Tuberculosis

Chronic infectious disease caused by Mycobacterium Tuberculosis

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Tuberculosis

Trasmission

- Airborne
- Airways-Lymphatic
- Ingestion (*M. Bovis*)

Mycobacteria : *aerobic bacteria forming single or branched chains*

- *Cell wall: mycolic acid (acid-alcohol fast)*

Reservoir for ***M. Tuberculosis***

- ***Subjects with active tuberculosis***
- Tuberculosis caused by *M. Bovis* (intestinal) still detected in countries with:
  - Infected cows
  - Non pasteurised milk

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Tuberculosis

Epidemiology: spread worldwide

- 1,7 billion people affected by TB
- 8-10 million new cases every year
- 1,7 million deaths each year.
- Second most frequent infectious disease (1° HIV)
- HIV infection makes patients prone to TB
- 50 millions people worldwide have HIV+TB
- In the U.S. from 1985 to 1992 >> than 20% of cases (>HIV) among homeless, immigrants, prisoners
- After 1993 < of cases, 16.0000 cases of TBC + among immigrants

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- TBC endemic in poor, overcrowded countries hit by chronic debilitating diseases
- In the U.S. typically affects the elderly, homeless and HIV patients
- Some diseases > the risk of TBC: diabetes mellitus, Hodgkin lymphoma, chronic lung diseases (silicosis), chronic renal failure, malnutrition, alcohol addiction and immune suppression.

Tuberculosis

Mycobacterium Tuberculosis (hominis / bovis)

- Presence of micro-organisms
- Acquired through transmissions of droplets of saliva from subjects with active TB
- Presence of a small calcified nodule at the site of infection indicates previous infection only (micro-organisms may be quiescent, but can become active in case of immune suppression)
- It causes delayed hypersensitivity to M.T. antigens (basis for the Mantoux test)

Tuberculosis

- ***Tuberculin skin test (Mantoux)***
  - Intradermal injection of purified protein derivatives (PPD) of M.T.
  - 48-72 hours later: appearance of palpable nodule
  - Positivity = Cell-mediated hypersensitivity to M.T. antigens
  - It doesn't distinguish between previous infection and active disease
- ***False negatives:***

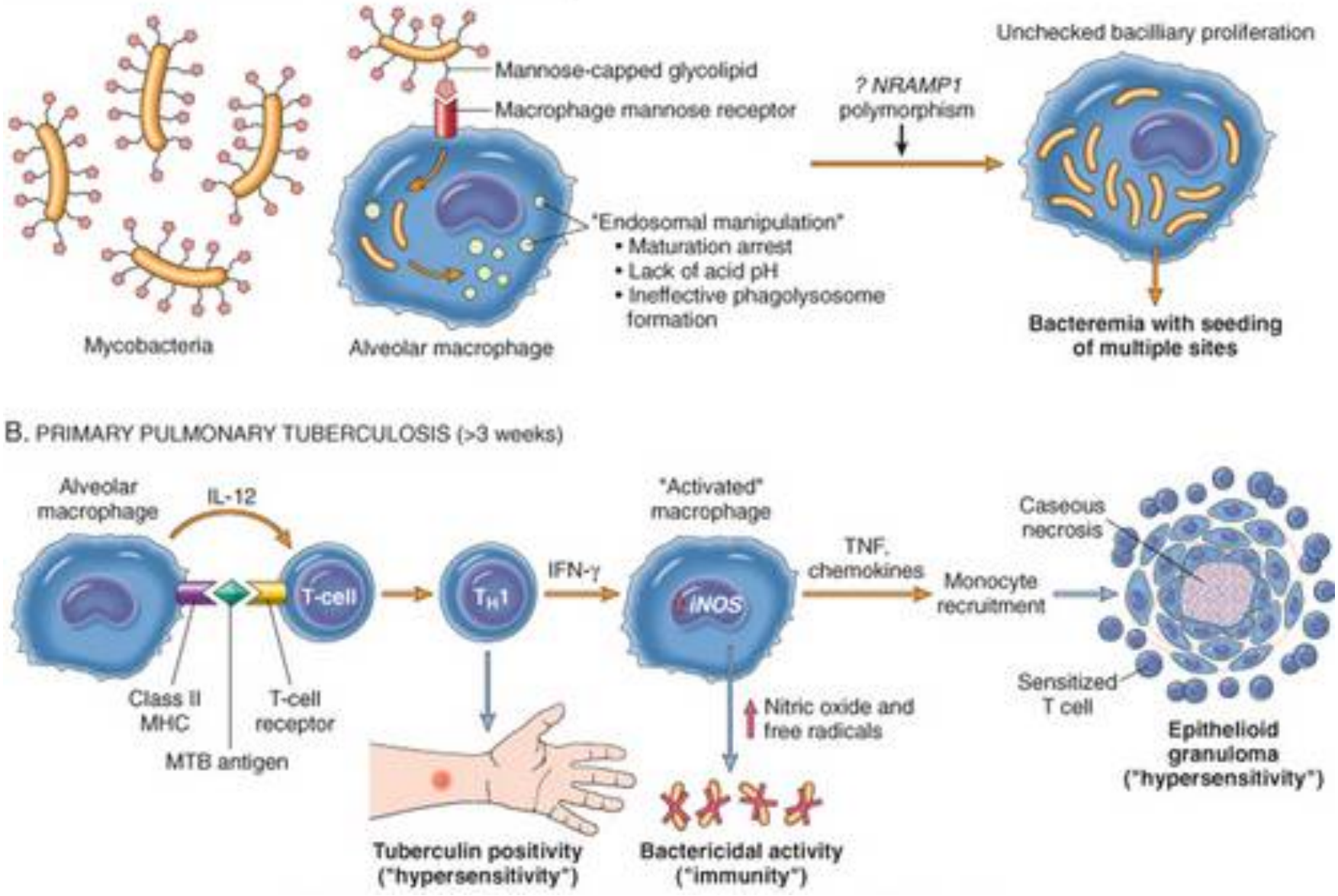
  Viral infections, sarcoidosis, malnutrition, Hodgkin disease, immune suppression and hyperacute tubercolosis (immune system hasn't reacted to the infection)
- ***False positives:***

  Infection by atypical mycobacteria

Tuberculosis

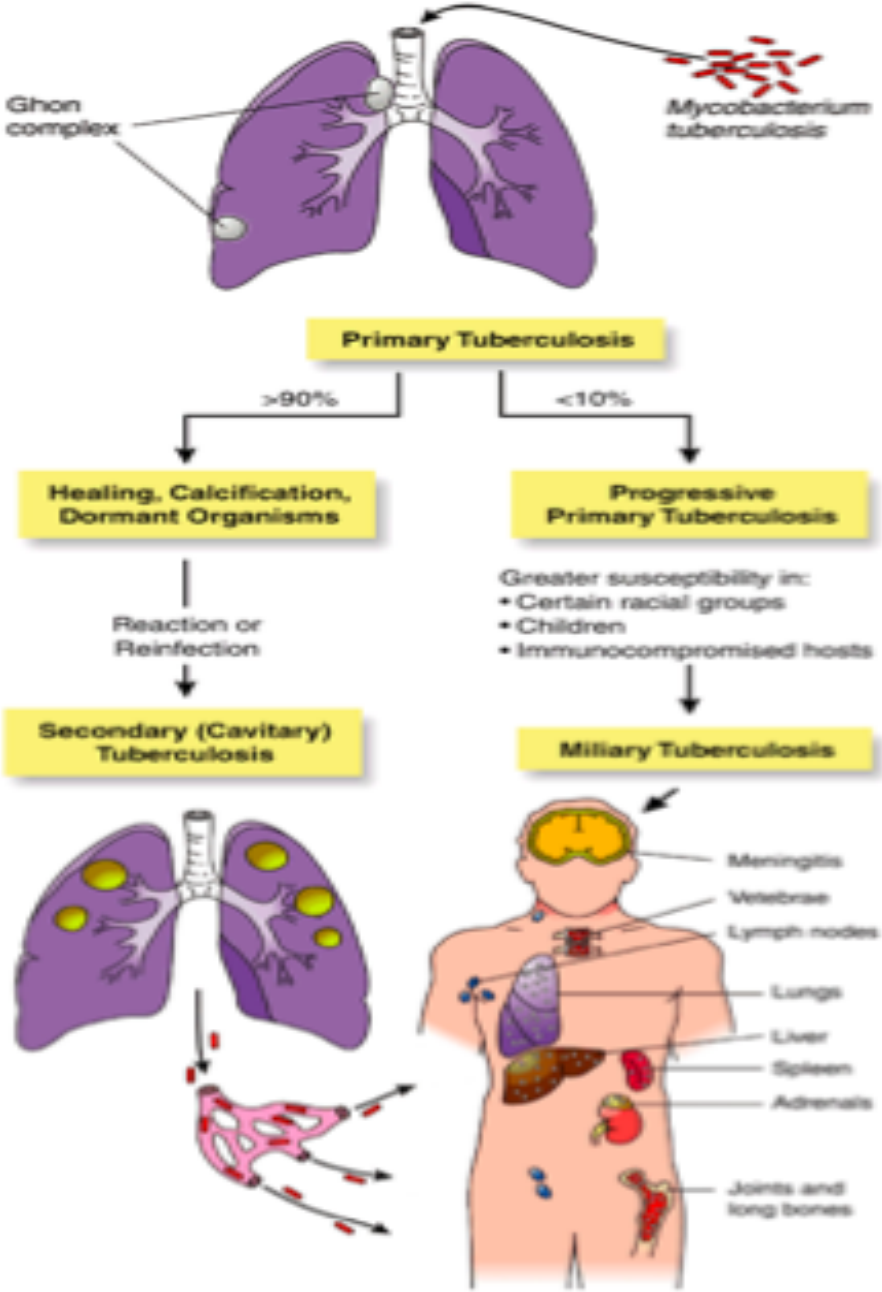
Pathogenesis:

- Immunocompetent subject with no previous exposure depends on:
  - Cell-mediated immunity, which allows resistance to mycobacteria and hypersensitivity against mycobacterial antigens
  - Clinical manifestations like caseous granulomas and formation of cavities inside the lung = hypersensitivity of the host, aquired immunity against the microorganism


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
? NRAMP1 polymorphism
Unchecked bacilliary proliferation
Bacteremia with seeding of multiple sites
B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)
Alveolar macrophage
IL-12
T-cell
Class II MHC
T-cell receptor
MTB antigen
T_H1
IFN-γ
"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")

Tuberculosis

- Immunocompetent subject with previous exposure to M.T. results in:
  - Rapid activation of immune response
  - Increased tissue necrosis
- Hypersensitivity and resistance appear at the same time
- Loss of hypersensitivity (PPD-) = loss of resistance to mycroorganisms


Ghon complex
Mycobacterium tuberculosis
Primary Tuberculosis
>90%
<10%
Healing, Calcification, Dormant Organisms
Progressive Primary Tuberculosis
Reaction or Reinfection
Greater susceptibility in:
• Certain racial groups
• Children
• Immunocompromised hosts
Secondary (Cavitary) Tuberculosis
Miliary Tuberculosis
Meningitis
Vetebrae
Lymph nodes
Lungs
Liver
Spleen
Adrenals
Joints and long bones

Tuberculosis

Primary infection:

- focus or primary complex (pulmonary or intestinal):
  - Most ventilated areas, subpleural
  - Exudative alveolitis (epithelioid)
  - Productive alveolitis (granulomatous)
  - Lymphangitis
  - Granulomatous lymphadenitis
- Anatomic healing
- Clinical healing with sclerosis / calcification
- Spread into lungs / other viscera
  - Lymphatic
  - Haematogenous
  - Canalicular

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Clinical characteristics of TB infection:

- *Primary tubercolosis occurs in subjects with no previous exposure*
  - Exogenous source
  - Elderly people and immune-compromised patients can lose their specific immunity against M.T. and so develop primary tubercolosis more than once
- *Clinical history*
  - Latent infection (>>>)
  - Progressive infection

Tuberculosis

Morphology

Primary tuberculosis:

- Starts in the lungs
- Upper lobe (lower part)
- Lower lobe (upper part)
- Peripheral (close to the pleura)
- Hypersensitivity develops
- Primary tubercle
  - Nodule cm 1-1,5
  - Grey-whitish
  - Caseous necrosis = ***primary complex (Ghon focus)***
- Bacilli are drained
  - Regional lymphonodes (caseous necrosis)

    = Ranke's complex

Cell-mediated immunity controls the infection

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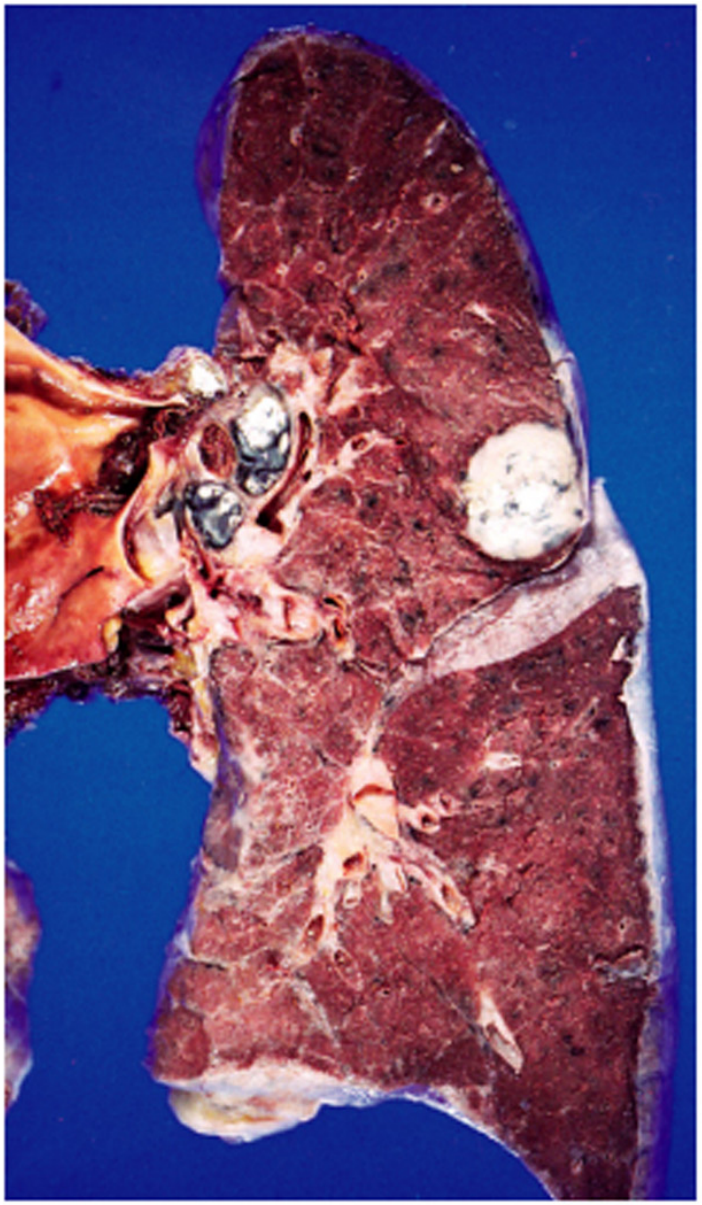

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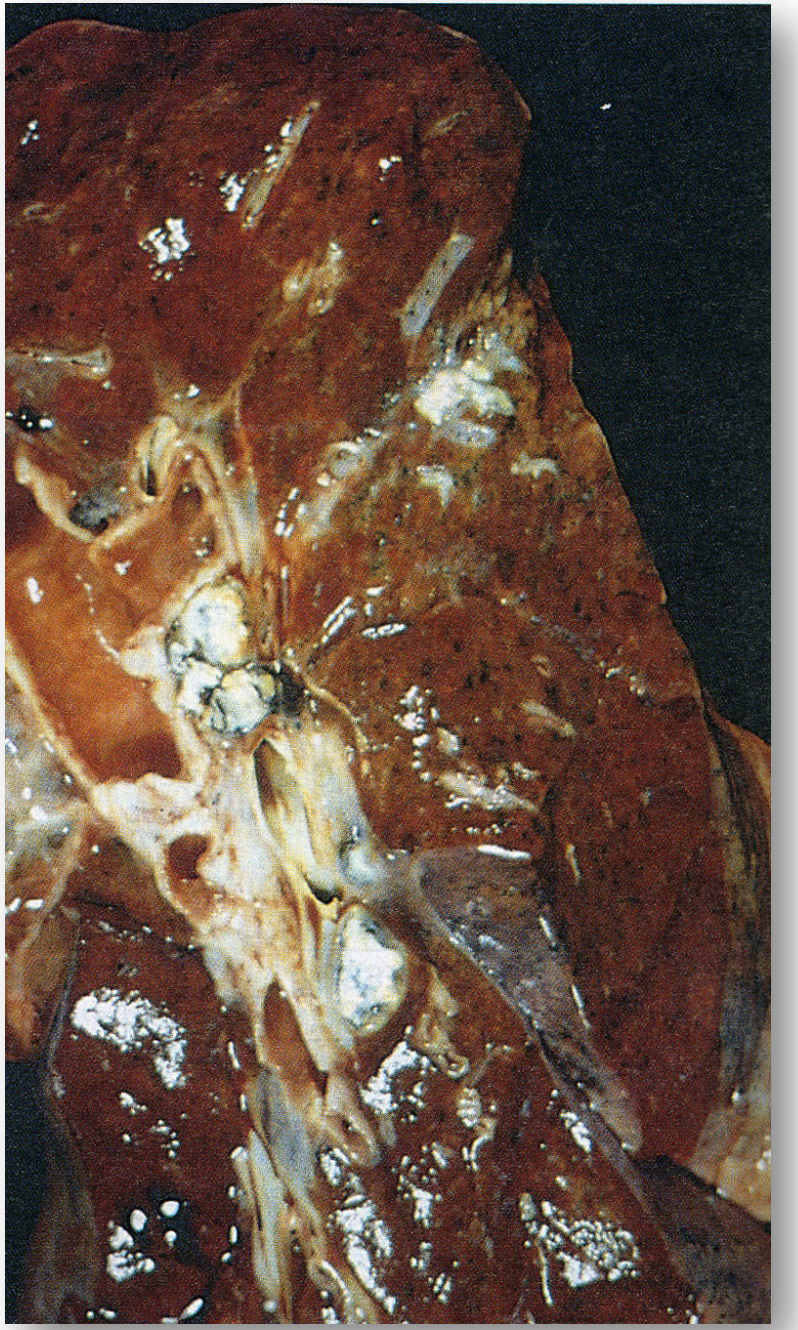
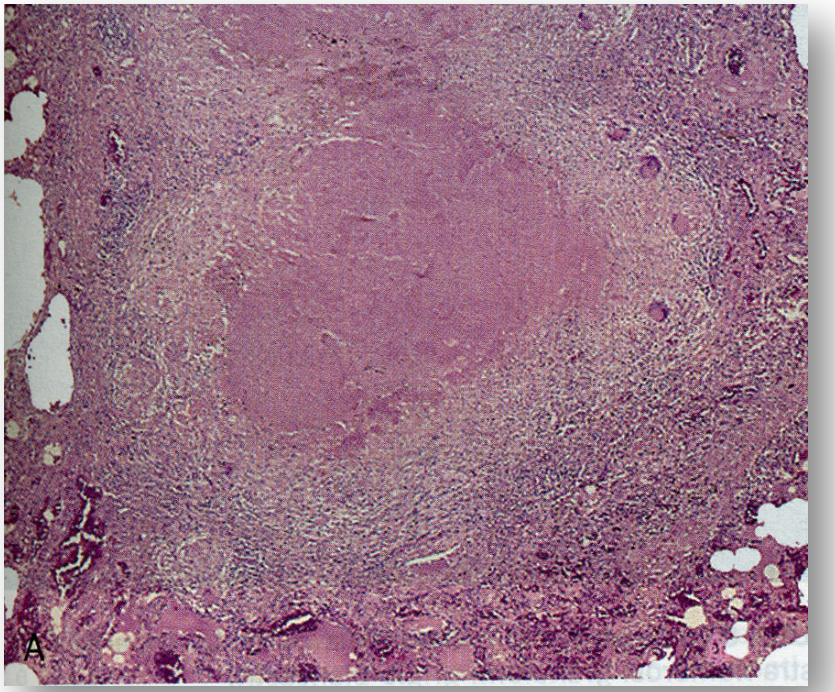
Histology:

- Granulomatous reaction with tubercles (caseating or not)
- Single tubercles are microscopic
- Confluent tubercles become macroscopically evident
- Surrounded by fibroblast reaction
- Presence of lymphocytes and multinucleated giant cells (Langhans cells)

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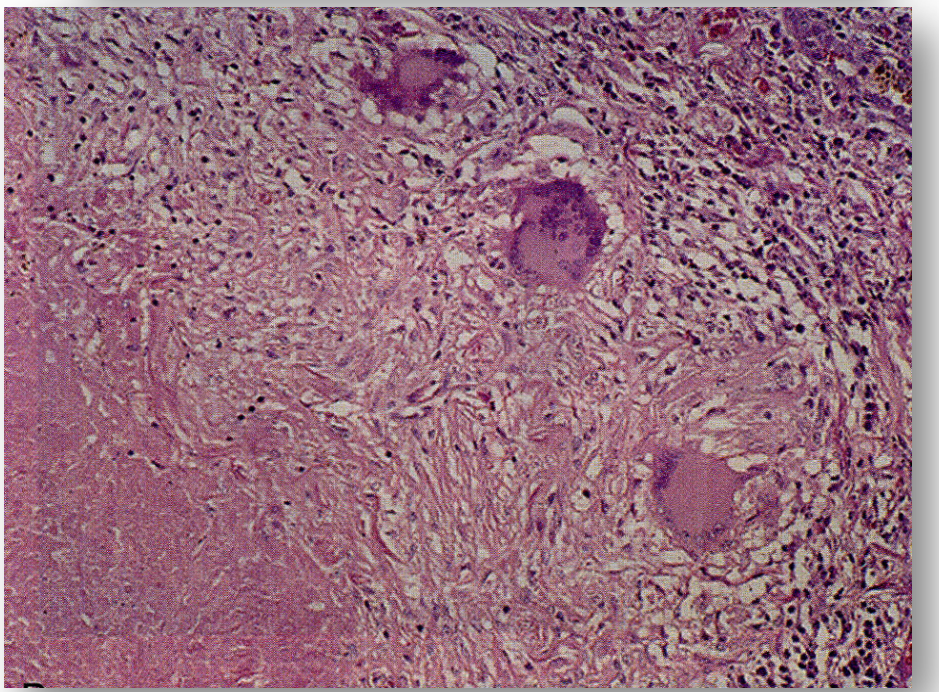

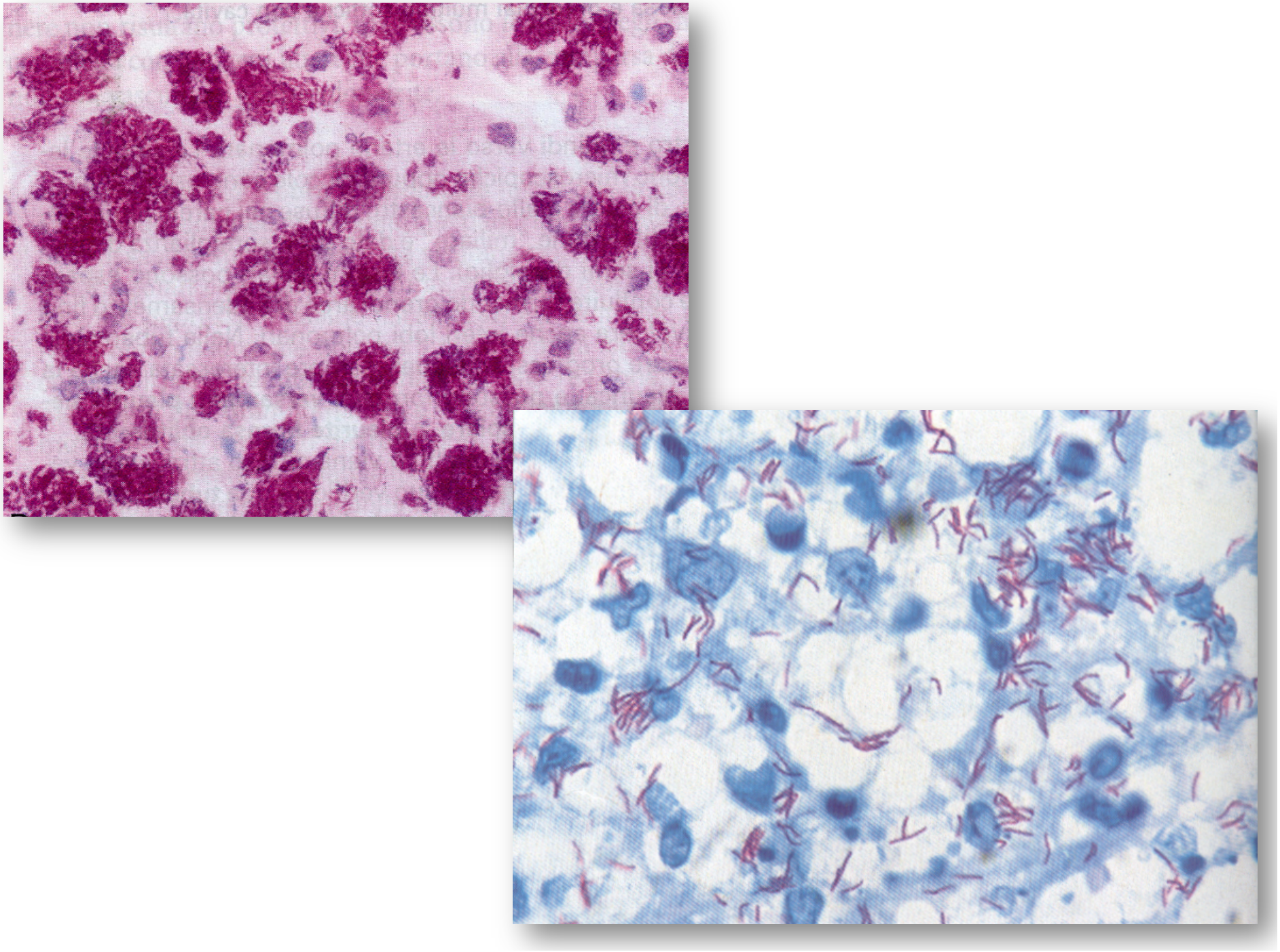

Tuberculosis

Immediate POST-PRIMARY TB (JUVENILE)

- Bronchopneumonia
- Caseous Pneumonia
- Miliary TB (hematogenous or lympho-hematogenous)
- Chronic apical tubercolosis of Aschoff-Puhl
- Fibro-sclerosis of the apex

Tuberculosis

Secondary (post-primary) TB

- Pulmonary
  - Early subclavicular infiltrate Assmann-Redeker type (epithelioid alveolitis of the apex)
  - Tubercular lobitis
  - Secondary bronchopneumonia
  - Caseous pulmonitis (lobitis)
  - Secondary Haematogenous Miliary
- Renal
- Uterine-salpingeal
- Cerebro-meningeal
- Lymph nodal

Tuberculosis

Secondary tuberculosis occurs in subjects with previous sensitization :

- After primary tubercolosis
- Reactivation of quiescent primary lesions (even after many years + lower resistance of host)
- External re-infection (virulent strains or immunosuppression)

- Reactivation: frequent in areas with low prevalence
- Reinfection: important in endemic areas

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Tuberculosis

Morphology ***Secondary tuberculosis***

- Initial Lesion:
  - Small focus of consolidation (< 2 cm)
  - Within 1-2 cm from the apical pleura
  - ***Small, hard, grey-whitish focuses, variable caseous necrosis, peripheral fibrosis***
  - Parenchymal focus develops a fibrous capsule – eventually calcified scar
- Histology: confluent tubercles with caseous necrosis
- Secondary tubercolosis of the lung can:
  - Heal spontaneously / after therapy
  - Progress

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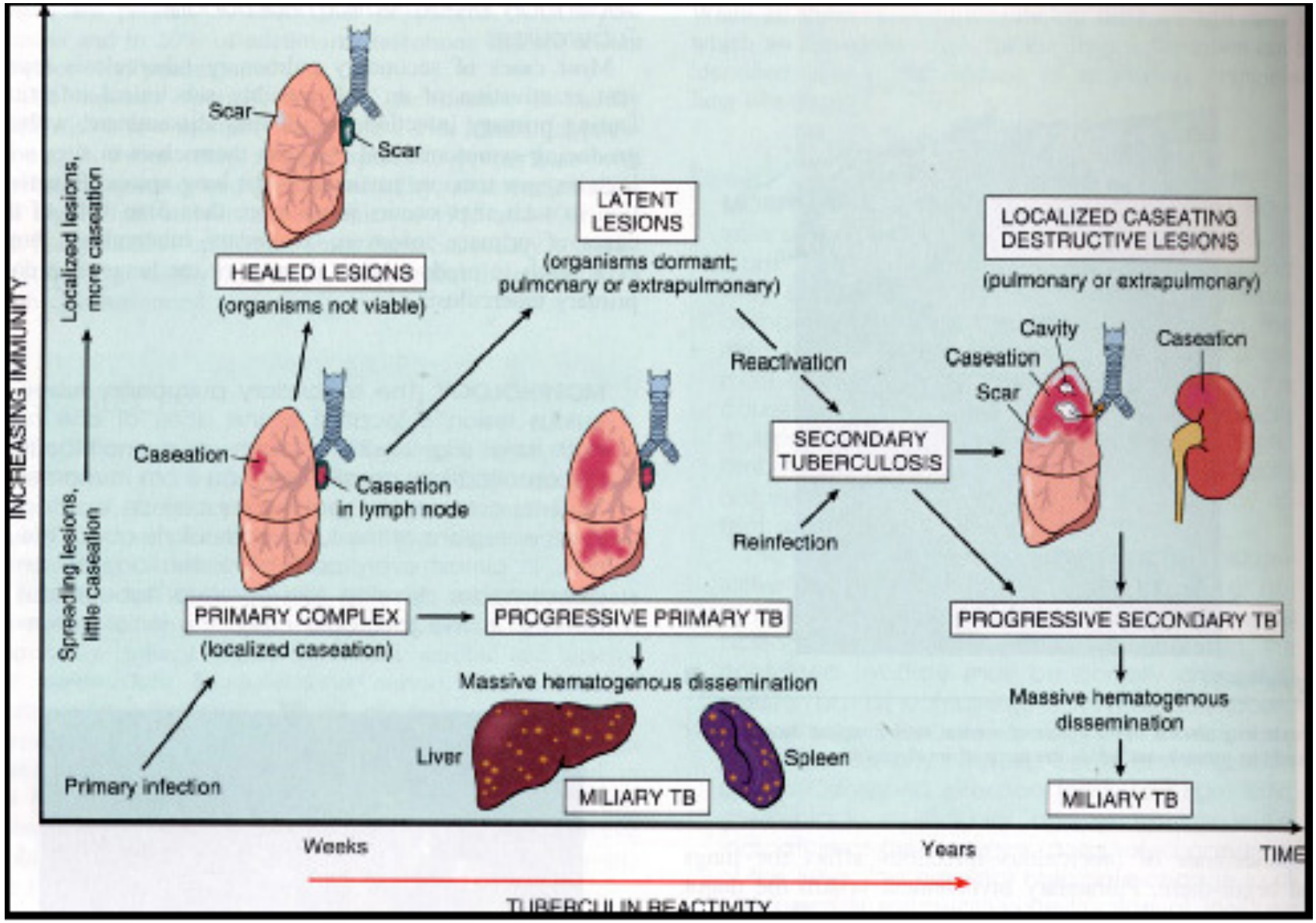
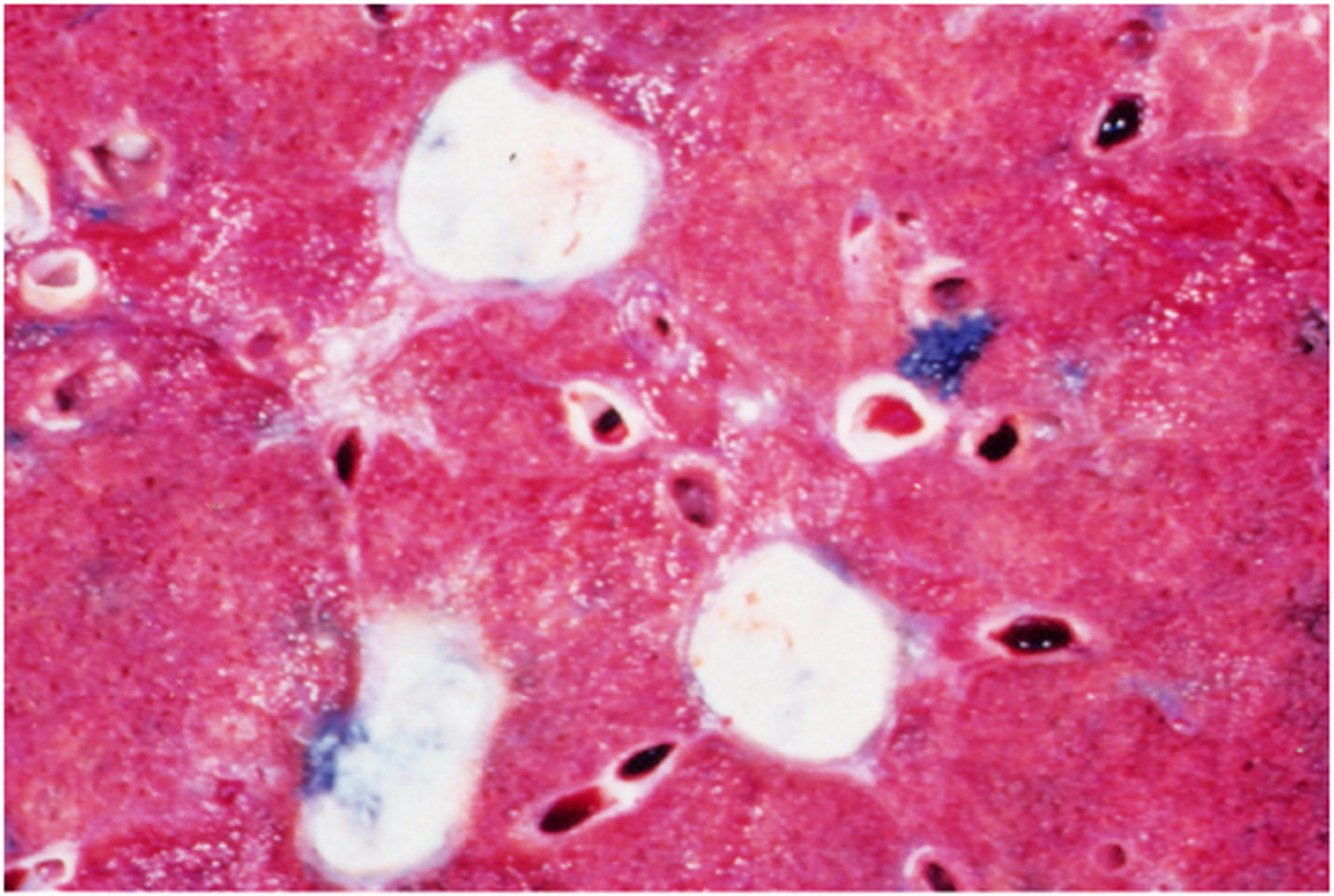


Tuberculosis Pathogenesis



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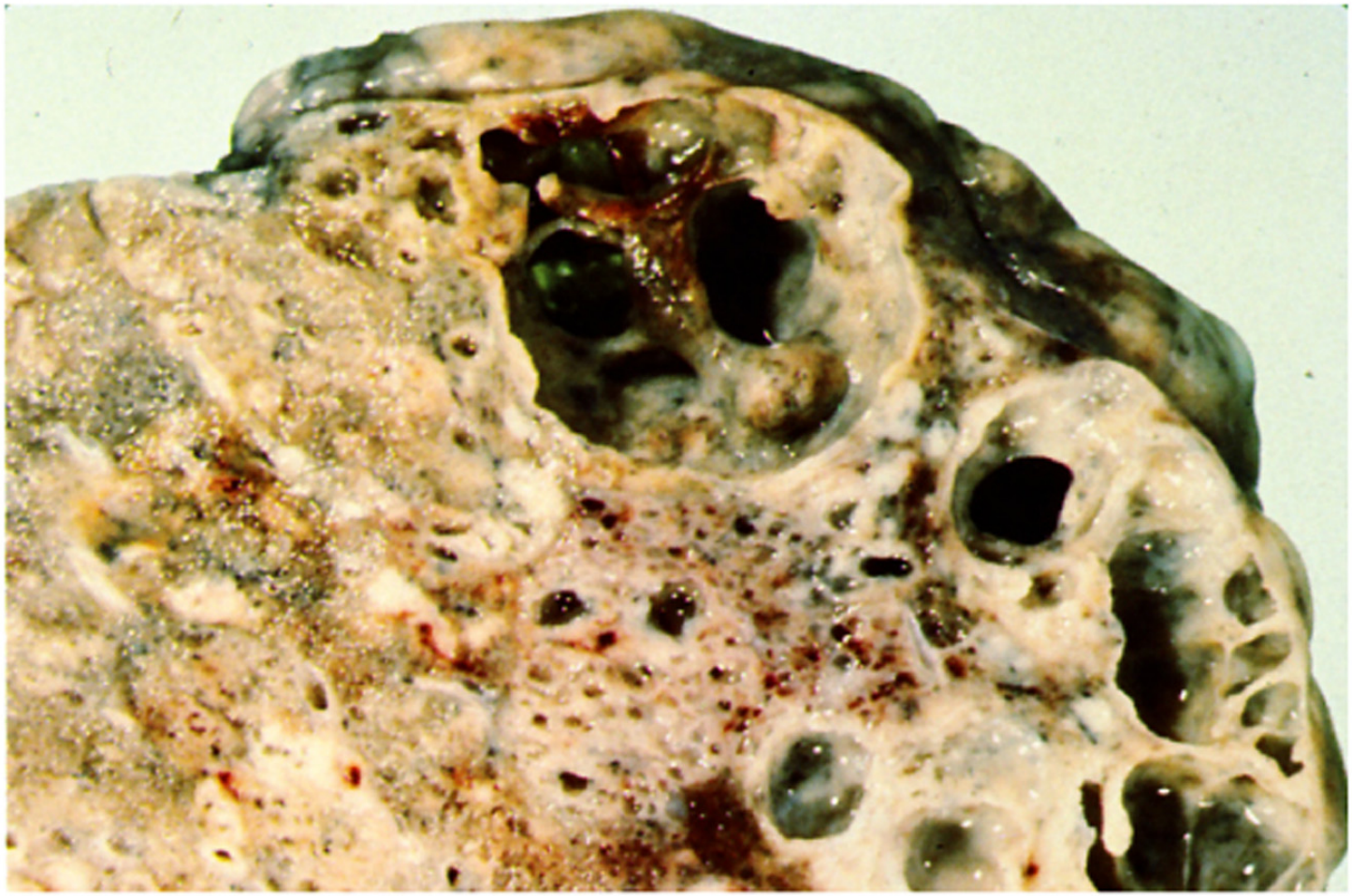
Complications (tertiary TB)

- Fibro-caseous tuberculosis
- Ulcero-cavernous tuberculosis
  - Necrotic layer
  - Granulomatous layer
  - Fibroticlayer
- Tubercle
- Pleuritis Tb
- Pyo-pneumothorax
- TB Meningitidis



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Progressive pulmonary TB

- Occurs in the elderly and immunocompromised patients
- Enlargement of the apical lesion with >> caseous necrosis
- Bronchial erosion with draining of caseous material
- Irregular cavity with indented borders, small amounts of fibrotic tissue
- Haemoptysis (erosion of blood vessels)

- Adequate treatment:
  - Fibrosis with bronchial distortion
- Inadequate treatment:
  - Infection spreads through airways, lymphatics, blood

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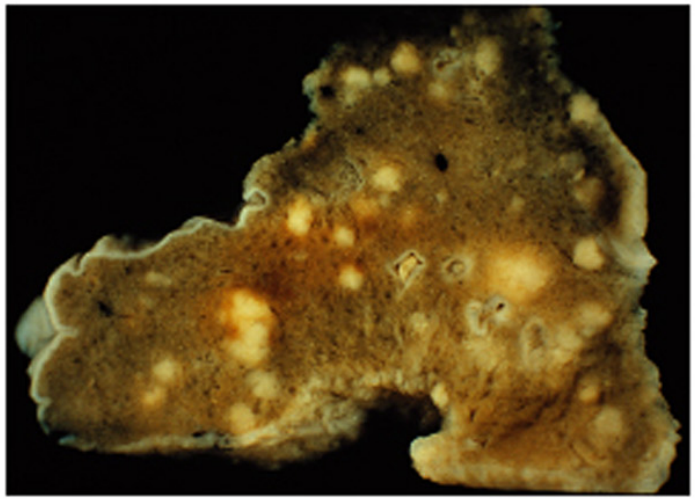
Miliary pulmonary TB

- Microrganisms are drained by lymphatic ducts
- Systemic veins > Right heart > Pulmonary artery
- Small lesions (2mm), yellow-whitish
- Spread throughout lungs
- Pleural cavity is involved
  - *Serous pleural effusions, tuberculous empyema, obliterating fibrinous pleuritis*

If infectious material spreads via lymphatics or sputum

- *Endobronchial, endotracheal or laryngeal tubercolosis*



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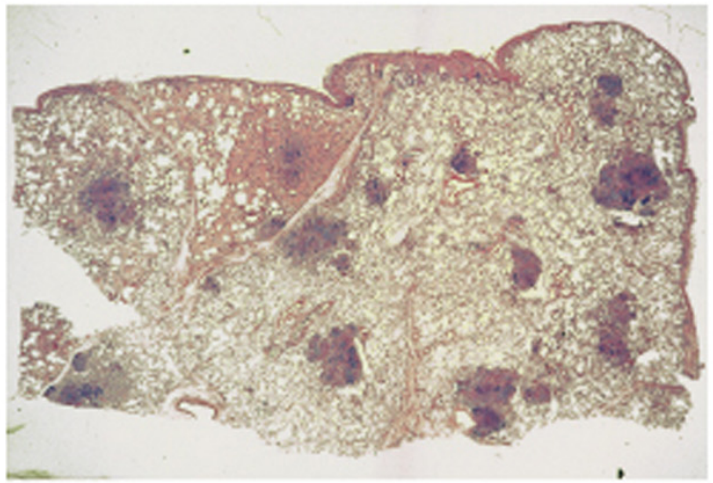

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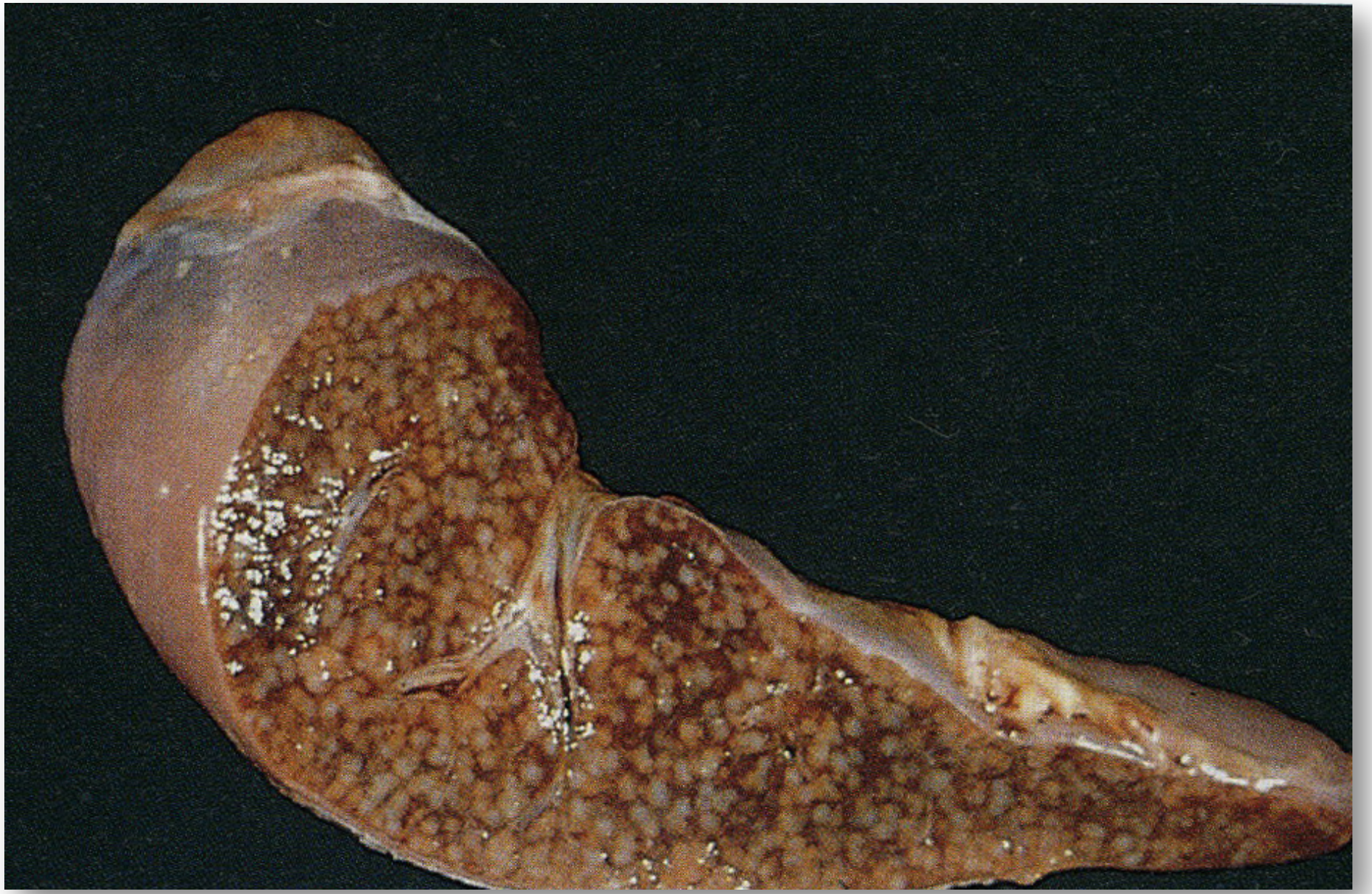
Systemic miliary TB

- Infectious lung foci spread through pulmonary veins > heart > arterial circulation > any organ

Granulomatous Tubercles

- *Liver, Bone Marrow, Spleen, Adrenal glands, Meninges, oviducts, epididymis*



Tuberculosis

Isolated organ TB

Can appear in any organ or tissue infected via blood and it can be the only manifestation of the disease

Meninges, Kidneys, Adrenal glands, Bones (osteomyelitis) Oviducts, Vertebrae (Pott's disease)

- ***Lymphadenitis***
  - Extra-pulmonary TB
  - Tuberculous cervical adenitis (scrofula)
  - HIV neg. = unifocal
  - HIV pos. = multifocal, systemic symptoms, lungs or other organs involved
- ***Intestinal TB***

Intestinal tuberculosis nowadays appears as secondary tuberculosis due to ingestion of infected sputum

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Tuberculosis

Oral tuberculosis

Primary lesions are rare

Secondary lesions are frequent, due to coughing of infected material from pulmonary lesions

Chronic ulcer, painless, undermined edge, covered by yellow-greyish eschar, tongue localisation

- *Gingival granular lesions*
- *Cervical lymphadenitis , intra- ed extra-parotideal*

Diagnosis

- Biopsy
- Detection of tubercular bacilli (specific stains or special cultural methods)

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