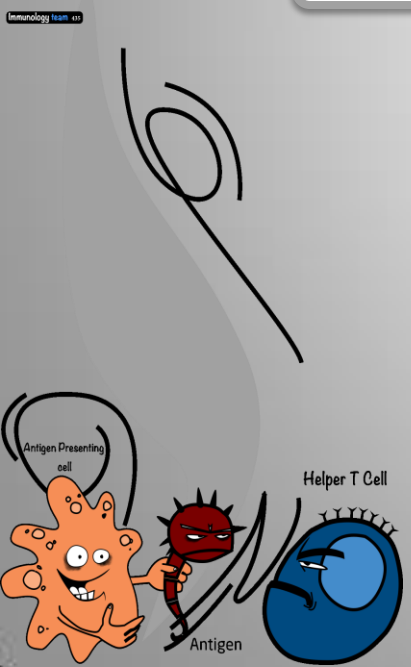
Interferon gamma

Makes macrophages stronger

- Further activation of macrophage
- Enhances the ability of macrophage to kill phagocytosed bacilli

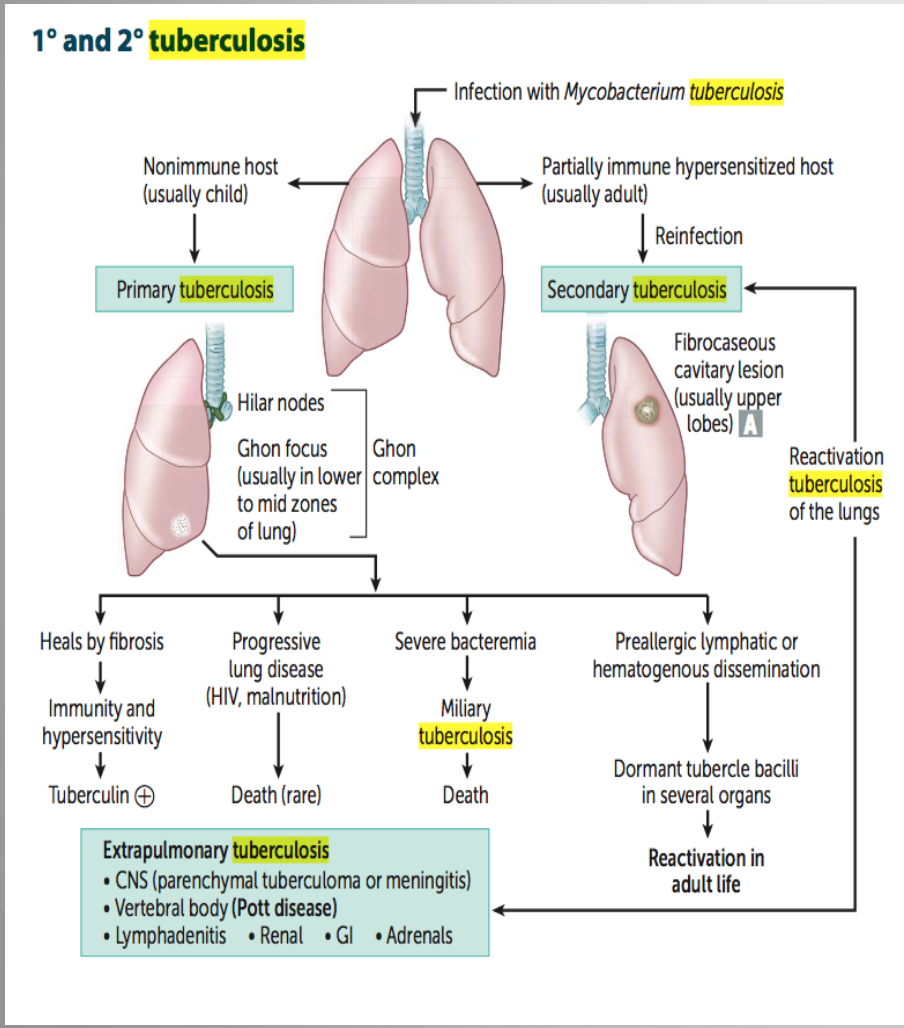
Outcomes:

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



Summary of primary and secondary tuberculosis

* Extra slide



Primary TB transmitted in aerosol droplets then deposits in lower lobes of lung ⟶ Ingested by alveolar macrophages , mycolic acid cell wall allows intacellular survival and proliferation ⟶ T cell and uninfected macrophages wall off and destroy infected macrophages and form caseous granuloma ⟶ Leave fibrotic, calcified scar (tubercles) with few dormant organisms ⟶ May spread to other sites by lymphatics and blood forming extrapulmonary tubercle

Secondary TB, weakend T-cell response will reactivates of pulmonary tubercle in apex (high oxygen favors aerobic growth) ⟶ Macrophages respond and form large caseous granuloma which creates cavitation in lung ⟶ May disseminate to other sites

Miliary and Chronic TB

- **How disseminated TB produced?**

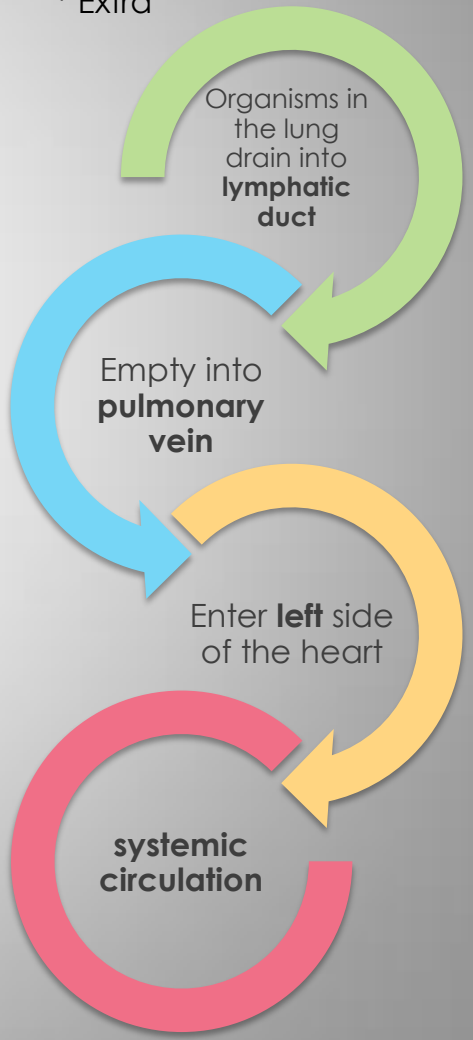
  Unchecked bacterial growth may lead to **hematogenous** spread (bacteremia).
  It may follow from **1ry** or **2ry** TB.

- **What will happen if the patient with active TB didn't take his medication?**

  In the 80% of cases, **Death** occurs due to the **absence of treatment.**
  The remaining 20% develop chronic disease or recover.
  You have to know that **complete spontaneous eradication** of the bacilli is rare.

Systemic miliary TB

* Extra



Latent TB

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)

Here the immune system works on the lymphocyte CD8+ more than CD4+(T **cytotoxic**) and that leads to more IFN-γ
which is good because the IFN-γ will be all the time against the bacteria (we don't get rid of bacteria, it's there but with low load)
Then the immune system will stop in this stage and become inactive (latent)
So, here the immune system try to deal with the bacteria as a virus

Most drugs acting on the DNA of the foreign body in latent TB there is no replication of the bacteria (latent Bactria) so, the drugs are not effective.

- Latent TB = Non-replicated bacilli
- Immune response is mainly directed towards **Ag secreted by growing bacilli**

Therefore

- Non-replicating bacilli will be **less** obvious to the protective cellular response.
- This correlates directly with an innate resistance to anti-MTB drugs

Note

أدوية الTB الحالية تعمل على proliferating bacteria only ، فلما تصير الحالة Latent TB ما راح تفيد هذي الحالة.
لكن توجد أبحاث حالية تقوم على علاج latent bacteria

Reactivation disease (2ry TB)

- Reactivation TB results from ➡ **proliferation of previously dormant bacteria** that seeded at the time of primary infection.
- Reactivation in healthy individuals without underlying medical problems occurs ~ **5-10%**
- The disease process in reactivation TB tends to be:

Process in reactivation of TB tends to be

- **Localize** in contrast to 1ry disease
  - Occurs typically in the **apex** of lung
  - Because it is localized, Little regional lymph node involvement early in disease and **less caseation**
- Disseminated disease is **unusual**

Factors associated with reactivation of TB

- **Immuno-suppressions.**

Associated condition include:

- HIV infection
- Diminution in cell mediated immunity associated with age
- Inhibition of TNF-a and its receptor
- Corticoster-oid use
- Malignant lymphoma
- Diabetes mellitus
- End-stage renal disease

What is the role of TNF-a?

Recruitment of monocyte, which in turn undergo action and differentiation into the epithelioid histocyte.

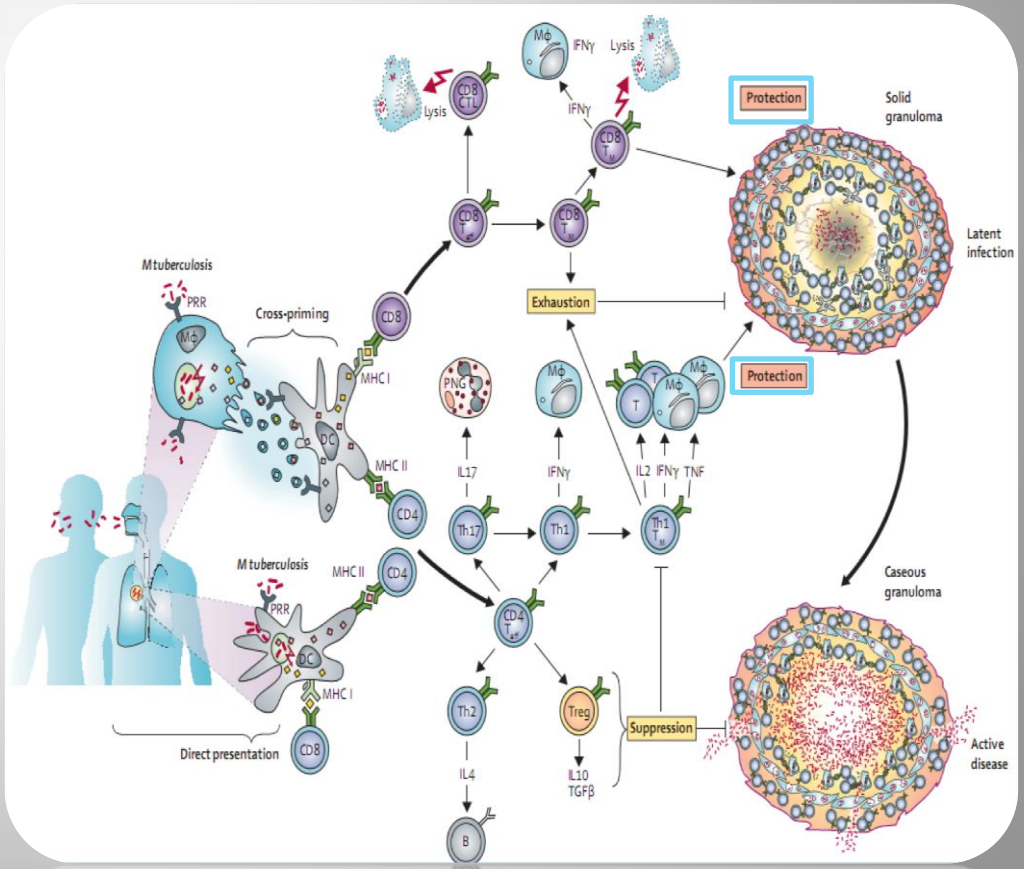
Test for immunity against TB

Delayed hypersensitivity skin test
Tuberculin test or (**Mantoux**)

1. Intradermal injection of **PPD** "purified protein derivative "
2. Correct interpretation of the result is unreliable in immuno-compromised states affecting CMI e.g. HIV
3. Test result is interpreted by measuring the diameter of the induration after 48 hours

Didn't get it? Click here.

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



DELAYED-TYPE HYPERSENSITIVITY (DTH) RESPONSE

A. 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.

B. As a result, the protective T cell response must be distinguished from the T cell response associated with DTH.

C. An in vitro interferon-gamma release assay has been developed. **(This tests helps us differentiate between DTH and latent)**

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.

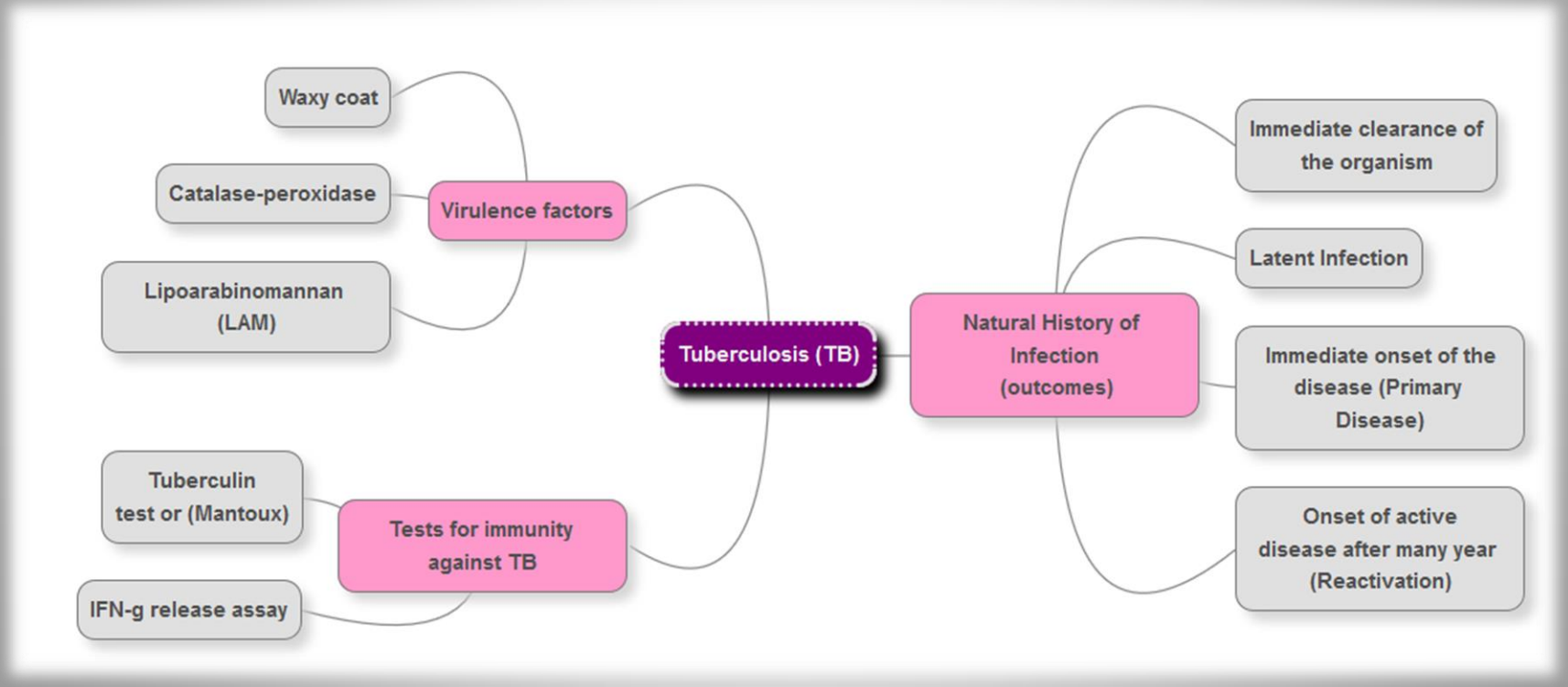
The tests use antigens specific to M. tuberculosis including the **early secretory antigenic target 6 (ESAT-6) and culture filtrate protein (CFP-10).**

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.


Antigen
Antigen Presenting cell
Helper T Cell
Immunology team 435

Summary


Tuberculosis (TB)
Virulence factors
Waxy coat
Catalase-peroxidase
Lipoarabinomannan (LAM)
Tests for immunity against TB
Tuberculin test or (Mantoux)
IFN-g release assay
Natural History of Infection (outcomes)
Immediate clearance of the organism
Latent Infection
Immediate onset of the disease (Primary Disease)
Onset of active disease after many year (Reactivation)

Tuberculosis (TB)

protective immunity & pathologic hypersensitivity

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.

Infection is acquired by inhalation of M. tuberculosis in aerosols and dust (airborne transmission)

Infected people cough up large numbers of mycobacteria

Virulence factors of tubercle

strategies to evade early intracellular killing mechanisms

Waxy coat:

- withstand drying and survive for long periods in air and house dust
- Inhibition of phagosome-lysosome fusion
- Inhibition of phagosome acidification
- Escape from the phagosomal compartment into the cytoplasmic space

Catalase-peroxidase:

- Resistance to reactive oxygen intermediates (ROIs)

Lipoarabinomannan (LAM):

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

Natural History of Infection

After exposure to M. tuberculosis, immune handling of the infection determines the final outcome.

Immediate clearance of the organism

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.

Latent Infection

1. Delayed type of hypersensitivity
2. Activation of CD4+ (Th1) lymphocytes
3. Later induction of high number of CD8+ with increased production of IFN-γ and cytotoxic activity
4. Bacterial load remains constant but non-replicating and infection is in latency
5. innate resistance to anti-Mtb drugs

Immediate onset of the disease (Primary Disease) (10%)

Innate defense system

- Tubercle bacillia carried to alveolar sacs
- proliferation in macrophage
- Cytokines and chemokines
- Attraction of phagocytic cells
- Granuloma formed (tubercle)
- Lymphadenopathy
- Granuloma + lymph node = ghon system
- Fibrosis + Calcification = Ranke Complex

Adaptive

After 2-6 weeks of infection
Cell mediated **Th1 (CD4)**

- IFN & TNF
- More macrophages
- More inflammation
- More lung destruction
- Caseating necrosis
- host becomes infectious to others

Miliary disseminated TB

- hematogenous spread
- TB meningitis

Chronic Disease

- In absence of treatment, death occurs in 80% of cases
- healing by fibrotic changes

Onset of active disease after many years (Reactivation)

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

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.

Test for immunity against TB

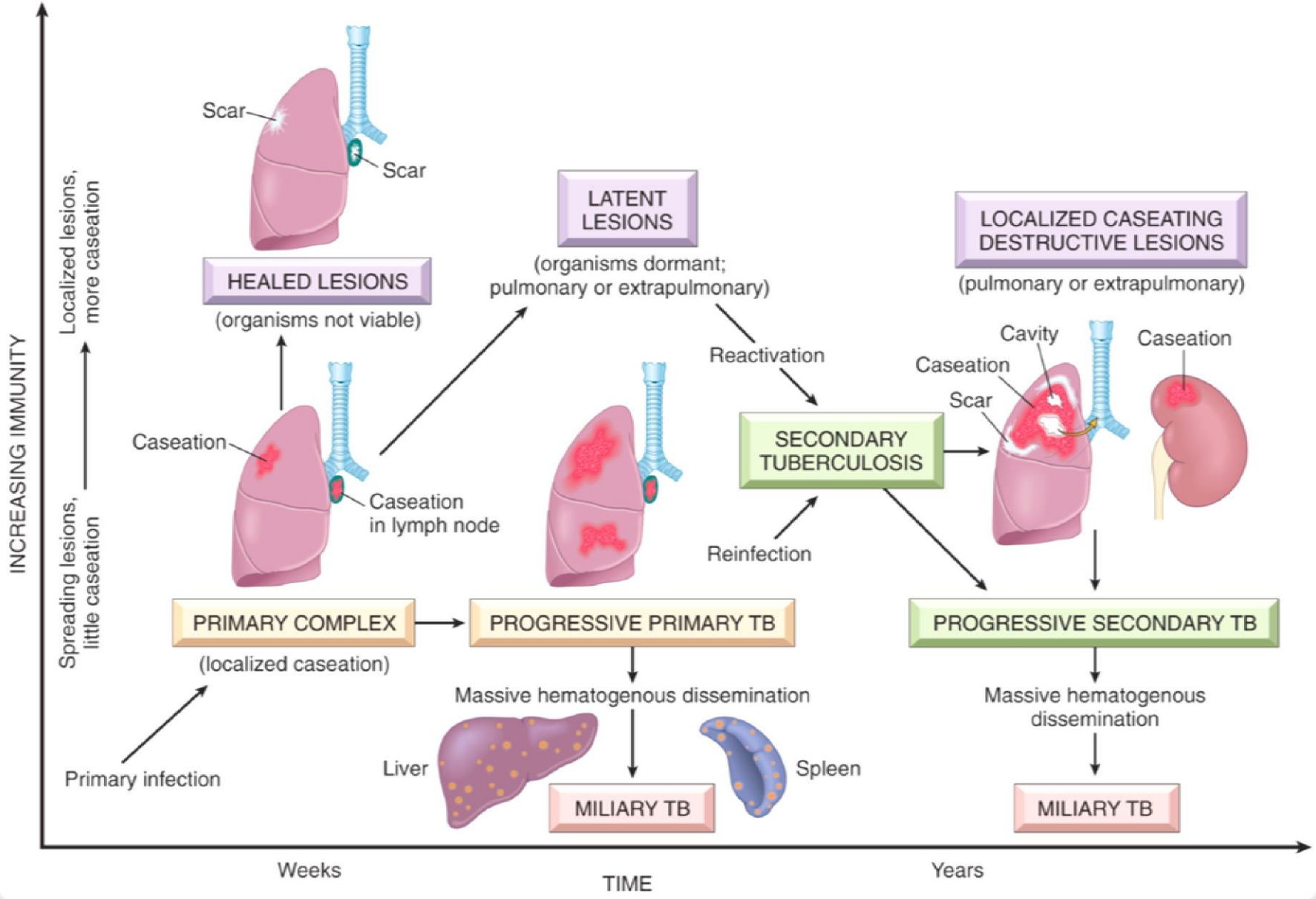
Tuberculin test or (Mantoux)

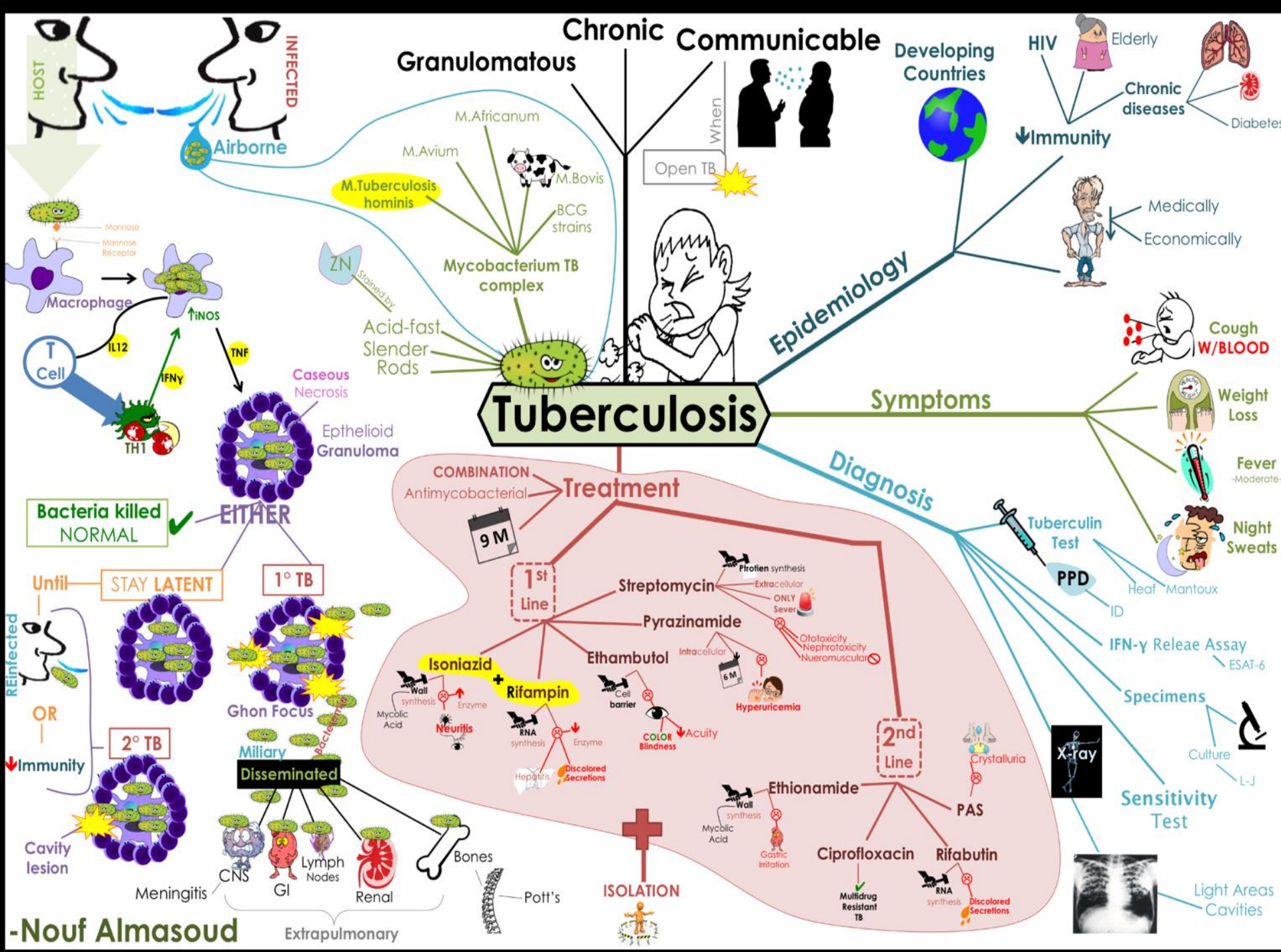
Delayed hypersensitivity skin test

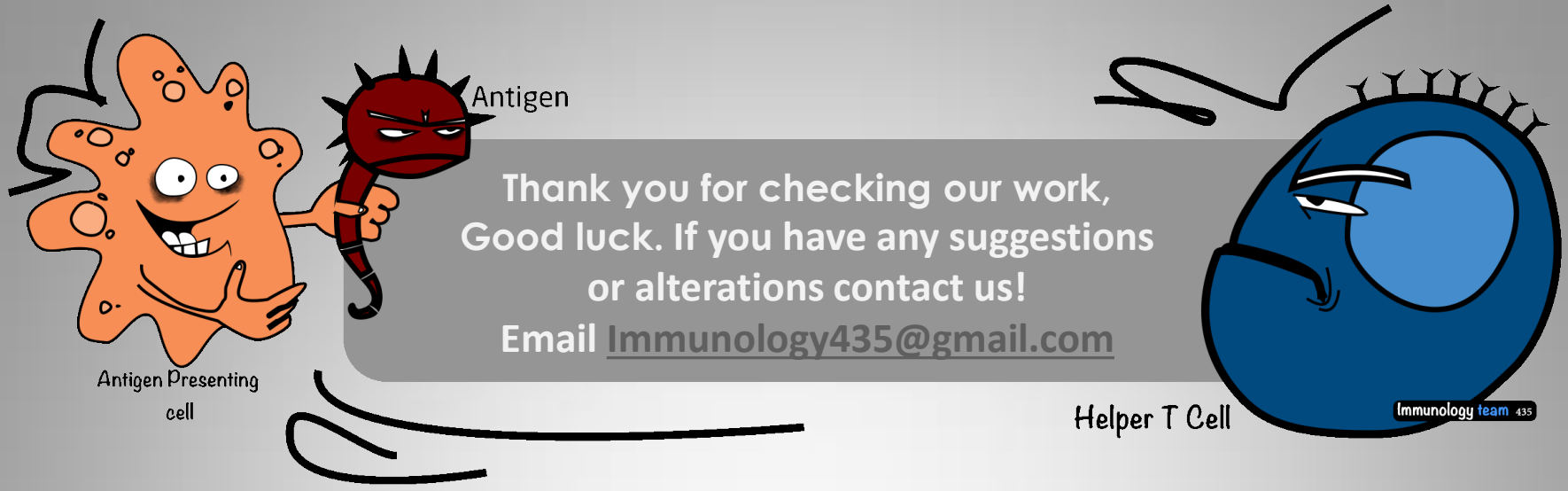
- Intradermal injection of PPD (protein)
- Tuberculin test should be interpreted with caution as it may be difficult to differentiate between DTH against M. tuberculosis and latent disease.

IFN-γ release assay

- The test measures interferon-gamma released into blood from T cells.
- The test can differentiate those latently infected with M. tuberculosis from those vaccinated with BCG.


INCREASING IMMUNITY
Localized lesions, more caseation
Spreading lesions, little caseation
Scar
Scar
HEALED LESIONS
(organisms not viable)
LATENT LESIONS
(organisms dormant; pulmonary or extrapulmonary)
LOCALIZED CASEATING DESTRUCTIVE LESIONS
(pulmonary or extrapulmonary)
Reactivation
Cavity
Caseation
Caseation
Scar
Caseation
Caseation in lymph node
SECONDARY TUBERCULOSIS
Reinfection
PRIMARY COMPLEX
(localized caseation)
PROGRESSIVE PRIMARY TB
PROGRESSIVE SECONDARY TB
Massive hematogenous dissemination
Massive hematogenous dissemination
Primary infection
Liver
Spleen
MILIARY TB
MILIARY TB
Weeks
TIME
Years


Tuberculosis
Chronic
Granulomatous
Communicable
When
Open TB
Airborne
HOST
INFECTED
M.Africanum
M.Avium
M.Bovis
M.Tuberculosis hominis
BCG strains
Mycobacterium TB complex
ZN
Stained by
Acid-fast Slender Rods
Epidemiology
Developing Countries
HIV
Elderly
Chronic diseases
Diabetes
Immunity
Medically
Economically
Symptoms
Cough W/BLOOD
Weight Loss
Fever
-Moderate-
Night Sweats
Diagnosis
Tuberculin Test
PPD
Heaf
Mantoux
ID
IFN-γ Releae Assay
ESAT-6
Specimens
Culture
L-J
Sensitivity Test
X-ray
Light Areas Cavities
Mannose
Mannose Receptor
Macrophage
↑iNOS
T Cell
IL12
IFNγ
TNF
TH1
Caseous Necrosis
Epthelioid Granuloma
Bacteria killed
NORMAL
EITHER
Until
STAY LATENT
1° TB
Ghon Focus
Bacteria
Miliary
Disseminated
2° TB
Immunity
OR
REinfected
Cavity lesion
CNS
GI
Lymph Nodes
Renal
Bones
Pott's
Meningitis
Extrapulmonary
COMBINATION
Antimycobacterial
Treatment
9 M
1st Line
Streptomycin
Protien synthesis
Extracellular
ONLY Sever
Ototoxicity
Nephrotoxicity
Nueromuscular
Pyrazinamide
Intracellular
6 M
Hyperuricemia
Ethambutol
Cell barrier
COLOR Blindness
Acuity
Isoniazid
+
Rifampin
Wall synthesis
Mycolic Acid
Enzyme
Neuritis
RNA synthesis
Hepatitis
Discolored Secretions
2nd Line
Ethionamide
Gastric Irritation
Crystalluria
PAS
Ciprofloxacin
Multidrug Resistant TB
Rifabutin
ISOLATION
-Nouf Almasoud



Thank you for checking our work,
Good luck. If you have any suggestions or alterations contact us!
Email Immunology435@gmail.com

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أسرار باطرفي
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فرح مندوزا
لولوة الصغير
منيرة العمري

إبراهيم البيشي
تركي العنزي
عبدالناصر الوابل
ماجد العسبلي
فيصل القحطاني
عبدالاله ابو خلف
محمد الفواز
ناصر المقبل