



# Pathology RS

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# TUBERCULOSIS

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# Tuberculosis

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

# Risk Factors

TB flourishes under conditions of :

**Poverty, crowding, and chronic debilitating illness.**

The following groups are the most common groups affected by TB in the USA

- 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

In areas of the world where HIV infection is prevalent, HIV infection is the dominant risk factor for the development of TB

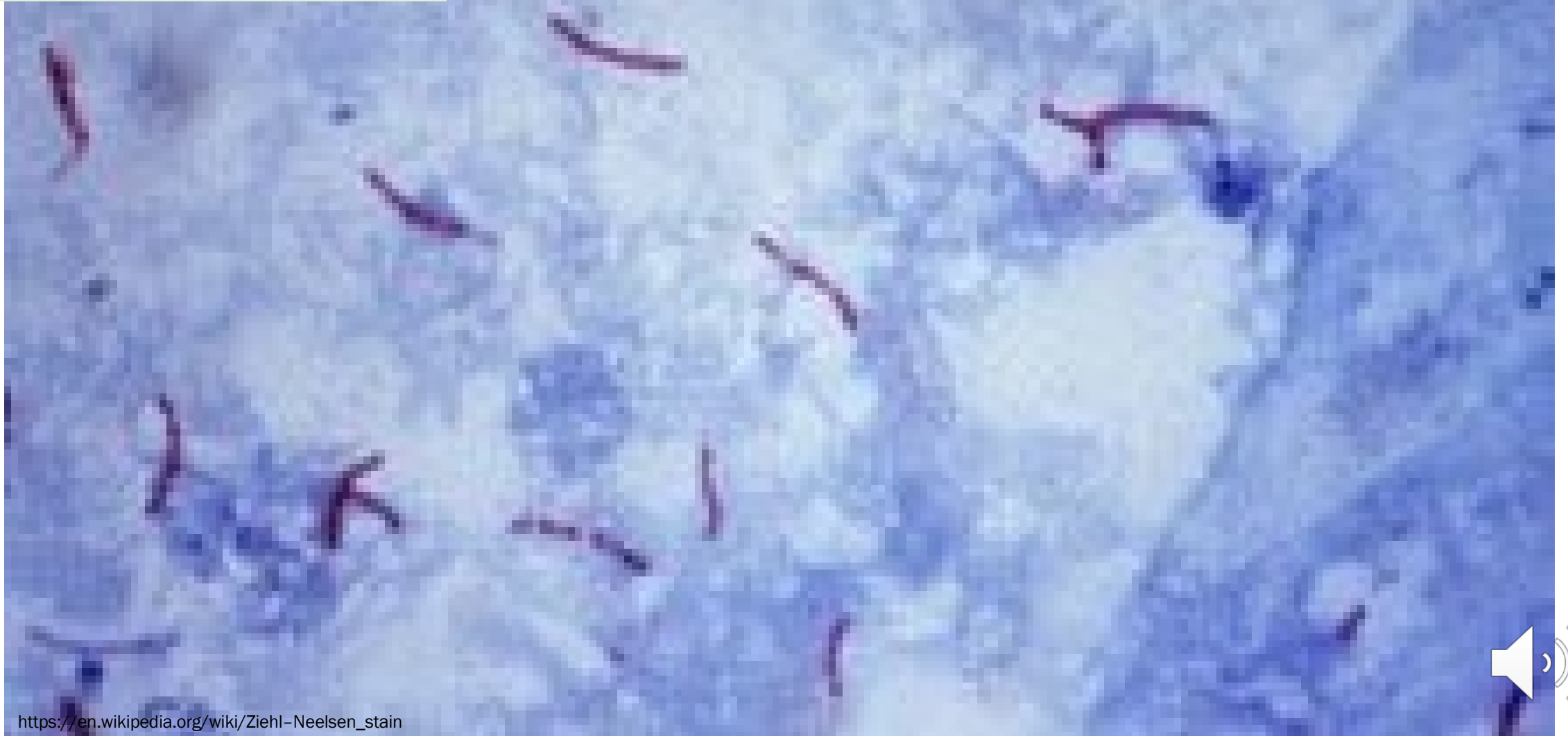


# Etiology:

## ■ 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).

This figure shows a Ziehl-Neelsen stained tissue section , as you can appreciate there are cylindrical rods that are stained with a purple color, those are the bacilli of mycobacterium tuberculosis





# **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**

This type of tuberculosis is rare except in countries with tuberculosis of dairy cows and sales of unpasteurized milk

- 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

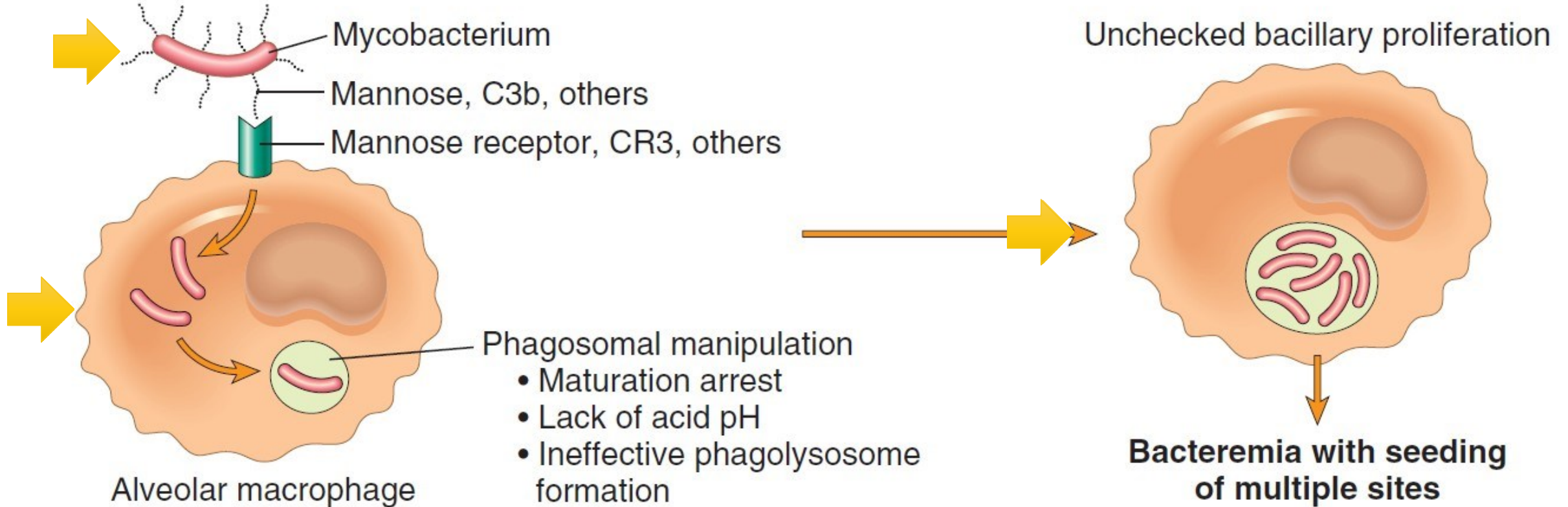


# Pathogenesis

- 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

## A INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY

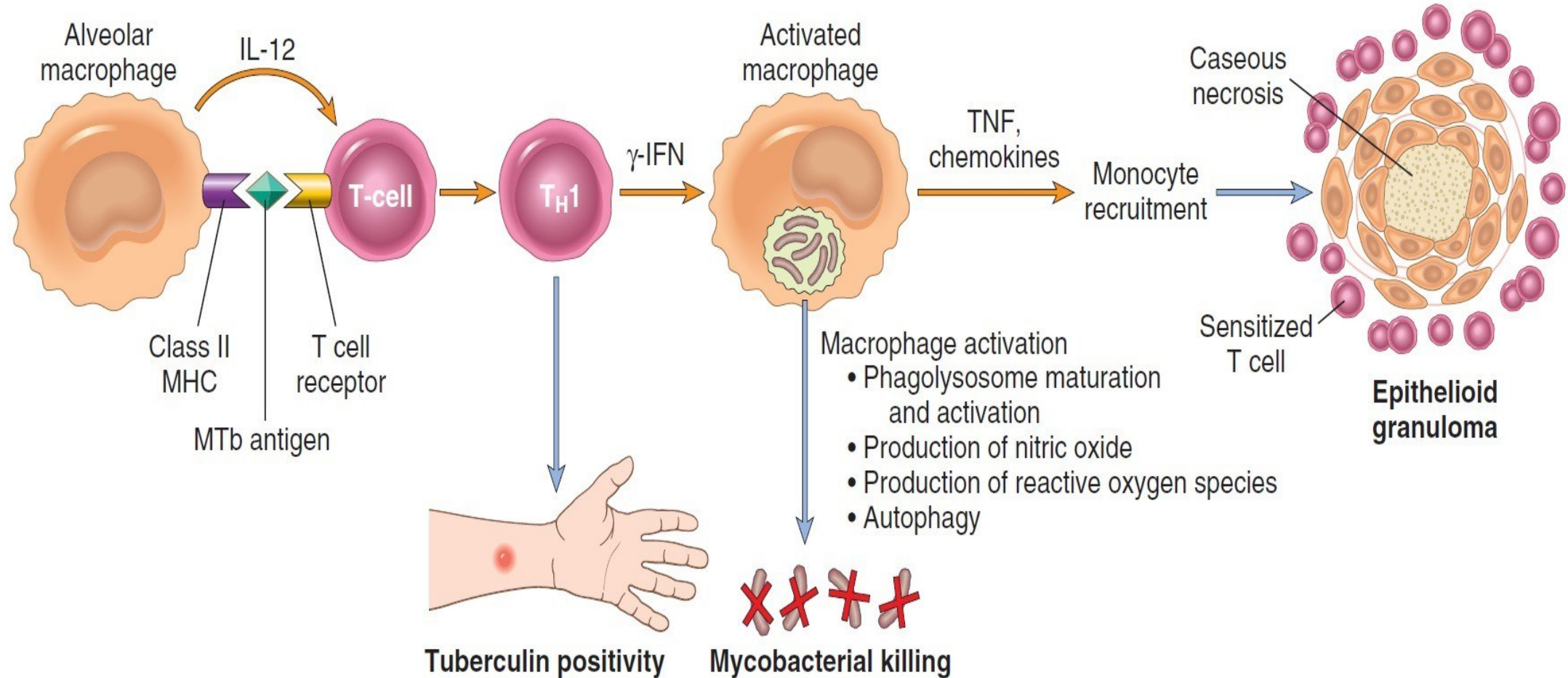


# Infection before activation of cell mediated immunity:

- 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

## B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY



# 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) à type 1 T helper lymphocytes response → type 1 T helper cells are generated and secret IFN- $\gamma$ .
- **IFN- $\gamma$**  is the critical mediator that enables **macrophages to contain the M. tuberculosis infection and to become bactericidal.**

## ■ IFN- $\gamma$ :

- stimulates maturation of the phagolysosome in infected macrophages
- stimulates expression of inducible nitric oxide synthase  $\rightarrow$  nitric oxide (NO)  $\rightarrow$  reactive nitrogen intermediates  $\rightarrow$  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- $\gamma$   $\rightarrow$  activates Macrophages  $\rightarrow$  differentiate into the “epithelioid histiocytes”  $\rightarrow$  aggregate to form granulomas (giant cells).
- Activated macrophages also secrete TNF and chemokines, which promote recruitment of more monocytes.

### q **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- $\gamma$ , TNF, or nitric oxide production)
  - poorly formed granulomas
  - absence of resistance
  - disease progression.



Individuals with inherited mutations in any component of type 1 helper pathway are extremely susceptible to infections with mycobacteria

- 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)

The test is positive if it induces a visible and palpable induration at least 5 millimeters in diameter that usually peaks within 48 to 72 hrs, so negative results mean that you most likely haven't been infected with bacteria that causes TB

- 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

In most individuals it's seen as self-limited asymptomatic focus of pulmonary infection

- Uncommonly may result in the development of fever and pleural effusions.

Because it's asymptomatic the only evidence of infection is a tiny telltale fibrocalcific nodule at the site of infection

- Viable organisms may remain dormant in a tiny, telltale fibrocalcific nodule at the site of the infection for several years (**infection, not active disease**)

Those individuals are infected but don't have active disease, therefore cannot transmit organisms to others, but :

- 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.



A grey-white parenchymal focus under the pleura in the lower part of the upper lobe

# MORPHOLOGY, grossly:

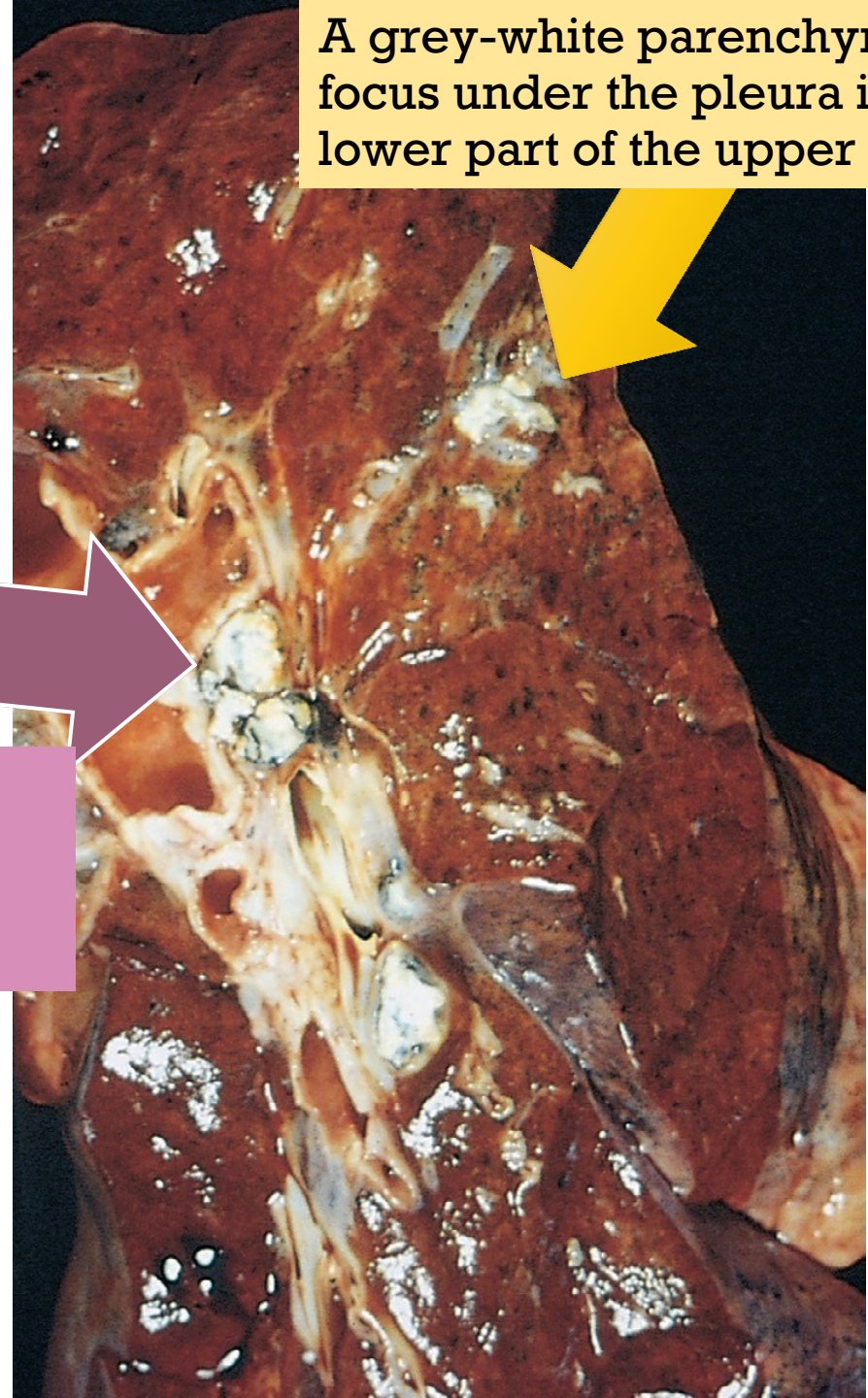
- Tubercle bacilli, free or within phagocytes, travel via the lymphatic vessels to regional lymph nodes.

Which also often caseates

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

Hilar lymph node that shows caseation

A grey-white parenchymal focus under the pleura in the lower part of the upper lobe





- 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:

Histologically, sites of infection are involved by a characteristic inflammatory reaction marked by the presence of caseating and non- caseating granulomas which consists of epithelioid histiocytes and multi nucleated giant cells

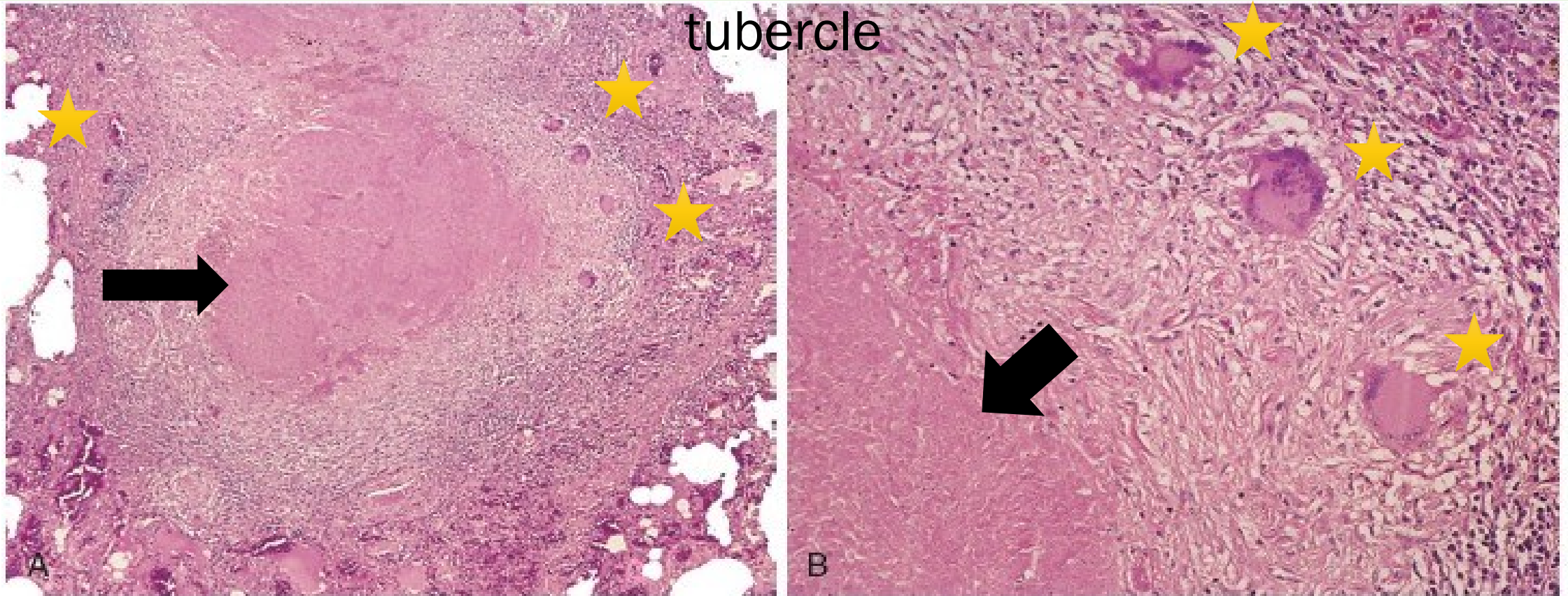
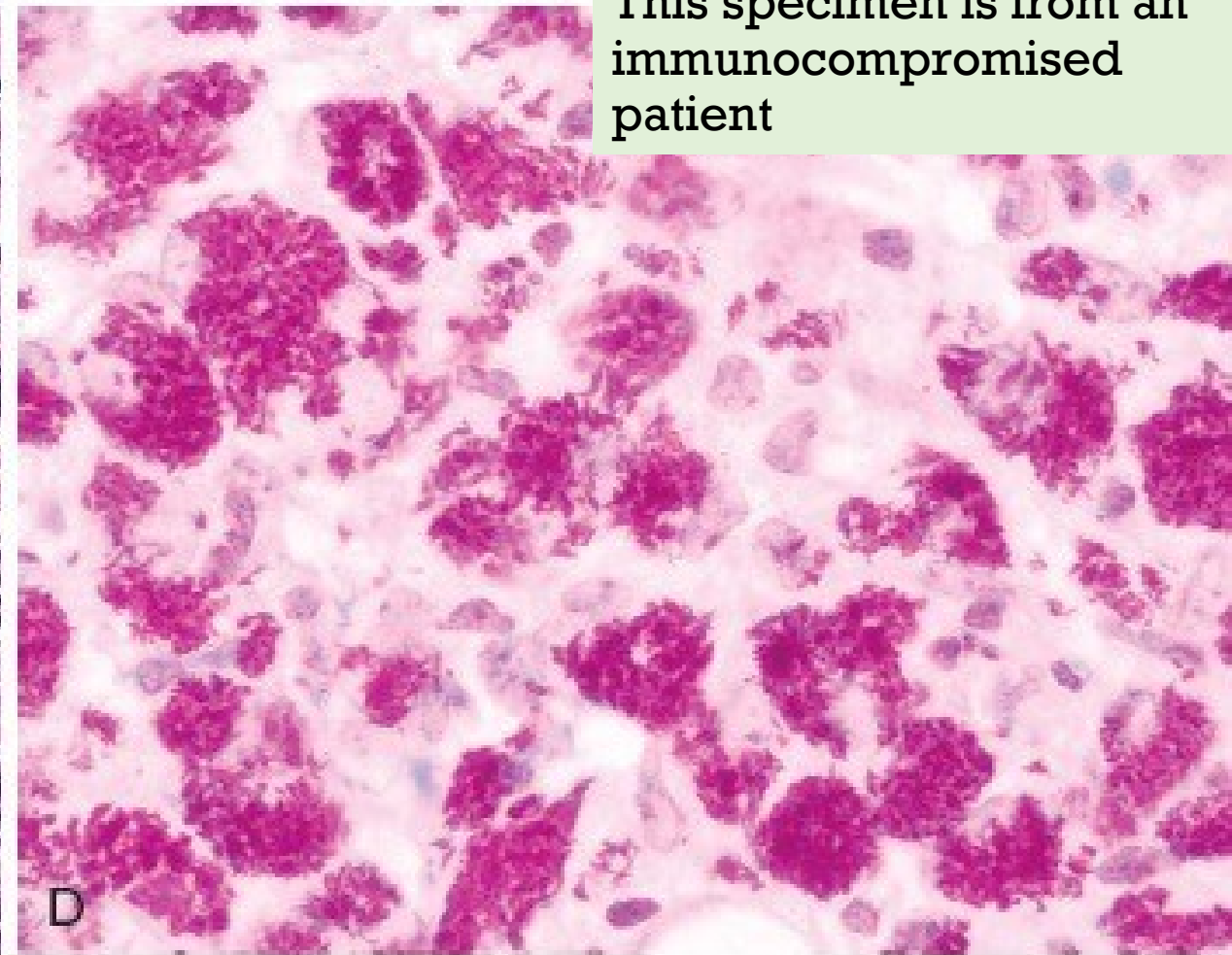
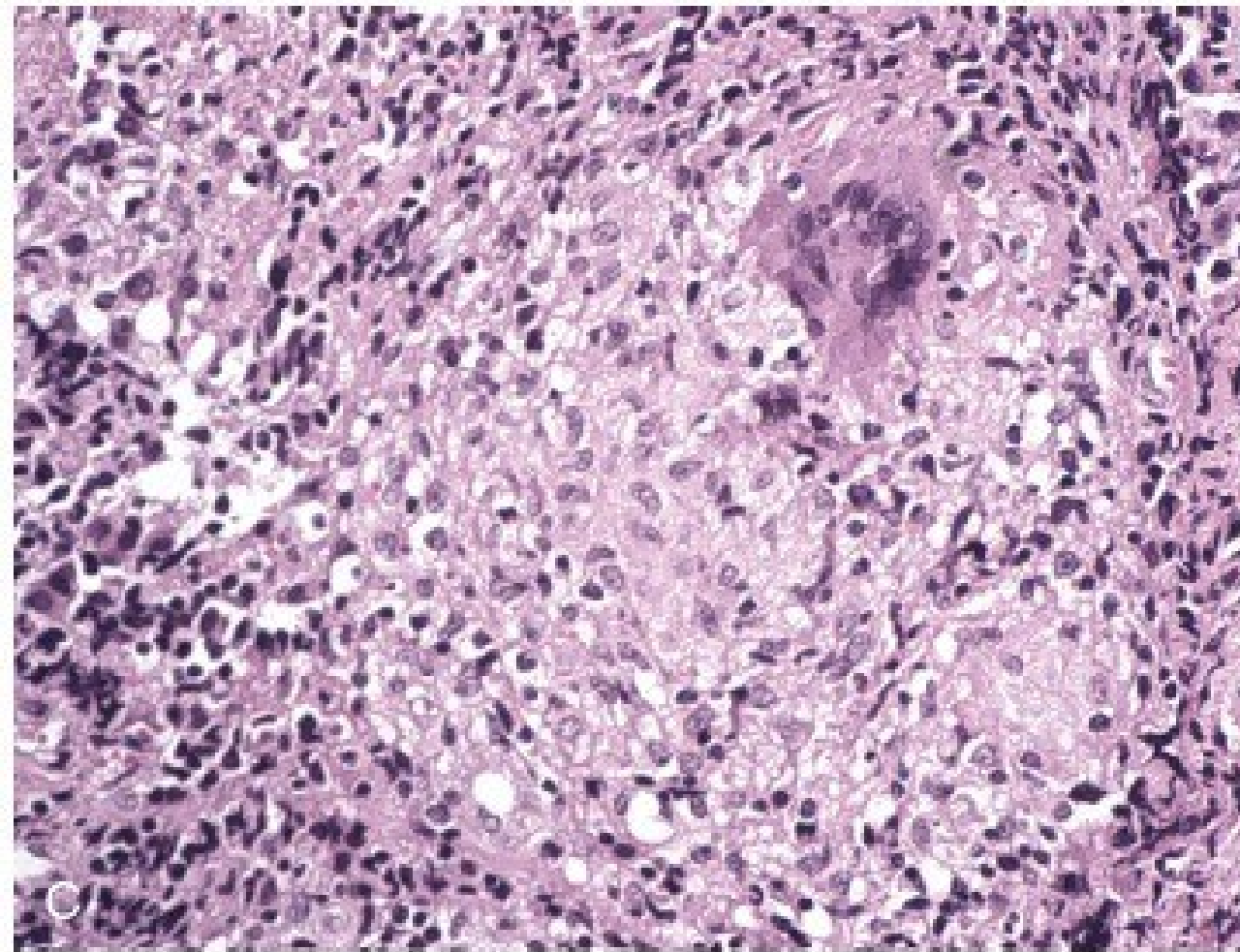


Figure A : shows the characteristic tubercle at a low magnification while figure B shows a higher magnification of the same focus , the black arrows points to central granular caseation surrounded by epithelioid & multinucleated giant cells highlighted by the yellow stars , this is the usual response in individuals who develop cell mediated immunity to the organism

This specimen is from an immunocompromised patient



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

# 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:**

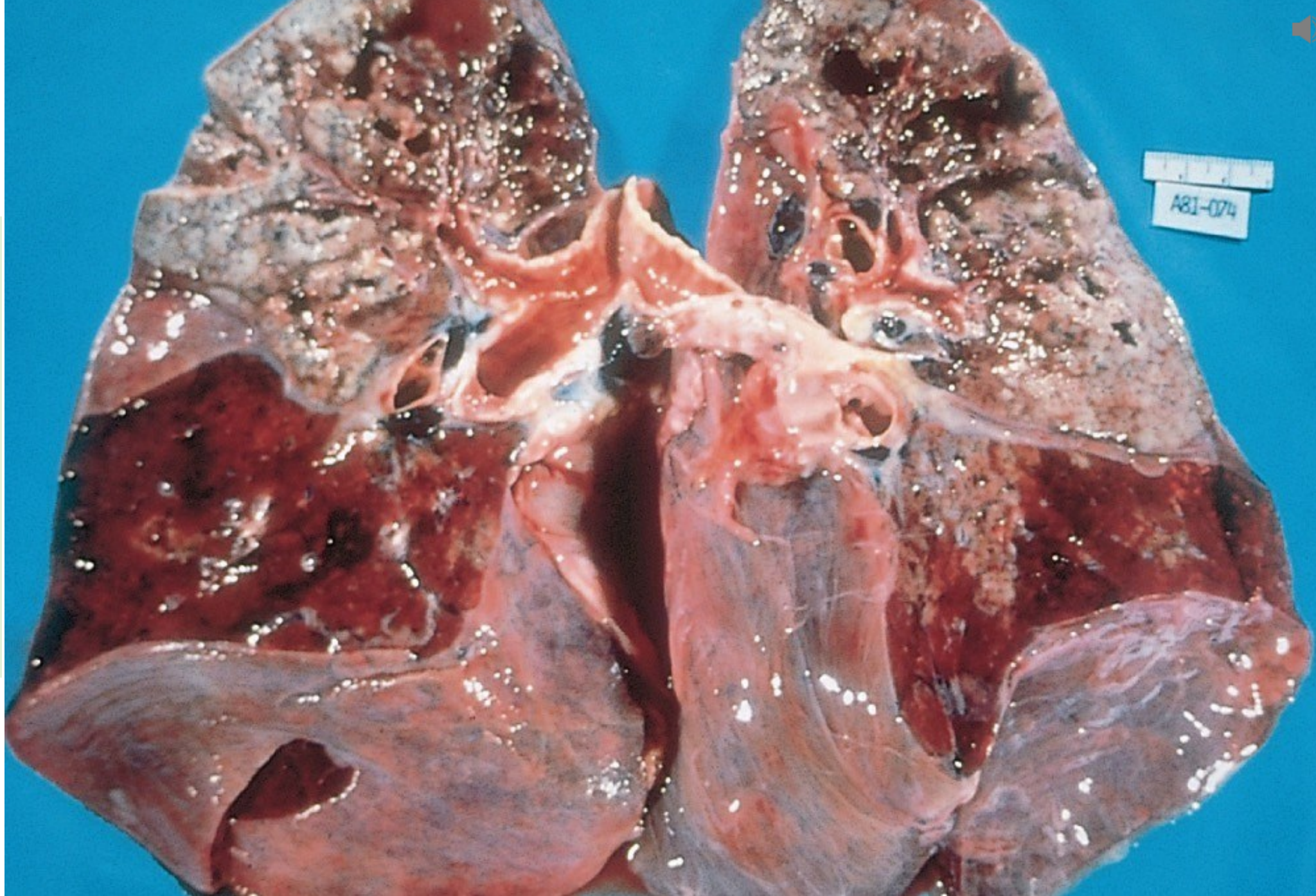
- **active lesions:** coalescent tubercles with central caseation.
  
- **tubercle bacilli:**
  - can be demonstrated by acid fast stain in early exudative and caseous phases of granuloma formation
  - Impossible to find them in the late fibrocalcific stages.
  
- **Localized, apical, secondary pulmonary 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.

This figure shows involvement of upper parts of both lungs by grey-white areas of caseation and multiple areas of softening & cavitation in a patient with secondary pulmonary TB





## ■ 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** Or obliterative fibrous pleuritis
  - **Endobronchial, endotracheal, and laryngeal tuberculosis**

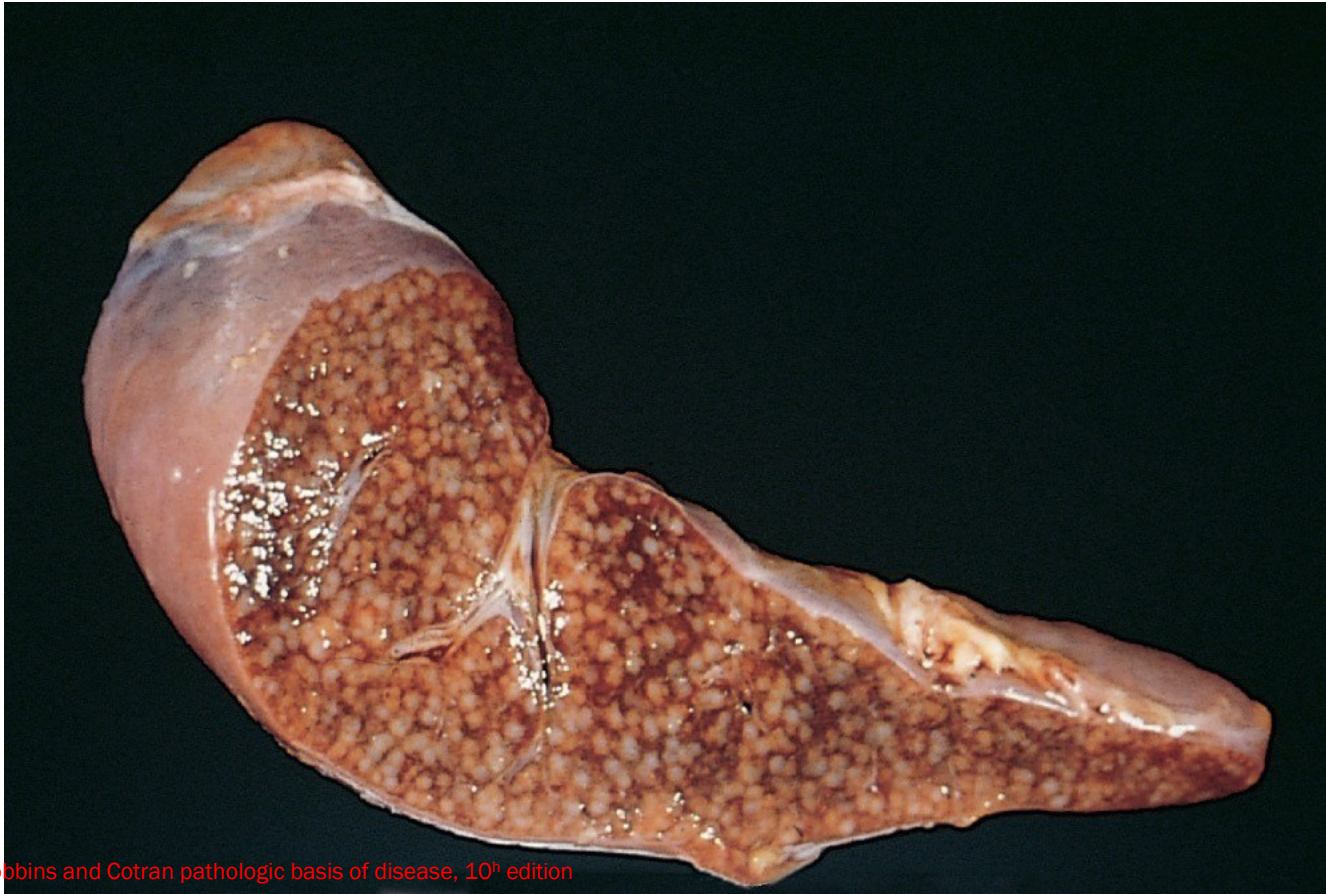
May develop when the infected material is spread either through the lymphatic channels or from the expectorated infectious material

The mucosal lining may show a minute granulomatous lesions that can be seen only sometimes under the microscope



## ■ **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



## ■ 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

Lymphadenopathy tends to be unifocal and most patients don't have a concurrent extranodal disease

HIV positive patients almost always have multifocal disease, systemic symptoms and either pulmonary or other organs involvement by active tuberculosis



# 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**

If it involves the Fallopian tube >> may present as infertility  
Involvement of the meninges >> may present with headache and neurologic defects  
Pott disease >> presents with back pain and paraplegia

# 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

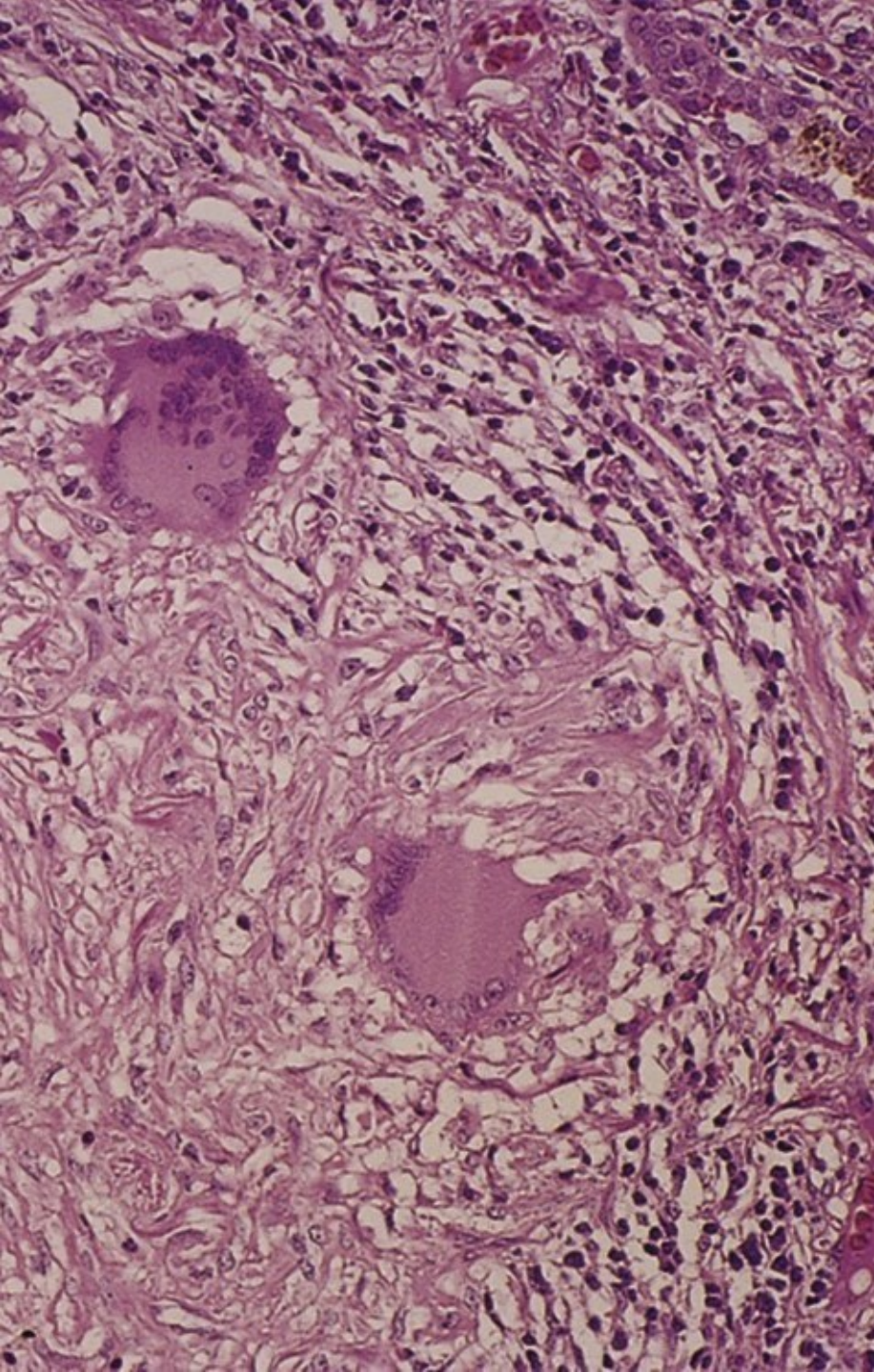
Because it can identify the occasional pcr negative cases & allow testing for drug susceptibility



# Prognosis :

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

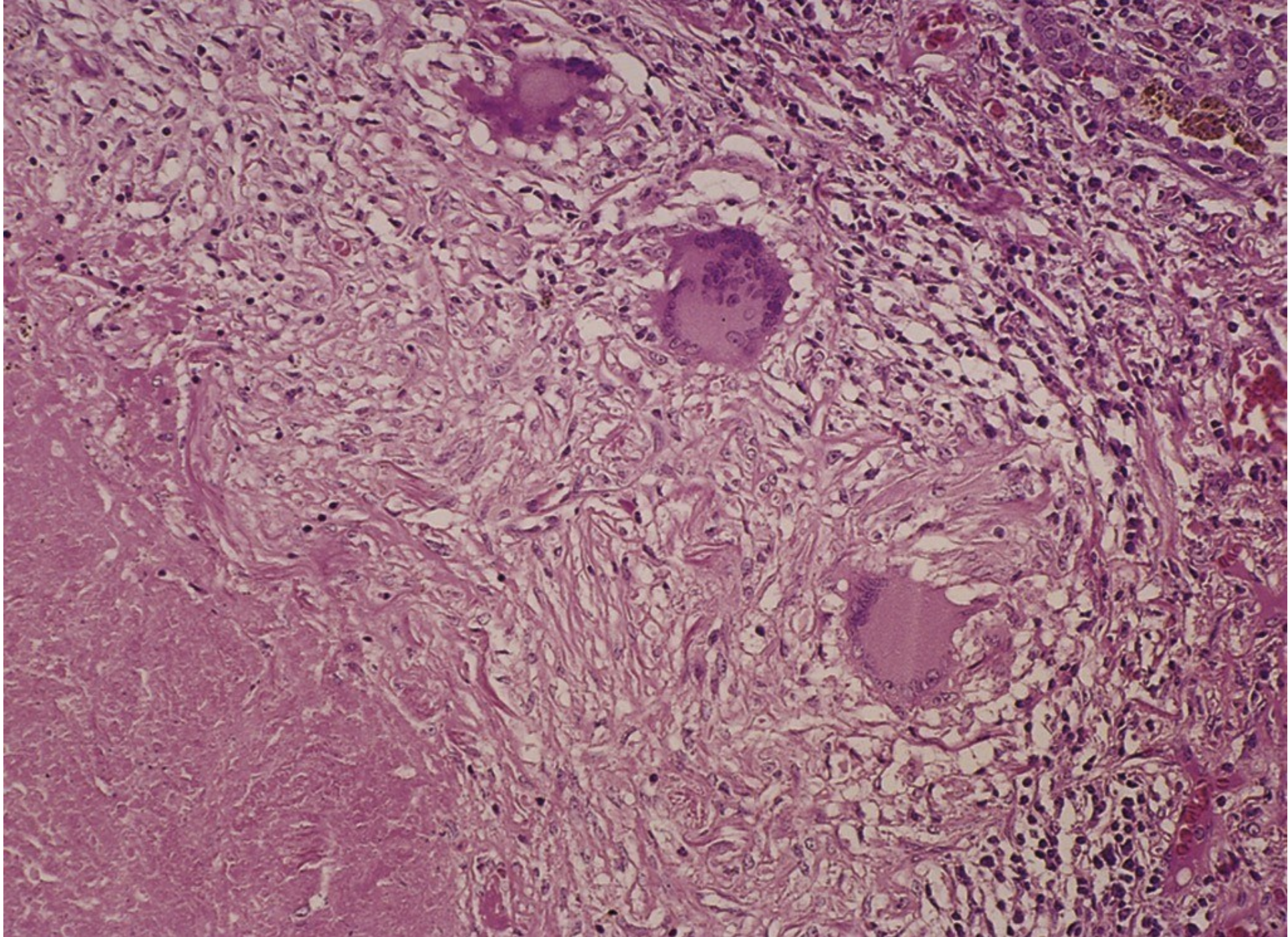


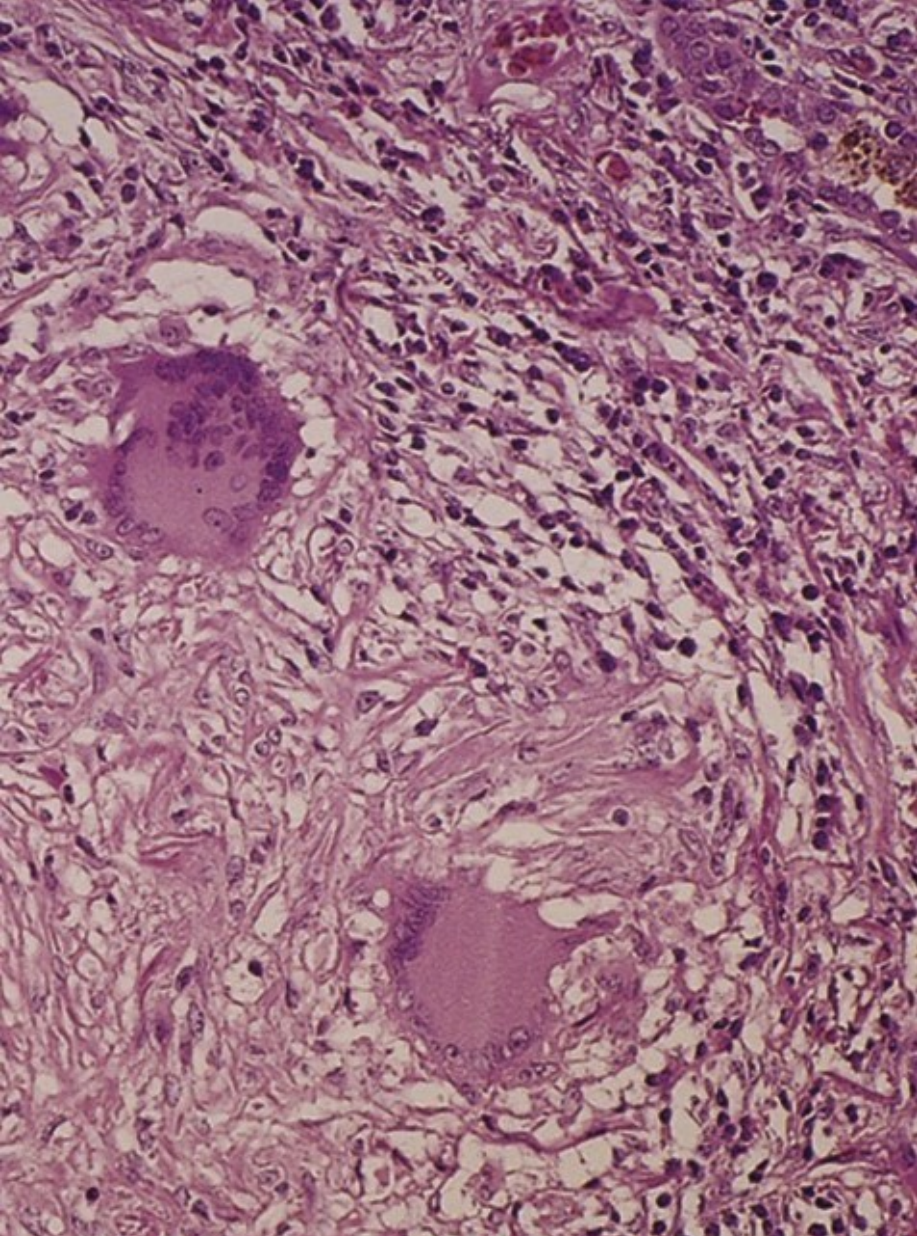


45-year-old lady has a routine health maintenance examination. On physical examination, there are no remarkable findings. Her body mass index is 22. She does not smoke. A tuberculin skin test is positive. A chest radiograph shows a solitary, 3-cm left upper lobe mass without calcifications. The mass 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







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**A pink amorphous tissue at the lower left representing caseous necrosis, The rim of the granuloma has epithelioid cells & langhans giant cells so we have caseating granulomatous inflammation > mycobacterium tuberculosis infection**



**THANK YOU!**