Comparative pathology of tuberculosis following infection from mice to men.

Dr. Sowmya Bharath

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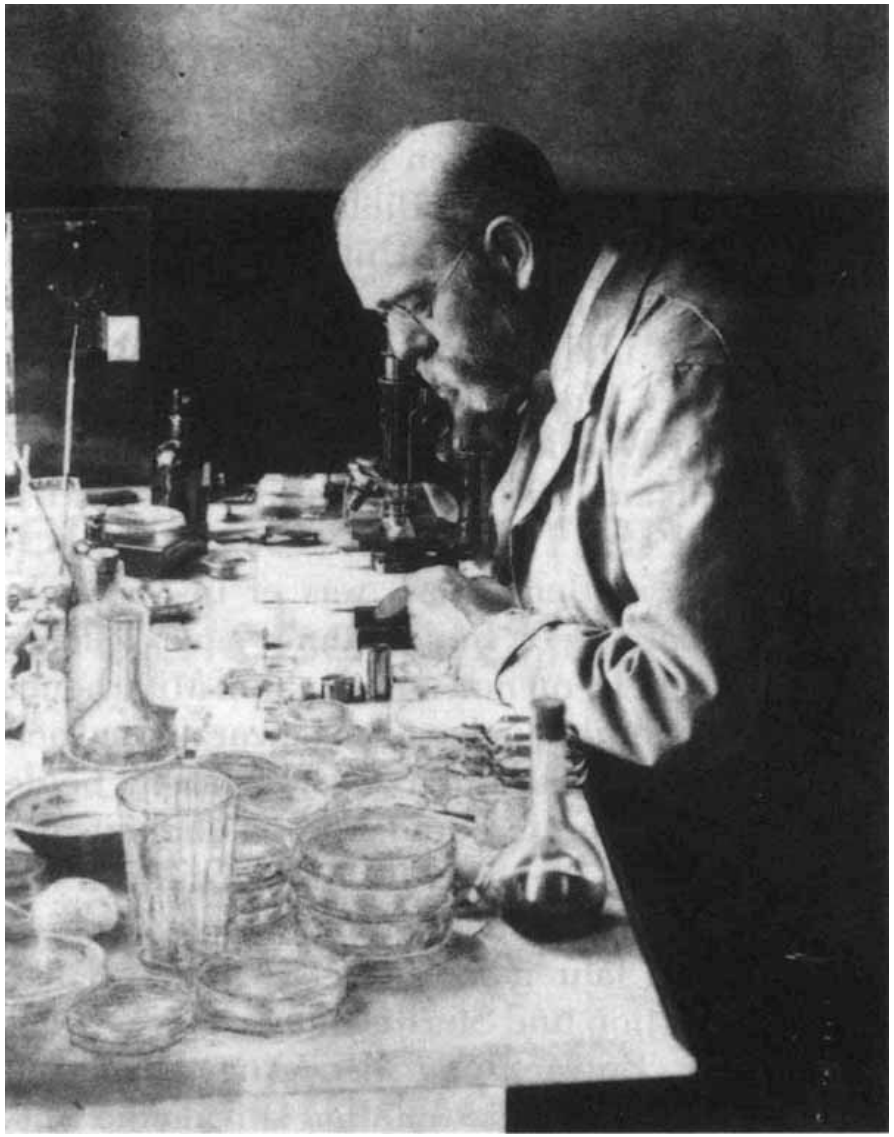
Milestones…

- 125th anniversary of the discovery of TB bacillus
- Decades ago, TB started disappearing, thanks to antibiotic era.
- Promised to eliminate it from the globe by the turn of the 20th century.



Today…

- But today, TB still remains a major disease afflicting all of mankind
- New forms of TB have appeared in many developed countries.
- And in developing nations it is spreading even faster, with two million people dying every year from the disease.

Two reasons

- Emergence of drug resistance
  - MDR and XDR TB
- HIV/AIDS epidemic

Tuberculosis: Medical Need

- "Worldwide Pandemic" - WHO
- Kills 5000 persons every day
- Incidence increasing by 1% / yr
- Leading cause of Death in HIV
- Drug Resistance in all countries
- 5% refractory to present therapy
- No new drug in the last 40 years

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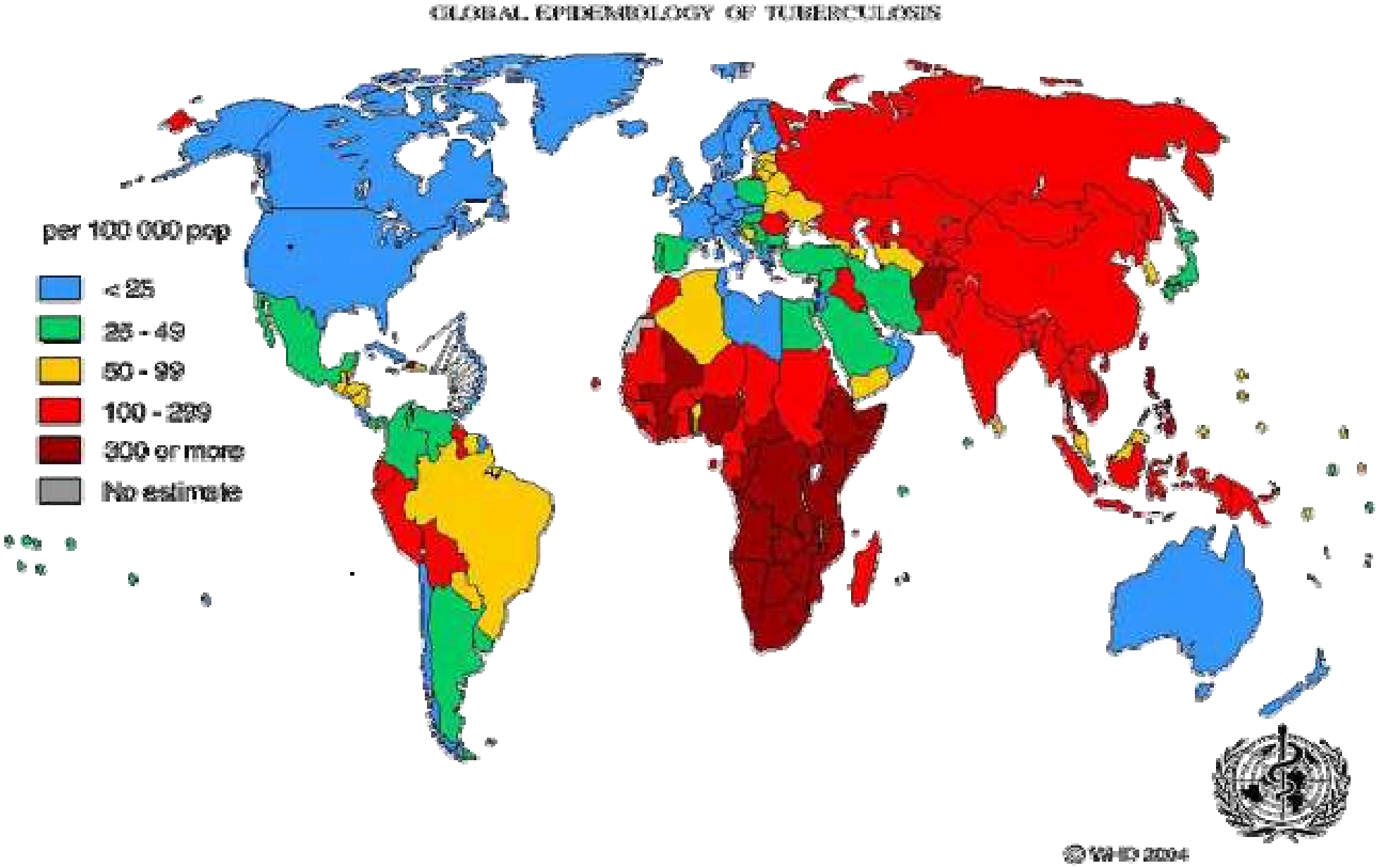
Distribution of TB Cases



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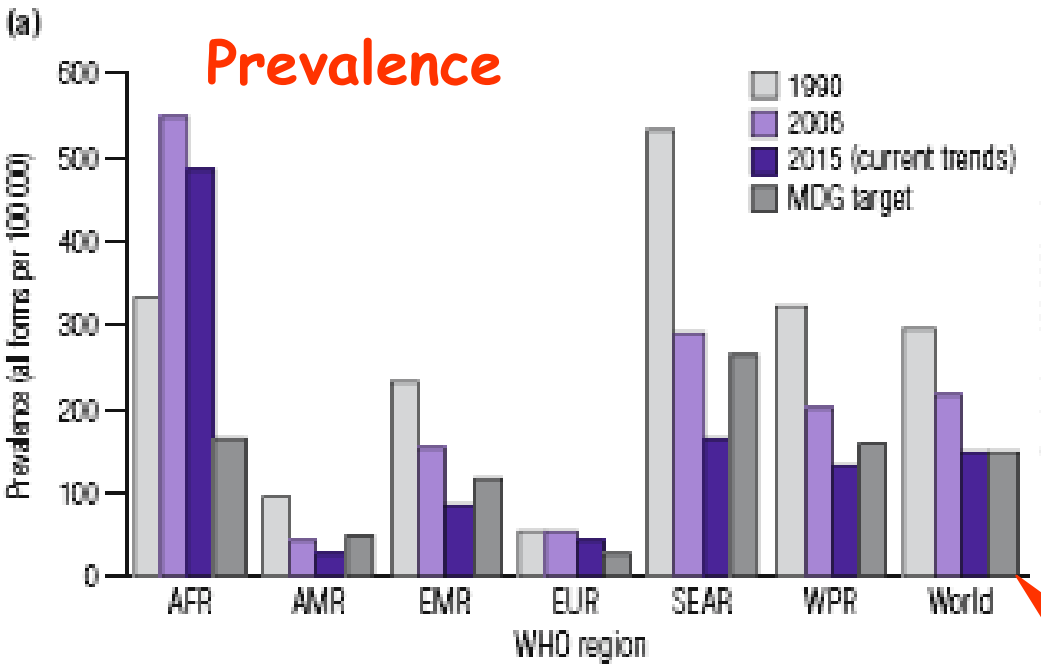
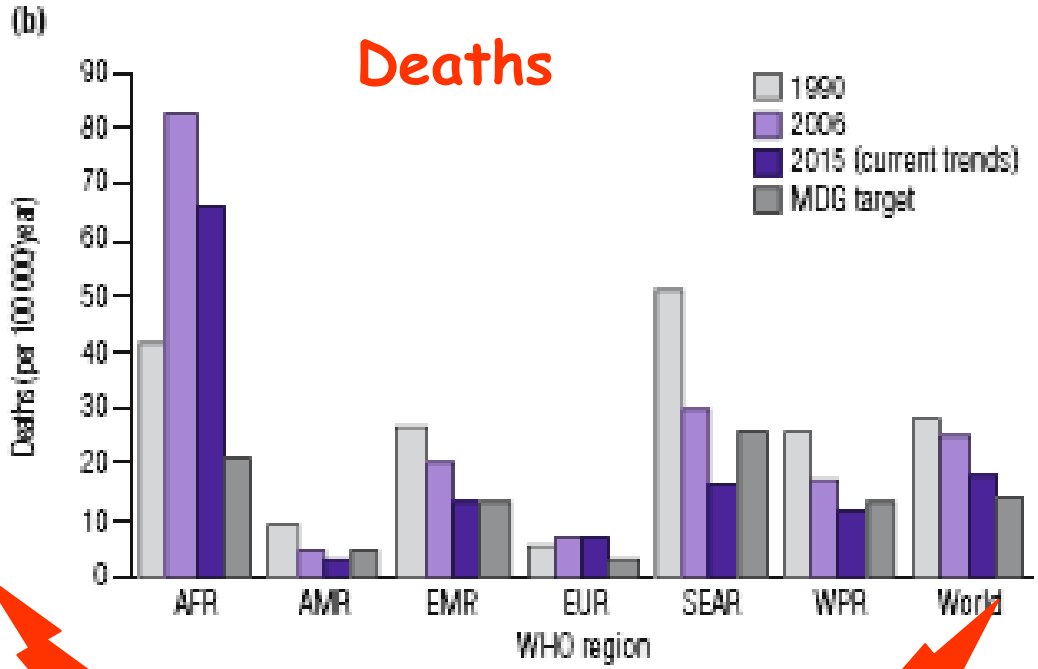
Prevalence and Deaths





AFR- Africa
AMR-America
EMR-Eastern Mediterranean
EUR- Europe
SEAR- South East Asia
WPR- Western Pacific
MDG- Millennium goal

By 2015 (worldwide):
10 million cases
1 million deaths

Ref: Global TB control. Surveillance Planning Financing. WHO Report 2008

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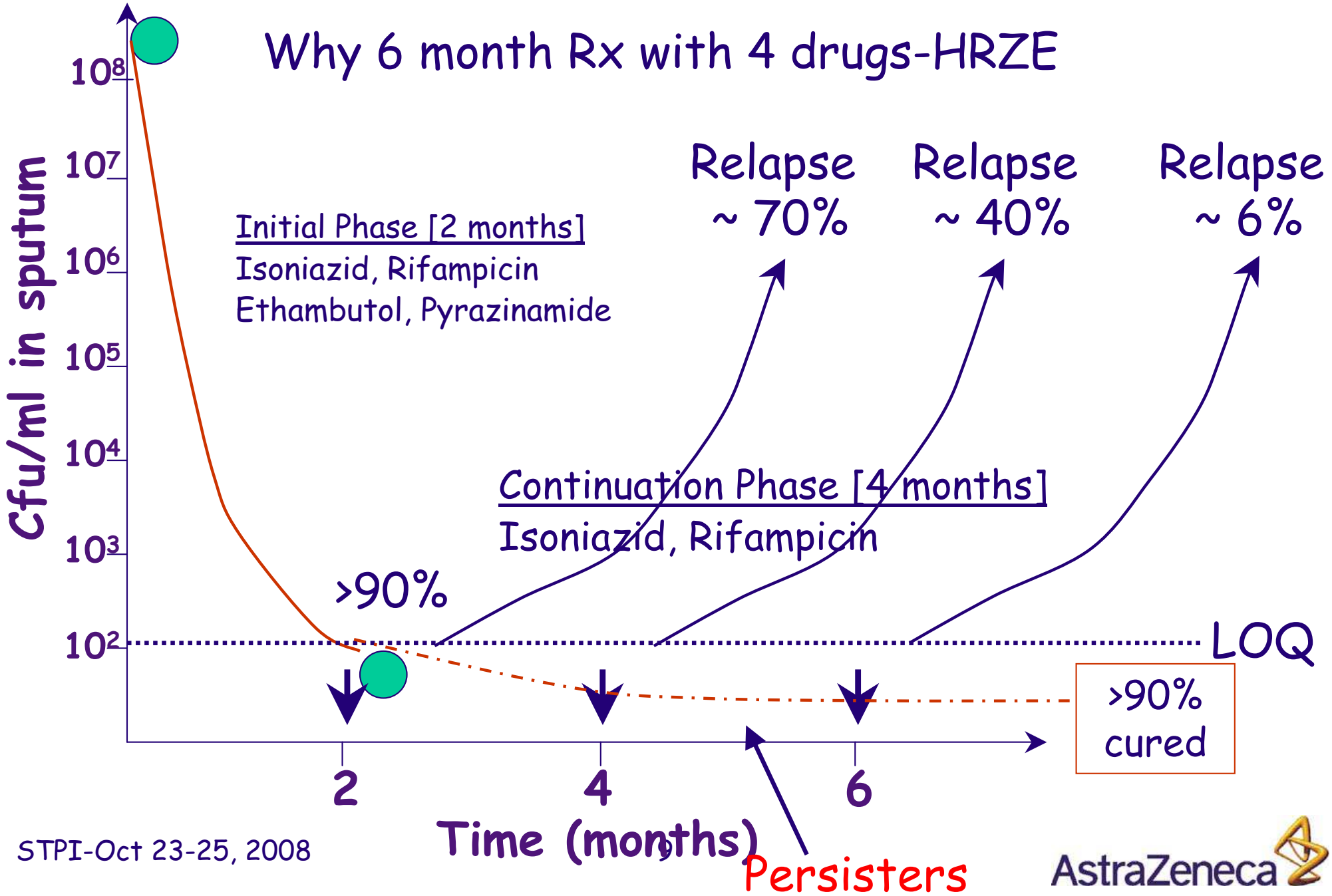
Complexities of tuberculosis

- Slow growing pathogen
- Granulomatous inflammation.
- Latency. Ability of the host to contain the organism.
- Spectrum of histological changes- varies with species.
- Immunological status of individual.

Complexity in TB Treatment



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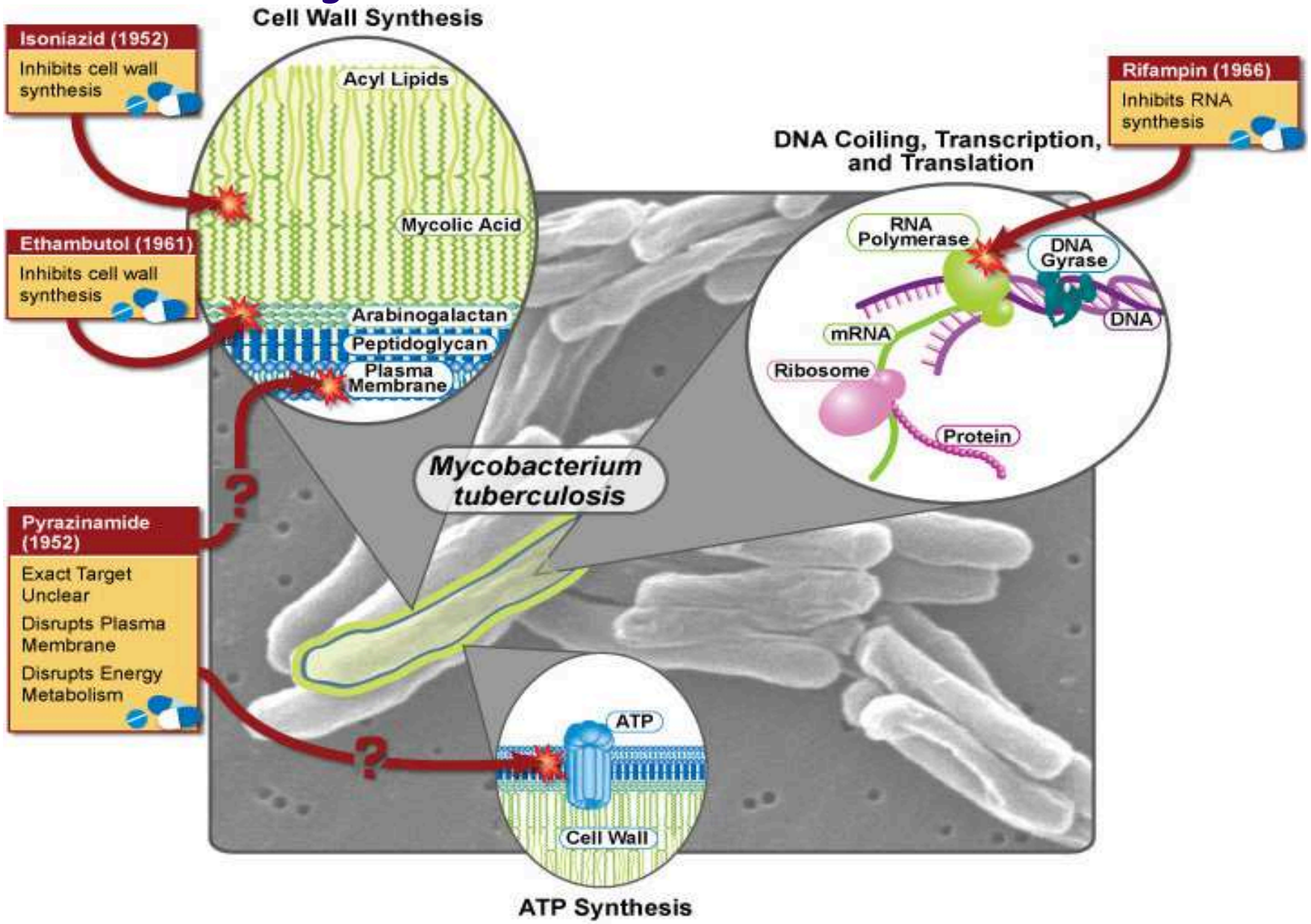
First-Line Treatment of Tuberculosis (TB) for Drug-Sensitive TB



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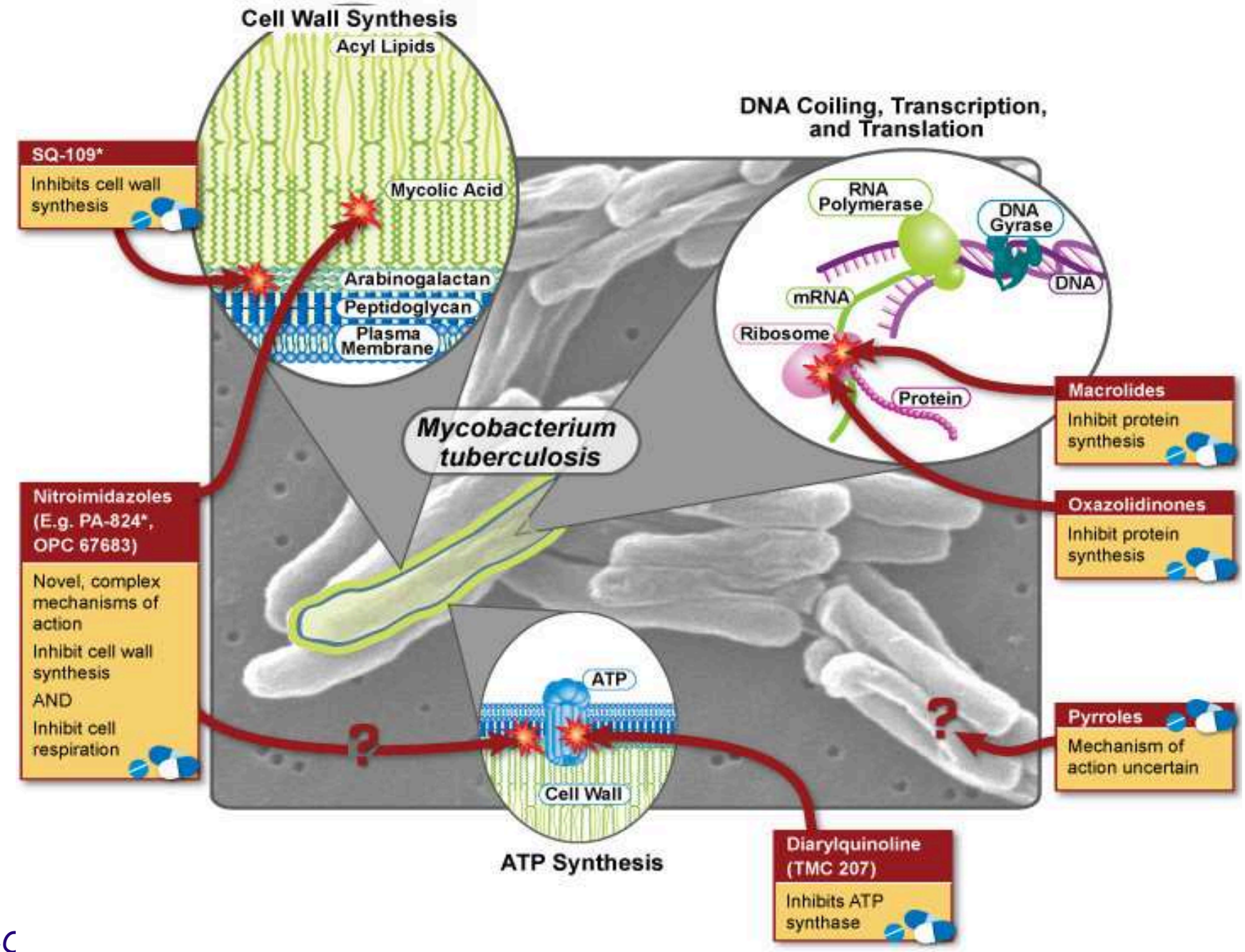
New Tuberculosis (TB) Drugs Under Development



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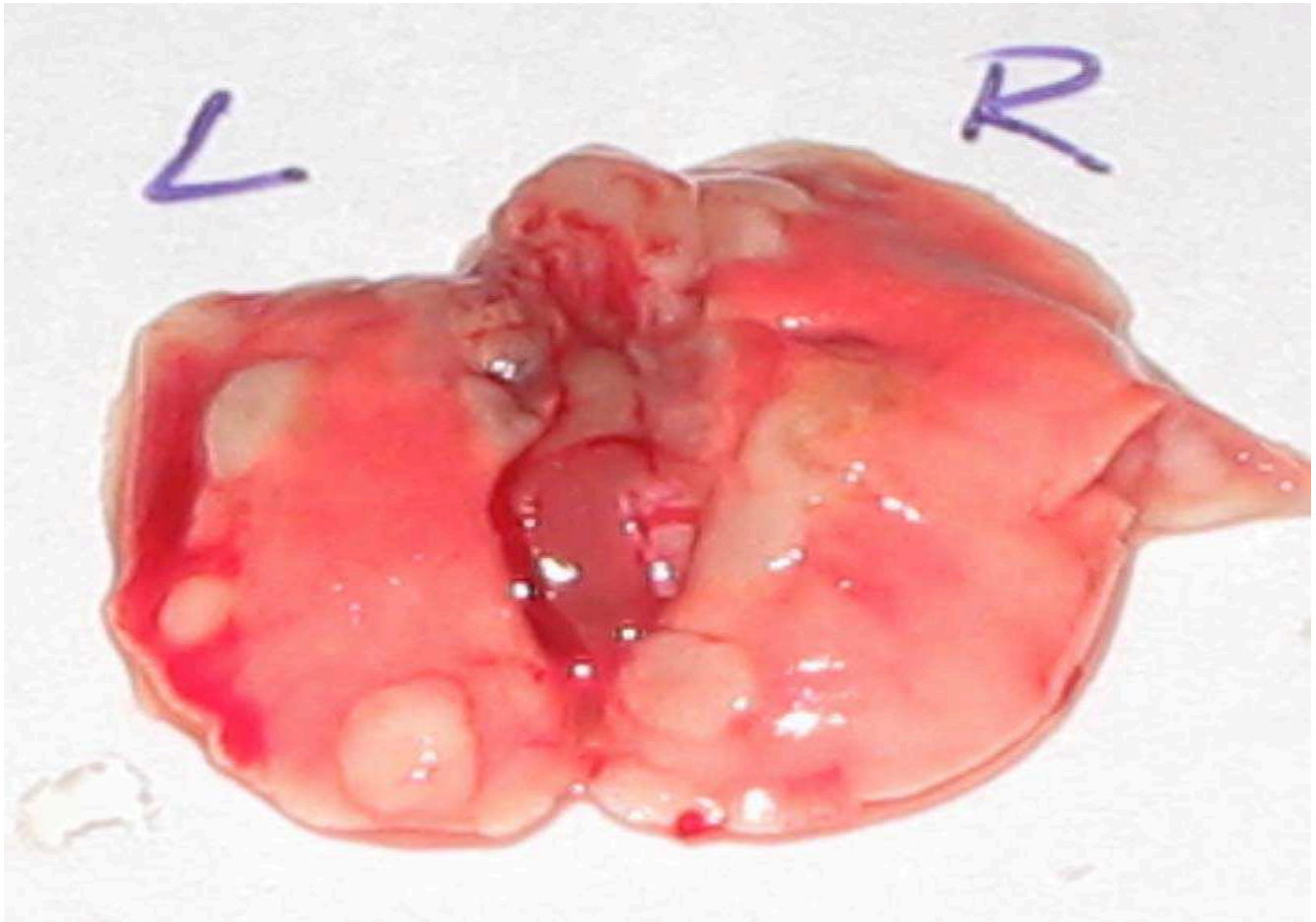
Variations in histopathology

- Nonnecrotizing granuloma which is dominated by the epitheloid histiocytes.
- Suppurative granuloma with a necrotic centre.
- Fibrotic/sclerotic granuloma with concentric fibrosis with minimal inflammatory cells.
- Calcified granuloma with a few cells at the periphery.
- Tuberculous pneumonia characterised by filling the airspaces by inflammatory cells.

Mouse lung granuloma



BALB/c mouse infected with *M.tuberculosis*- aerosol infection . 8 wks. Post infection

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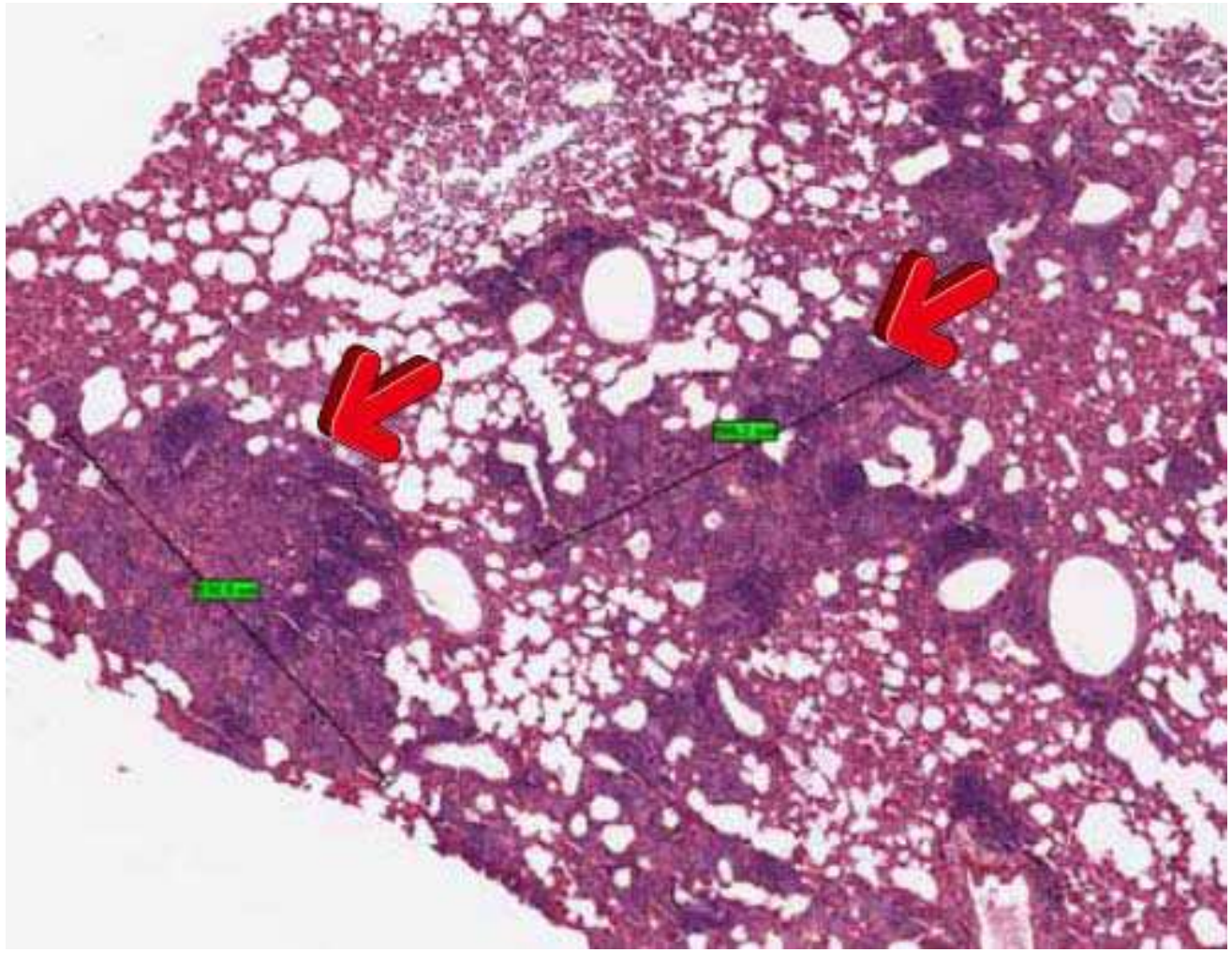
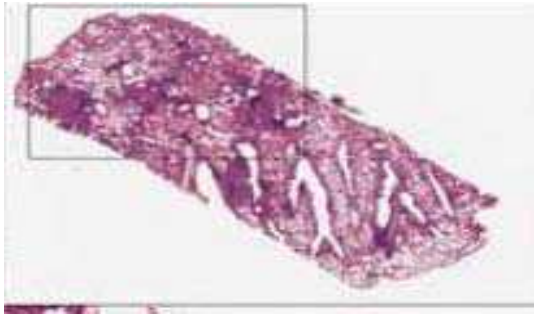
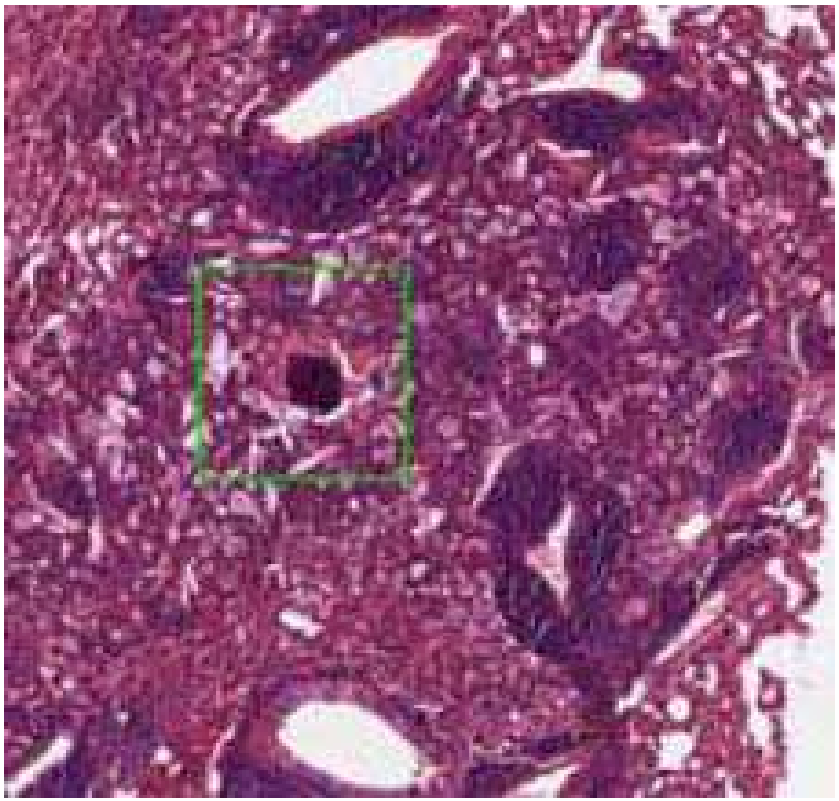
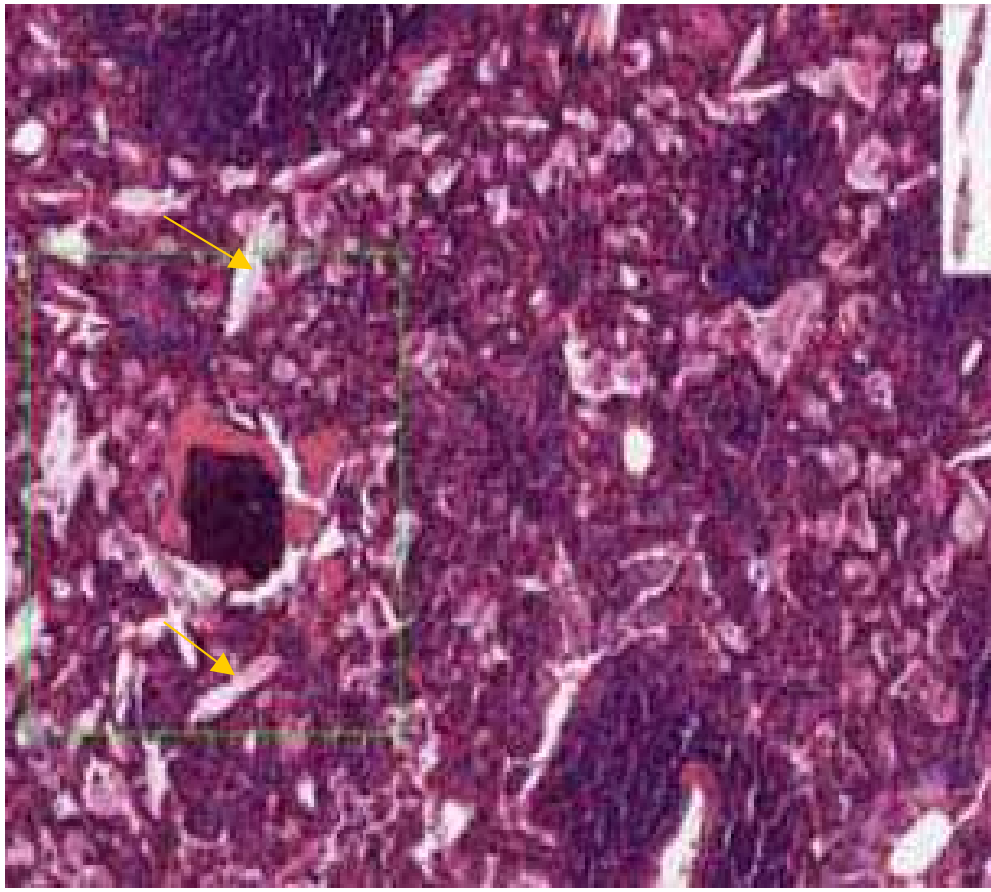




Granuloma from BALB/c mouse. 8 weeks post infection. Nonnecrotising granuloma, predominantly lymphocytic.





Granuloma from BALB/c mouse with calcification and cholesterol clefts. 21 weeks post infection.

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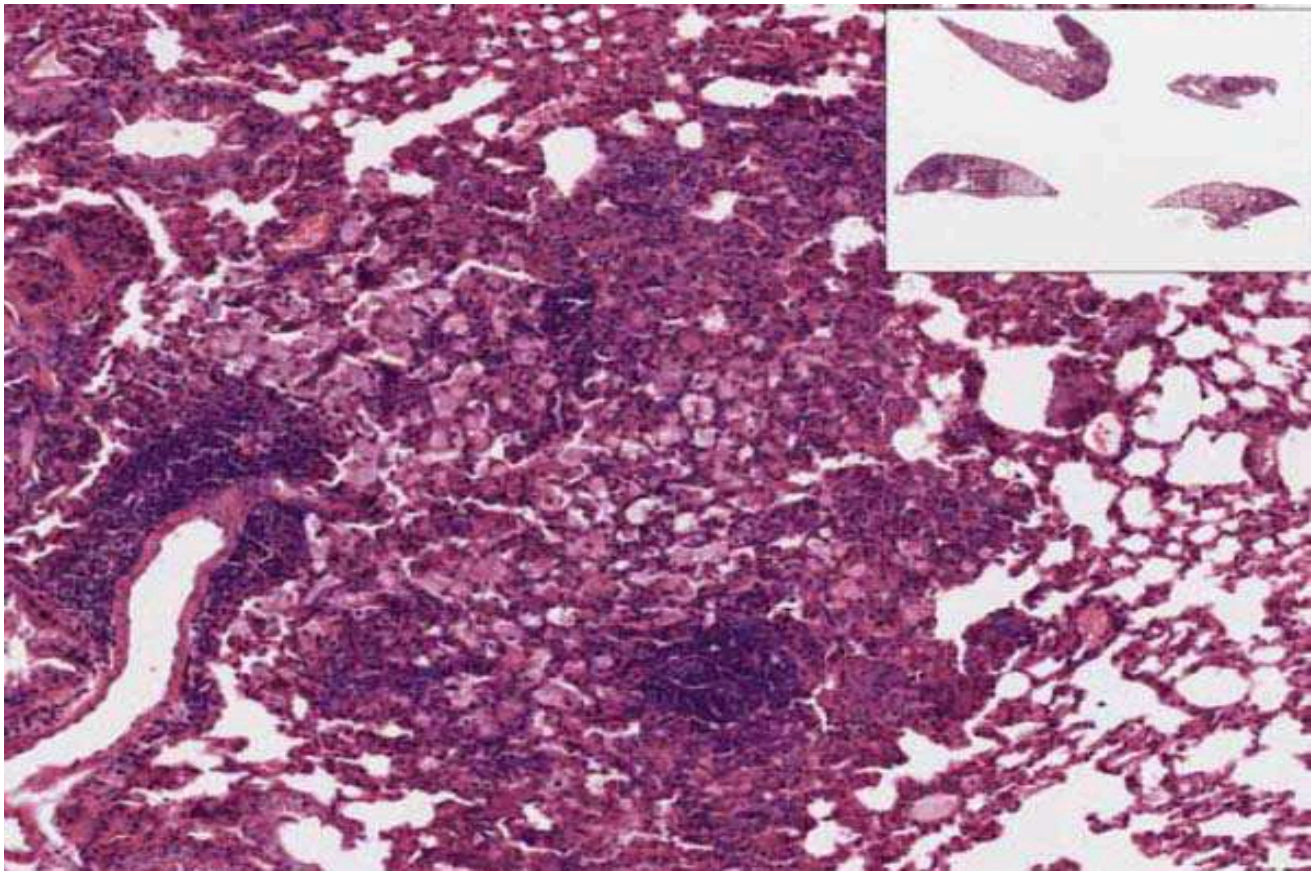
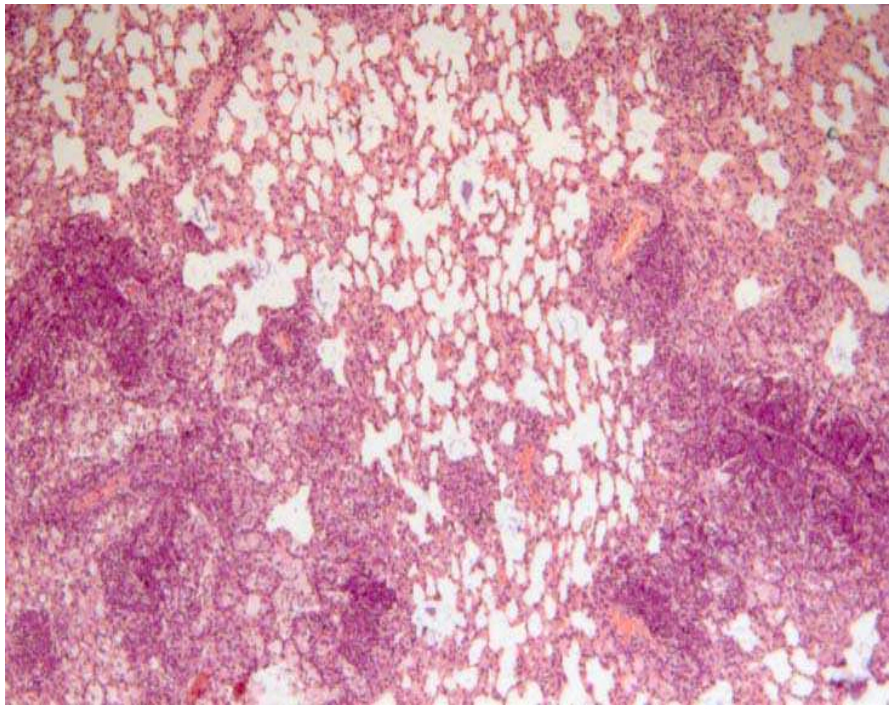


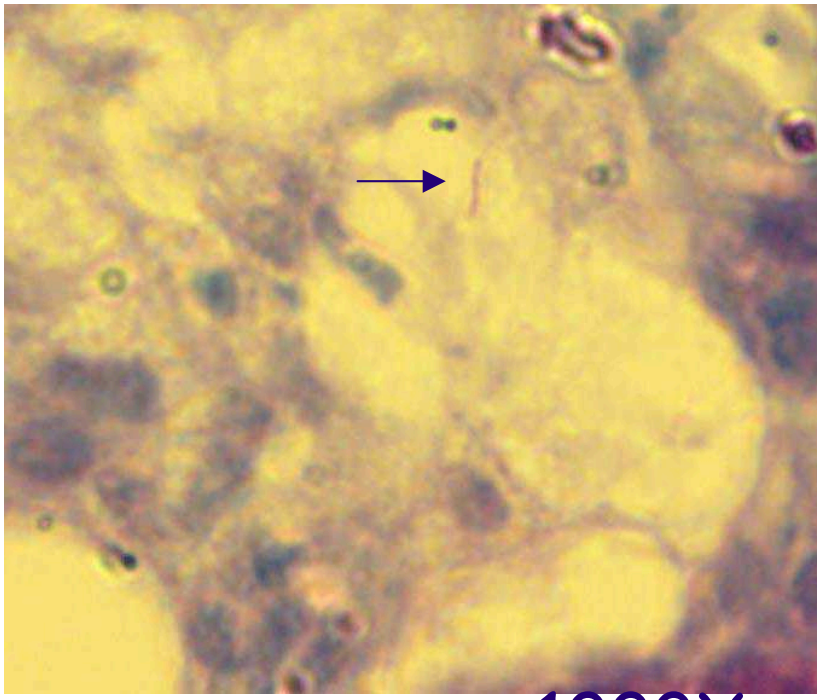
Granuloma from BALB/c mouse 21 weeks post infection. Aggregation of epithelioid histiocytes.Foamy macrophages.

BALB/c mouse infected with *M.tuberculosis* H37Rv



50X

8 wks PI. H&E



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8 wks PI. ZN

Predominatly lymphocytes, epitheloid and foamy macrophages

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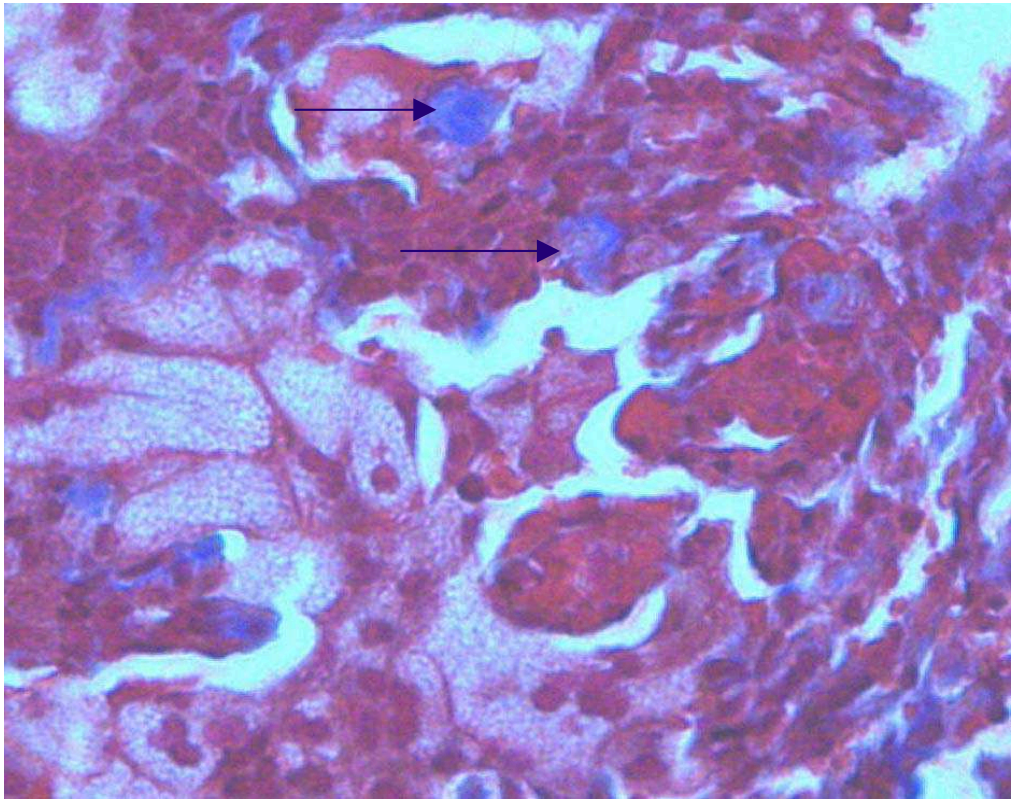
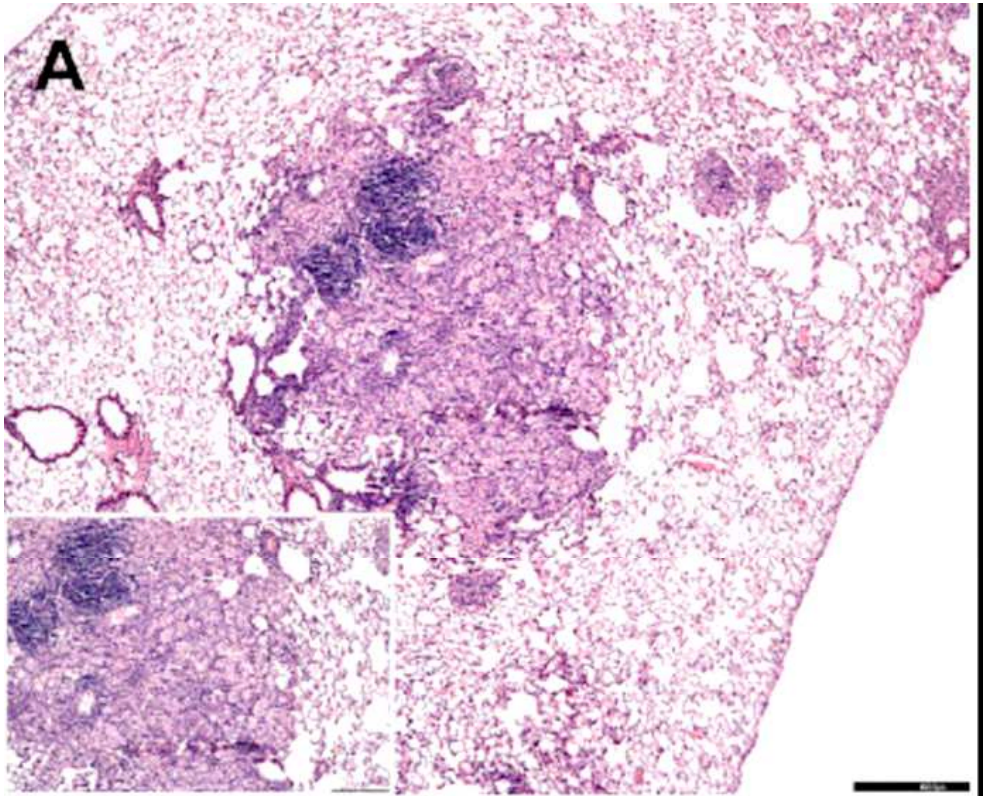
BALB/c mouse infected with *M.tuberculosis* H37Rv



34 wks PI- Trichrome staining

Scanty connective tissue interspersed within the granuloma. Foamy macrophages and epitheloid cells are present

C57Bl/6 mouse infected with M.tuberculosis



8 wks post infection. Consisting of Infiltration of predominantly lymphocytes and macrophages and no necrosis.

Randall.J.Basaraba , Tuberculosis, 2008

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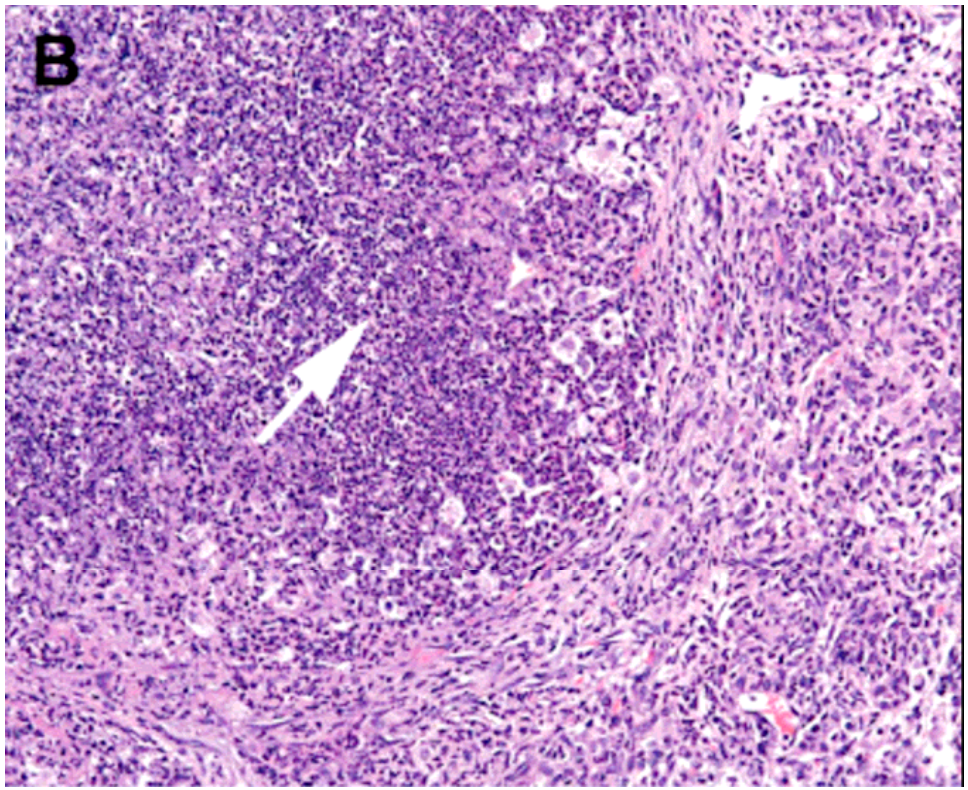

IFN-G KO mouse showing extensive lesion with infiltration of neutrophils

Randall.J.Basaraba ,Experimental tuberculosis, Tuberculosis,: 2008 ,88, suppl. 1, S35-S47

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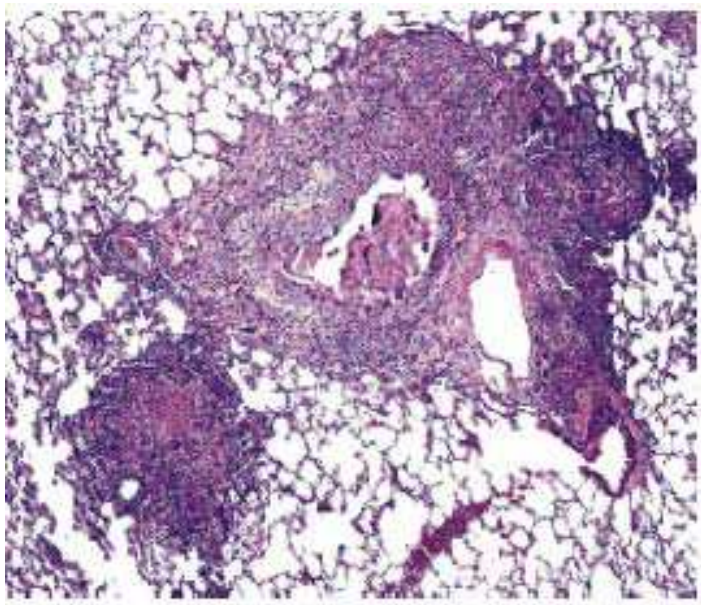

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Lungs from *M.tuberculosis* infected G.pigs . Primary granuloma showing Dystrophic calcification.

Lenearts et al, AAC, 2007

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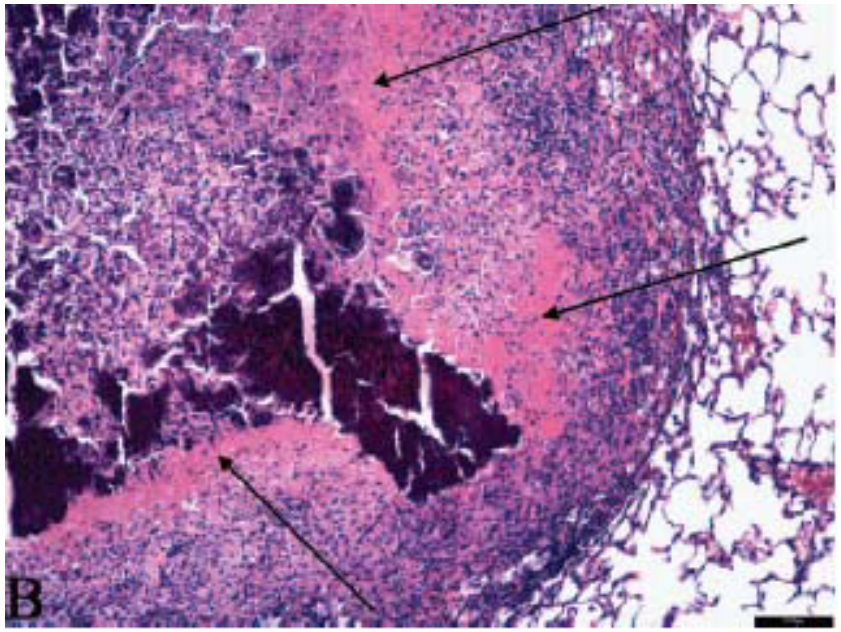
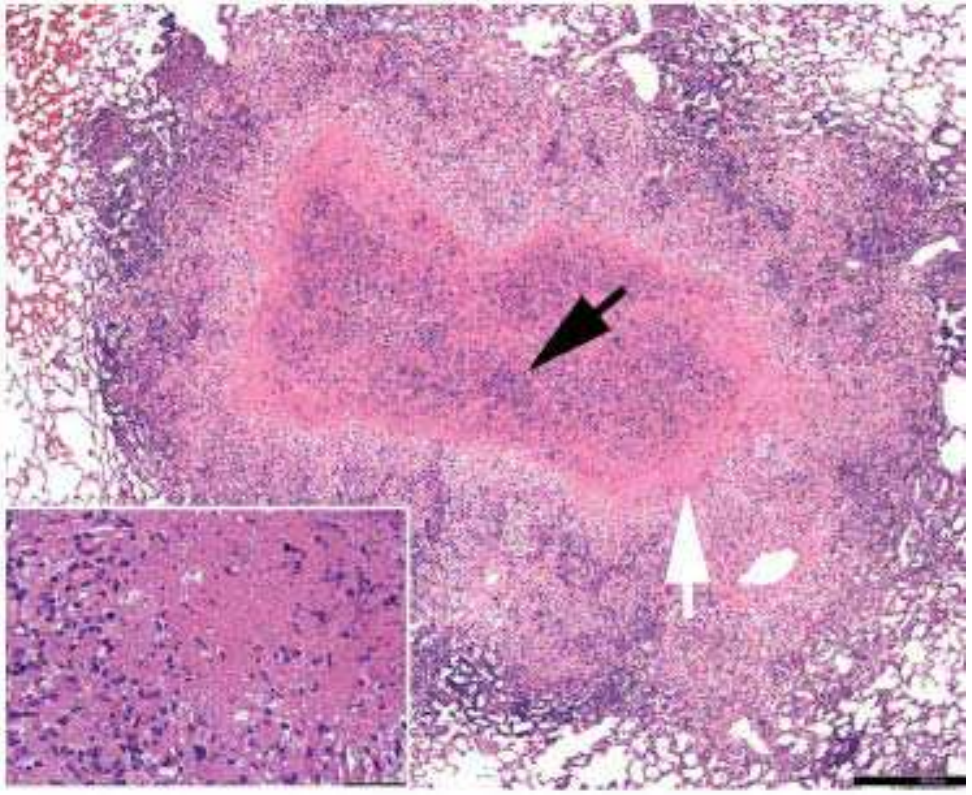
G.pig lung infected with *M.tuberculosis*



dystrophic calcification at the centre and delineated by acellular rim that blends with fibrous capsule which contains predominantly Lymphocytes and fewer macrophages.

Lenearts et al, *AAC*, 2007

Cotton rats infected with *M.tuberculosis*



Immunologically naïve cotton rats show – necrotic lesion in 30 days.

Randall.J.Basaraba , Tuberculosis, 2008

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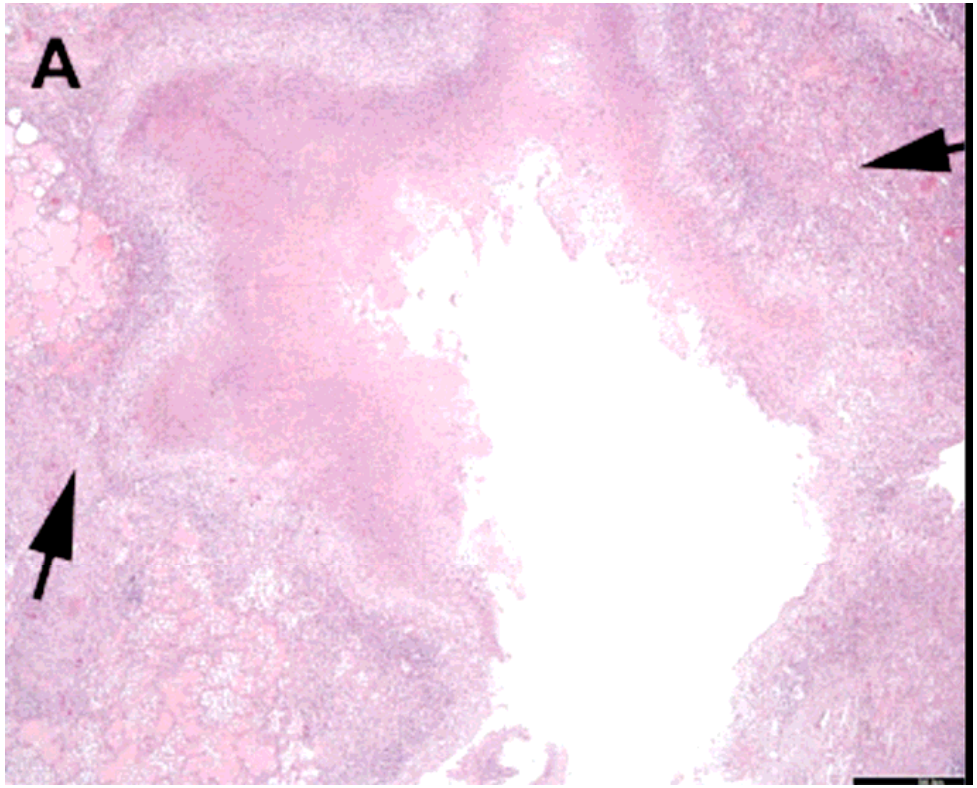
Non-human primate (Rhesus macaque, *Macaca mulatta)* -



Form a large cavity as a result of lung tissue necrosis.
Liquefactive necrosis

Randall.J.Basaraba , Tuberculosis, 2008

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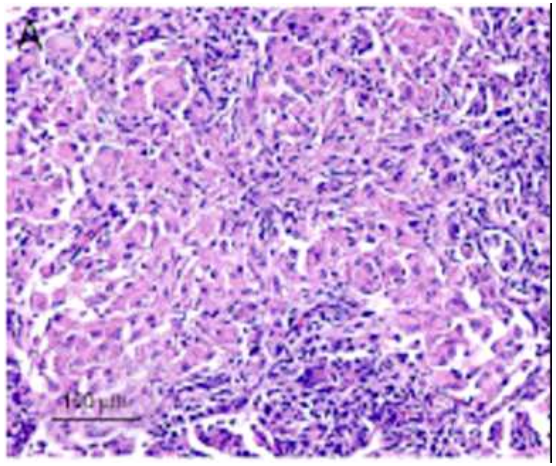
Rabbit infected with *M.tuberculosis* H37Rv



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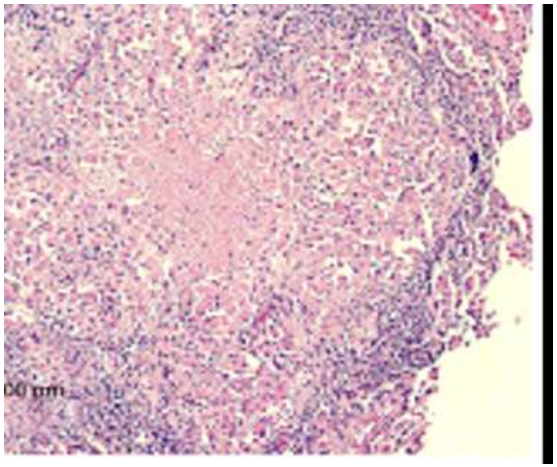
5 wks post infection



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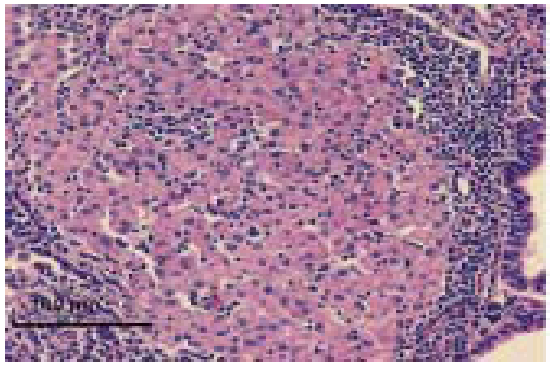
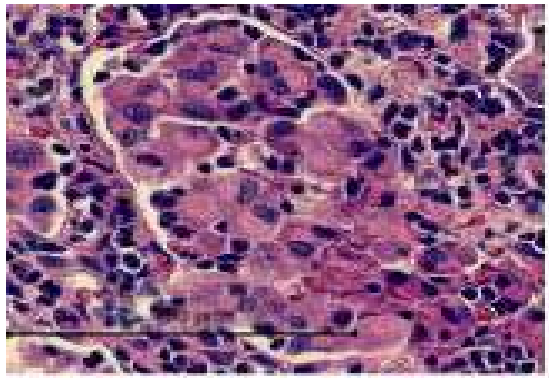
10 wks post infection



200x

15 wks: caseous center has been replaced by epitheloid macrophages

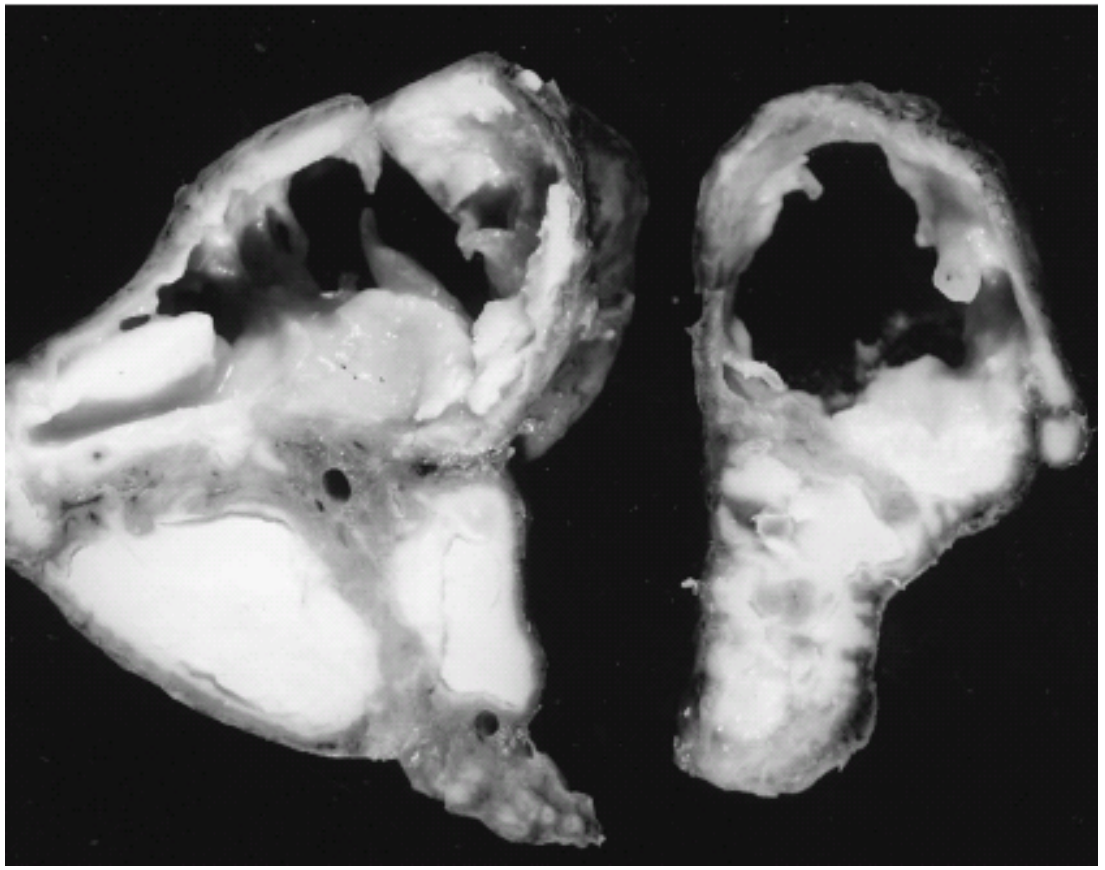


400x

15 wks : Intraalveolar plug of Epitheloid macrophages- after Immunosupression.

Manabe et al. Tuberculosis: 2008

Rabbit lungs- cavitary lesion



18 wks post infection – high dose aerosol infection

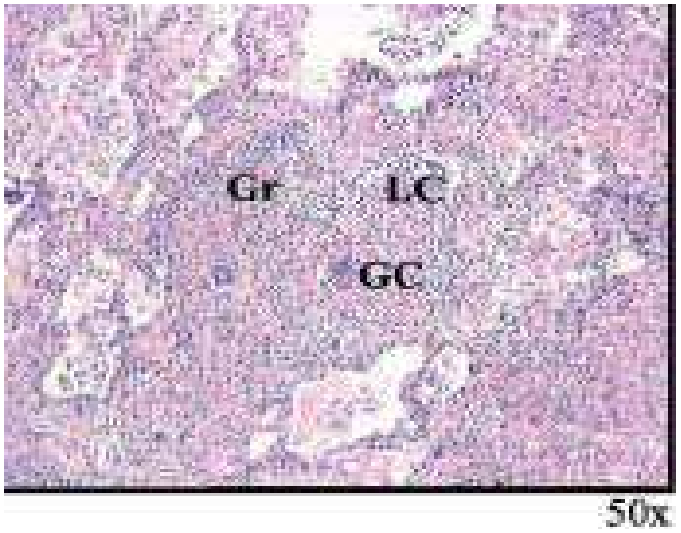
Paul J. Converse et al., Infection and Immunity, 1996

Cavitary lesion

- Seen in human tuberculosis.
- Rabbit and non-human primates develop this lesion, however there is a difference in pathogenesis
- Rabbits develop cavitary lesion as apart of primary lesion.
- In humans, the cavitary lesions typify post primary or reactivation TB that can develop decades after initial infection

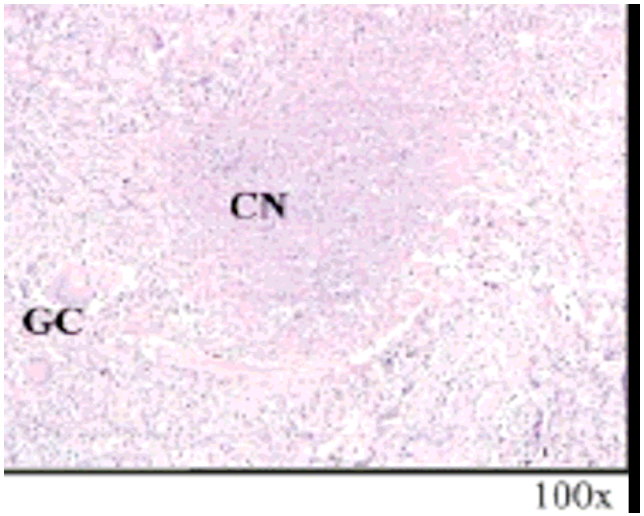
Human Lesions

50X



Human TB case- Nonnecrotic granuloma with Giant Cell(GC) Surrounded by lymphocytic infiltration.

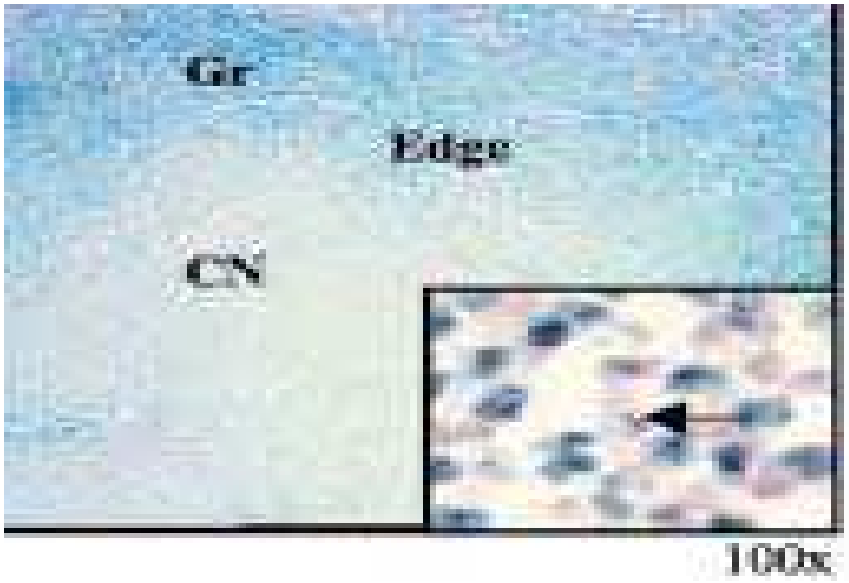
100X



Human TB case- containing caseous necrosis and Giant cells

Fenhalls et al. J .Microbiol Methods.(2002)

Human Lesions



Human granuloma with necrotic center
Detection of Mtb by ZN technique.
Some acid fast bacilli are not detected by ZN stain
(are they in a different state- cell wall deficient state?)

Fenhall et al. J .Microbiol Methods.(2002)

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Summary

- TB is not a single disease entity
- Multiplicity of physiological states of the bacilli
  - Extracellular, Intracellular, Hypoxic etc
- Multiplicity of pathophysiological conditions in the lesions
  - Necrotic,Nonnecrotic, fibrous, calcification and cavitary lesions etc.

Acknowledgements

- AstraZeneca India Pvt Ltd.
- Dr. Balganesh.T
- Dr.Balasubramanian.V
- Dr.R.K.Shandil
- Dr.Sheshagiri Gaonkar
- Dr.Naveen Kumar
- Dr.Sowmyasree Lingegowda

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