Tuberculosis (TB)

Dr. S.K. Liyanage
Department of Pathology

Objectives

At the end of this lecture, student should be able to

- describe the pathogenesis of TB
- describe the macroscopy and microscopy of the lung in primary and secondary TB
- list the sequale of primary and secondary TB

TB

- A communicable, chronic granulomatous inflammatory disease

- Most cases are due to

  - ***Mycobacterium tuberculosis hominis***

  - *Mycobacterium bovis – rare*

TB - Pathogenesis

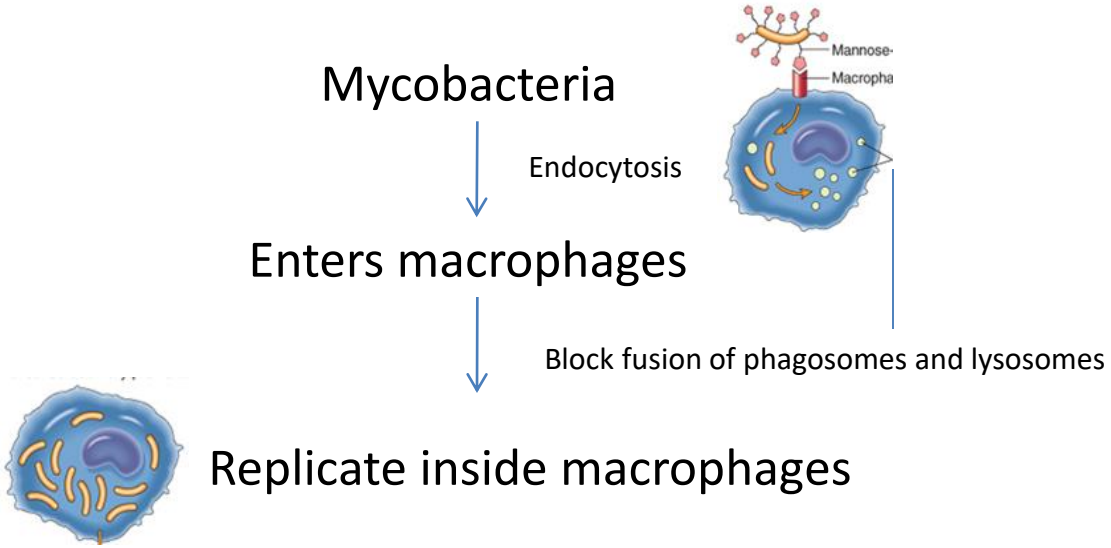
- Depends on development of anti-micobacterial cell mediated immunity (CMI)

Development of hypersensitivity

- granulomas
- cavitations
- tissue destruction

Immunity to TB bacilli

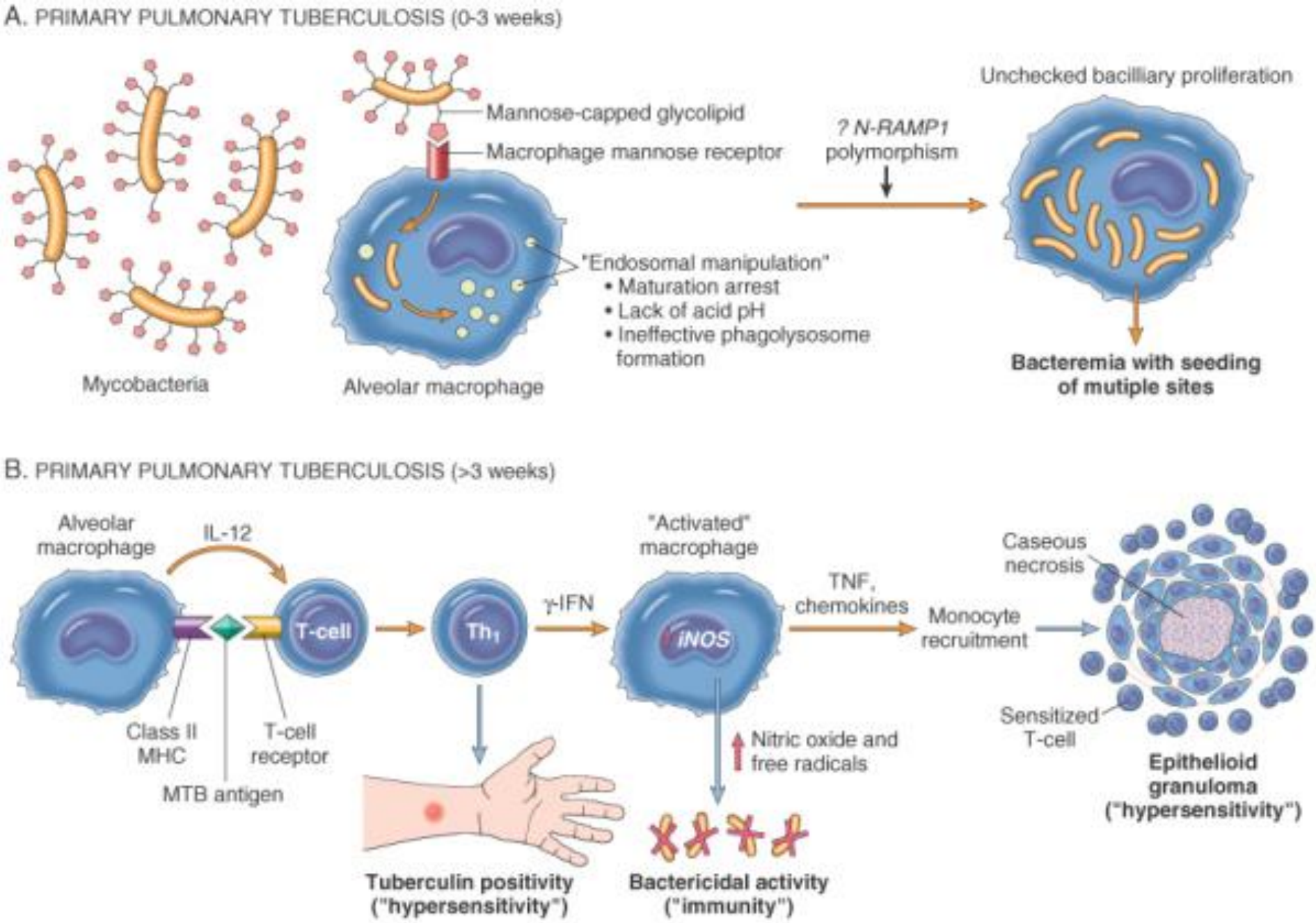
CMI and granuloma formation

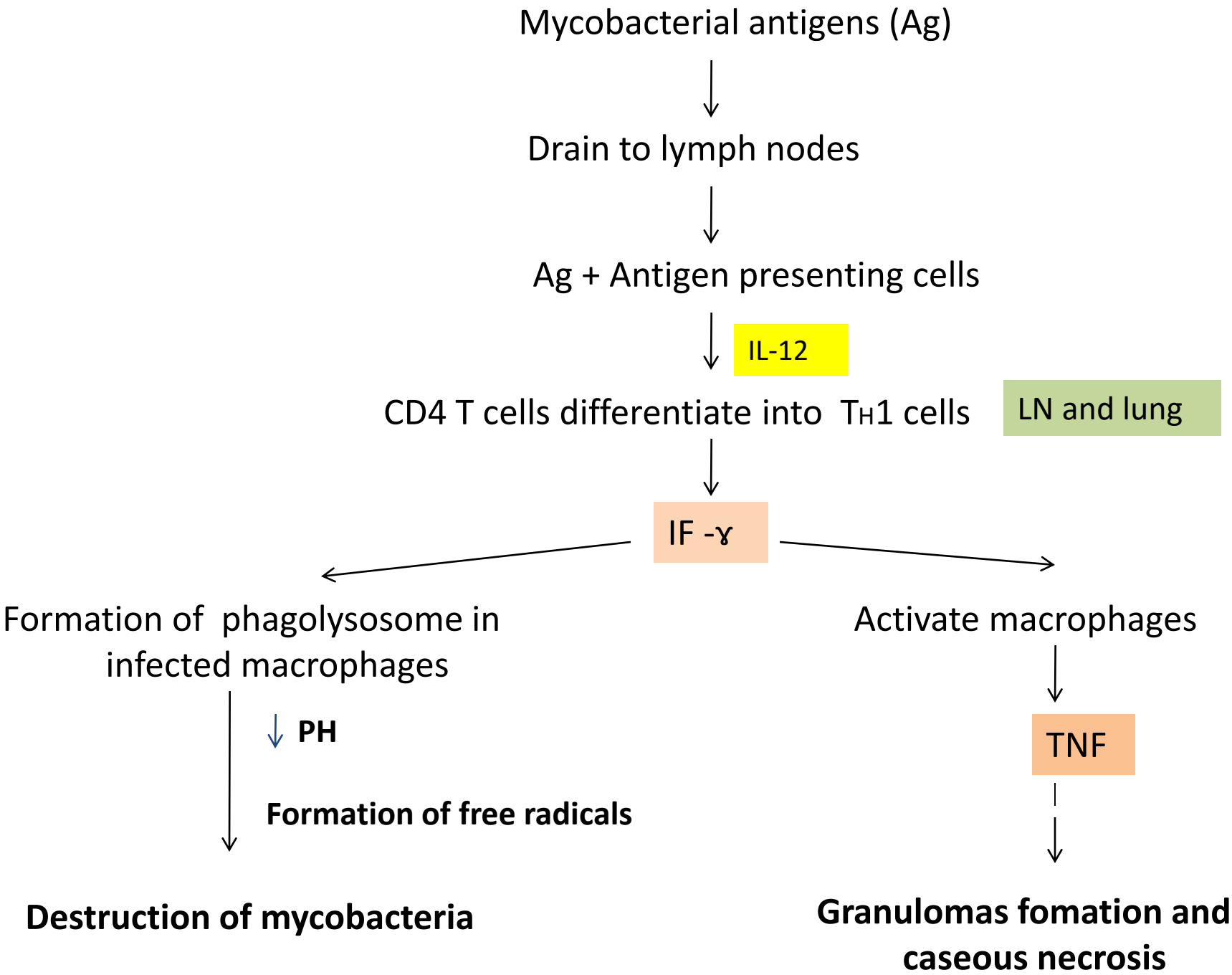


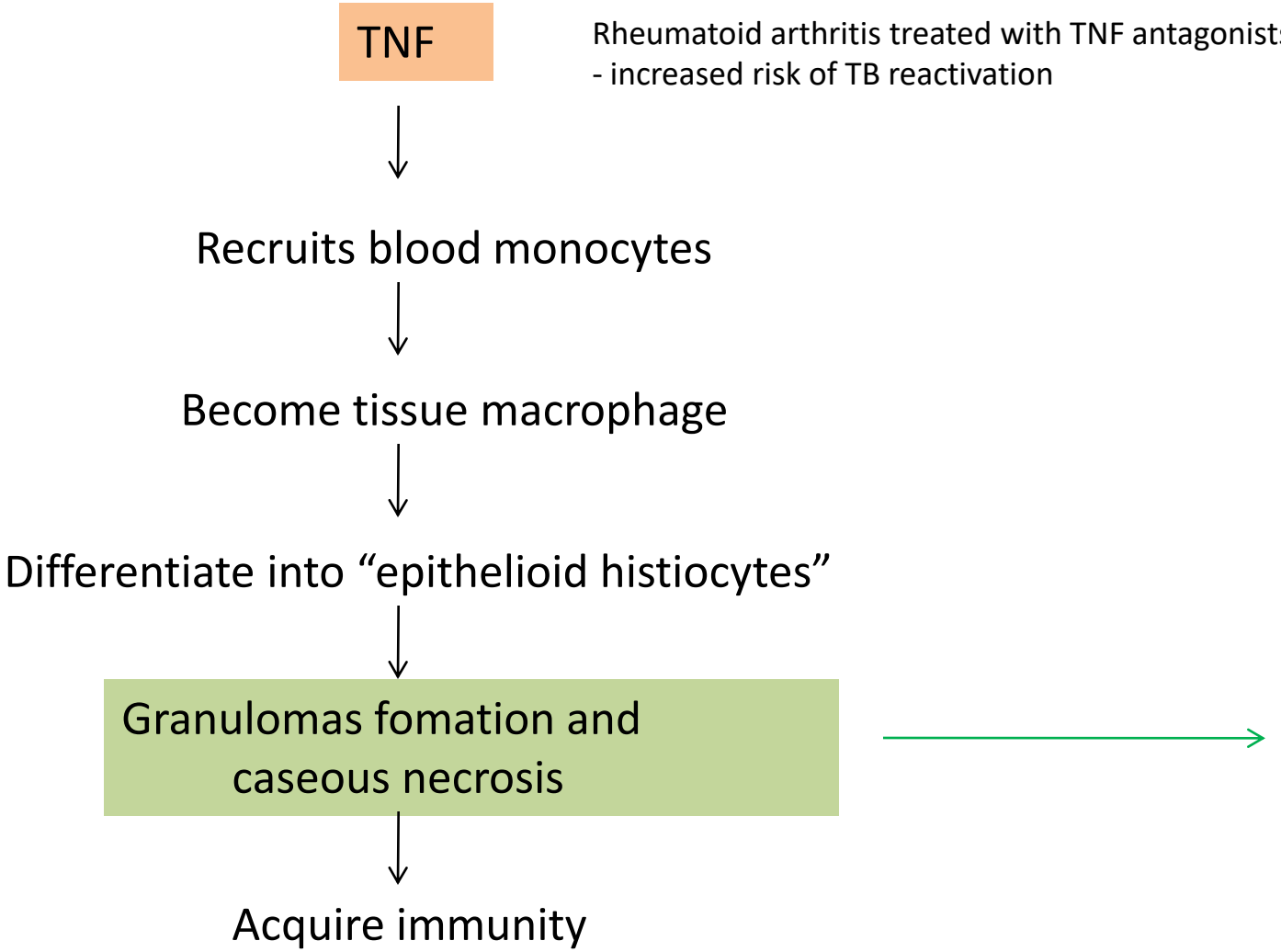
Earliest stage of primary TB (<3 weeks), in non-sensitized individuals

- Bacteria proliferate in the pulmonary alveoli macrophages and air spaces
- Results in bacteraemia and seeding of multiple sites

Most patients - Asymptomatic / get mild fever

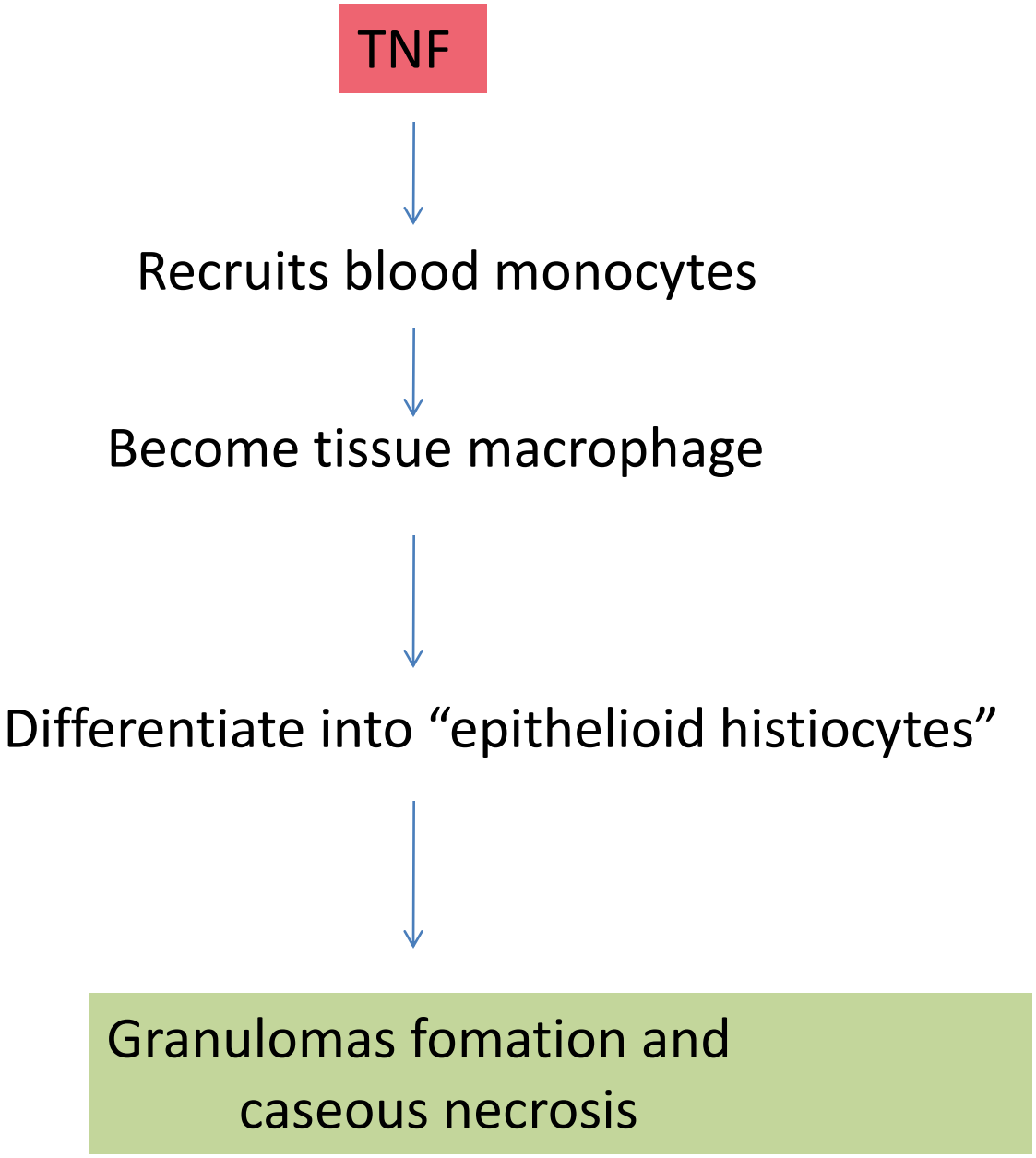

A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)
Mycobacteria
Mannose-capped glycolipid
Macrophage mannose receptor
Alveolar macrophage
"Endosomal manipulation"
• Maturation arrest
• Lack of acid pH
• Ineffective phagolysosome formation
? N-RAMP1 polymorphism
Unchecked bacilliary proliferation
Bacteremia with seeding of mutiple sites
B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)
Alveolar macrophage
IL-12
T-cell
Class II MHC
T-cell receptor
MTB antigen
Th1
γ-IFN
"Activated" macrophage
iNOS
TNF, chemokines
Monocyte recruitment
Caseous necrosis
Sensitized T-cell
Epithelioid granuloma ("hypersensitivity")
Nitric oxide and free radicals
Tuberculin positivity ("hypersensitivity")
Bactericidal activity ("immunity")


Mycobacterial antigens (Ag)
Drain to lymph nodes
Ag + Antigen presenting cells
IL-12
CD4 T cells differentiate into TH1 cells
LN and lung
IF -ɣ
Formation of phagolysosome in infected macrophages
PH
Formation of free radicals
Destruction of mycobacteria
Activate macrophages
TNF
Granulomas fomation and caseous necrosis



In many - No significant tissue destruction

In some - Infection progresses (old age/ immunosuppression)


TNF
Recruits blood monocytes
Become tissue macrophage
Differentiate into “epithelioid histiocytes”
Granulomas fomation and
caseous necrosis

Immunity to TB

Mediated by differentiated CD4 T cells (T_H1 cells)

↓

Cell mediated immunity (CMI)

↓

- Stimulate macrophages to kill bacteria
- Effective protective immunity
- Hypersensitivity and tissue destruction
- Rapid activation of defensive mechanisms in re-infection or reactivation

What is a granuloma?

"A focus of chronic inflammation consists of aggregates of epithelioid histiocytes surrounded by mononuclear leukocytes, principally lymphocytes and occasionally plasma cells"

Older lesions may have peripheral fibroblastic proliferation

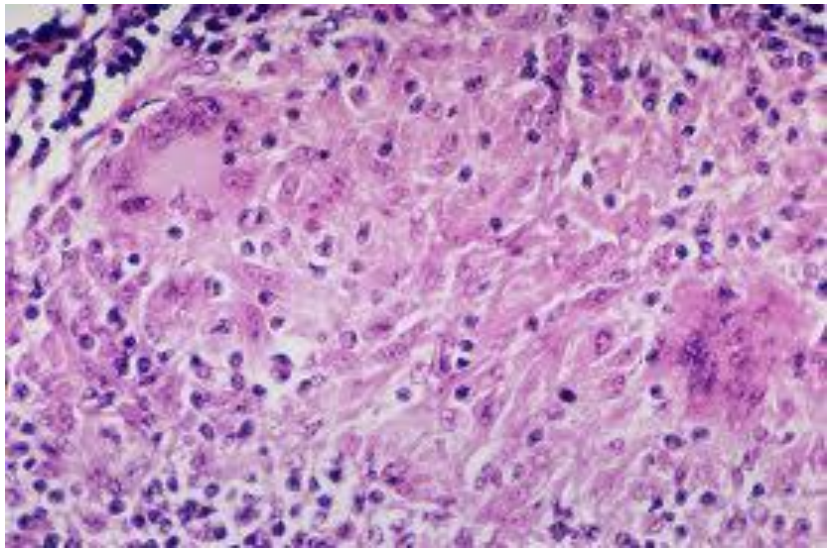
TB granuloma - Microscopy

- Epithelioid cells - Large histiocytes

Nuclei

- elongated, plump
- fused together

"multinucleated giant cells"



Cytoplasm

- pale pink, abundant and granular
- indistinct cell borders

TB granuloma - Microscopy

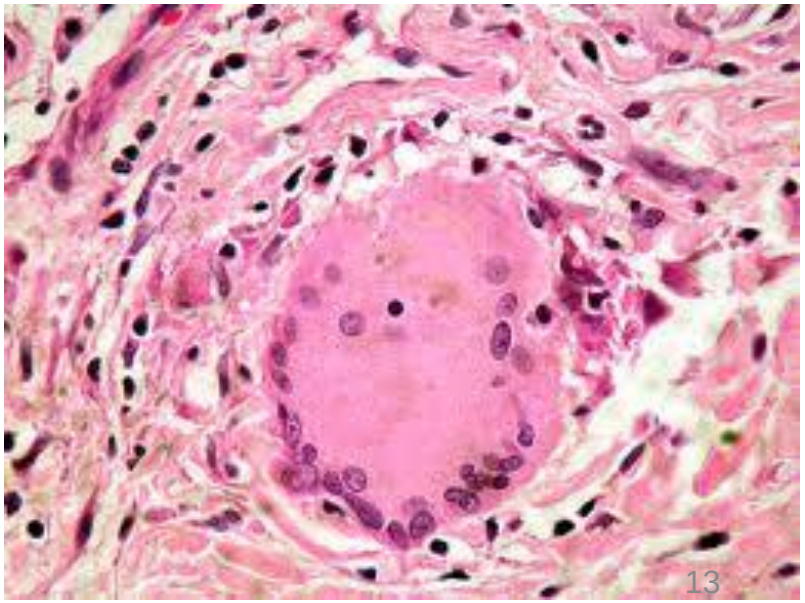
- **Multinucleated giant cells**

  Cytoplasm - abundant , pale pink

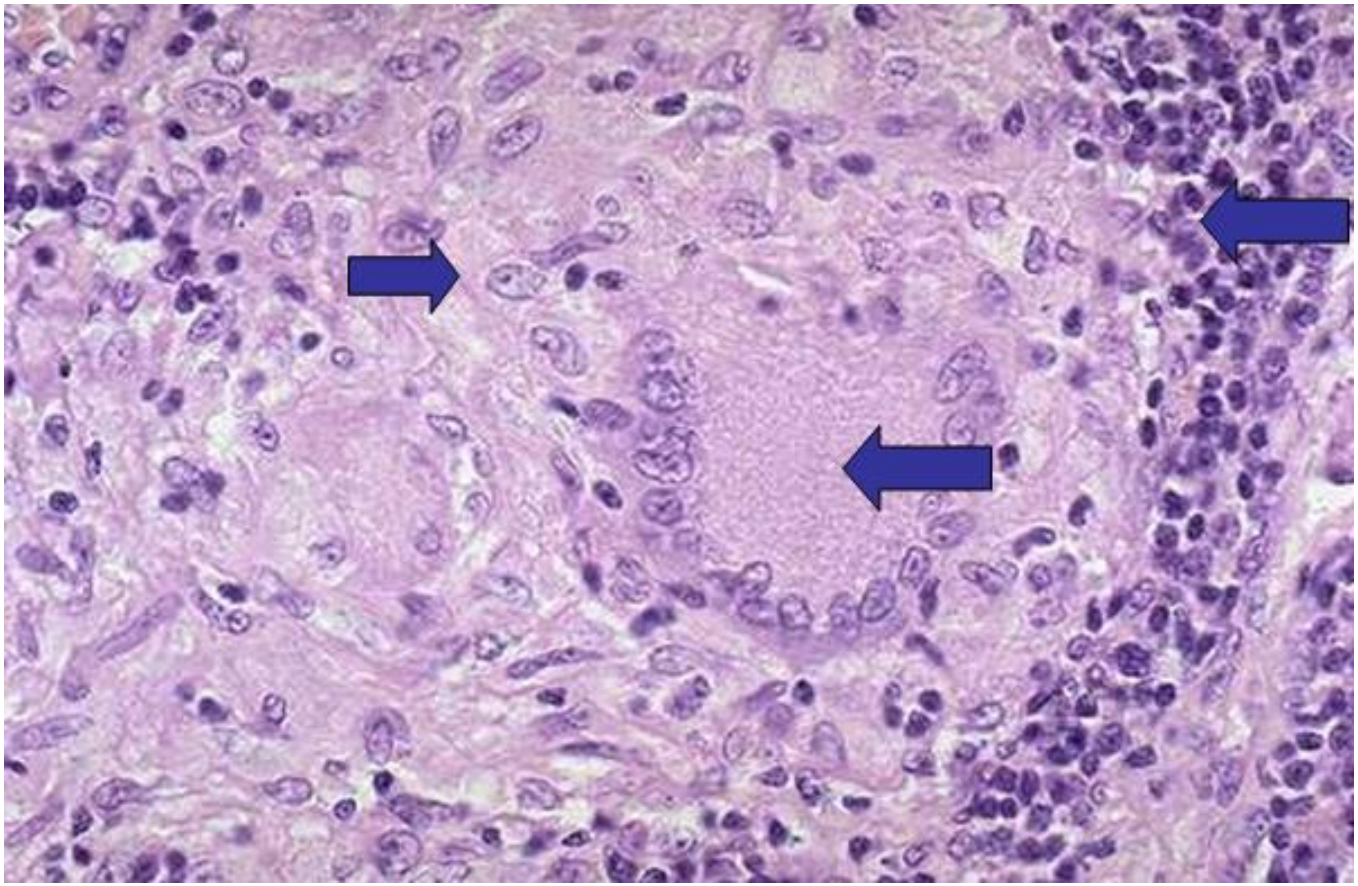
  Nuclei - 20 or more small nuclei

  - arranged at the cell periphery (horse shoe shape)

  "Langhans-type giant cells"

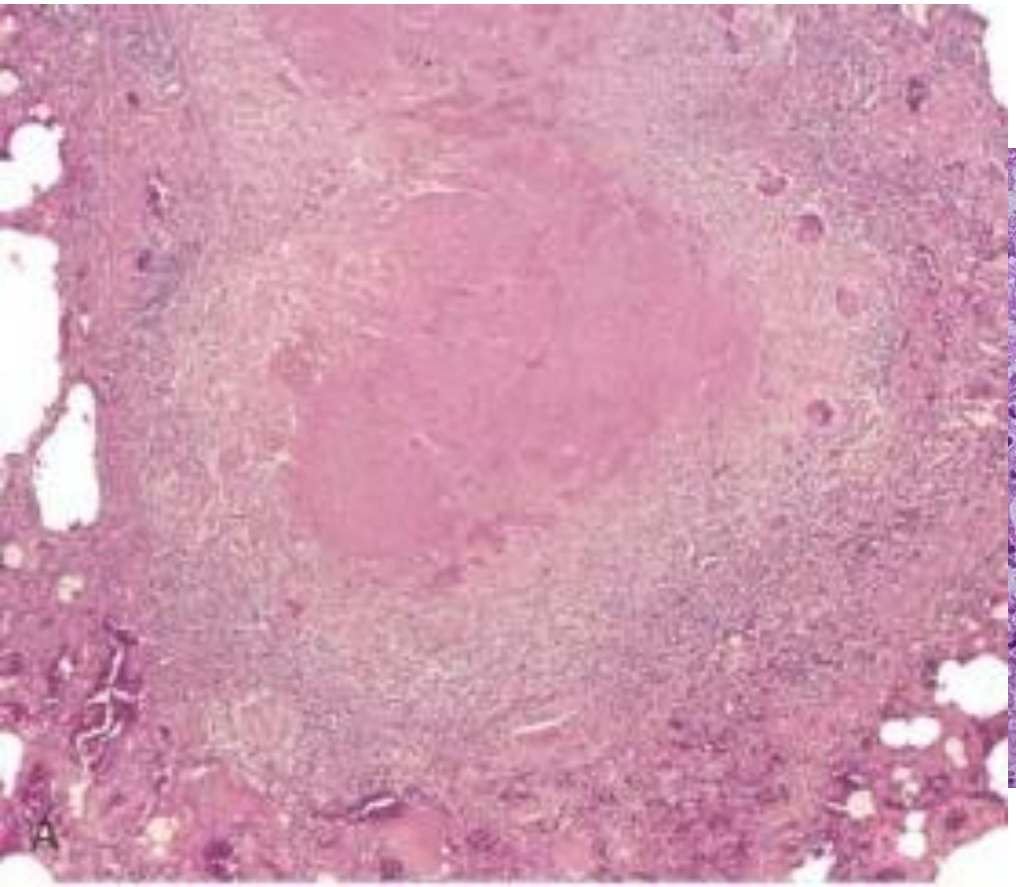


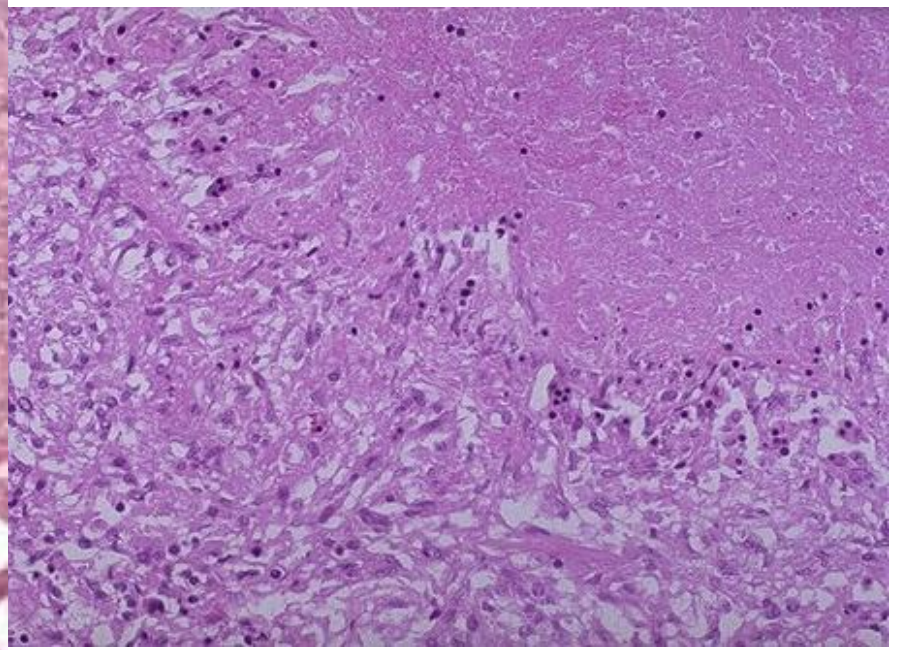
TB granuloma - Microscopy



Collections of epithelioid histiocytes , multinucleated giant cells
Surrounded by mononuclear cells ,lymphocytes and plasma cells
Recognize the cells marked by the arrows

TB granuloma - Microscopy





Central area of **caseous necrosis**

- acellular , eosinophilic granular material

Clinicopathologic patterns of TB

- Primary TB
- Secondary TB

Progressive pulmonary TB (in primary and secondary TB)

miliary pulmonary disease

pleural effusion, tuberculous empyema,

obliterative fibrous pleuritis

Systemic miliary TB

Isolated-organ TB

} Extra-pulmonary TB

Primary TB

- Most patients have no active disease

  Bacilli remain dormant (Latent infection)

- **Some have progressive infection** with continued lung pathology

Primary TB

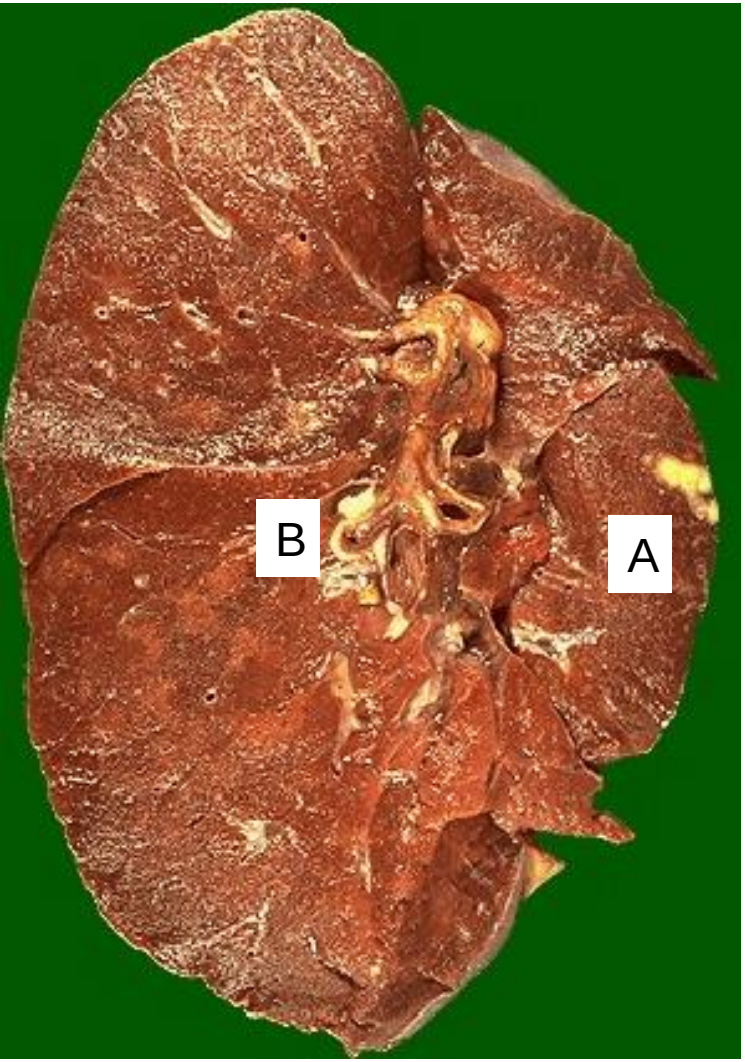
- Almost always begins in the lungs (M.bovis - rare)

- The inhaled bacilli implant in the distal air spaces
  - lower part of the upper lobes or
  - upper part of the lower lobes
  - usually close to the pleura

Primary TB - Macroscopy

- **Lung parenchyma**
  - Pale yellow lesions, close to the pleura (1-1.5 cm)
    "Ghon focus"
  - Central pale yellow caseous (cheese like) material
- **LNs** (tubercle bacilli, free/ within macrophages drain to the hilar LNs)
  - Enlarged hilar lymph nodes
  - Central pale yellow caseous material

Primary TB - Macroscopy



A- Pale yellow lesion in the upper part of the lower lobe,

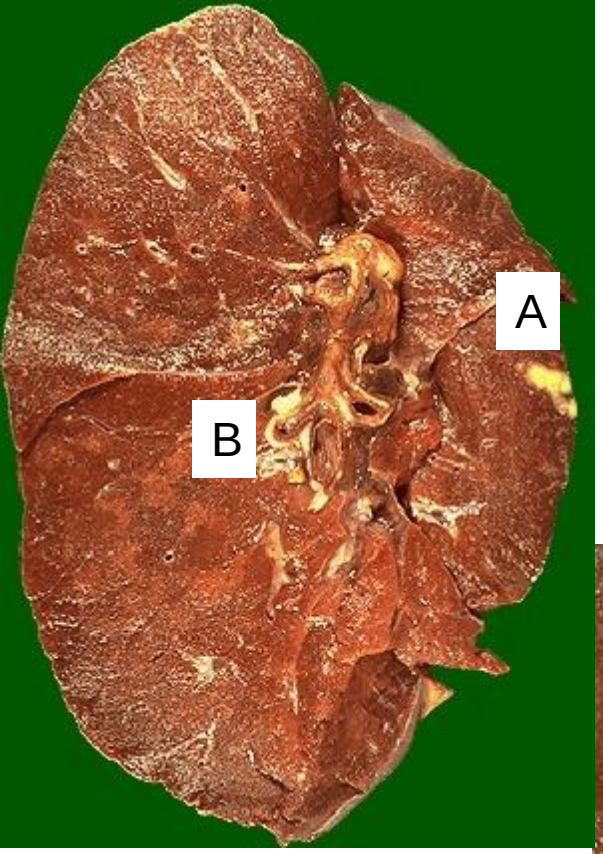
close to the pleura

Cut surface - soft caseous material

B - Enlarged hilar lymph nodes

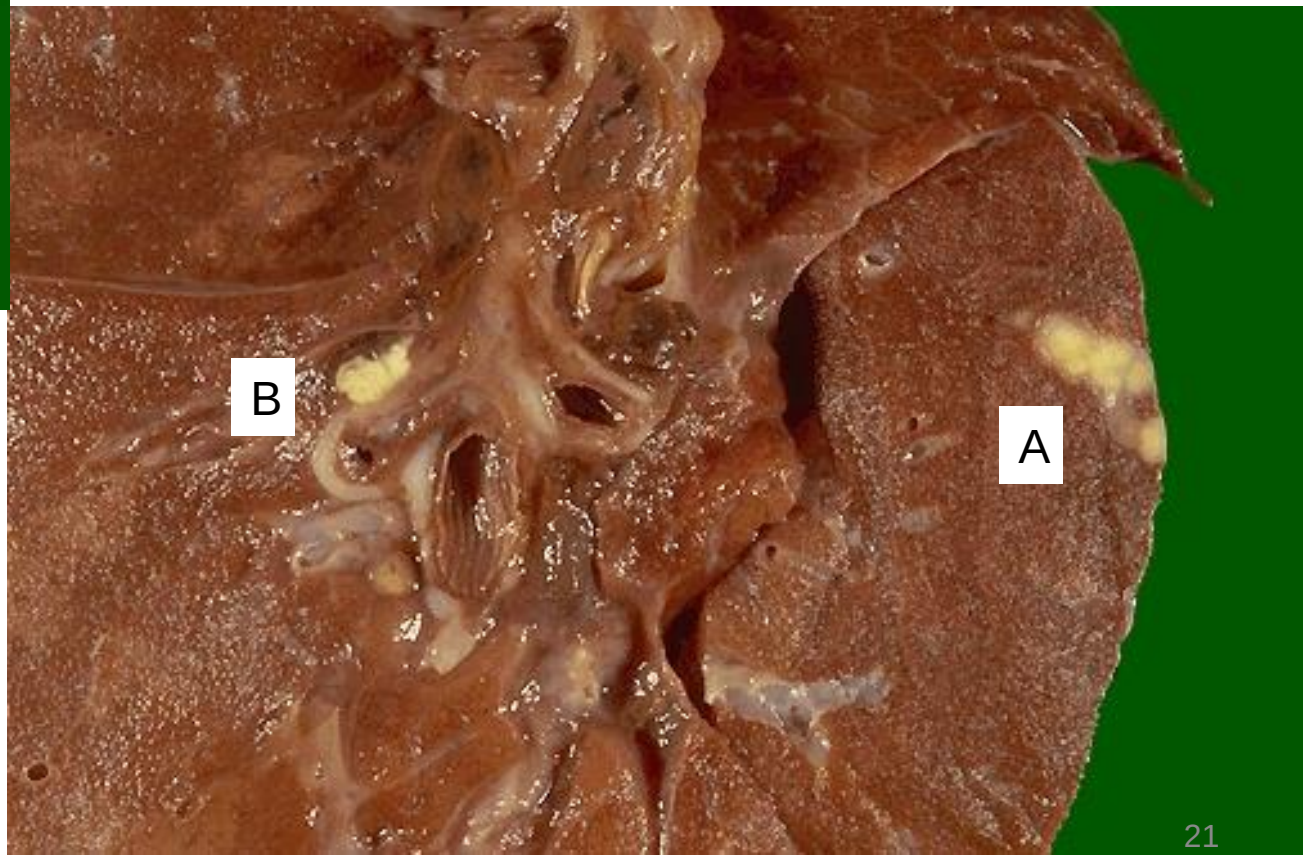
Cut surface - Soft caseous material

A+B “Ghon complex”



A - Lung parenchma

B - Hilar lymph nodes



Primary TB - Microscopy

- Lesions show granulomatous inflammation
- Forms both caseating and non-caseating granulomas
- Individual tubercles – microscopic lesions
- Multiple coalescent granulomas
  - may visible macroscopically

Primary TB

- During first few weeks
  - lymphatic and haematogenous spread to the other parts of the body
- 95% of cases - CMI controls the infection
- Ghon complex undergoes progressive fibrosis

- Despite seeding of other organs, no lesions develops

Primary TB - Sequela*

- 90% undergo fibrosis and calcification
- Lymphohaematogenous dissemination

  - Tuberculous meningitis

  - Miliary TB

  Similar to progressive disease in secondary TB

*any abnormal condition that follows and is the result of a disease, treatment, or injury

Secondary pulmonary TB

Secondary pulmonary TB

- Develops in previously sensitized hosts
- Usually arises from

  - Reactivation of dormant primary lesion

    Decades after initial infection

    Due to weakened host resistance

  - Exogenous re-infection

    Due to weakened host immunity

    Large inoculum of virulent bacilli

- May follow shortly after primary TB

Secondary pulmonary TB

- Localized , apical lesions

  - may heal with fibrosis, spontaneously/ after therapy

Or

  - May progress along several different pathways

Secondary pulmonary TB

- Progressive pulmonary TB
- Miliary pulmonary disease
- Pleural effusion , tuberculous empyema
  obliterative fibrous pleuritic
- Endobronchial, endotracheal and laryngeal TB

- Systemic miliary TB
  Isolated-organ TB

} Extra-pulmonary TB

Secondary pulmonary TB

- Classic site - Apex of the upper lobes of one or both lungs
- Because of the preexisting hypersensitivity, there is marked tissue response
  - Infection is localized to the lung parenchyma
  - Regional LNs are less prominently involved

Progressive pulmonary TB

- Elderly and immunosuppressed
- Apical lesions enlarges with expansion of the area of caseation
- Erosion into a bronchus evacuates the caseous centre, creating a ragged irregular cavity

  lined by caseous material , poorly walled off by

  fibrous tissue
- Erosion of blood vessels - Haemoptysis

Progressive pulmonary TB

- With adequate treatment, progression may be arrested
- If the treatment is inadequate / host defense is impaired, infection may spread by

  - direct expansion of the pulmonary lesion
  - via dissemination through airways, lymphatic channels / vascular system

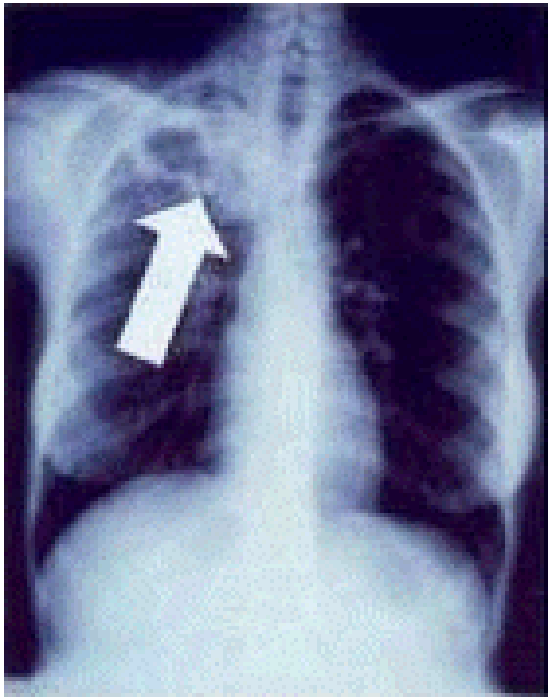
Secondary pulmonary TB - Macroscopy

- Initial lesion
  - Apex of the lung
  - Sharply demarcated , firm, grey - white to yellow , consolidated area, usually < 2cm
  - within 1-2 cm of the pleura
  - Central pale yellow , soft caseous necrosis
  - peripheral fibrosis

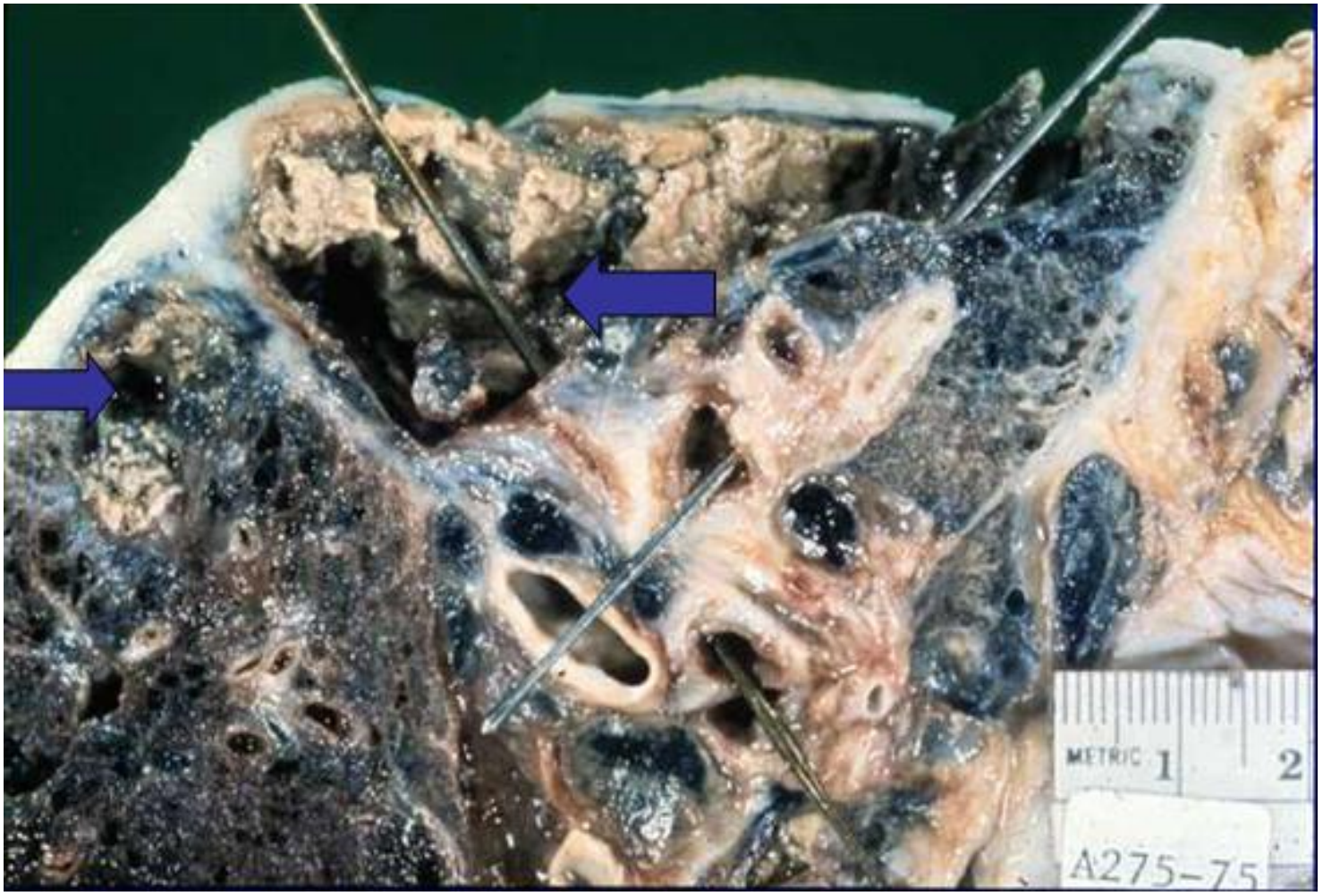
- Later , with a good immune response these lesions undergo fibrosis and calcification

Secondary pulmonary TB - Macroscopy

- Central caseation leads to **cavity formation**
  - lined by caseous material
  - base contains thickened vessels
  - surrounded by an area of consolidation



Lung - Cavity formation



Secondary pumonary TB - Microscopy

- Granuloma formation
  - coalescent granulomas
  - central caseous necrosis

- Early lesion - bacilli+
  Later - bacilli are difficult to find

Miliary pulmonary TB

Tuberculosis bacilli

Lymphatics

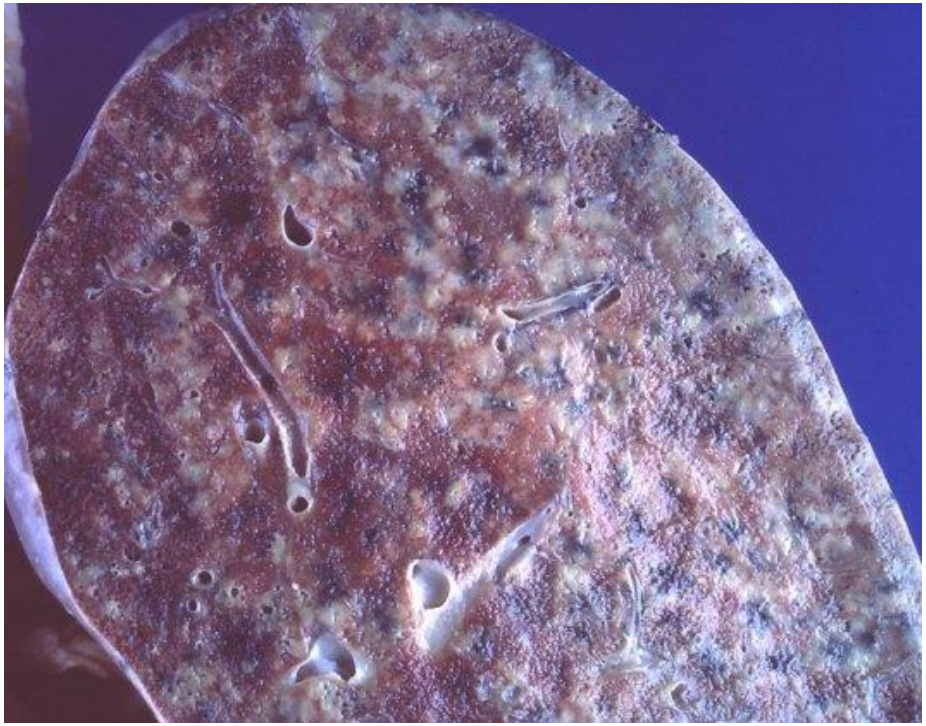
Lymphatic ducts

Venous return

Right side of the heart

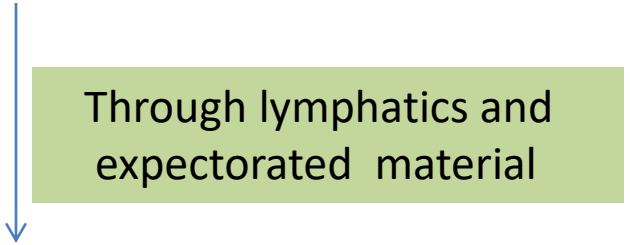
Pulmonary arteries

Lesions scattered through the lung parenchyma



Endobronchial, endotracheal and laryngeal TB

Tuberculosis bacilli in the lungs



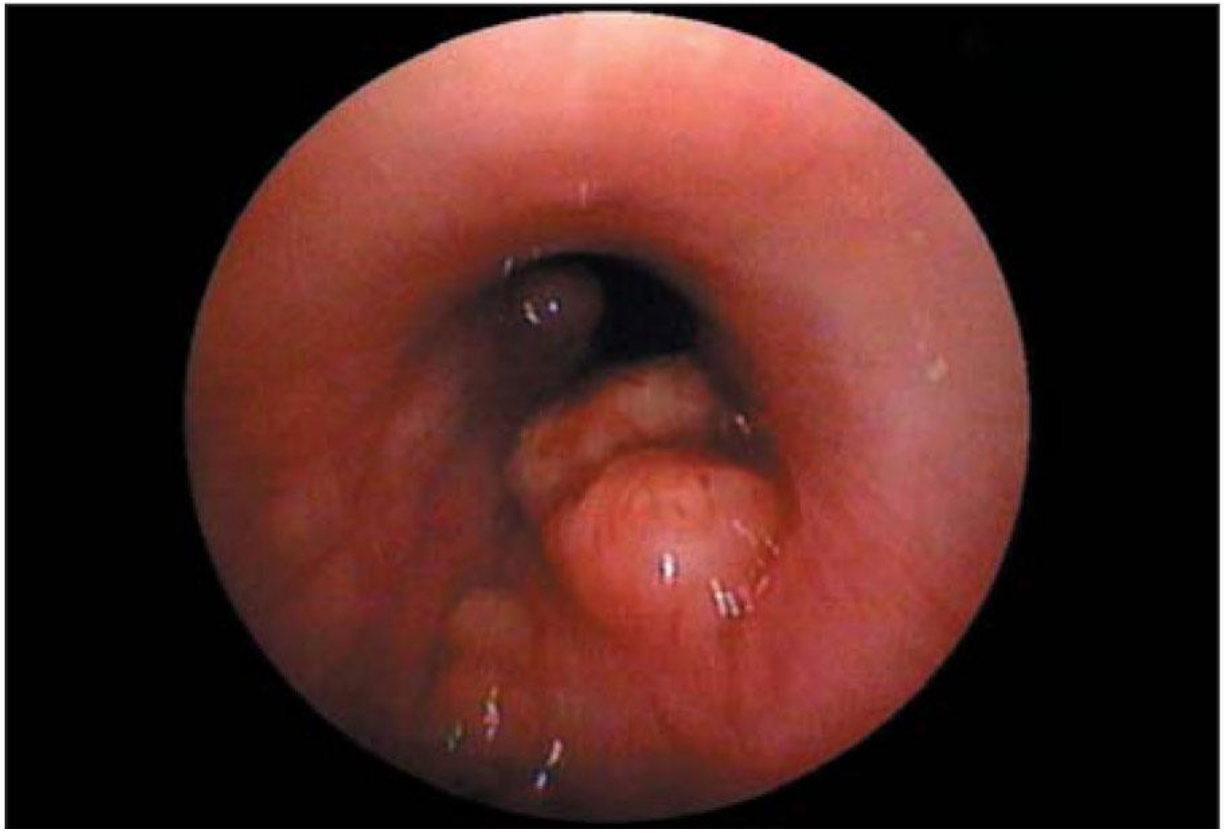
Bronchus, trachea and larynx

Macroscopy

Mucosal lining may studded with multiple ,yellow-white lesions

Sometimes these may be visible only microscopically

Microscopy - Granulomas



Bronchoscopic image of the left main bronchus and polypoid lesions.

Systemic miliary TB

Tuberculosis bacilli in the lungs

pulmonary venous return

Heart

Systemic circulation

Any organ

Liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, epididymis

Secondary pulmonary TB - sequela

- Usually lesions undergo fibrosis and calcification
- Lesions may open into a bronchus

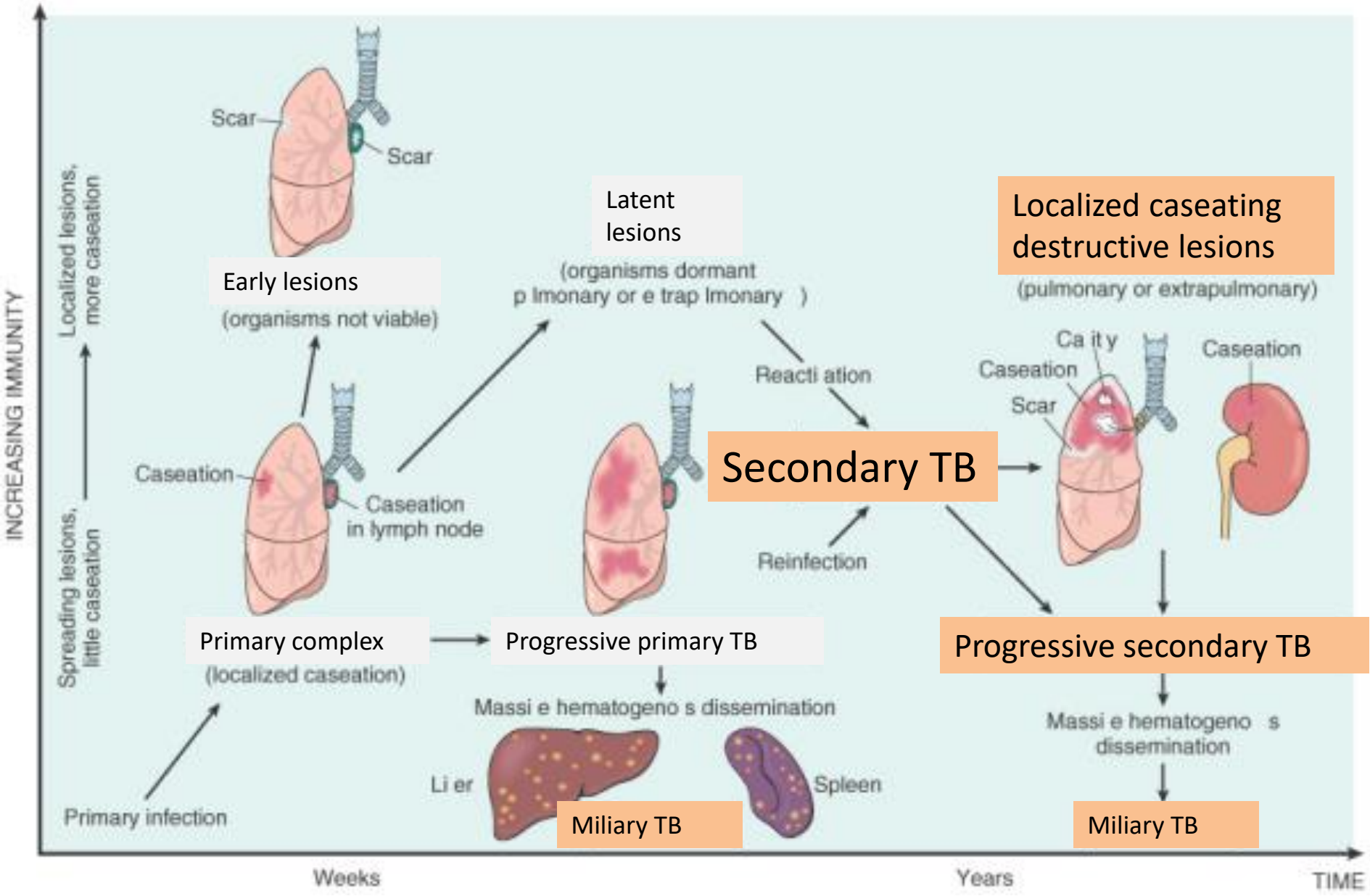
  - discharge bacilli → Sputum+

  Spread to bronchus, trachea, larynx, intestine

- Cavity formation
- Erosion of blood vessels → Haemoptysis
- Pleural involvement → Pleural effusion

Secondary pulmonary TB - sequela

- Spread - direct
  - lymphatic
  - haematogenous
- In immunocompromised persons
  - Bronchopneumonia
  - Miliary pulmonary TB
  - Dissemination → other organs


INCREASING IMMUNITY
Localized lesions, more caseation
Spreading lesions, little caseation
Scar
Scar
Early lesions
(organisms not viable)
Latent lesions
(organisms dormant
p lmonary or e trap lmonary)
Localized caseating destructive lesions
(pulmonary or extrapulmonary)
Reacti ation
Secondary TB
Ca it y
Caseation
Scar
Caseation
Caseation
Caseation in lymph node
Reinfection
Primary complex
(localized caseation)
Progressive primary TB
Progressive secondary TB
Massi e hematogeno s dissemination
Massi e hematogeno s dissemination
Li er
Spleen
Miliary TB
Miliary TB
Primary infection
Weeks
Years
TIME

Summary

- Discussed the pathogenesis of TB
- Described the macroscopy and microscopy of the lung in primary and secondary TB
- Listed the sequale of primary and secondary TB

HIV/AIDS and Tuberculous infection

- Reading assignment

Extra-pulmonary TB

Extrapulmonary TB

- Appear in any of the organs or tissues seeded haematogenously
- May be the presenting manifestation
- Typically involved organs

  Meninges - TB meningites

  Kidneys - Renal TB

  Adrenals

  Bones - Osteomyelitis

  Fallopian tubes - Salpingitis

  Vertebrae (Pott disease) - Paraspinal abscesses / abdominal or pelvic mass

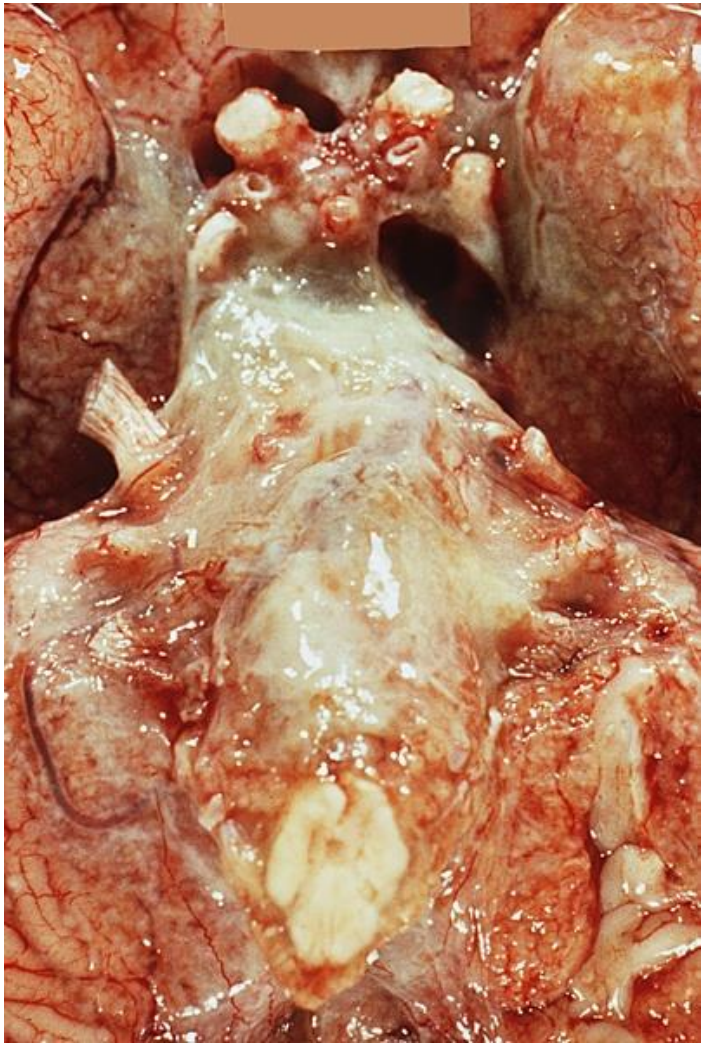
TB - Central nervous system

- Tuberculous meningitis
- Tuberculoma

TB-Meningitis

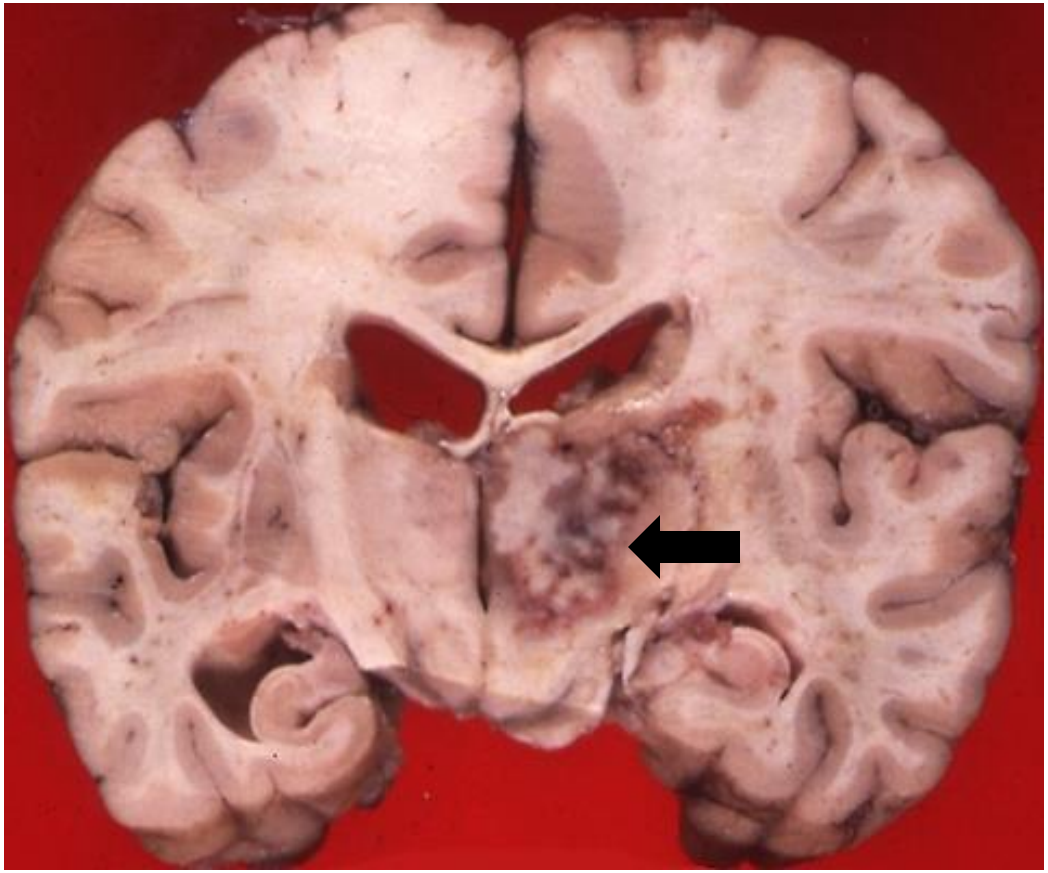
- Haematogenous spread
- Occasionally from infection in the vertebral body
- Chronic course
- Caseous material – prominent at the base of the brain
- Obstruction to CSF flow - hydrocephalus
- Small tubercles may form and cover the meninges
- Obliterative endarteritis results in small foci of infarction

Tuberculous meningitis



Thick exudate covering the base of the brain

Tuberculoma



- Space occupying lesion (SOL)
- Adults - cerebral hemisphers
- Children - cerebellum

Renal TB

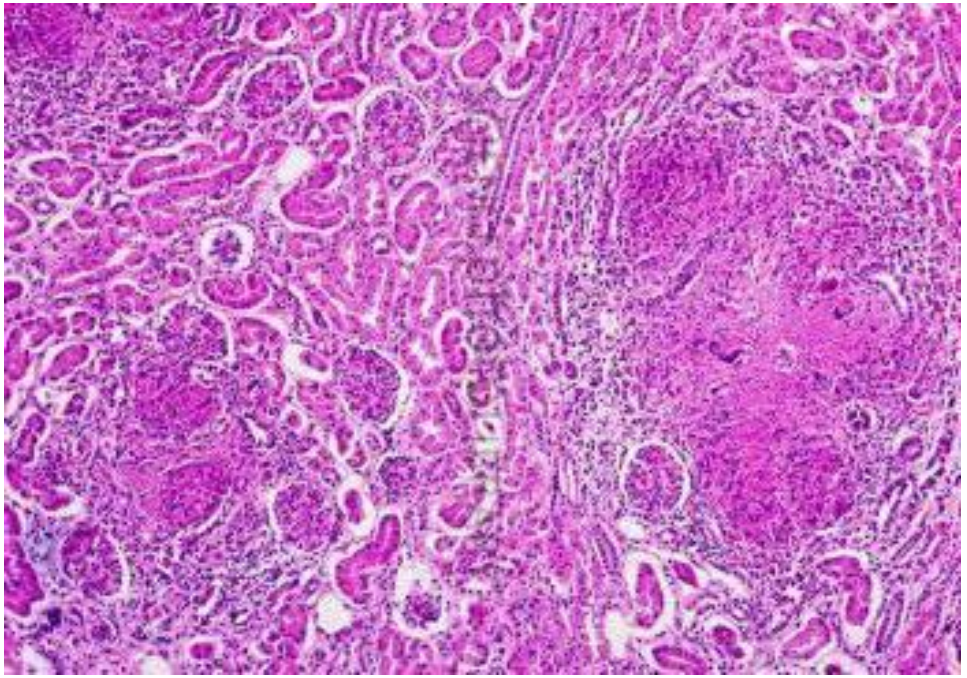
- Haematogenous spread/ascending infection from the uro-genitary system
- Milliary tubercles

Tuberculous pyelonephritis

Dilated peivicaleceal system

Filled with white-yellow caseous material

Renal parenchyma is distorted



Intestinal tuberculosis

- Primary type is unusual
- Secondary TB – ingestion of infected sputum
- Commonly affects the ileum

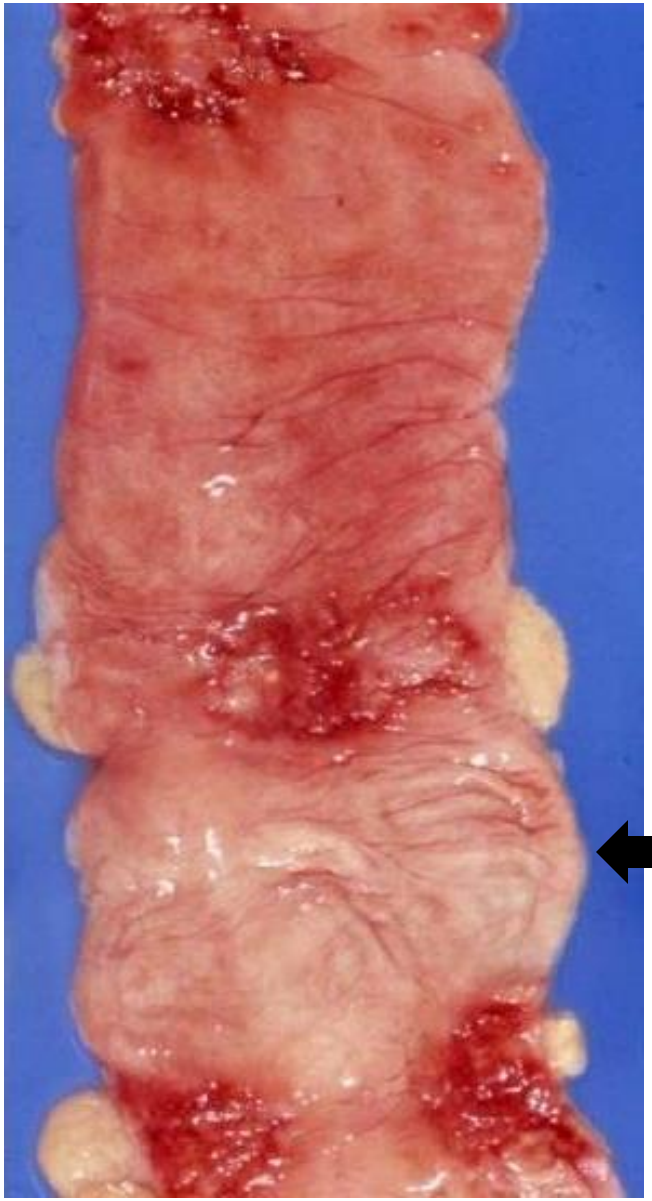
  Deep transverse ulcers

  Heal with stricture formation

  Ileo - caecal region involvement

  DD - crohn’s disease

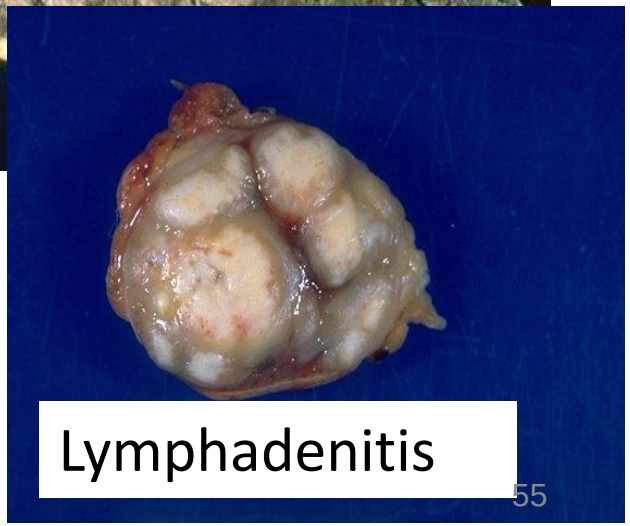
TB- intestine



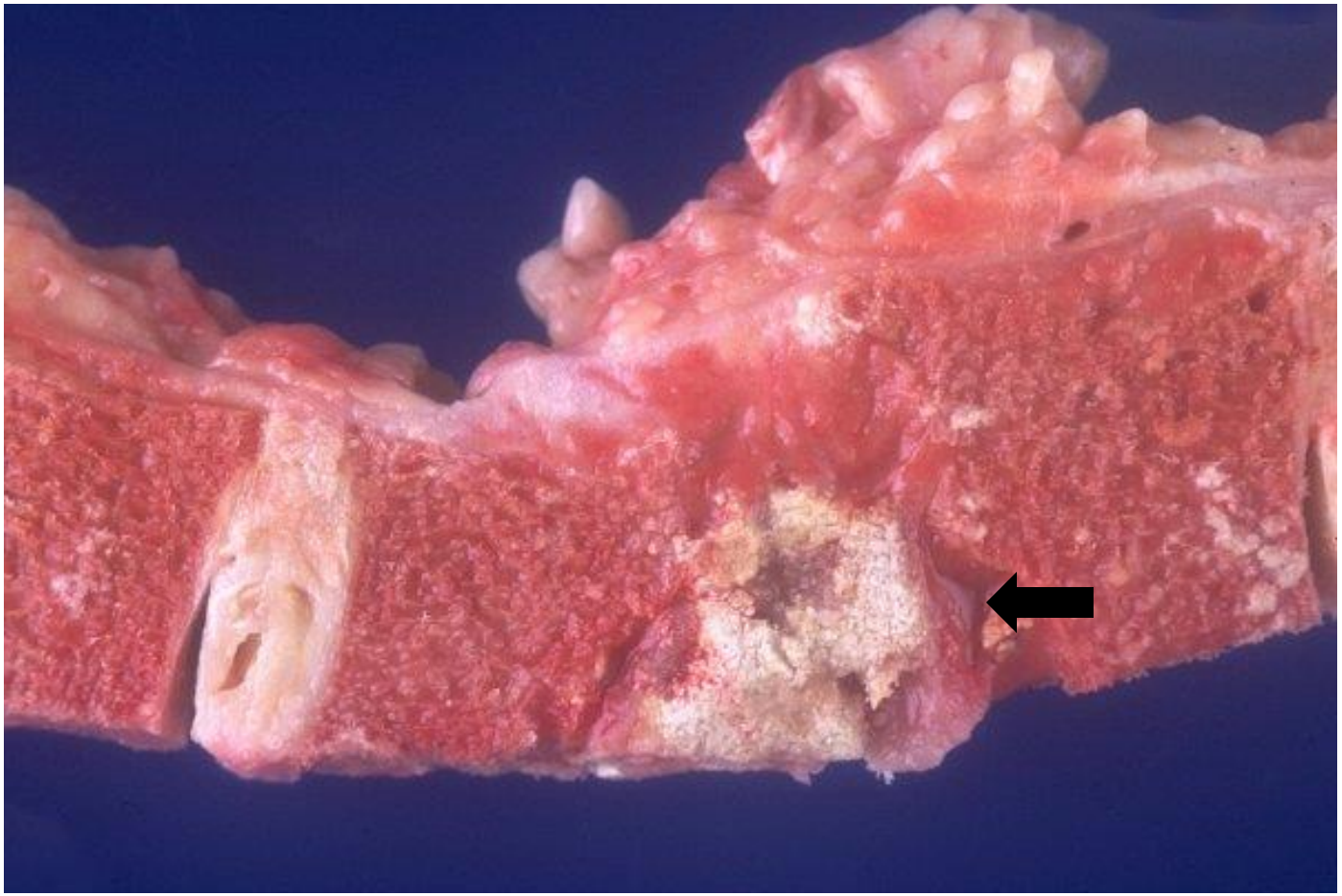
Ileum – Transverse ulcers

TB

Epididymorchitis



TB- Vertebrae (Pott disease)



TB- Bones and joints

- Haematogenous spread
- Commonly involves the spine
- Usually lower thoracic and lumbar vertebrae
- Vertebral body → leads to collapse of the vertebrae
- Paraspinal abscess → spreads to other vertebrae
- Spread along the sheath of psoas muscle → psoas abscess

TB bone

Cord compression

- Compression by abscess/bone material/ disc material
- Later due to kyphosis

TB - Joints

- Haematogenous / from the bone
- Hip and knee joints commonly affected
- Inflammed synovium with inflammation extending to the subchondral bone and dissect it from the articular cartilage

Lymphadenitis

- Most frequent form of extrapulmonary TB
- Usually in cervical region (scrofula)

- HIV negative individuals

  Unifocal lymphadenopathy

  HIV – positive individuals

  Almost always multifocal lymphadenopathy

Mantoux test

- Read