

1/3 of world's population = infected

- ↳ NTB Infection ≠ Disease
- ⇒ Latent TB (Robert Koch)
- ⇒ Huge Reservoir for future disease

Active Infection = "tuberculosis" (> 9M new/year)

- ↳ TB = leading cause of death due to bacterial infection!

Interplay $\left\langle \begin{matrix} \text{HIV} \\ \text{NTB} \end{matrix} \right\rangle$ Especially in SA!

MDR & XDR TB strains are on Rise = Super easy for Medicine!

NTB Antibiotic Responsibility = NTB!

NTB Transmission:

must do fit test (tight seal)

- ↳ Aerosolized droplet nuclei ⇒ N95
- ↳ families = not an issue

- ⇒ Particles airborne for long time
- ⇒ Single cough = 8000 infectious droplets

↳ Deposited in terminal Airways!

⇒ occurs mainly indoors after prolonged Exposure & multiple inocula

Risk: closeness of contact
Must take NTB seriously
↳ normal surgical mask not protect against TB

HIV (-) generally need cavities for transmission
HIV (+) can transmit without having cavities

↳ not all who are exposed get infected.
1/3 (not too sure why)

Impaired immunity may lead to TB disease

- (Host Genetics)
- HIV/AIDS (↑ TB [3] among Medical students)
- Malnutrition
- Alcoholism
- Renal failure
- Immunosuppressive therapy
- Diabetes Mellitus

The Stages of Latent Infection → Disease:

Latent infection = Asymptomatic & ID based on a T-cell response against NTB antigens

- (+) tuberculin test
- (+) Interferon γ release Assay (IGRA)

Latent & Active = oversimplification

NTB Infection = 4 Response Spectra:

- 1) Innate Immune Stage: → sent Dr
Host innate immune sys able to eradicate infection.
No Acquired Involvement = No memory
- 2) Acquired Immune Stage:
Both innate & Acquired immune sys operate to eliminate infection (granuloma's ^{heat})
- 3) Quiescent Immune Stage: most people here (= granuloma)
Host immune sys still control infection but there are still viable (non-replicating) organisms
- 4) Active Infection Stage:
Bacteria = viable + replicate
Host immune sys fight but start to show apparent symptoms ⇒ The Active Disease
from Active → 1/3 live
→ 1/3 die
→ 1/3 Chronic Infection

Immune Dx of NTB infection:

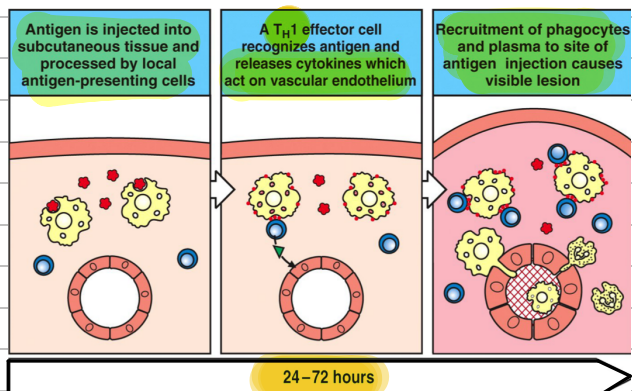
Delayed type 4 Hypersensitivity (cell mediated) (Th1 mediated)

- TB cultures & supernate inject TB Antigens into skin (NTB not specific) Also multiple punches like Tine, Heat tests
- Tuberculin Skin test
- PPD → Purified Protein Derivative
- Mantoux test

Response after 24-72h
Rash > 10mm = (+) test

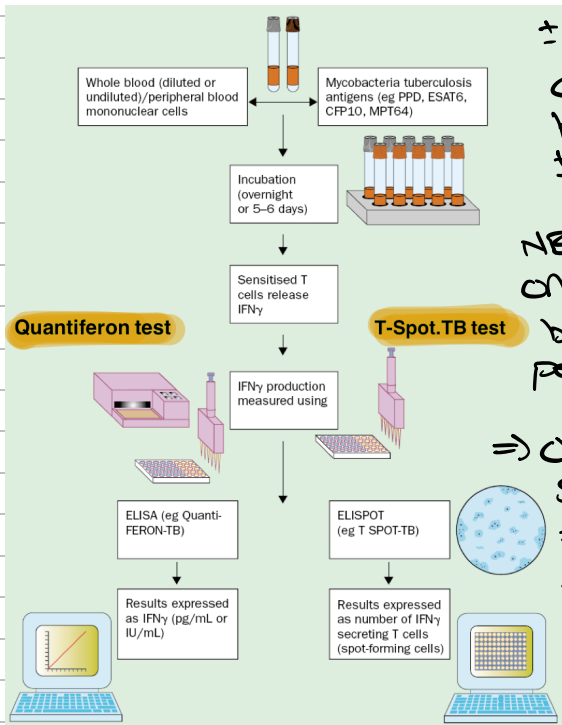


⇒ Means you have memory Against TB proteins



New tests for MTB Infection:

Interferon gamma release Assays (IGRA)

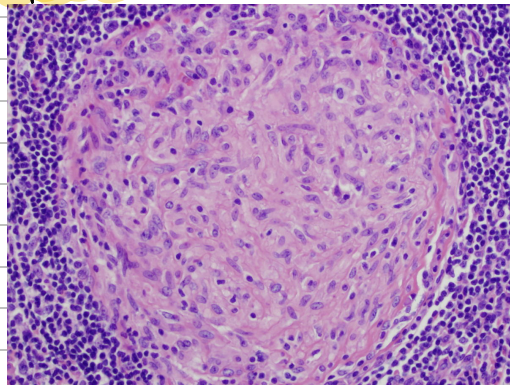


± 500 000 cells in the test & only ± 5 will be (+)

NB in SA only + xnt children below 5 & people with HIV

⇒ Child below 5 & contact = immediate prophylaxis!

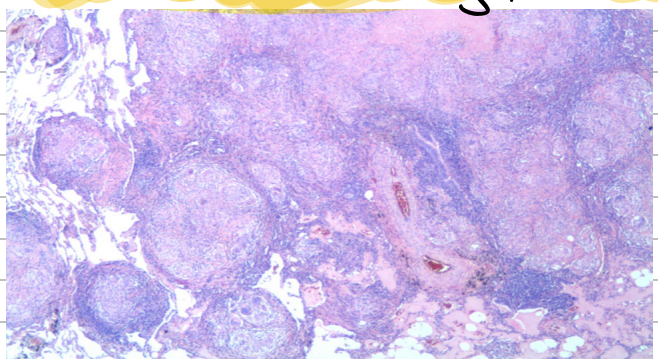
Granuloma:



↳ centre = macrophages with ingested TB = giant cells = some Neutrophils
↳ surrounded by T-cells & fibrotic wall

↳ Body try to "contain"
↳ centre can become necrotic, later fibrotic (Space-occupying lesion)

MTB = contained & dormant unable to cause disease until host weakened
Below = Multiple Caseating Granulomas in lung



Inside Granuloma = Hypoxic conditions
↳ MTB = ↓ metabolism (DosR Regulator)
No Growth + ↓ Respiration & ↓ metabolism

↳ Become Non-stainable by conventional methods (AFB'S → ZN)

⇒ Lesion Disruption: MTB ^{DNA} DNA Synthesis = Recultured → act as pheromones
↳ (RPF'S) → Regus Promoting factors
↳ Dissolve cell walls

↳ caseating centre may liquefy
↳ = MTB flourish & transmitted in blood stream all over body!

Quantiferon: Whole Blood

T-Spot-TB: Peripheral blood mononuclear cells

• Rely on pre-existing memory T-cells against MTB Antigens

- More specific than TST
- As sensitive as TST
- More Expensive than TST (> 10 \$)
- Requires lab
- More standardised than TST
- Require only 1 visit to HC-worker (prior results in)

→ Lung: Draining Lymph Nodes
Pathogenesis: Inhaled immune cells induce T-cells

Infected Alveolar macrophages / Interstitial dendritic cells (DC'S)

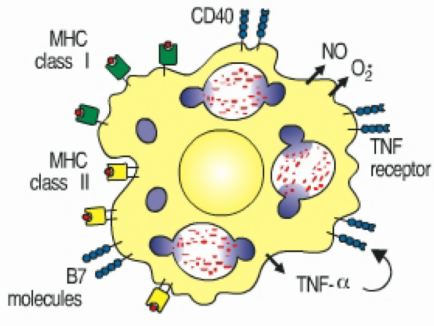
↓
Migrate to Draining Lymph nodes & stimulate Antigen specific T-cells

⇒ Lung lesion + Lymph nodes = Gran complex ARE'S Attract T-cells

OR
Enter Lung Parenchyma, Attract macrophages from blood = macrophage (Histocytes) = Granuloma forms (orchestrated by T-cells)

Many ways to subvert macrophage function during MTB Infection:

Activated macrophage



- Interference with phagosome (lysosome fusion) = Prevention of phagolysosome Acidification
- ↓ interaction by IFN-γ

- ↓ Regulation & degradation of MHC II
- Lack of expression of co-stimulatory molecules

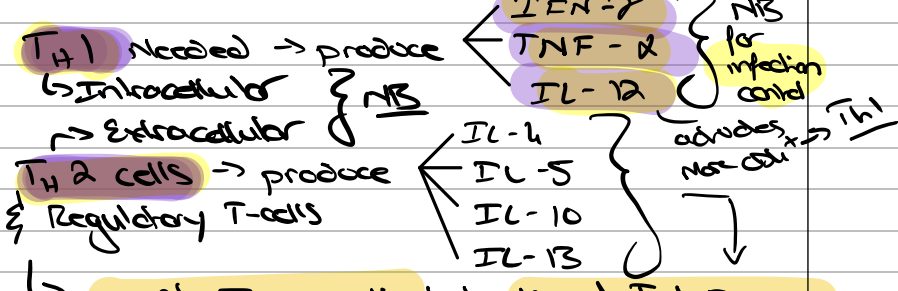
Why with TB = Loss of Immune Memory?

- ↳ **MTB Δ's Antigens**
∴ MTB = 4000 genes; may stop expressing antigens that were expressed during early infection
↳ memory cells that were specific for early infection = not useful now since MTB not expressing those antigens anymore

- ↳ **Exhaustion of Memory:**
Persistent antigen coupled with strong stimulation = leads to loss of memory cells

- ↳ **Wrong T-cell phenotype:** -T_{H2} instead of T_{H1}

MTB = Best fought with a T_{H1} Response
But MTB release things that induces a T_{H2} Response instead



↳ prevent Immunopath but also ↓ T_{H1} Response
= if balance disturbed MTB = evade immune system

TB tries to ↑ T_{H2} Response since a T_{H1} Response eradicates it better!
ie. TB induces wrong immune response

Susceptibility to TB:

Susceptibility to TB

- Acquired Immune suppression
 - HIV infection - loss of CD4 T cells, 10%/year get TB
 - Diabetes - macrophages are suppressed. 3x higher rate
 - 'Biologicals' = TNF inhibitors
 - Other immune suppressive drugs, i.e. after organ transplantation, anti-cancer chemotherapy
- ↳ macrophage activation
- Mendelian susceptibility to mycobacterial infection (genetic defects)
 - IFN-gamma signalling (receptor 1 and 2)
 - IL-12 (IL-12p40 or receptor beta 1)
 - STAT-1
 - NFκB kinase (NEMO) - reduced TLR and TNF activation
- ↳ Th1 stimulation
- Other
 - Concurrent helminth infection (induce IL-4, IL-5, IL-10, IL-13, and regulatory T cells, which suppress TH1 cells)
 - Age, especially <5yrs, or old age
 - Malnutrition
 - Alcoholism
 - Smoking

IL-12 (CD4⁺ → Th1)
IL-4 (CD4⁺ → Th2)