TUBERCULOSIS

Maram abdaljaleel, MD
Dermatopathologist &Neuropathologist

Tuberculosis

- Tuberculosis is a communicable chronic granulomatous disease caused by Mycobacterium tuberculosis involving lungs usually but may affect any organ.

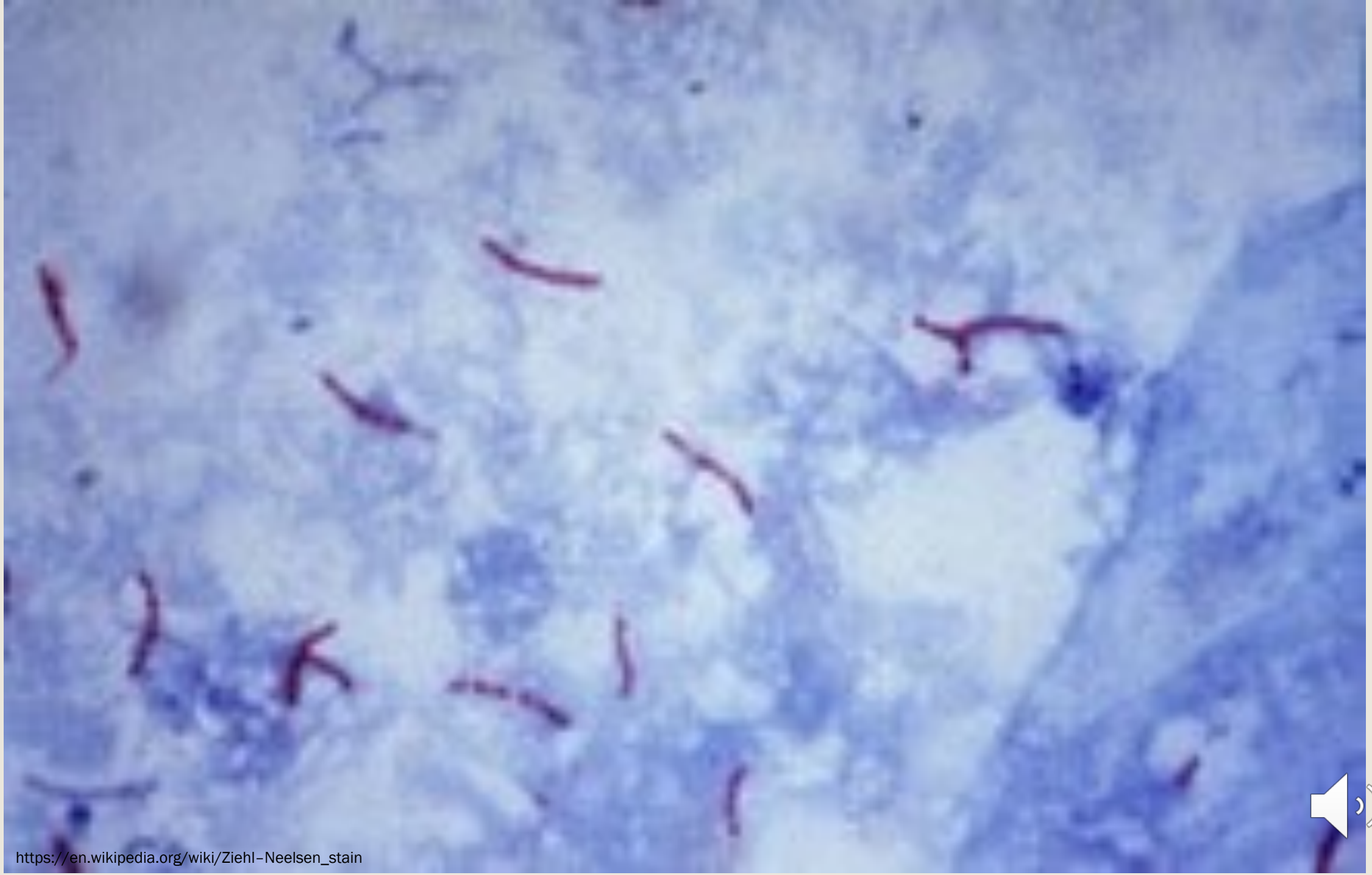
Risk Factors

Poverty, crowding, and chronic debilitating illness.

- older adults
- the urban poor
- AIDS
- and members of minority communities.
- African Americans
- Native Americans
- the Inuit (from Alaska)
- Hispanics
- immigrants from Southeast Asia
- diabetes mellitus
- Hodgkin lymphoma
- Chronic lung disease (silicosis)
- chronic renal failure
- Malnutrition
- Alcoholism
- Immunosuppression

Etiology:

- **Mycobacteria:**
  - slender rods
  - acid-fast (i.e., they have a high content of complex lipids that readily bind the Ziehl-Neelsen stain and subsequently stubbornly resist decolorization).



https://en.wikipedia.org/wiki/Ziehl–Neelsen_stain

M. tuberculosis hominis

- Most cases of tuberculosis.
- The reservoir of infection found in individuals with active pulmonary disease.
- Transmission
  - direct, by inhalation of airborne organisms in aerosols generated by expectoration
  - exposure to contaminated secretions of infected individuals.

Mycobacterium bovis

- Oropharyngeal and intestinal tuberculosis
- contracted by drinking contaminated milk

Mycobacterium avium complex

- Less virulent than M. tuberculosis
- Rarely cause disease in immunocompetent individuals.
- Cause disease in 10% to 30% of patients with AIDS.

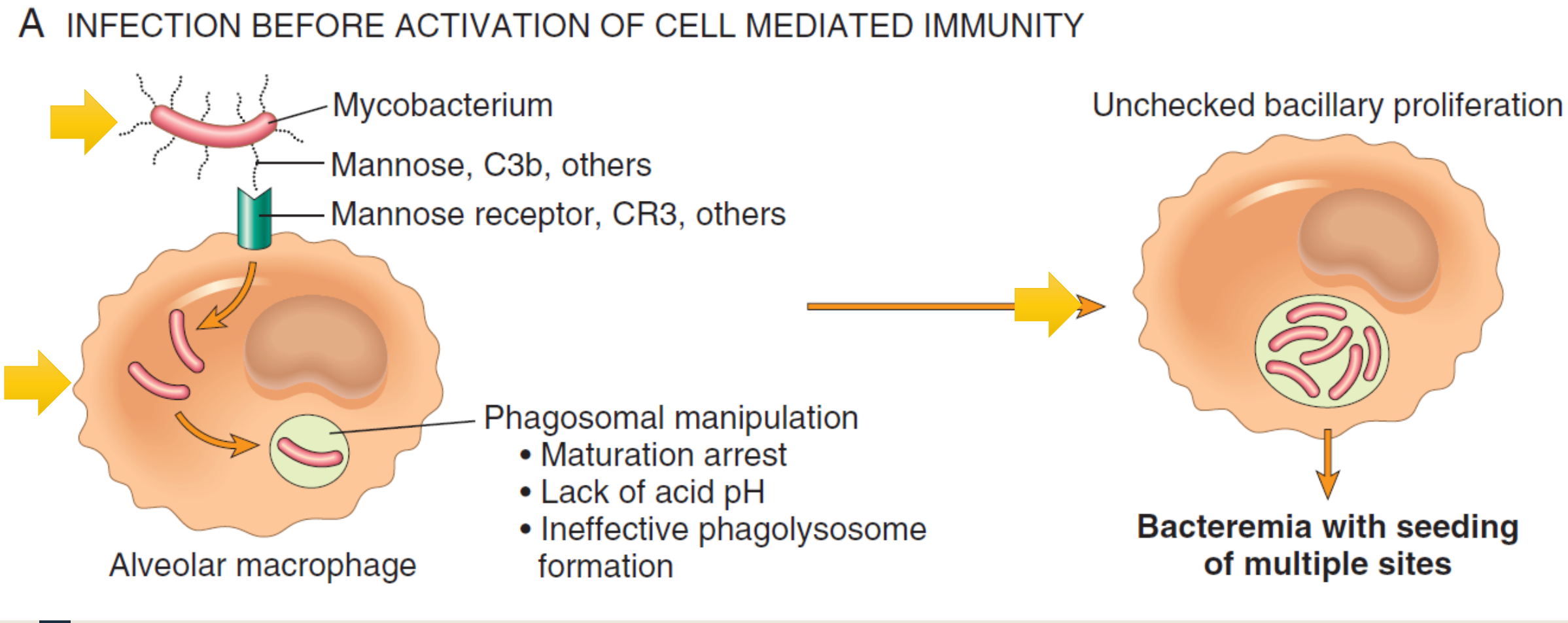
Infection vs. disease

- Infection implies seeding of a focus with organisms.
- Disease is a clinically significant tissue damage
- Routes of transmission
  - Airborne droplets

Pathogenesis

- **In the previously unexposed immunocompetent individual**
  - Development of cell-mediated immunity
    - To resist the organism
    - To develop tissue hypersensitivity to tubercular antigens.
  - Destructive tissue hypersensitivity as a part of the host immune response:
    - Caseating granulomas
    - Cavitation
    - immunity to the organism.

Natural history of primary pulmonary tuberculosis



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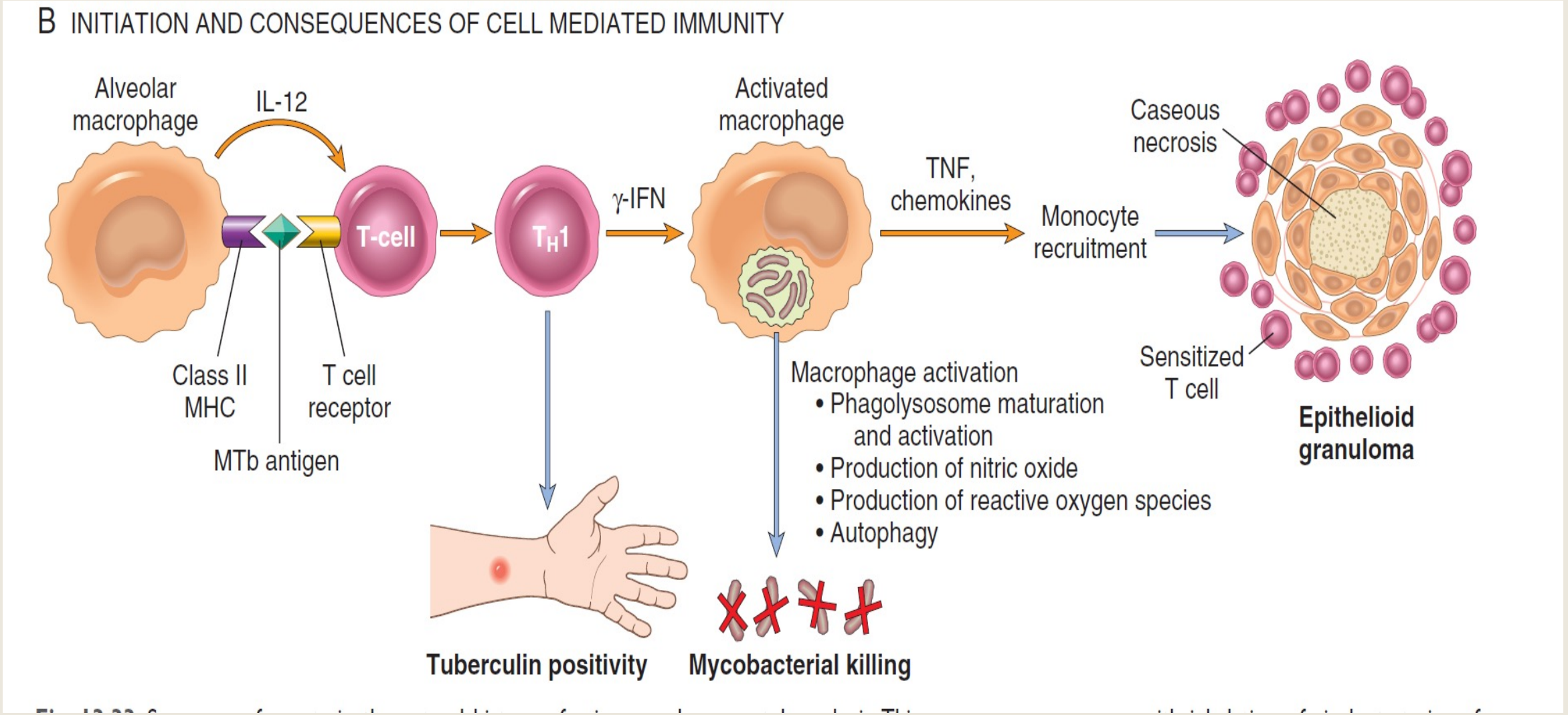
Infection before activation of cell mediated immunity:

- in the first 3 weeks after initial exposure (inhalation of virulent strains of Mycobacterium) → entry of a virulent strain of mycobacteria into macrophage endosome
  - This process is mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors that recognize several components of the mycobacterial cell walls.

- After entry the **organisms inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole,** allowing the mycobacterium to persist and proliferate within the pulmonary alveolar macrophages and air spaces → bacteremia and seeding of the organisms to multiple sites.
- Despite the bacteremia, most individuals at this stage are asymptomatic or have a mild flulike illness.

Natural history of primary pulmonary tuberculosis



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Development of cell mediated immunity:

- **3 wks** after exposure cell-mediated immunity is developed **(TH1 response)**

- IL- 12 released by antigen presenting cells (dendritic cells) → type 1 T helper lymphocytes response → type 1 T helper cells are generated and secret IFN-γ.

- **IFN-γ** is the critical mediator that enables **macrophages to contain the M. tuberculosis infection and to become bactericidal.**

- **IFN-γ:**
  - stimulates maturation of the phagolysosome in infected macrophages
  - stimulates expression of inducible nitric oxide synthase→ nitric oxide (NO) → reactive nitrogen intermediates→ killing of mycobacterium.
  - mobilizes antimicrobial peptides (defensins) against the bacteria.
  - stimulates autophagy, a process that sequesters and then destroys damaged organelles and intracellular bacteria such as M. tuberculosis.

- **Granulomatous inflammation and tissue damage:**
  - IFN-γ → activates Macrophages→ differentiate into the "epithelioid histiocytes" → aggregate to form granulomas(giant cells).
  - Activated macrophages also secrete TNF and chemokines, which promote recruitment of more monocytes.

- **Outcome:**
  - Majority: mycobacterial killing off before significant tissue destruction or illness.
  - In other people the infection progresses due to advanced age or immunosuppression, and the ongoing immune response results in caseation necrosis.

TH1 response:

1. Mycobacterial killing (bactericidal).
2. formation of granulomas, caseous necrosis and tissue destruction

Summary:

- Immunity to a tubercular infection is primarily mediated by TH1 cells, which stimulate macrophages to kill mycobacteria.

- Immune response, while largely effective, comes at the cost of hypersensitivity and the accompanying tissue destruction

- Defects in any of the steps of a TH1 T cell response (including IL-12, IFN-γ, TNF, or nitric oxide production)
  - poorly formed granulomas
  - absence of resistance
  - disease progression.

- Reactivation of the infection or re-exposure to the bacilli in a **previously sensitized host** results in rapid mobilization of a defensive reaction but also increased tissue necrosis.

- **Hypersensitivity (**T-cell immunity**) and resistance appear in parallel**

  - The loss of hypersensitivity (indicated by tuberculin negativity in a M.tuberculosis-infected patient) is an ominous sign of fading resistance to the organism.

Tuberculin (Mantoux) test:

- Delayed hypersensitivity
- intracutaneous injection of 0.1 mL of sterile purified protein derivative (PPD)
- A positive tuberculin skin test does not differentiate between infection and disease.

Primary Tuberculosis

- The form of disease that develops in a previously unexposed and unsensitized patient.
- 5% of newly infected acquire significant disease.

Primary Tuberculosis

- self-limited
- Uncommonly may result in the development of fever and pleural effusions.
- Viable organisms may remain dormant in a tiny, telltale fibrocalcific nodule at the site of the infection for several years **(infection, not active disease)**
- If immune defenses are lowered, the infection may reactivate a potentially life-threatening disease.

Primary Tuberculosis, presentation:

- In otherwise healthy individuals:
  - Mostly the only consequence are the foci of scarring. Which may harbor viable bacilli and serve as a nidus for disease reactivation at a later time if host defenses wane.

- Uncommonly, new infection leads to progressive primary tuberculosis:
  - Affected patients are:
    - overtly immunocompromised
    - have subtle defects in host defenses, (malnourished)
    - Certain racial groups, such as the Inuit
    - HIV-positive patients with significant immunosuppression

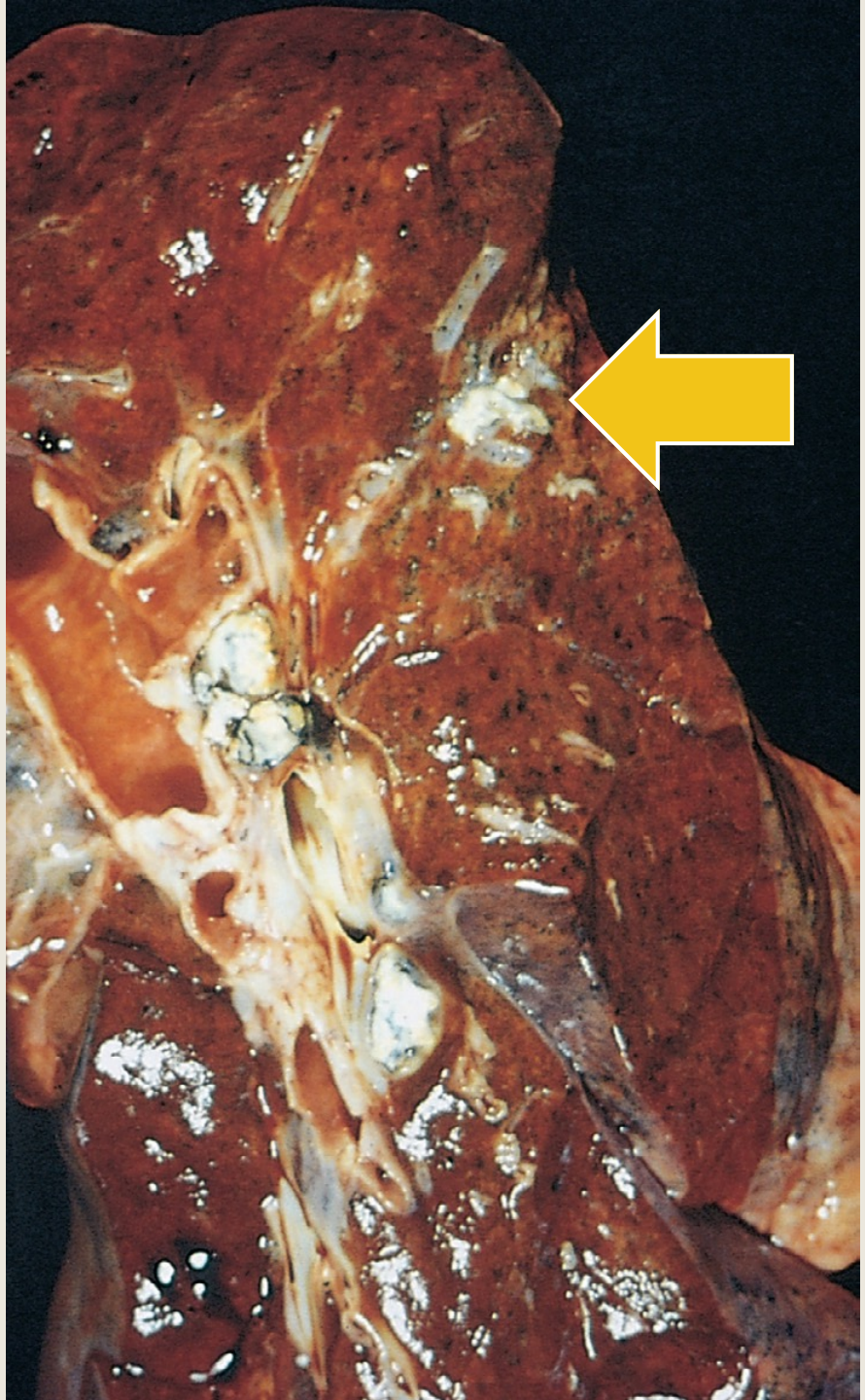
MORPHOLOGY

- Almost always begins in the lungs.

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

MORPHOLOGY, grossly:

- **Ghon focus.**
  - ✓ a 1-cm to 1.5-cm area of gray-white inflammatory consolidation emerges during the development of sensitization
  - ✓ In majority of cases→ central caseous necrosis.



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MORPHOLOGY, grossly:

- Tubercle bacilli, free or within phagocytes, travel via the lymphatic vessels to regional lymph nodes.

- **Ghon complex** :This combination of parenchymal and nodal lesions

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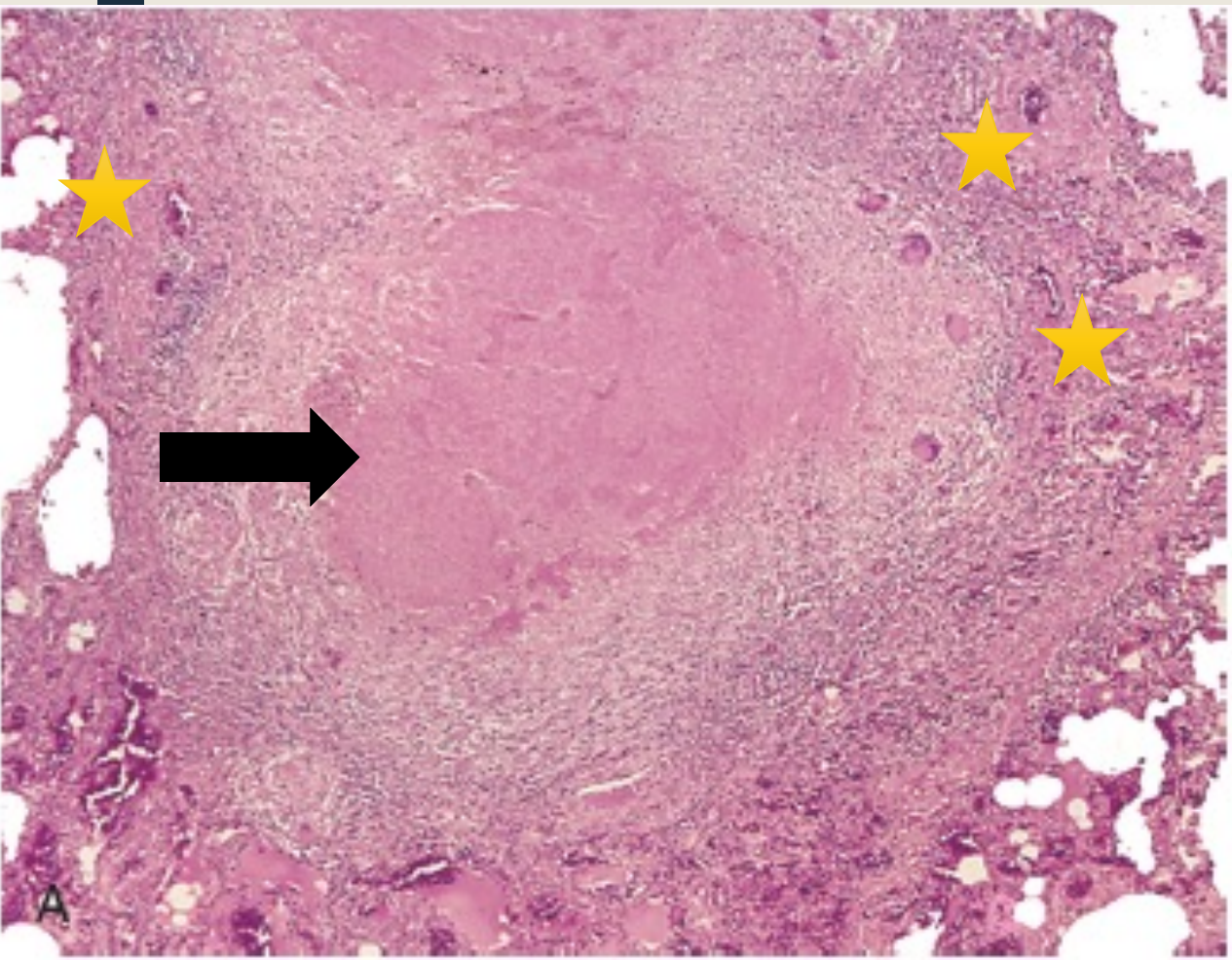
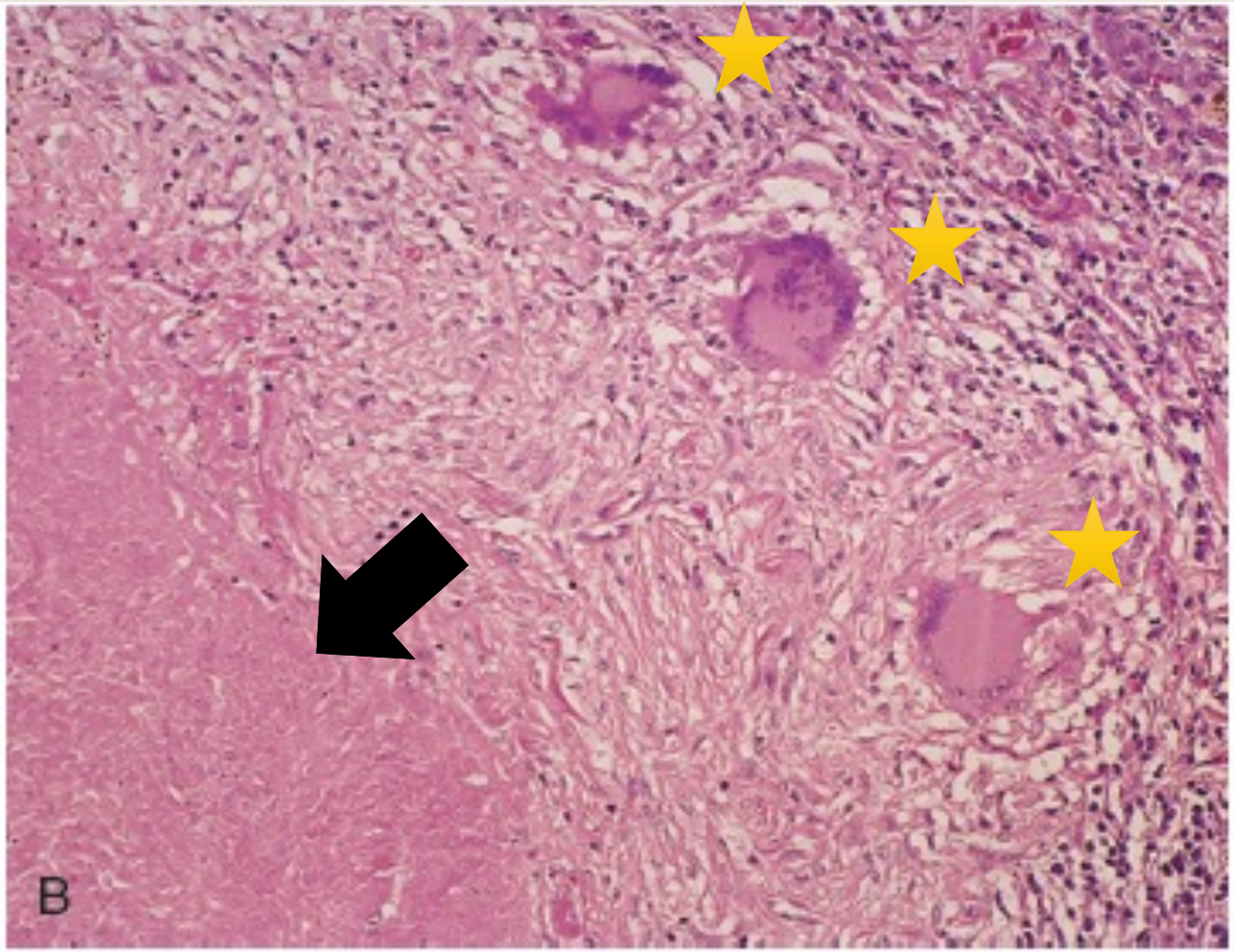
- In the first few weeks, Lymphatic and hematogenous dissemination
- In 95% cell-mediated immunity controls the infection.
- Ghon complex undergoes progressive fibrosis and calcification
- Despite seeding of other organs, no lesions develop.

MORPHOLOGY, microscopic:





tubercle

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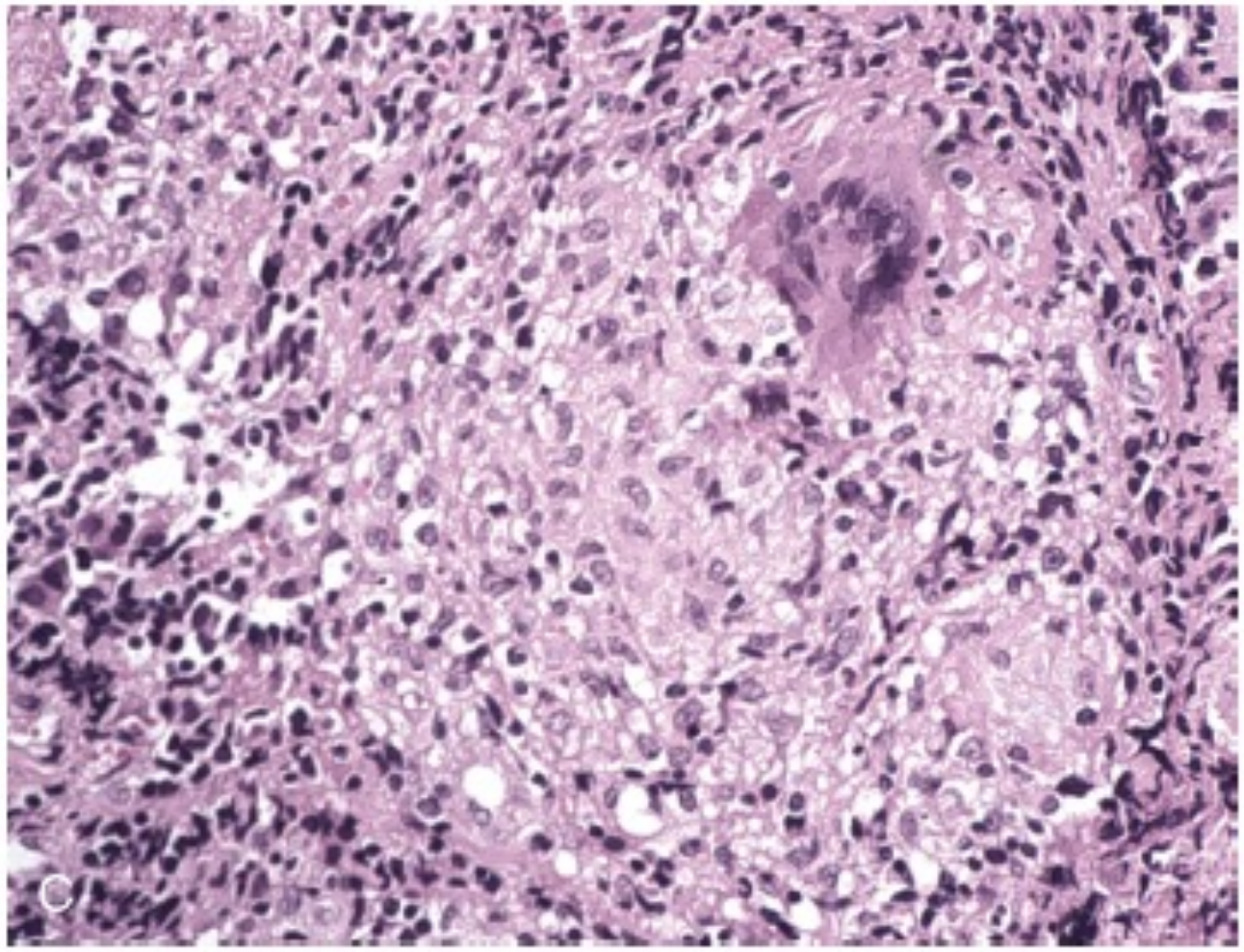

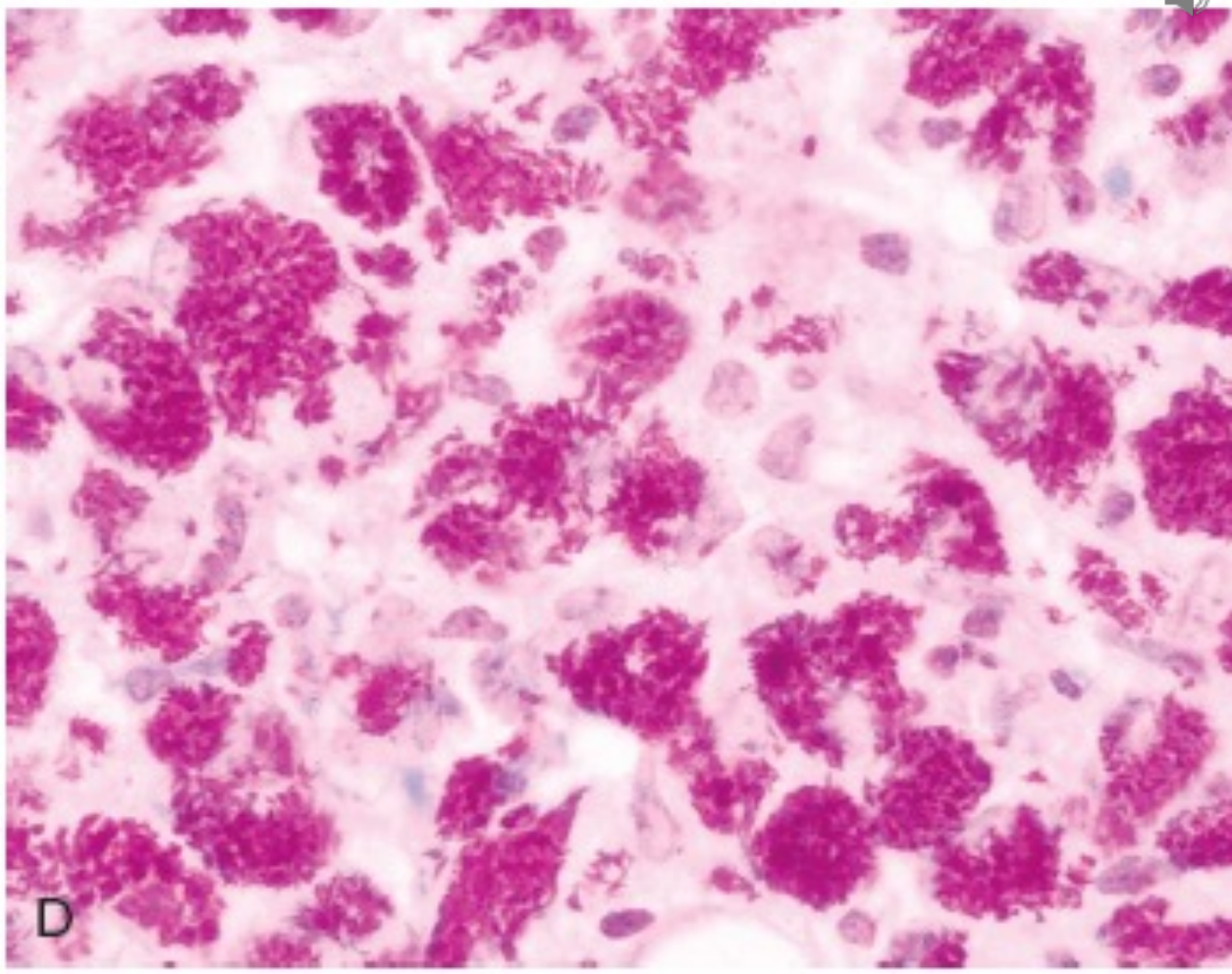

tubercular granulomas without central caseation

ZN stain→ sheets of macrophages packed with mycobacteria

irrespective of the presence or absence of caseous necrosis special stains for acid-fast organism

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Secondary Tuberculosis (Reactivation Tuberculosis)

- Arises in a previously sensitized host when host resistance is weakened Or due to reinfection
- <5% with primary disease develop secondary tuberculosis.

- Secondary pulmonary tuberculosis:
  - classically localized to the apex of one or both upper lobes.
  - the bacilli induce a marked tissue response to wall off the focus (localization)
    - So regional lymph nodes are less involved early in the disease than they are in primary tuberculosis.
  - cavitation leading to erosion into and dissemination along airways→ important source of infectivity, because the patient now produces sputum containing bacilli.

MORPHOLOGY, grossly:

- initial lesion is a small focus of consolidation, <2 cm, within 1-2 cm of the **apical pleura.**

- sharply circumscribed, firm, gray-white to yellow with variable amount of central caseation and peripheral fibrosis

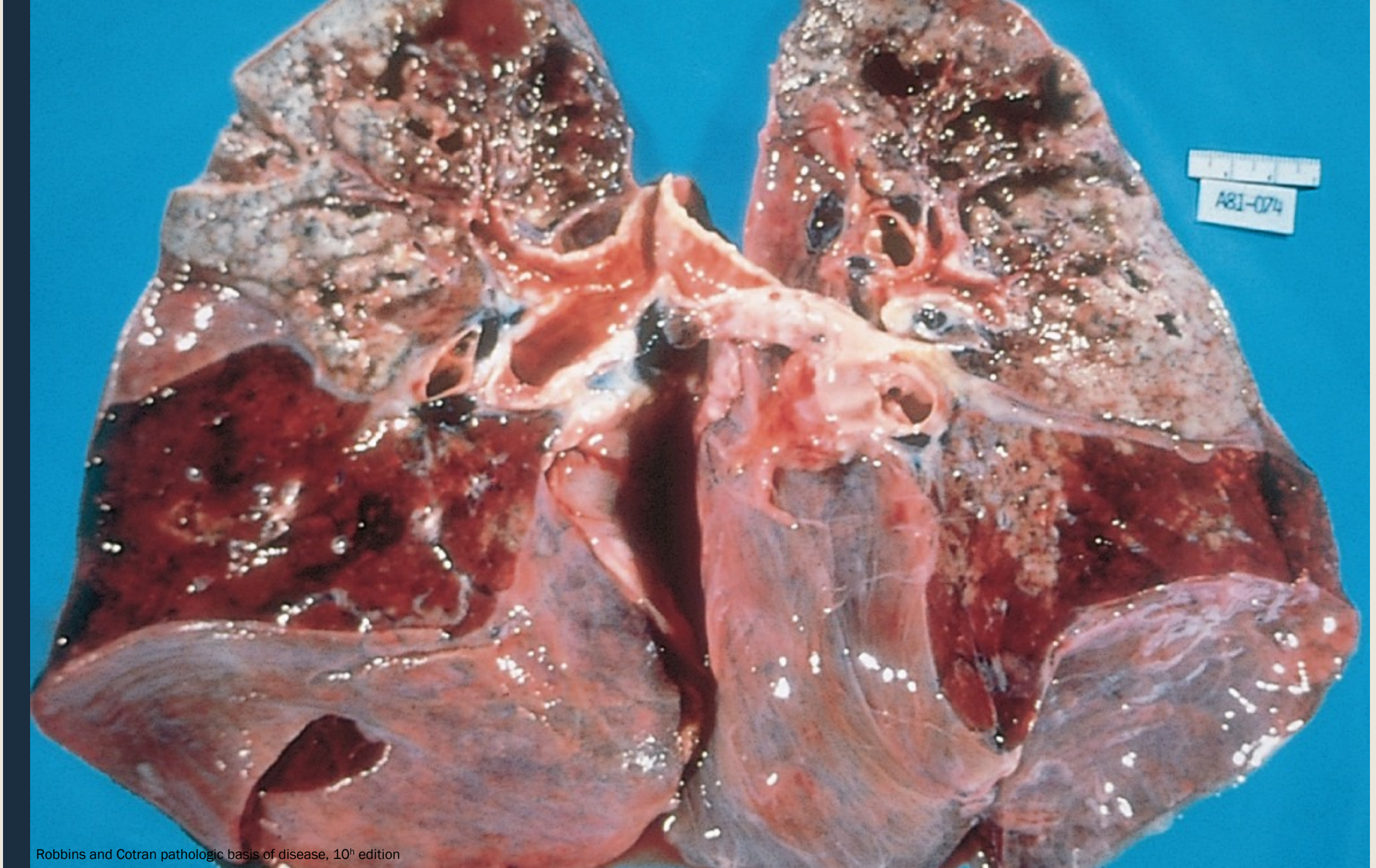
MORPHOLOGY, microscopic:

- **active lesions:** coalescent tubercles with central caseation.

- **tubercle bacilli:**
  - can be demonstrated by acid fast stain in early exudative and caseous phases of granuloma formation
  - Impossible to find them in the late fibrocalcific stages.

- **Localized, apical, secondary pulmonary tuberculosis either:**
  - heal with fibrosis either spontaneously or after therapy
  - or may progress and extend along several different pathways.

- **progressive pulmonary tuberculosis:**
  - apical lesion enlarges with expansion of caseation area.
    - Erosion into a bronchus evacuates the caseous center
    - Erosion of blood vessels results in hemoptysis.
  - **With adequate treatment**, the process may be arrested
  - **If the treatment is inadequate or host defenses are impaired**, the infection may spread by direct extension and by dissemination through airways, lymphatic channels, and the vascular system.



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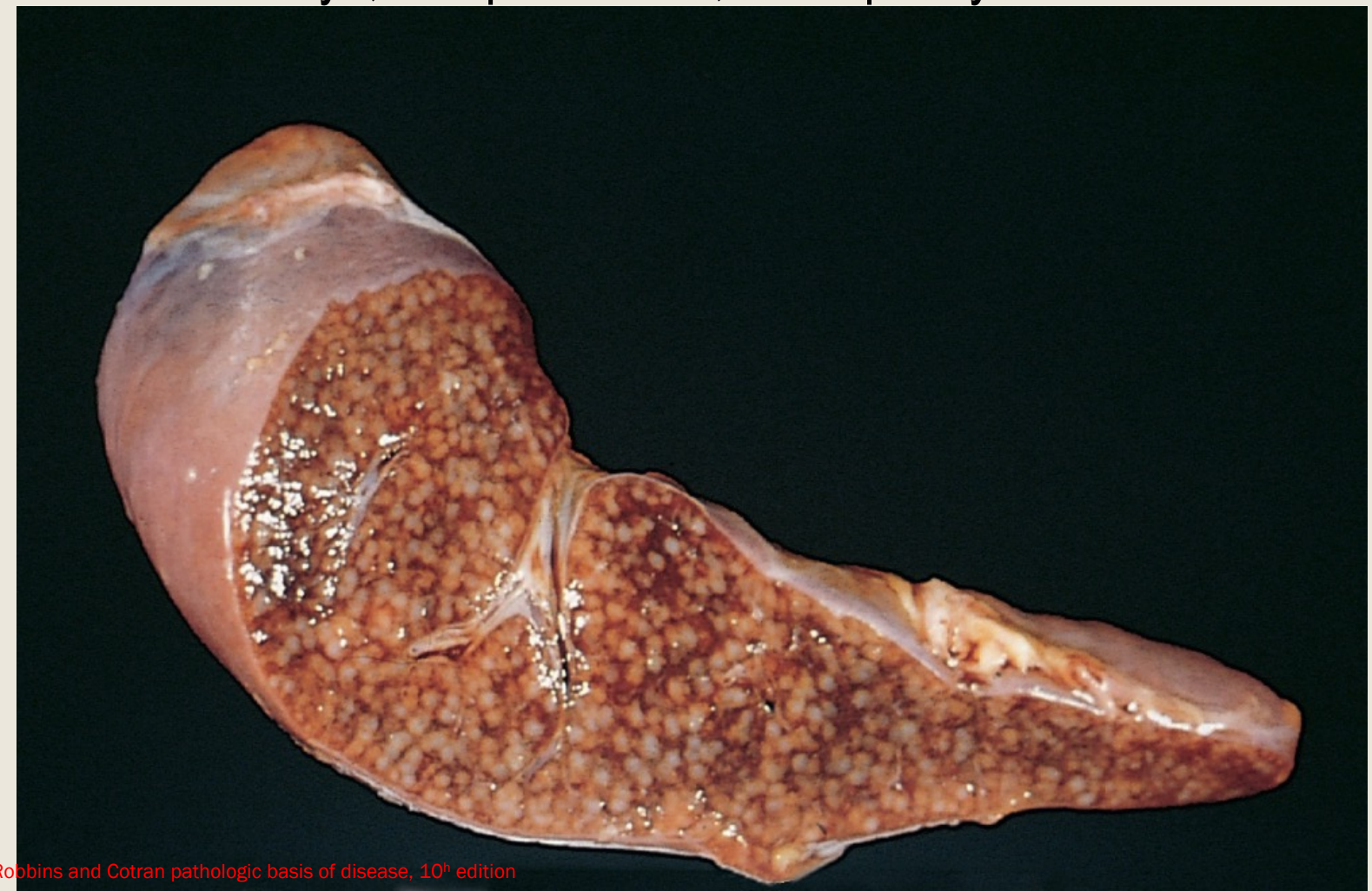
- **Miliary pulmonary disease :**
  - when organisms reach the bloodstream through lymphatic vessels and then recirculate to the lung via the pulmonary arteries.
  - small (2-mm), yellow-white consolidation scattered through the lung parenchyma
  - the word miliary is derived from the resemblance of these foci to millet seeds.
  - With progressive pulmonary tuberculosis:
    - pleural cavity is involved →**pleural effusions or tuberculous empyema**
    - **Endobronchial, endotracheal,** and **laryngeal tuberculosis**

- **Systemic miliary tuberculosis :**
  - when the organisms disseminate hematogenously throughout the body.
  - It is most prominent in the liver, bone marrow, spleen, adrenal glands, meninges, kidneys, fallopian tubes, and epididymis



Spleen: numerous gray-white granulomas

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- **Isolated-organ tuberculosis:**
  - any organs or tissues seeded hematogenously
  - can be the presenting manifestation of tuberculosis.
  - meninges (tuberculous meningitis), kidneys (renal tuberculosis), adrenal glands, bones (osteomyelitis), and fallopian tubes (salpingitis), vertebrae (**Pott disease).**

- **Lymphadenitis :**
  - **the most frequent form of extrapulmonary tuberculosis**
  - cervical region

Clinical Features

- **Asymptomatic,** especially in Localized secondary tuberculosis

- Insidious onset, with gradual development of both systemic and localizing symptoms and signs.

- **Systemic manifestations**:
  - probably related to the release of cytokines by activated macrophages (TNF and IL-1),
  - appear early in the disease course
  - include malaise, anorexia, weight loss, and fever.
  - Fever: low grade and remittent +/- night sweats.

- **Pulmonary**:
  - increasing amounts of sputum, at first mucoid and later purulent.
  - When cavitation is present, the sputum contains tubercle bacilli.
  - Hemoptysis (50%).
  - Pleuritic pain: from extension of the infection to the pleural surfaces

- **Extrapulmonary manifestations depend on the organ or system involved**

Diagnosis:

- based on the **history , physical and radiographic findings** of consolidation or cavitation in the apices of the lungs.

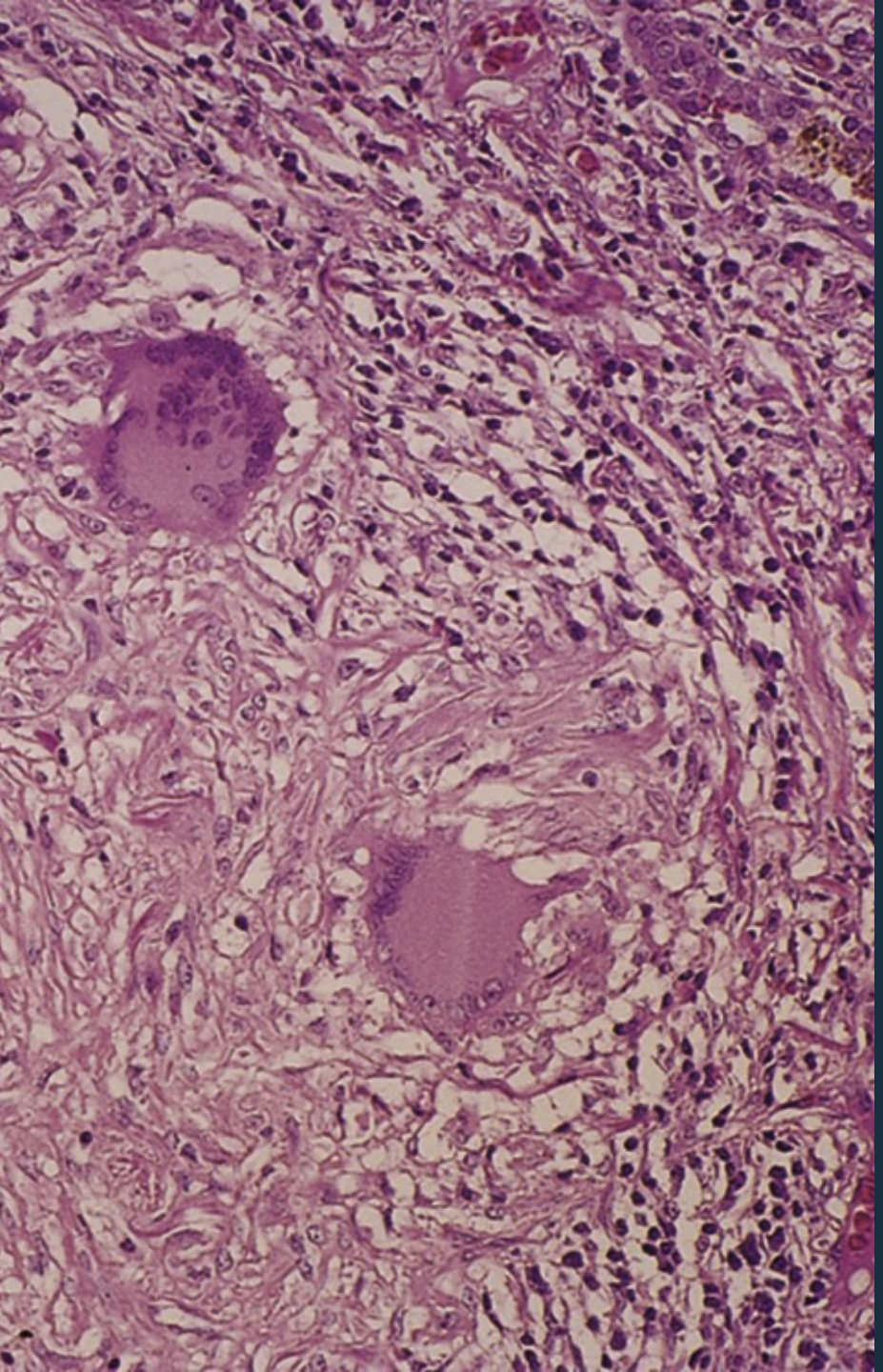
- Ultimately**, tubercle bacilli must be identified**:
  - The most common methodology for diagnosis of tuberculosis remains demonstration of acid-fast organisms in sputum by staining or by use of **fluorescent auramine rhodamine.**
  - **Conventional cultures (10 weeks)**
  - **liquid media–based radiometric assays (2 weeks).**
  - **PCR amplification** on liquid media with growth, as well as on tissue sections, to identify the mycobacterium.

culture remains the standard diagnostic modality

Prognosis :

- determined by :
  - the extent of the infection (localized versus widespread)
  - the immune status of the host
  - the antibiotic sensitivity of the organism

https://baytowncrimestoppers.com/baytowns-most-wanted/unsolved-crimes/



45-year-old lady has a routine health maintenance examination. On physical examination, there are no remarkable findings. Her body mass index is 22. She does not smoke. A tuberculin skin test is positive. A chest radiograph shows a solitary, 3-cm left upper lobe mass without calcifications. The mass is removed at thoracotomy by wedge resection. The microscopic appearance of this lesion is shown in the figure. Which of the following is the most likely diagnosis?

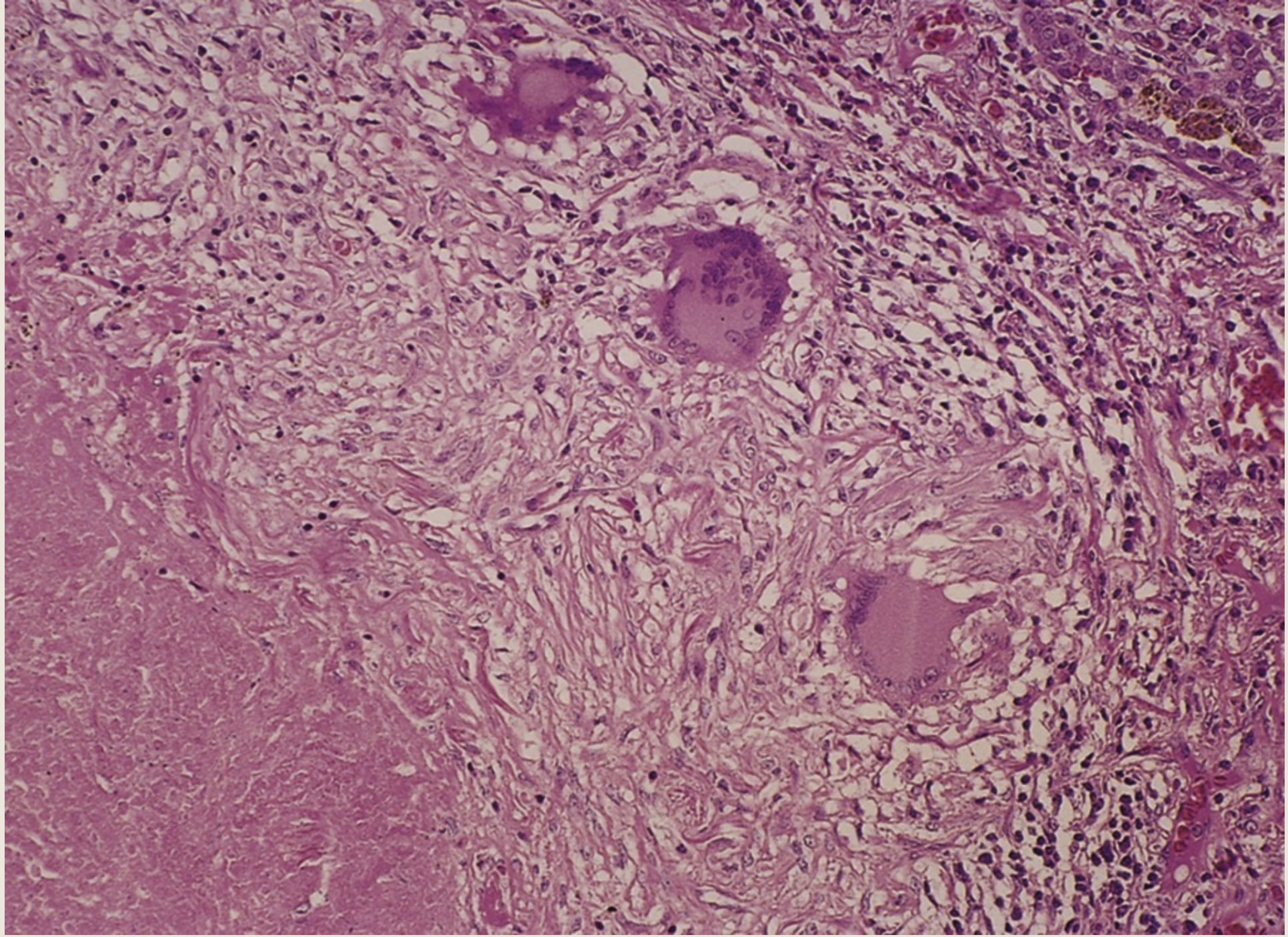
A Mycobacterium tuberculosis infection

B Necrotizing granulomatous vasculitis

C Poorly differentiated adenocarcinoma

D Staphylococcus aureus abscess

E Thromboembolism with infarction



THANK YOU!