

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.

Epidemiology

- ❑ The most common cause of death resulting from a single infectious agent.
- ❑ 1.7 billion individuals are infected worldwide.
- ❑ 1.5 million deaths per year.
- ❑ The incidence of tuberculosis in U.S.-born individuals has declined since 1992.

Risk Factors

Poverty, crowding, and chronic debilitating illness.

- older adults
- the urban poor
- patients with 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 (particularly silicosis)
- chronic renal failure
- Malnutrition
- Alcoholism
- Immunosuppression
- HIV

Infection vs. disease

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

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.

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.

- False-negative reactions or skin test anergy:
 - certain viral infections
 - Sarcoidosis
 - Malnutrition
 - Hodgkin lymphoma
 - immunosuppression
 - overwhelming active tuberculous disease.

- False-positive reactions may result from infection by atypical mycobacteria.

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).

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

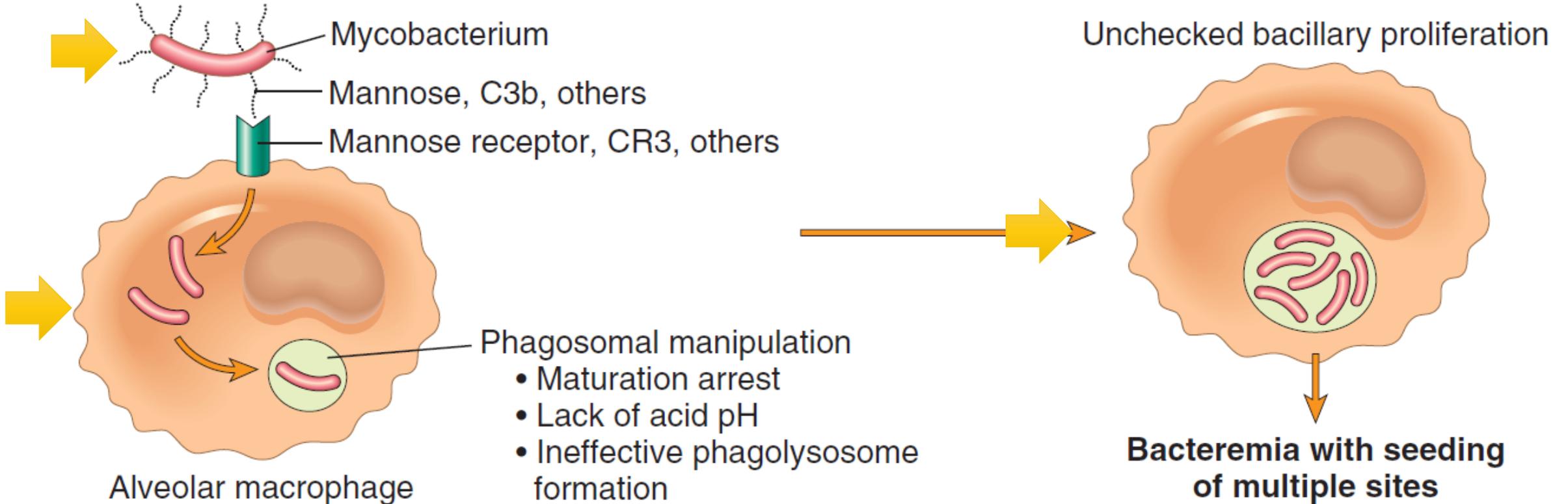
- Less virulent than *M. tuberculosis*
- Rarely cause disease in immunocompetent individuals.
- Cause disease in 10% to 30% of patients with AIDS.

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
 - Acquisition of immunity to the organism.

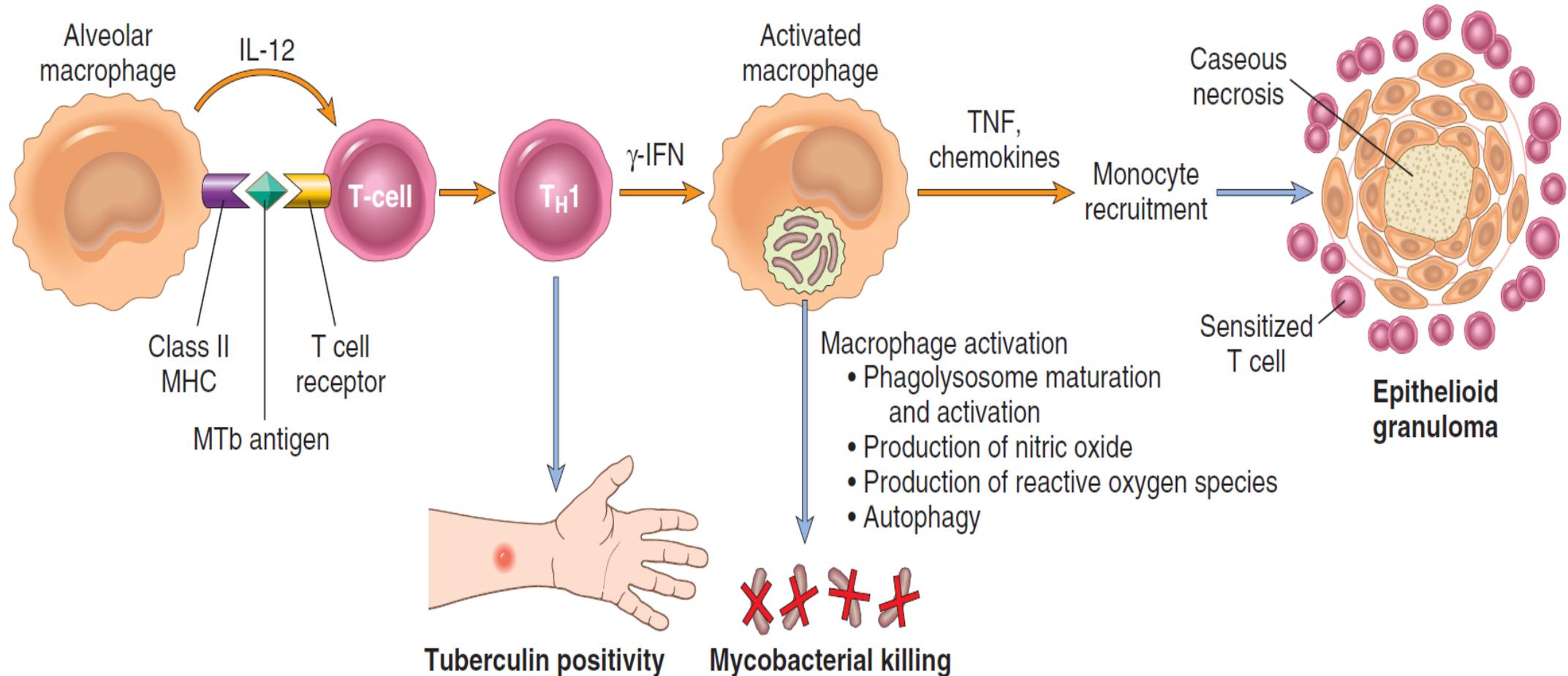
Natural history of primary pulmonary tuberculosis

A INFECTION BEFORE ACTIVATION OF CELL MEDIATED IMMUNITY



Natural history of primary pulmonary tuberculosis

B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY

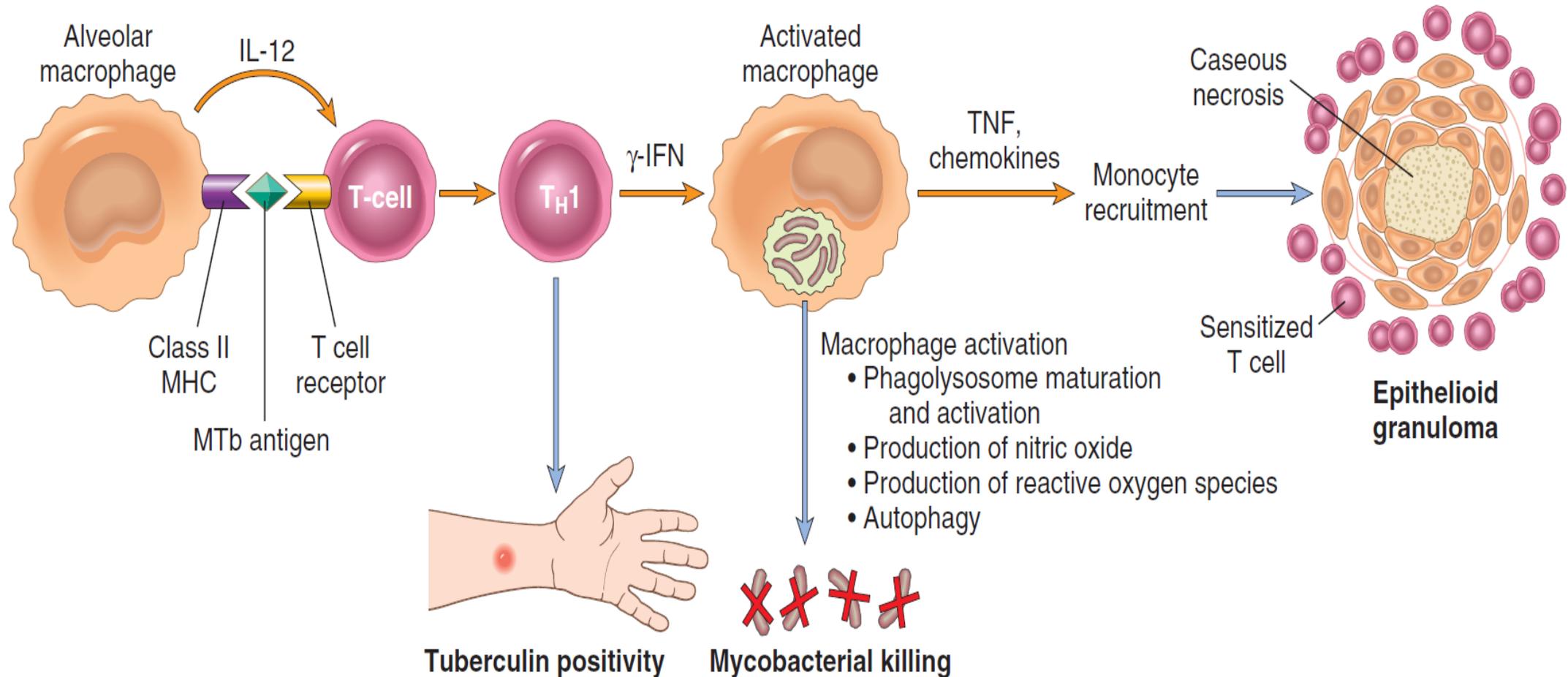


Activated macrophages

- **TNF**
 - Monocytes recruitment , activation and differentiation into the “epithelioid histiocytes” that characterize the granulomatous response
- **Inducible nitric oxide synthase (iNOS)**
 - raises nitric oxide (NO) levels, helping to create reactive nitrogen intermediates that are important in killing of mycobacteria
- **anti-microbial peptides (defensins)**
 - toxic to mycobacterial organisms.

Natural history of primary pulmonary tuberculosis

B INITIATION AND CONSEQUENCES OF CELL MEDIATED IMMUNITY



Pathogenesis, 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 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.

Primary Tuberculosis

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

Primary Tuberculosis, presentation:

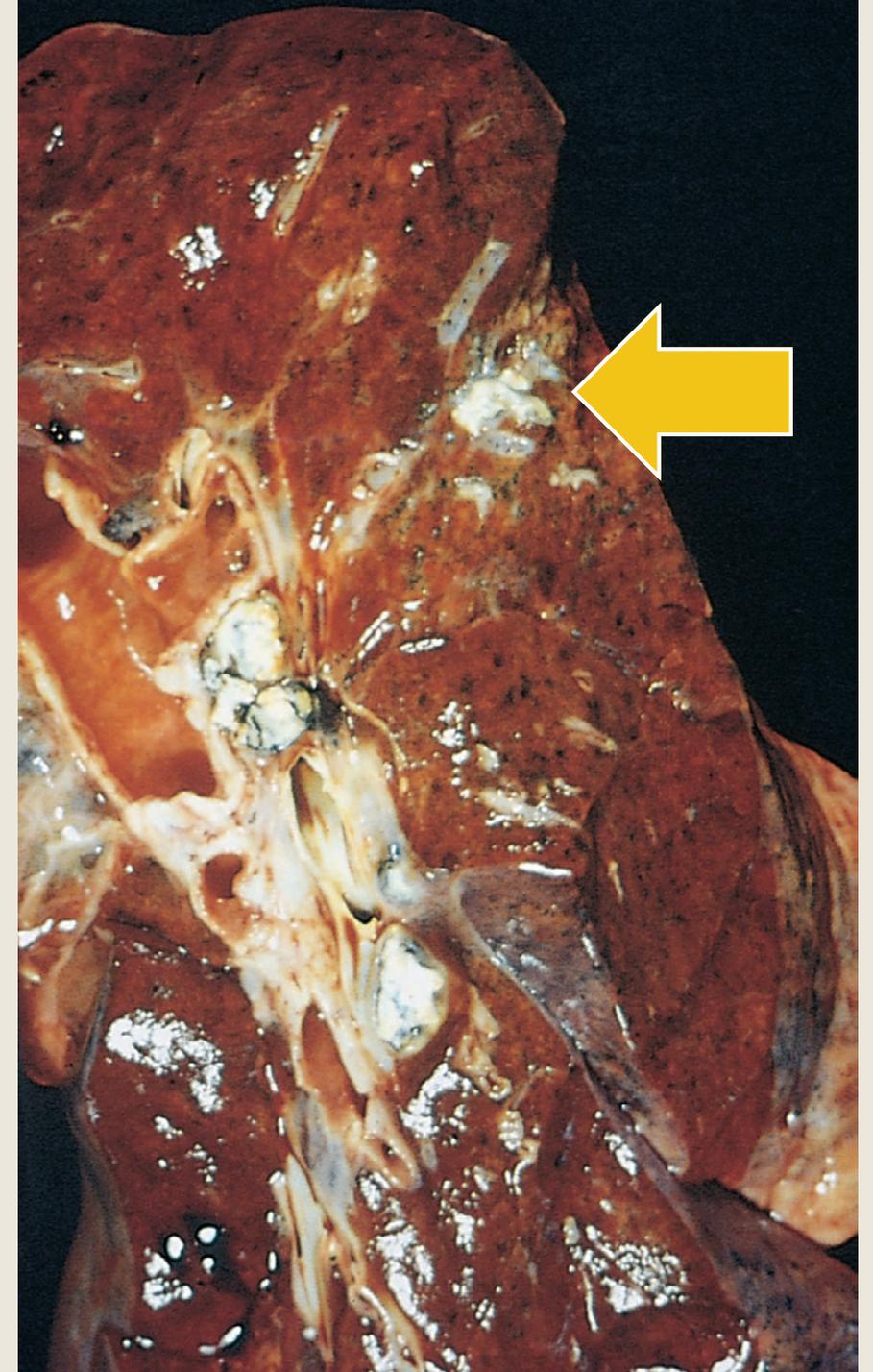
- In otherwise healthy individuals:
 - Mostly the only consequence are the foci of scarring. Which may harbor viable bacilli and serve as a nidus for disease reactivation at a later time if host defenses wane.
- Uncommonly, new infection leads to progressive primary tuberculosis:
 - Affected patients 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.

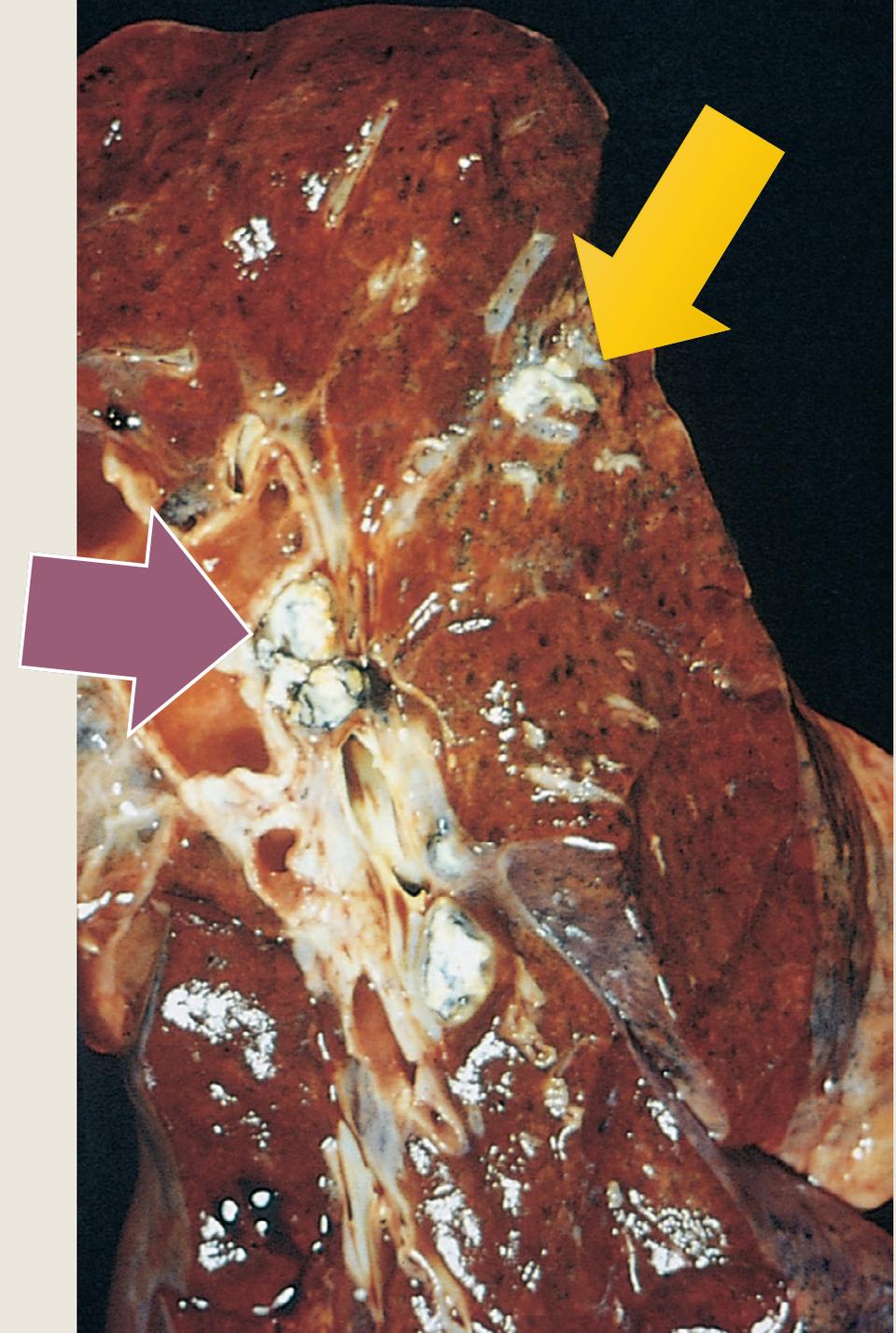
MORPHOLOGY, grossly:

- Ghon focus.
 - ✓ a 1-cm to 1.5-cm area of gray-white inflammatory consolidation emerges during the development of sensitization
 - ✓ caseous necrosis.



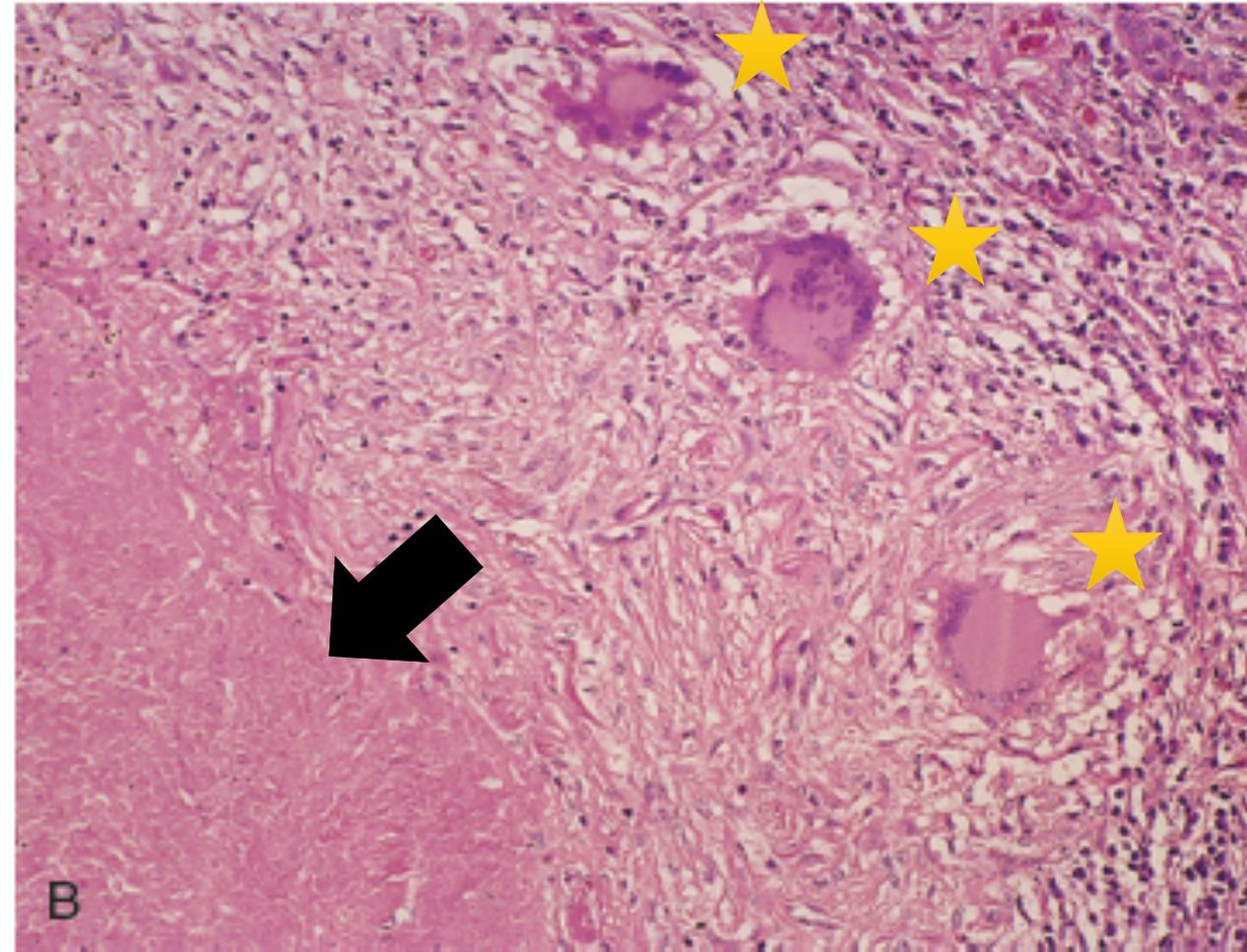
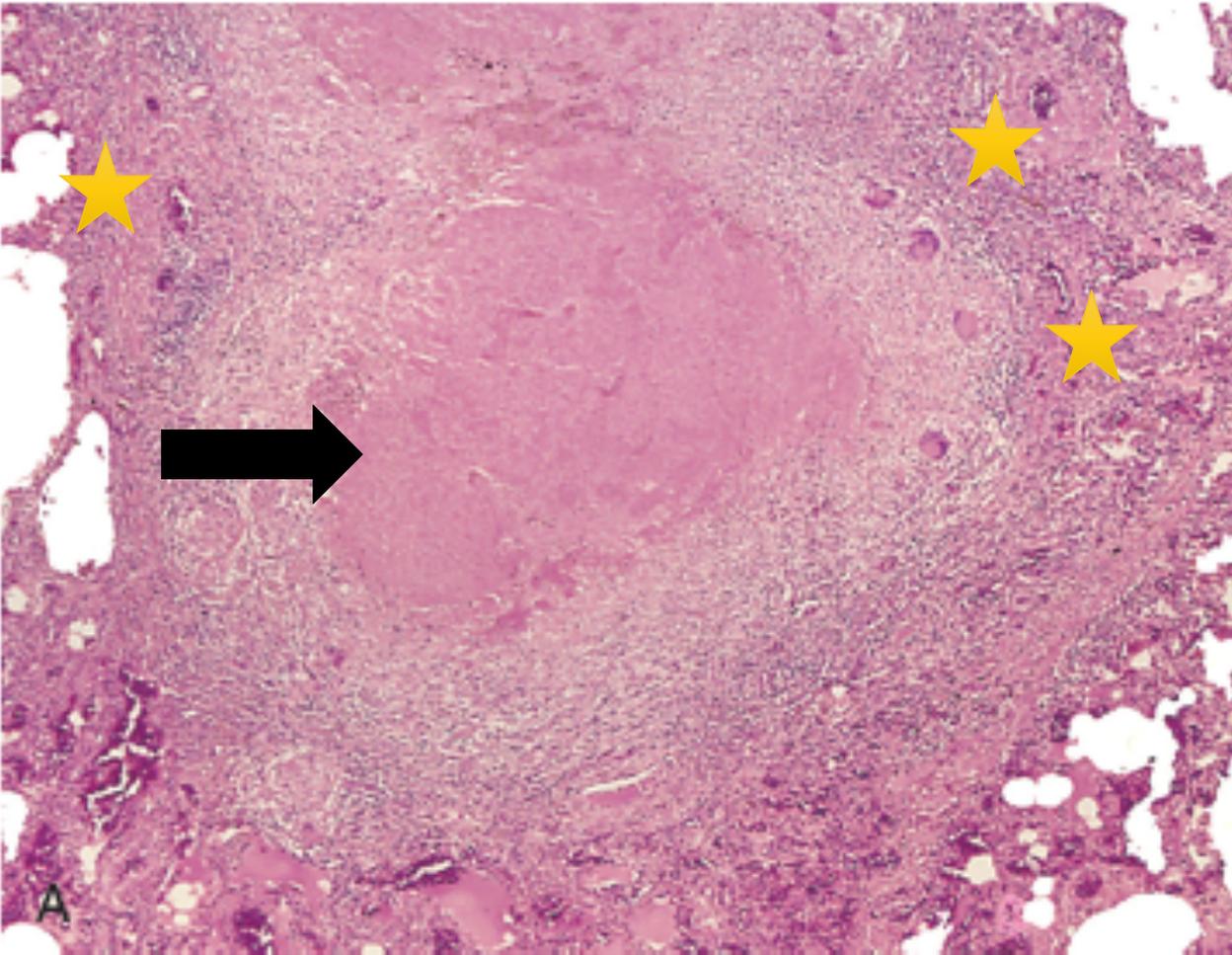
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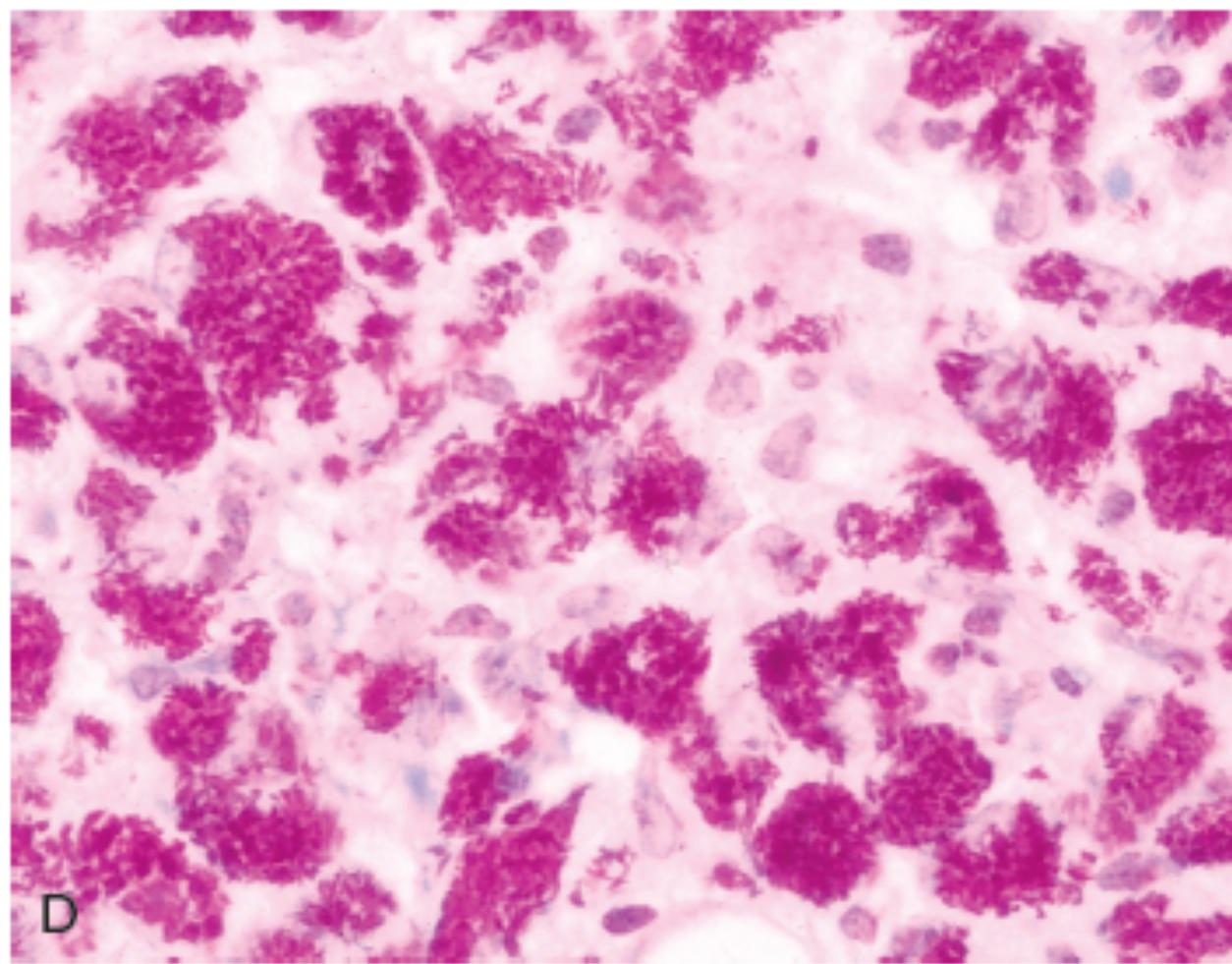
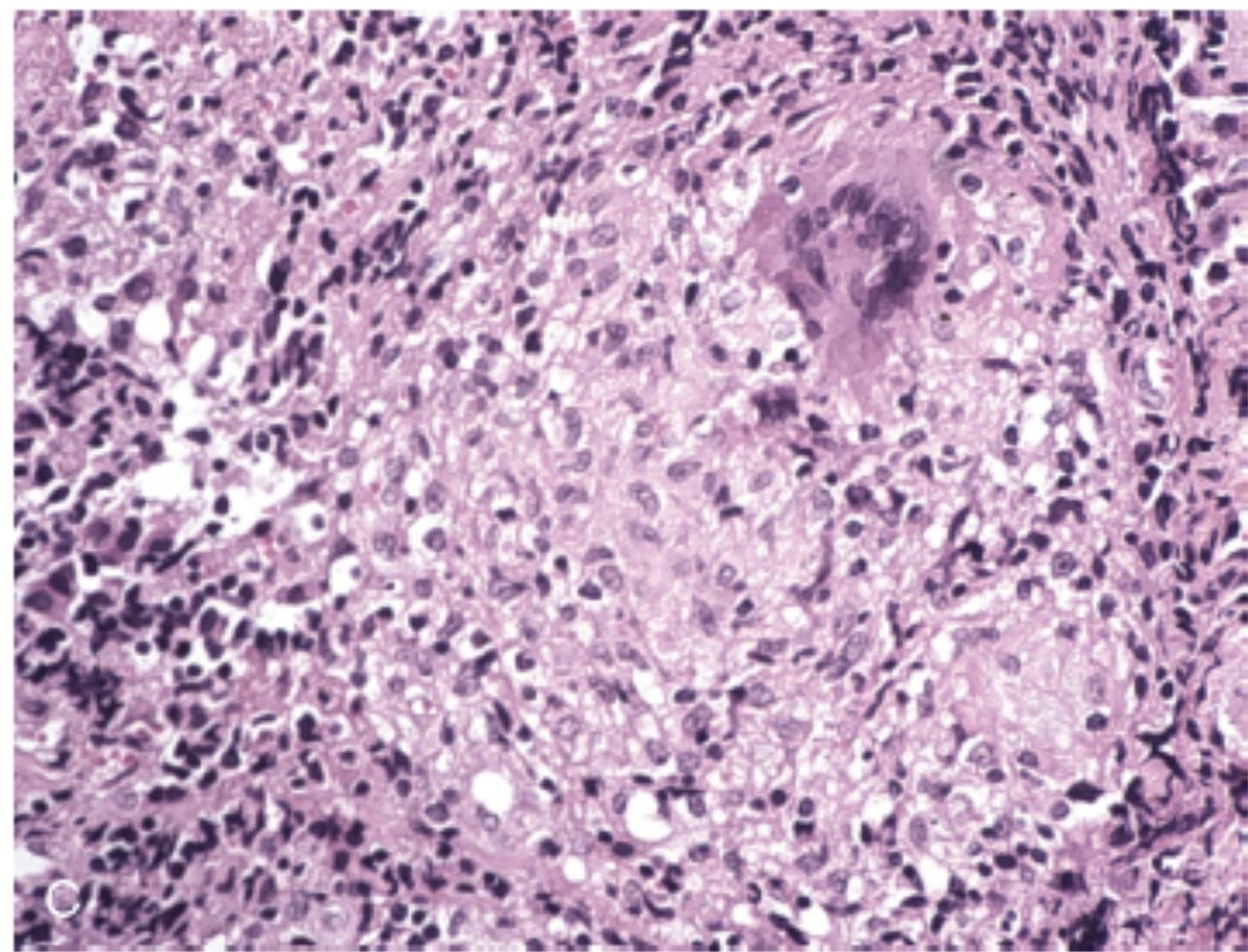
- Tubercle bacilli, free or within phagocytes, travel via the lymphatic vessels to regional lymph nodes.
- **Ghon complex** :This combination of parenchymal and nodal lesions



- 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:





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 excite a marked tissue response that tends to wall off the focus (localization)
 - 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:

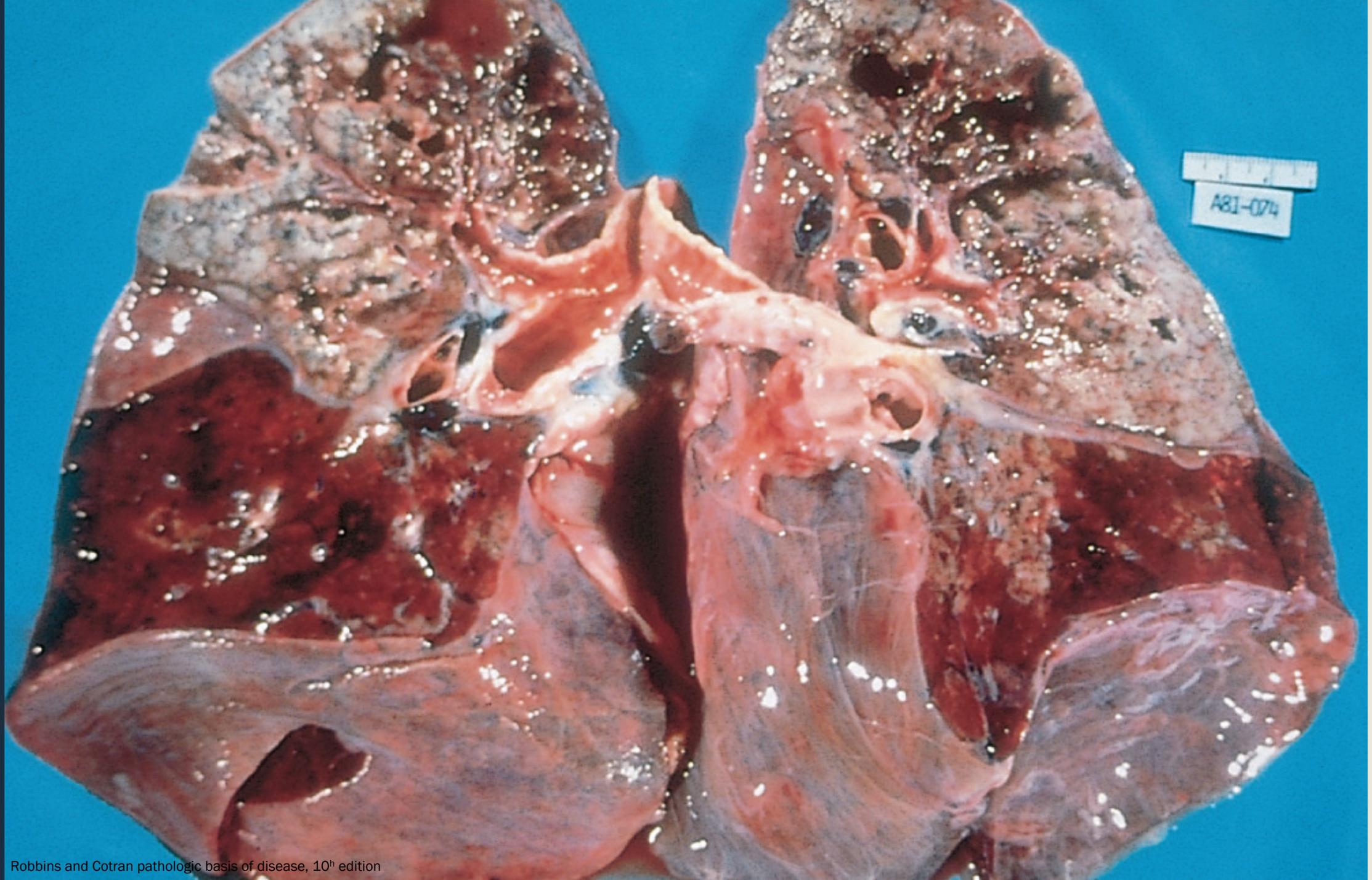
- initial lesion is a small focus of consolidation, <2 cm, within 1-2 cm of the **apical pleura**.
- sharply circumscribed, firm, gray-white to yellow with variable amount of central caseation and peripheral fibrosis

MORPHOLOGY, microscopic:

- **active lesions:** coalescent tubercles with central caseation.
- **tubercle bacilli:**
 - can be demonstrated by appropriate methods in early exudative and caseous phases of granuloma formation
 - Impossible to find them in the late fibrocalcific stages.
- **Localized, apical, secondary pulmonary tuberculosis:**
 - 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, creating a ragged, **irregular cavity lined by caseous material**
- 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.

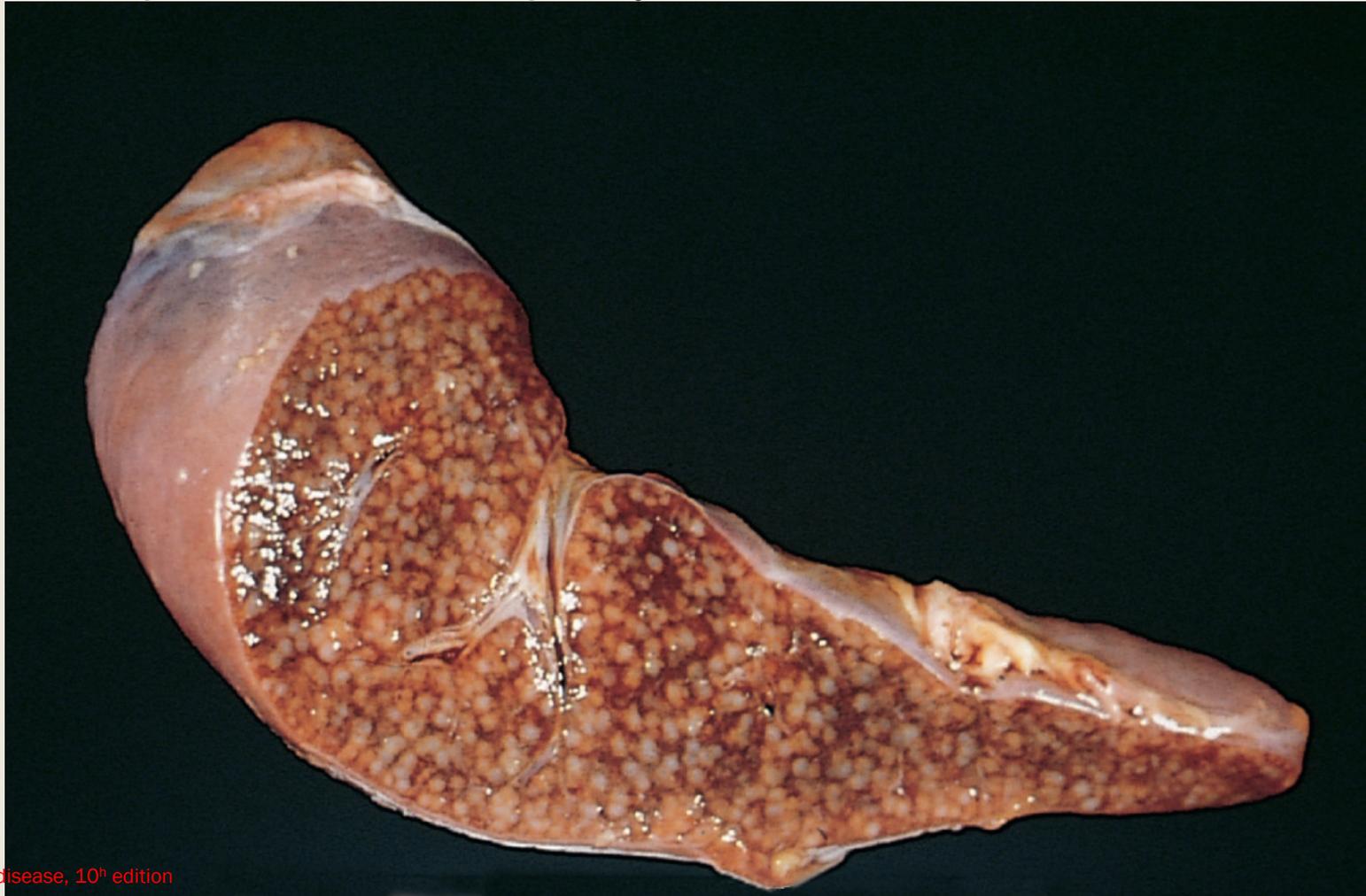


■ Miliary pulmonary disease :

- 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, the pleural cavity is invariably involved and serous **pleural effusions, tuberculous empyema, or obliterative fibrous pleuritis** develop.
- **Endobronchial, endotracheal, and laryngeal tuberculosis**
- The mucosal lining may show minute granulomatous lesions

■ 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



■ Isolated-organ tuberculosis:

- any organs or tissues seeded hematogenously and may 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
- unifocal, and most patients do not have concurrent extranodal disease.
- HIV-positive patients, have multifocal disease, systemic symptoms, and either pulmonary or other organ involvement by active tuberculosis.

Clinical Features

- **Asymptomatic**
- 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

– **Extrapulmonary manifestations:**

- infertility, headache, neurologic deficits, 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

Prognosis :

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



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THANK YOU!