Pathology of Tuberculosis

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Epidemiology

- Single most important infectious disease
- Affects 1/3 of world population
- Kills about 3 million patients each year
- PNG prevalence rate is 648 per 100 000 (WHO 2013).
- Mortality rate is around 57 per 100 000 (WHO 2013).

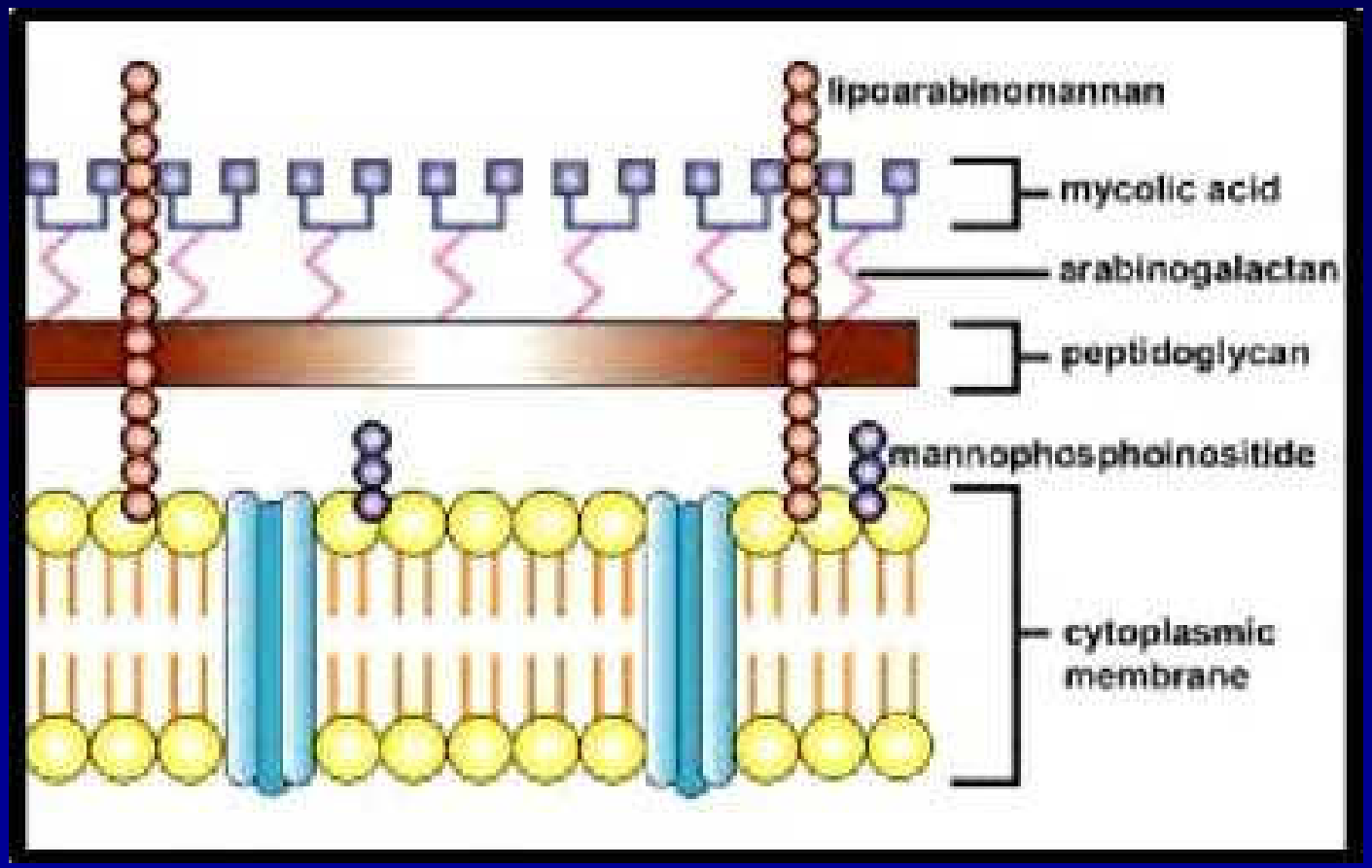
Etiology & Pathogenesis

- Infection is caused by M.tuberculosis & M.bovis.
- Aerobic, non-spore-forming, non-motile bacilli with a waxy coat (which is responsible for retaining the red dye in acid-fast stains).
- Transmitted by inhalation of infective droplets or when sneezed into air by infected person.
- M.bovis transmitted by consumption of unpasteurized milk from infected animals.

Etiology & Pathogenesis

- M.avium & M.intracellulare cause disseminated infection in 15-24% of AIDS patients.
- Pathogenicity: Related to its ability to escape killing by macrophages and induce delayed type hypersensitivity.
- Attributed to its cell wall components (Mycosides):
  - Cord factor – glycolipid found on virulent strains. Inhibits neutrophil migration & damages mitochondria
  - Lipoarabinomannam (LAM) – heteropolysaccharide, similar structure to gram negative endotoxin. Inhibits macrophage activation by interferon gamma.

Mycolic Acid Structure



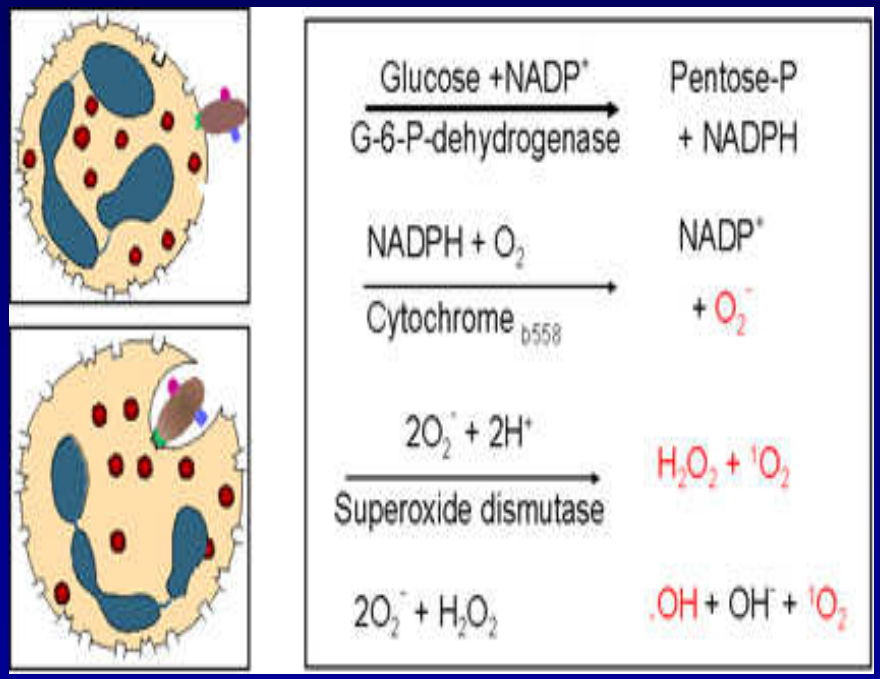
Ref: Yale School of Medicine, Laboratory Medicine Website

Pathogenesis

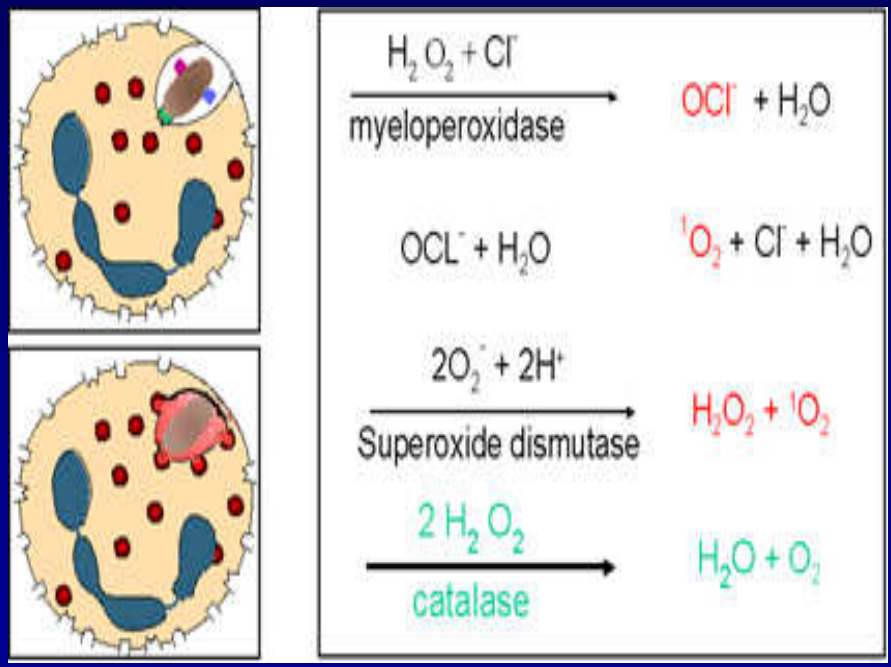
- LAM also induces macrophages to secrete TNF-α, which causes wt loss, tissue damage
  - Induce macrophage to secrete IL-10 which suppresses mycobacterium-induced T-cell proliferation.
- Complement activated on mycobacterium surface opsonize organism, facilitate its uptake by macrophages via complement receptor CR3 (MAC-1 integrin) without triggering respiratory burst necessary for killing intracellular organisms.

Intracellular Respiratory Burst

O2 depdendent myleoperxodase-independent intracellular killing



O2 dependent myeloperoxidase-dependent intracellular killing



Ref: Online Microbiology & Immunology, University of Carolina School of Medicine

Pathogenesis

- A highly immunogenic 65-kD heat shock protein – M. tuberculosis heat shock protein plays a role in autoimmune reactions induced by M. tuberculosis.
- M.tuberculosis resides in phagosomes which are not acidified into lyososomes.
  - Inhibition of acidification is by a urease secreted by myocobacterium. Sulfatides (cell wall) also inhibit fusion of phagosome with lysosome.
- Uptake of mycobacterium is by compliment – or mannose binding proteins rather than Fc receptors.

Pathogenesis

- Development of cell mediated immunity or type IV hypersensitivity reaction explains organisms destruction to tissues & emergence of resistance to organism.
- Primary infection is controlled via cellular immunity
- Secondary infection results from re-infection by virulent stains or reactivation and reduction in cellular immunity of infected individual.

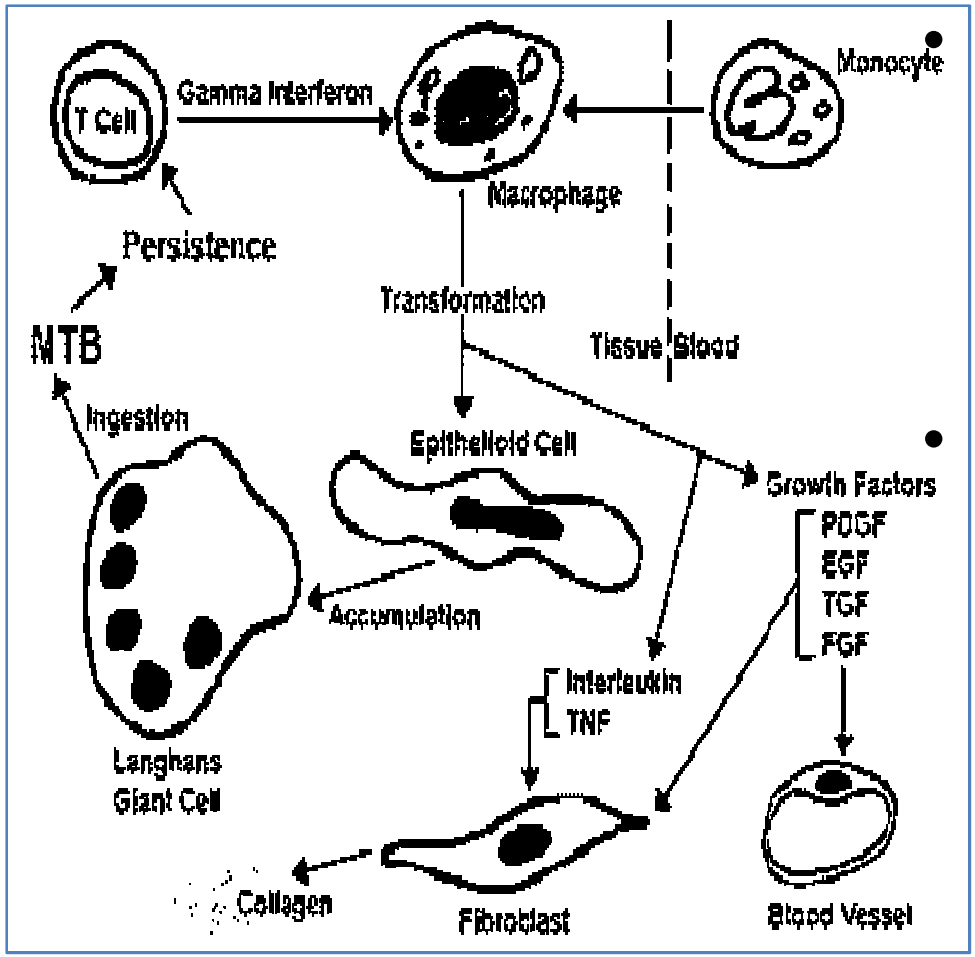
Primary Infection - Events

- Inhalation of mycobacterium & ends with T-cell mediated immunity response killing 95% of organism.
- Events in sequence:
  - Phagocytosis of organism by alveolar macrophages
  - And transportation to hilar lymp nodes.
  - Naïve macrophages unable to kill organism therefore bacilli multiply within macrophages

Primary Infection

- Bacilli lyse (kill) host macrophages and infect other macrophages.
- Bacilli disseminate to other parts of the lungs and other parts of the body.
- T-cell immunity against mycobacterium develops after a few weeks (3-4 weeks).
- Development of T-cell immunity is demonstrated by a positive purified protein test (PPD or Mantoux).
-

Type IV (delayed) Hypersensitivity

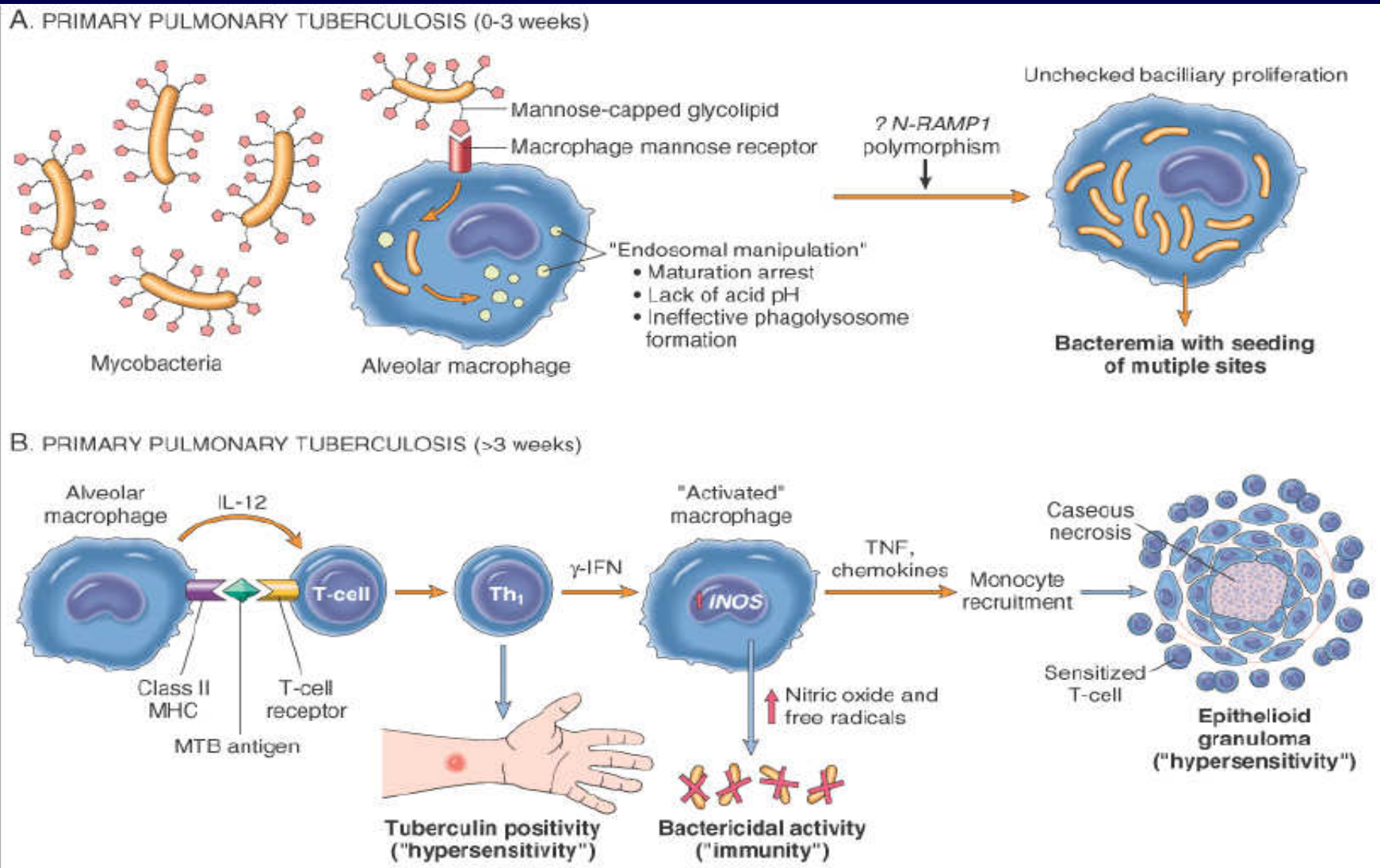


- Sensitised CD4+ cells process Ag and release lymphokines in association with MHC Class II molecules.
- Rxn begins in hrs & peaks in 2-3 days.

Primary Infection

- Mycobacterium activated T cells cause:
- CD4+ helper T cells secrete interferon-γ which activates macrophages to kill intracellular mycobacterium via NO, NO2 & HNO3. **This results in formation of epitheliod cell granulomas** & clearance of organism.
- CD8+ suppressor T cell lyse infected macrophages through a Fas-dependent, granule-dependent reaction & kill mycobacterium.

Primary Infection



Ref: Robins Pathological Basis of Diseases, 7th Ed.

Primary Infection

- CD4-CD8- (double negative) T cells lyse infected macrophages without killing mycobacterium
- **Lyses of macropahges results in formation of caseating granulomas.** Direct toxicity of mycobacterium to macrophages also contributes.
- Mycobacterium cannot grow in this acidic, extracellular environment, low in oxygen hence infection is controlled.

Primary Infection

- Calcified hilar lymp node is called a Ghon focus
- Together with calcified scar in the lung parenchyma is called a Ghon complex.
- This is ***latent TB infection.***
- LTBI diagnosed via PPD (low specificity, low sensitivity) and Quantiferon Function Test/QFT (high specificity, high sensitivity).
- Minimal lung changes. CXR normal most often. Look for Ghon complex/Focus.
- CXR screening for primary infection is not cost-effective.

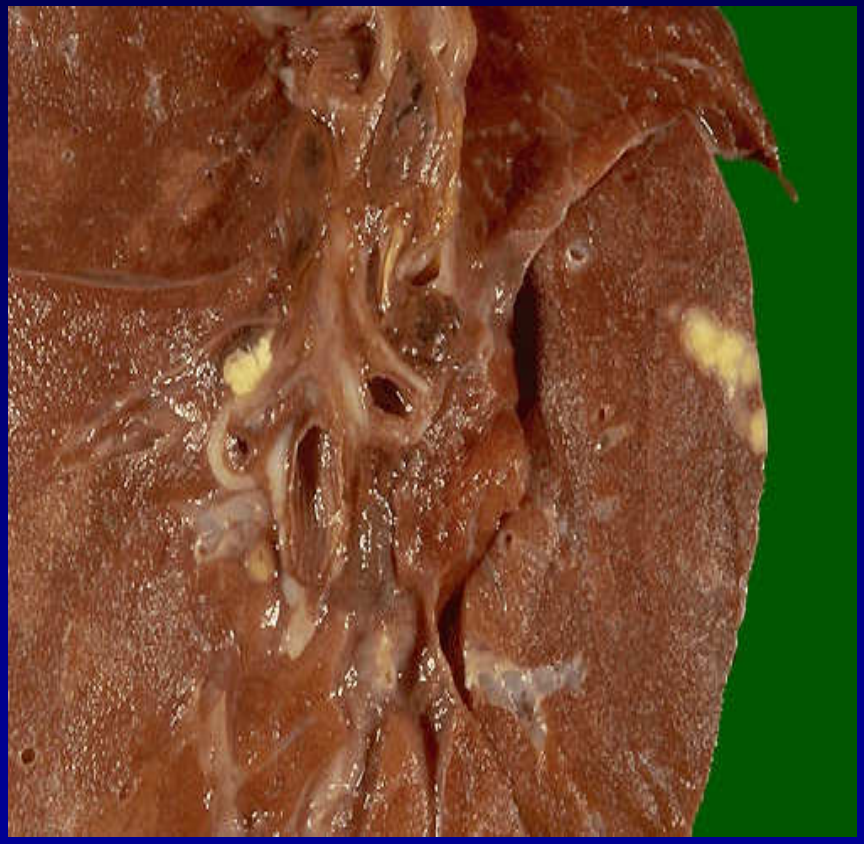
Secondary Infection

- Secondary infection results from re-infection by virulent strains or activation of latent TB infection and drop in cellular immunity in host.
- Secondary infection can be disseminated through out the lung, kidneys, meninges and elsewhere.
- Granulomas of secondary infection most evident in lung apeces. But maybe widespread.
- Formation of granulomas is cause of tissue damage (delayed type hypersensitivity).

Secondary Infection

- 2 characteristic features are: caseous necrosis & cavities.
- Necrosis may rapture into blood vessels spreading organism throughout the body (miliary TB).
- Or break into airways releasing infectious mycobacterium in aerosols.

Morphology – Primary Infection



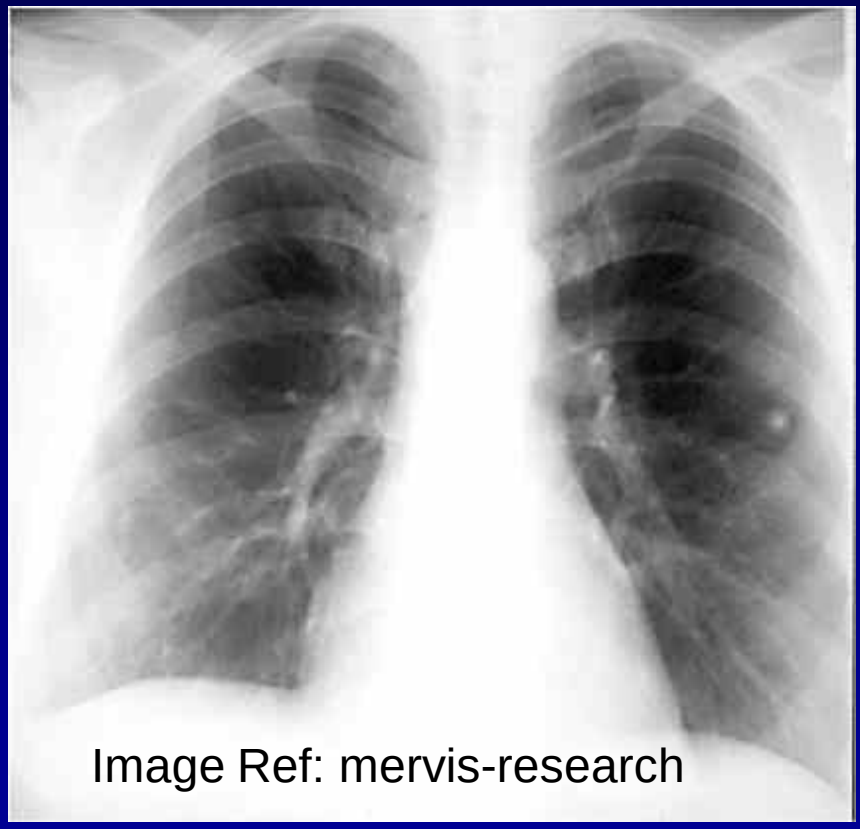


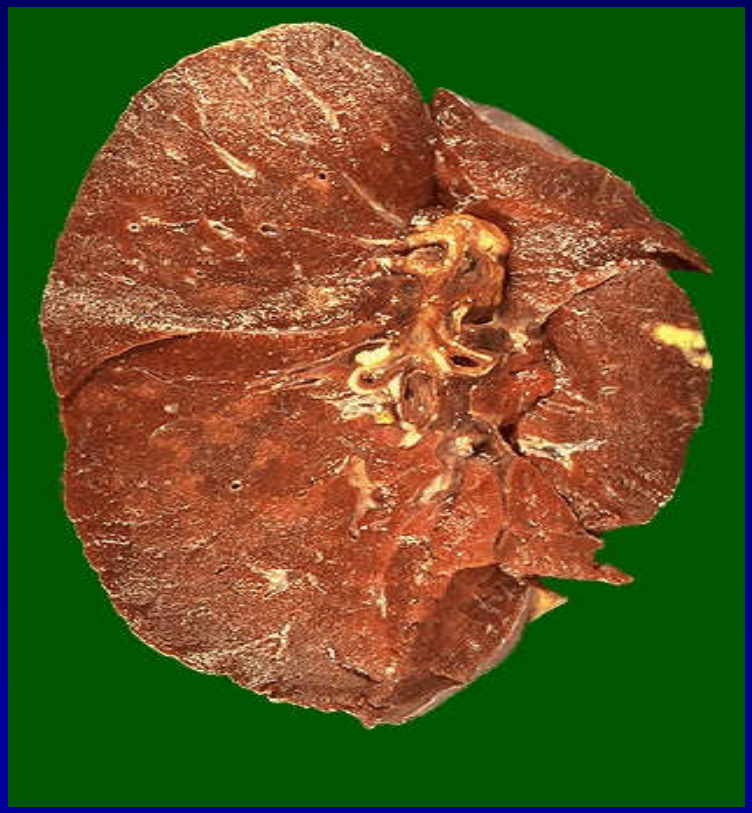
Image Ref: mervis-research

Ghon complex: hilar lymph node plus peripheral scar (yellow tan lesion).

Ref: Internet Pathology Laboratory, University of Utah.

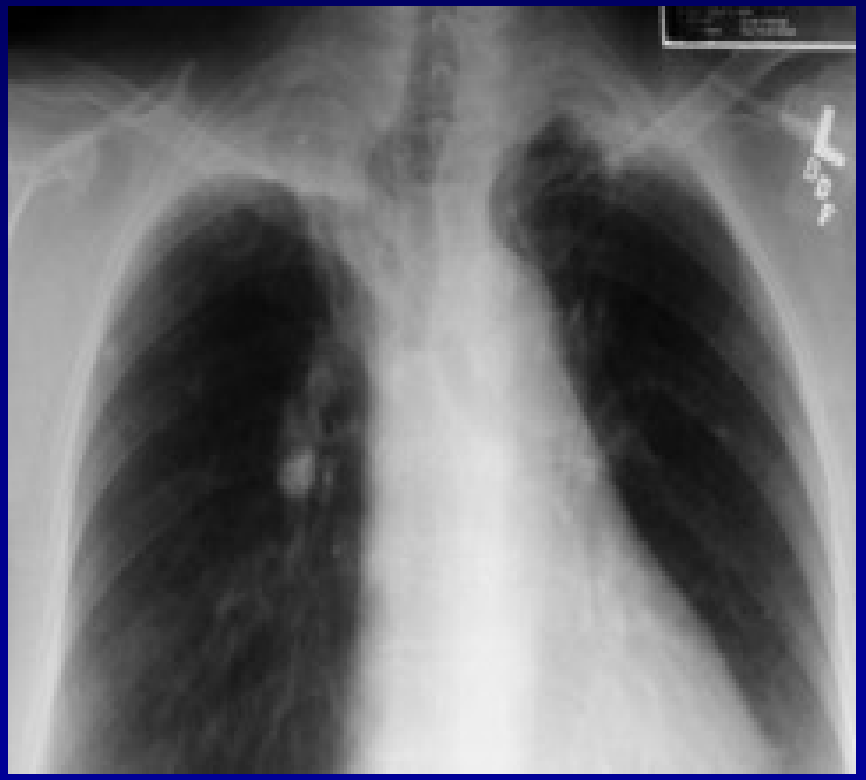
Primary Infection

Ghon Complex



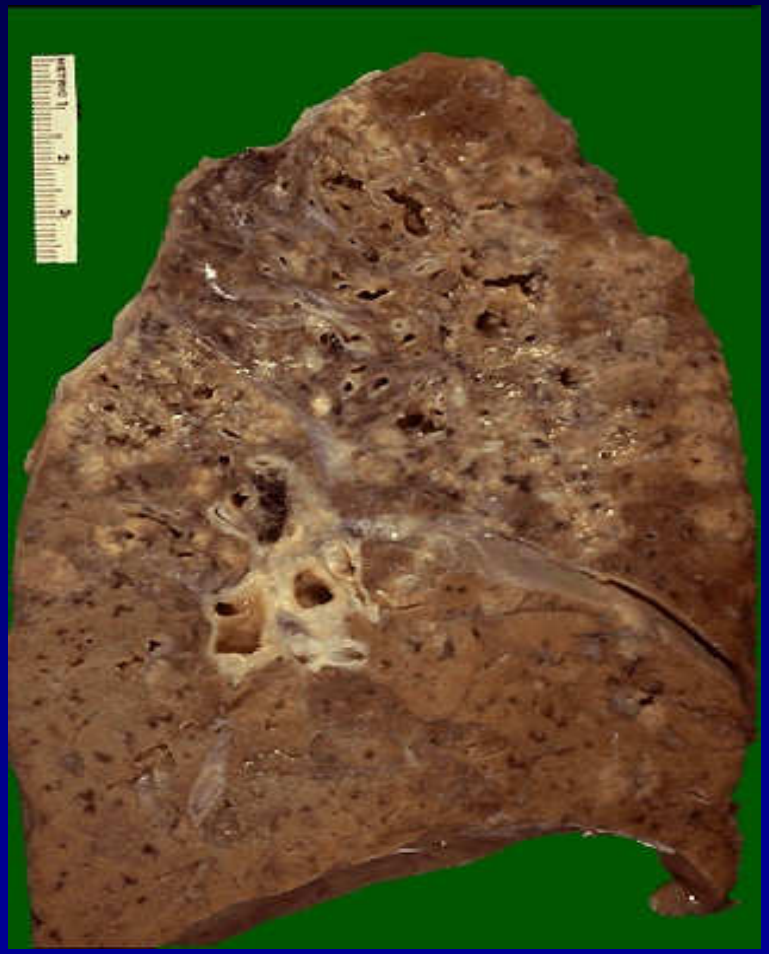
Ref: University of Utah

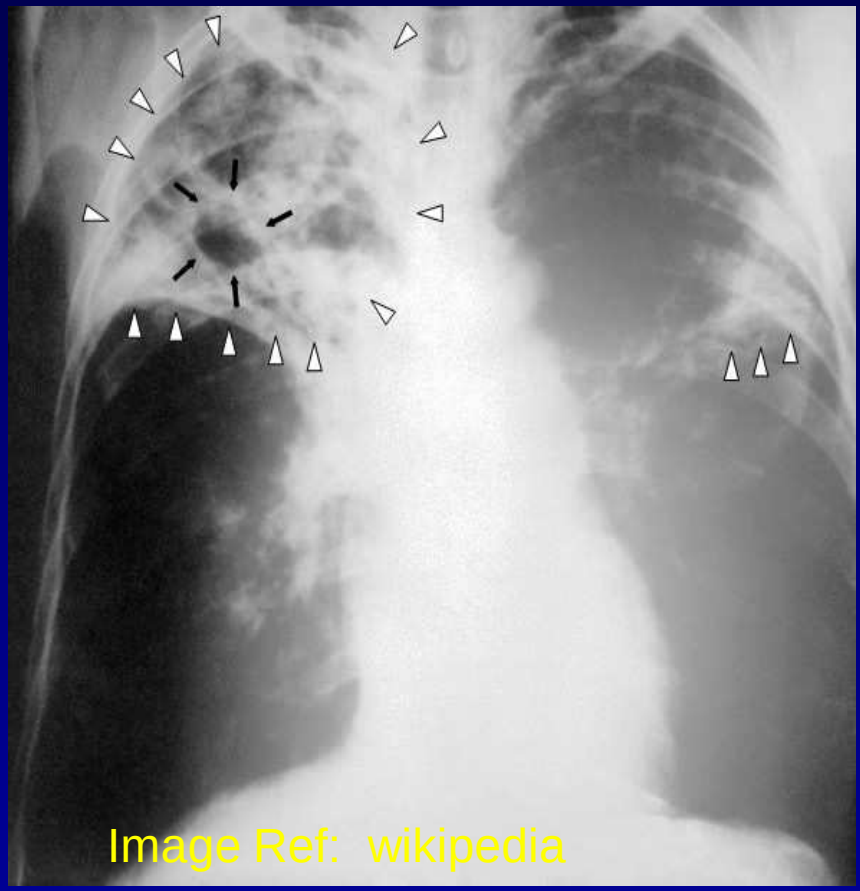
Ghon Focus



Ref: Quizlet.com

Secondary Pulmonary TB



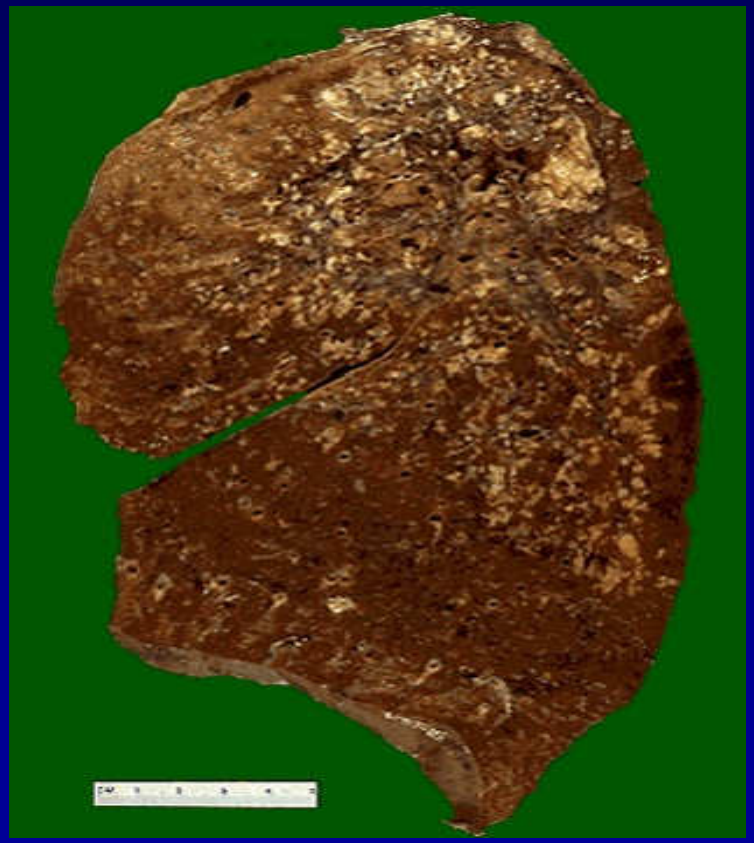


Cavity formation, multiple yellow tan granulomas. Propensity for apex

Ref: Internet Pathology Laboratory, University of Utah.

TB Morphology

Multiple yellow tan granulomas



Ref: University of Utah

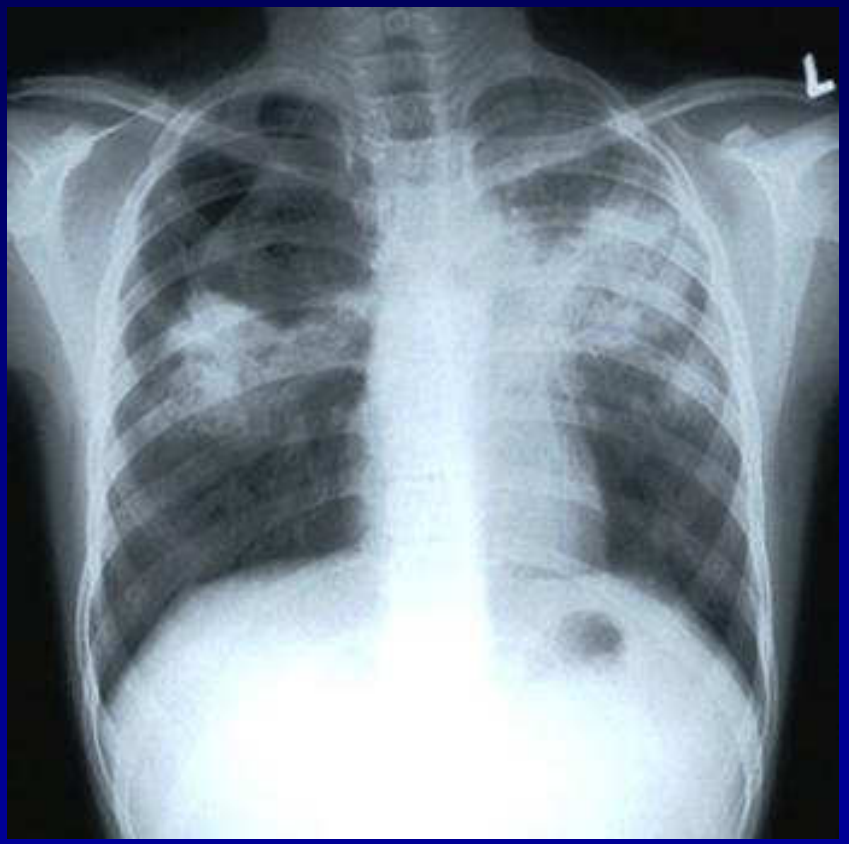
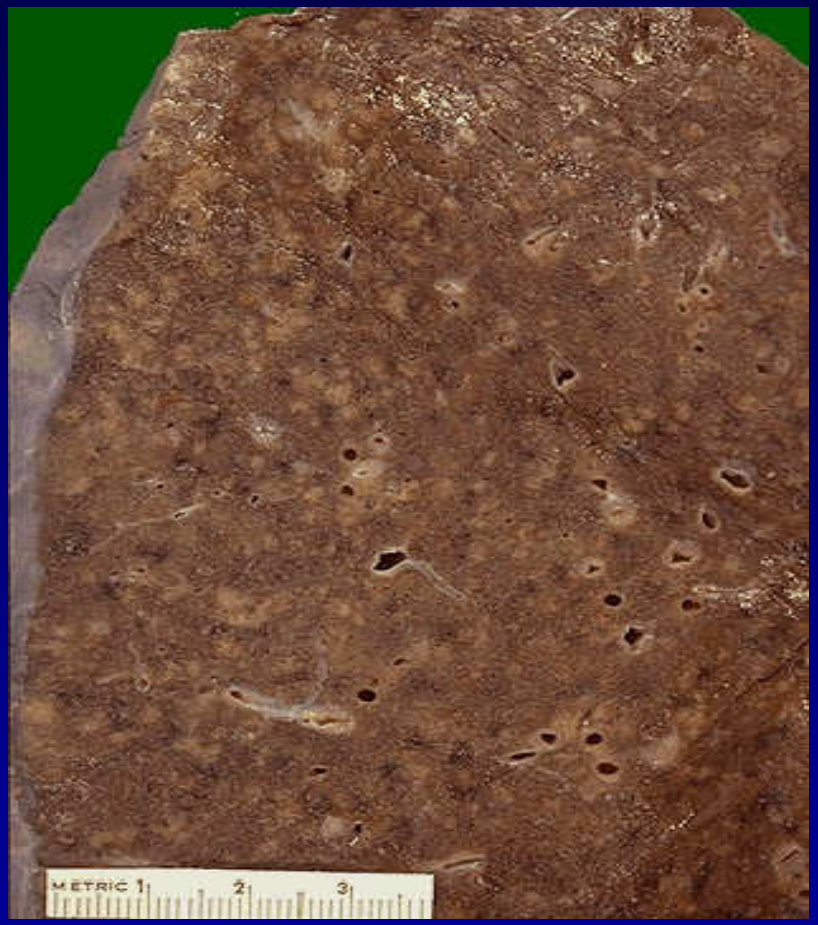
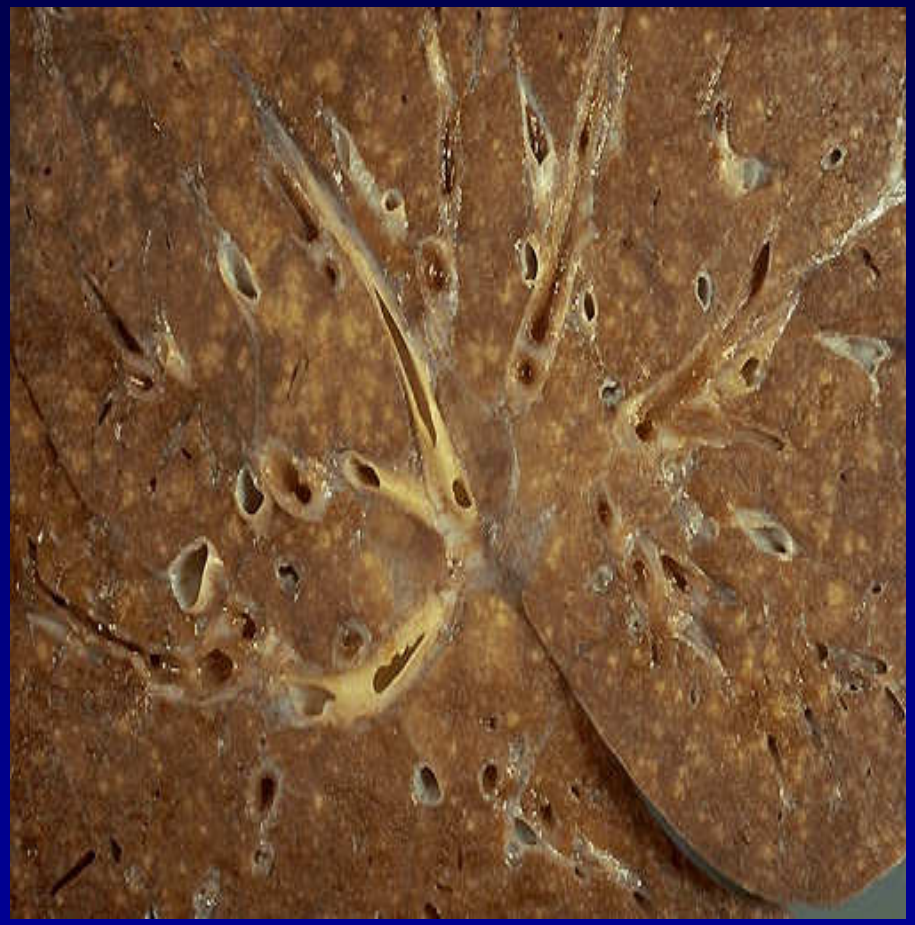


Image Ref: CDC

Morphology – Miliary TB

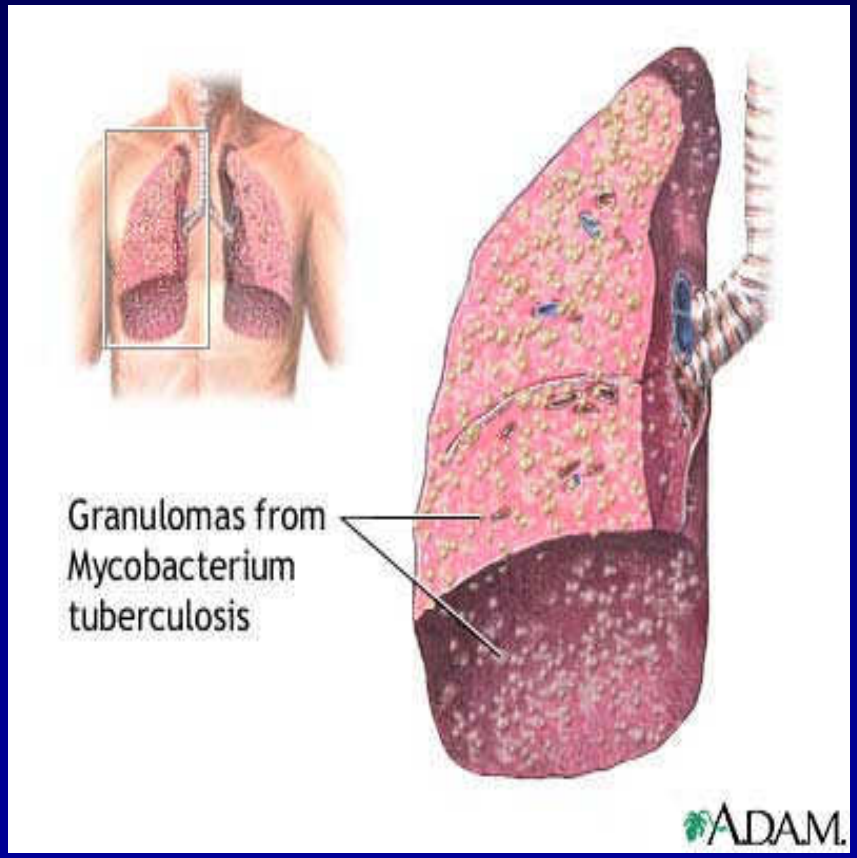




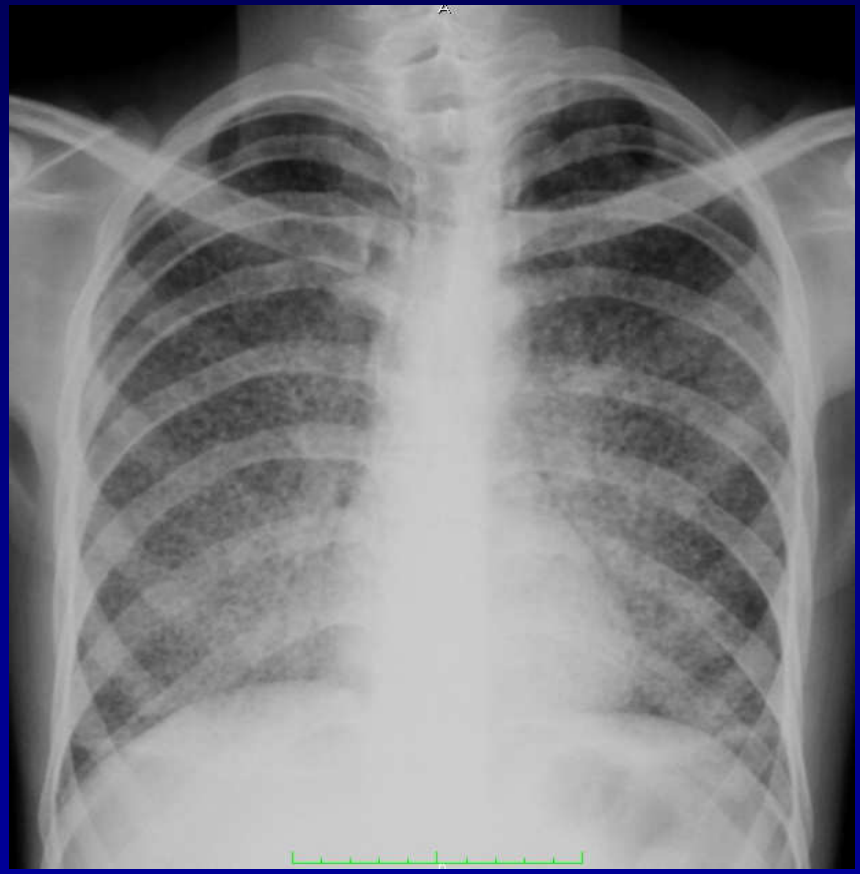
Multitude of small yellow tan granulomas 2-4mm in size resembling millet seeds.

Ref: Internet Pathology Laboratory, University of Utah

Miliary TB

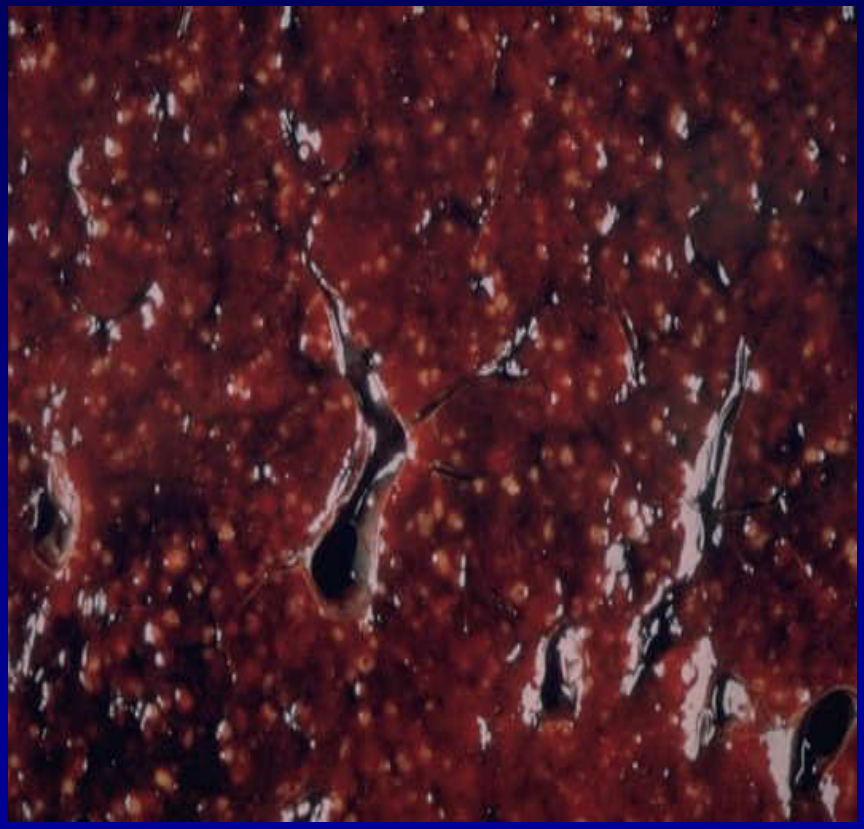


Ref: wikipedia

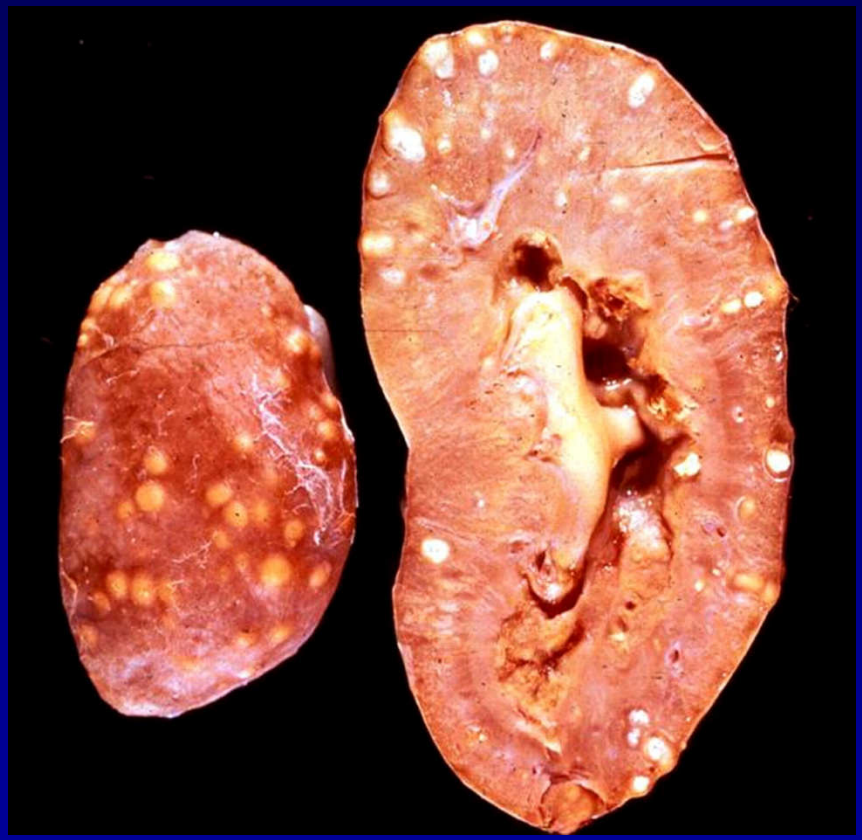


Ref: siamhealth.net

Miliary TB – Spleen & Kidney

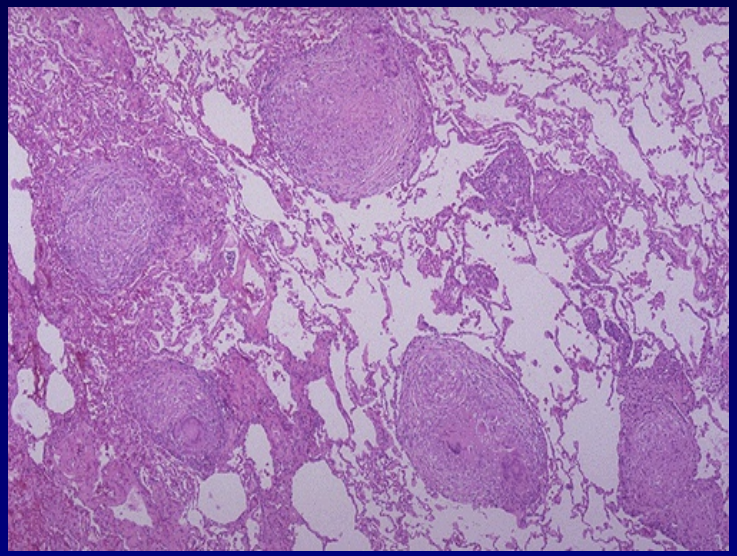


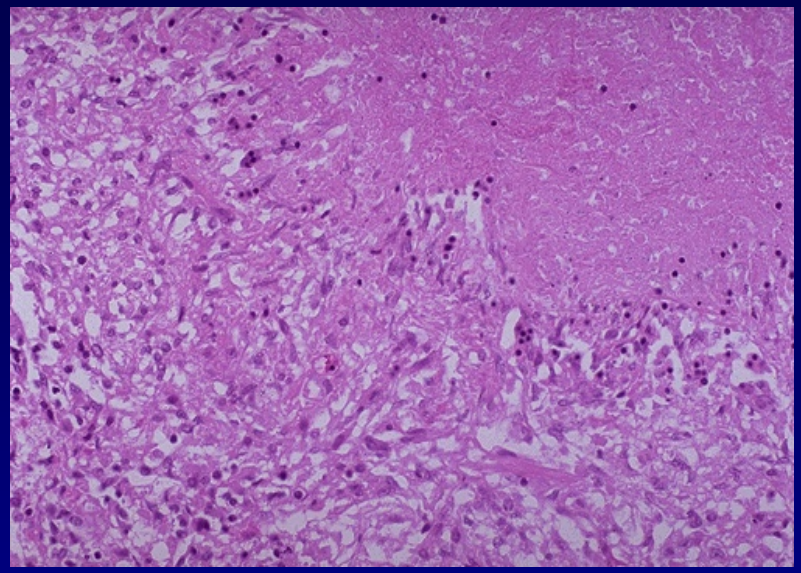
Ref: granuloma-homestead.com



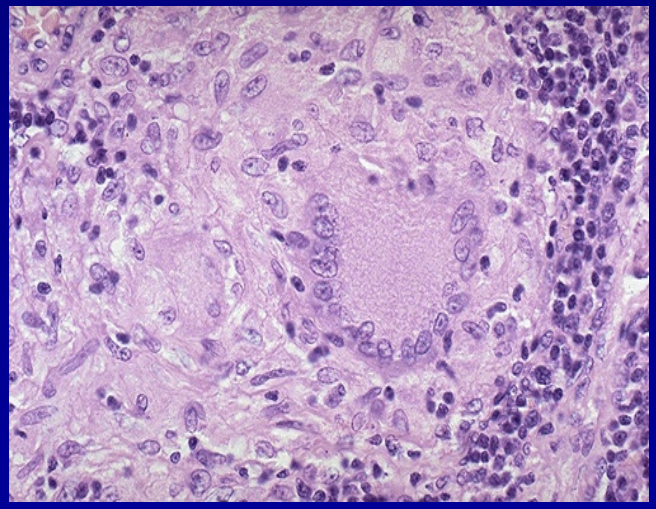
Ref: radiographics.rsna.org

TB Lung - Micro



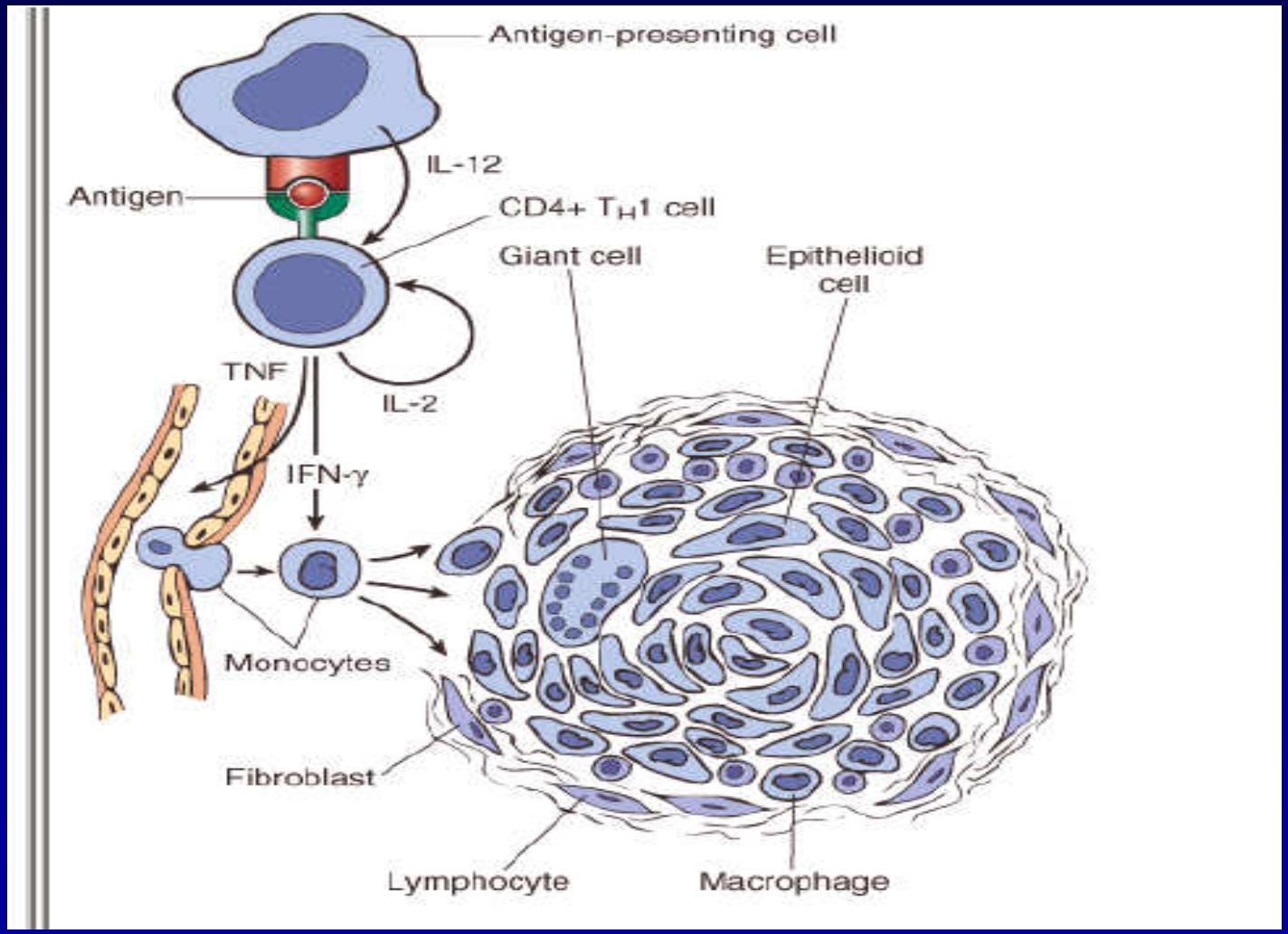


- Multiple granulomas
- Langhans giant cells
- Caseous necrosis ringed by chronic inflammatory cells, epitheloid cells



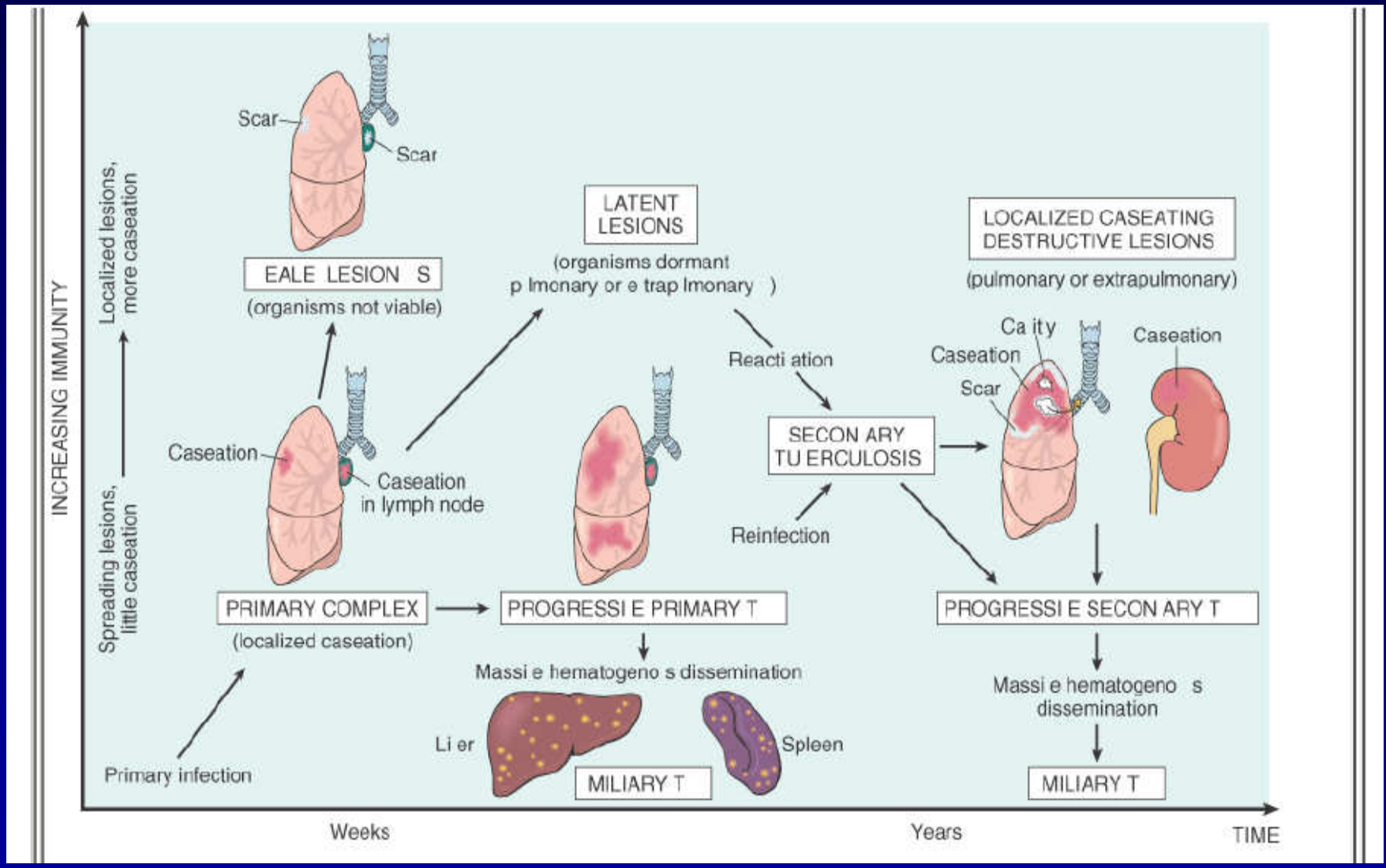
Ref: Internet Pathology Laboratory, University of Utah

Role of T cell in granuloma formation



Ref: Robins Pathological Basis of Diseases, 7th Ed

Progressive Pulmonary TB



Ref: Robins Pathological Basis of Diseases, 7th Ed.

Variable Forms of TB

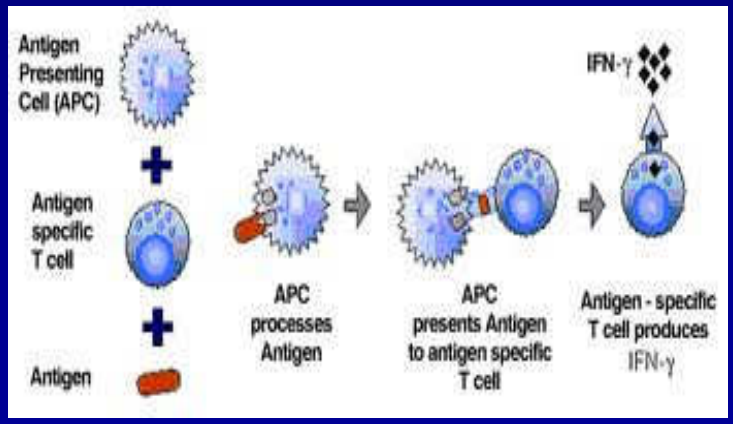
- Cavitary fibrocaseous tuberculosis
  - Cavity formation (usually apex) and walled off by fibrous tissue.
  - May affect more than one lobe of the lung.
  - Involvement of pleura leads to serous pleural effusions.
- Tuberculous bronchopneumonia – large areas of lung parenchyma and lobar exudate.
- Miliary TB results from lymphohematogenous dissemination.
  - Common sites include liver, kidneys, BM, adrenals, retina.

Laboratory Diagnosis

Latent TB Diagnosis

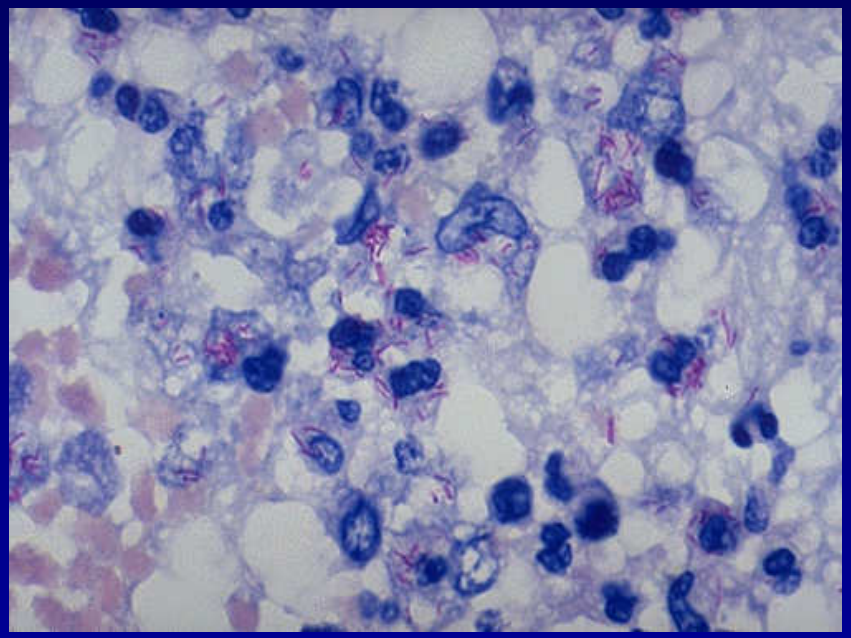
- Mantoux (PPD) & QFT
- PPD false positive from BCG vaccindation
- CXR – poor sensitivity, not cost effective.
- Serology – Banned by WHO

QFT

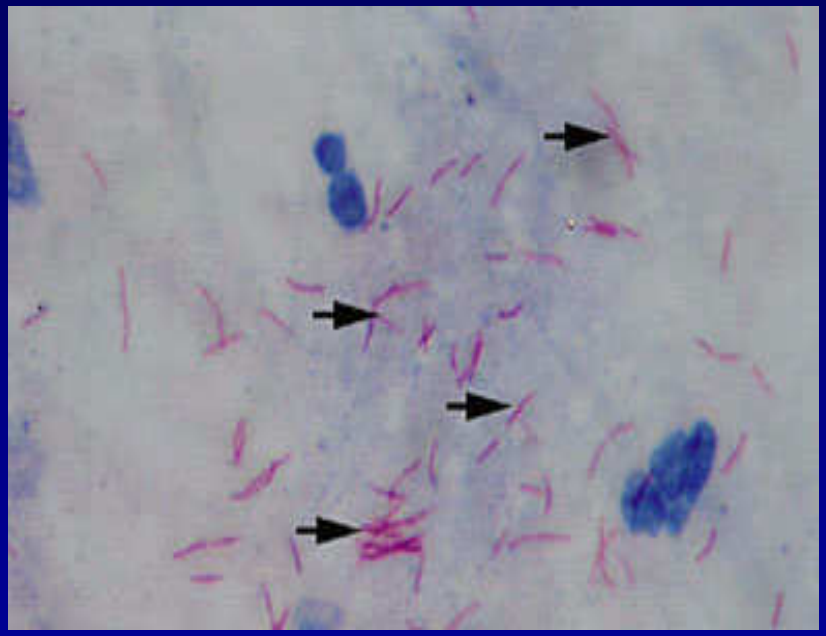


Laboratory Diagnosis

- Sputum/Tissue – AFB.



Ref: Internet Pathology Laboratory



Ref: Sharma & Tiwari, Rural & Remote Health Journal, May 2007

Laboratory Diagnosis

- Molecular biology – GenXpert, PCR
- Culture – identification, drug sensitivity and specificity testing. Different methods of culture.
- GenXpert can also test for RIF and INH resistance by isolating and amplifying genes.

- **Sample collection, storage, transporting and processing all determine test outcome!**
- ***If rubbish goes in, rubbish comes out!***

END

Ref: Robins Pathological Basis of Diseases.

Images: Internet Pathology Laboratory, University of Utah.

http://library.med.utah.edu/WebPath/

Download PDF copy of seminar notes at:

www.pathologyatsmhs.wordpress.com