بسم الله الرحمن الرحيم

PATHOLOGY

FINAL | Lecture 6

Tuberculosis

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﴿وَلَقَدْ نَعْلَمُ أَنَّكَ يَضِيقُ صَدْرُكَ بِمَا يَقُولُونَ ﴿٩٧﴾ فَسَبِّحْ بِحَمْدِ رَبِّكَ وَكُن مِّنَ السَّاجِدِينَ﴾

سبحان الله وبحمده، سبحان الله العظيم

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.**

- **These groups are the most groups affected by TB in US:**

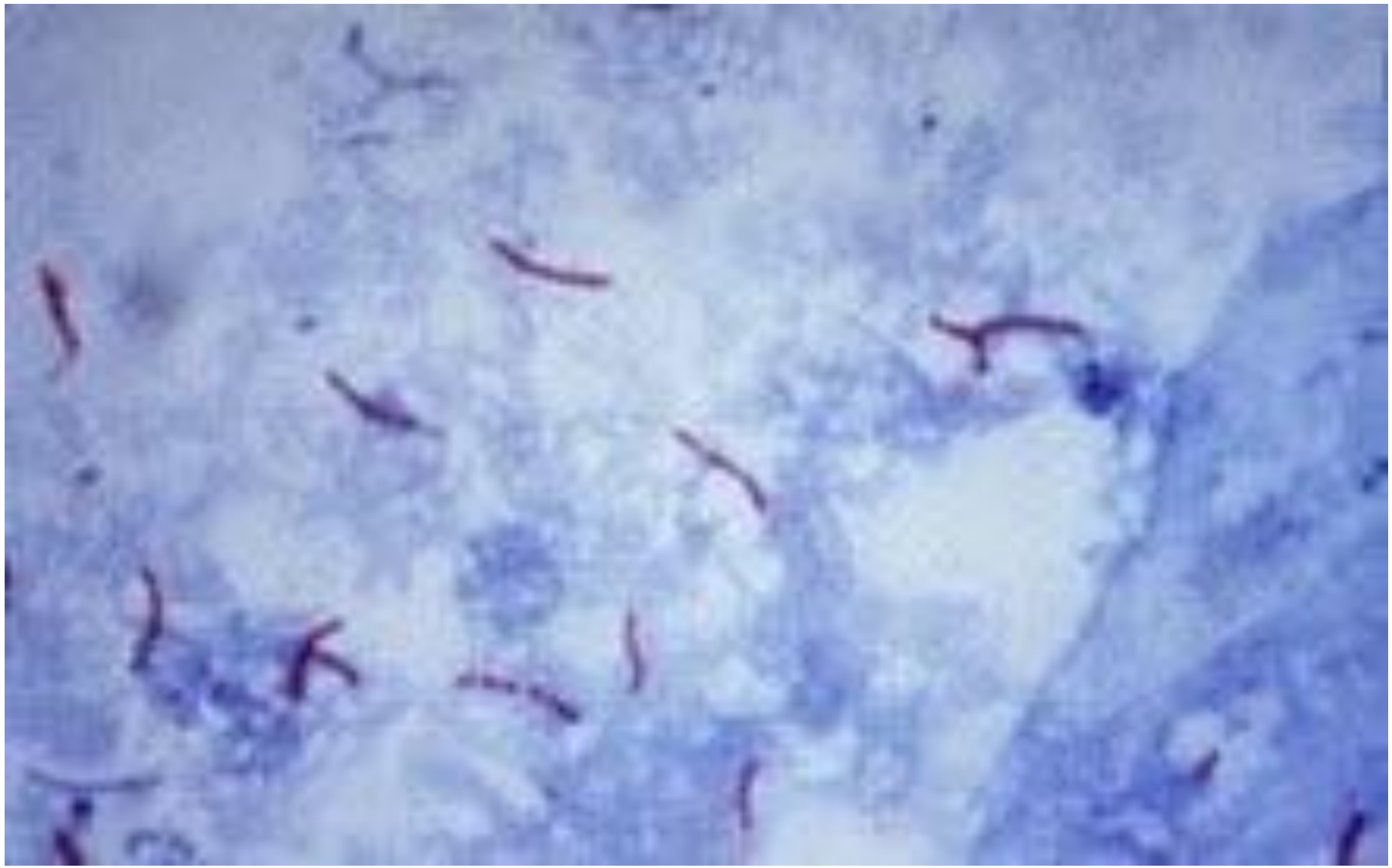
- older adults
- the urban poor
- patients with AIDS
- and members of minority communities.
- African Americans
- Native Americans
- Hispanics
- immigrants from Southeast Asia
- diabetes mellitus
- Hodgkin lymphoma
- Chronic lung disease (particularly silicosis)
- chronic renal failure
- Malnutrition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

In parts of the world where HIV infection is prevalent, HIV 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).

- **Mycobacterium tuberculosis appears as red, slender rod-shaped bacilli against a blue background on Ziehl-Neelsen staining.**



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.
- Rare type of TB, except in countries with tuberculosis in cows and unpasteurized milk sales.

Mycobacterium avium complex

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

Tuberculin (Mantoux) test:

- **Mycobacterial infection leads to:**

- Delayed hypersensitivity rxn.

  Which can be detected by *tuberculin test*.

- **The test consists of** intracutaneous injection of 0.1 mL of sterile purified protein derivative (PPD).

- The test is considered positive if it induces a visible, palpable induration of at least 5 mm in diameter, which usually peaks within 48–72 hours. A negative result therefore means that you have most likely not been infected with the bacteria that cause TB, while A positive tuberculin skin test does not differentiate between infection and disease.

The test have some limitations:

- **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.**

Infection vs. disease

- Infection implies seeding of a focus with organisms.
  Which may or may not cause clinically significant tissue damage

- Disease is a clinically significant tissue damage

- Routes of transmission
- Most infections are acquired by direct persons-to-person transmission of an Airborne droplets from an active case to a susceptible host.

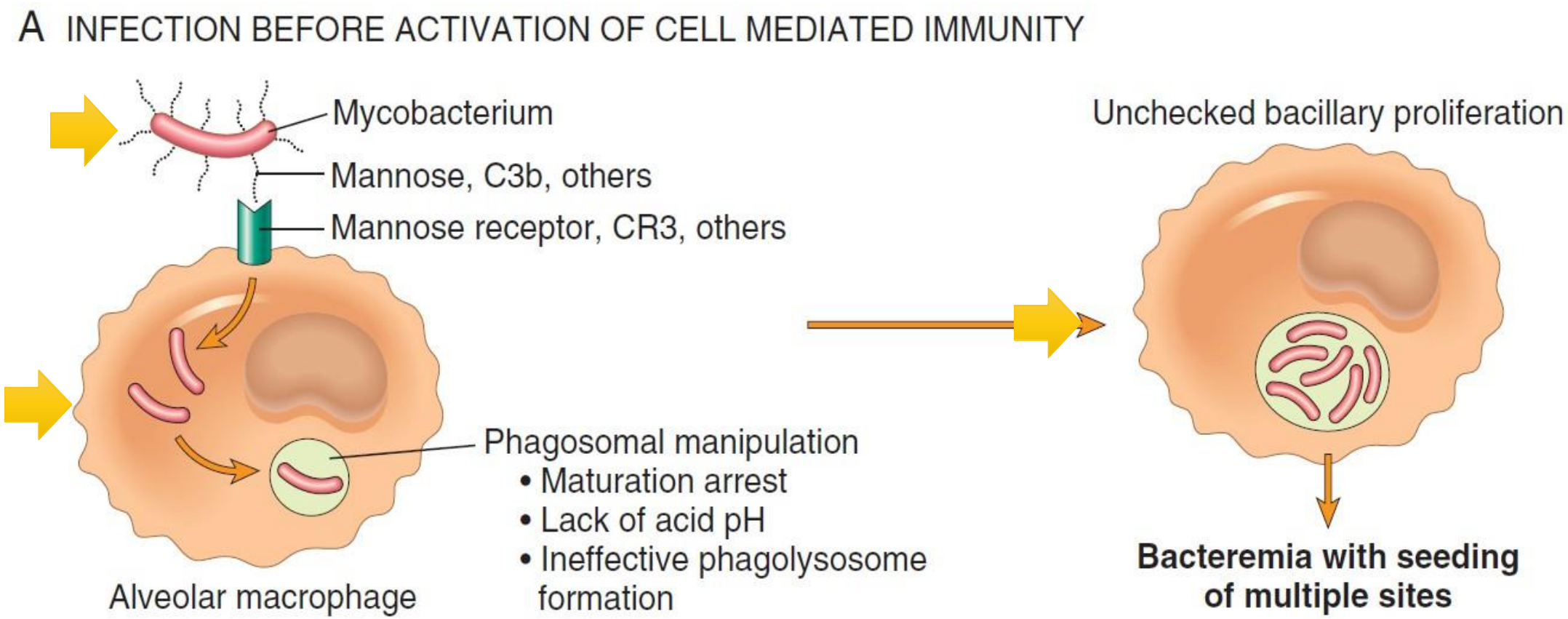
Pathogenesis

- **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

The figure shows the first step of a primary pulmonary tuberculosis:
(See the following page for clarification)



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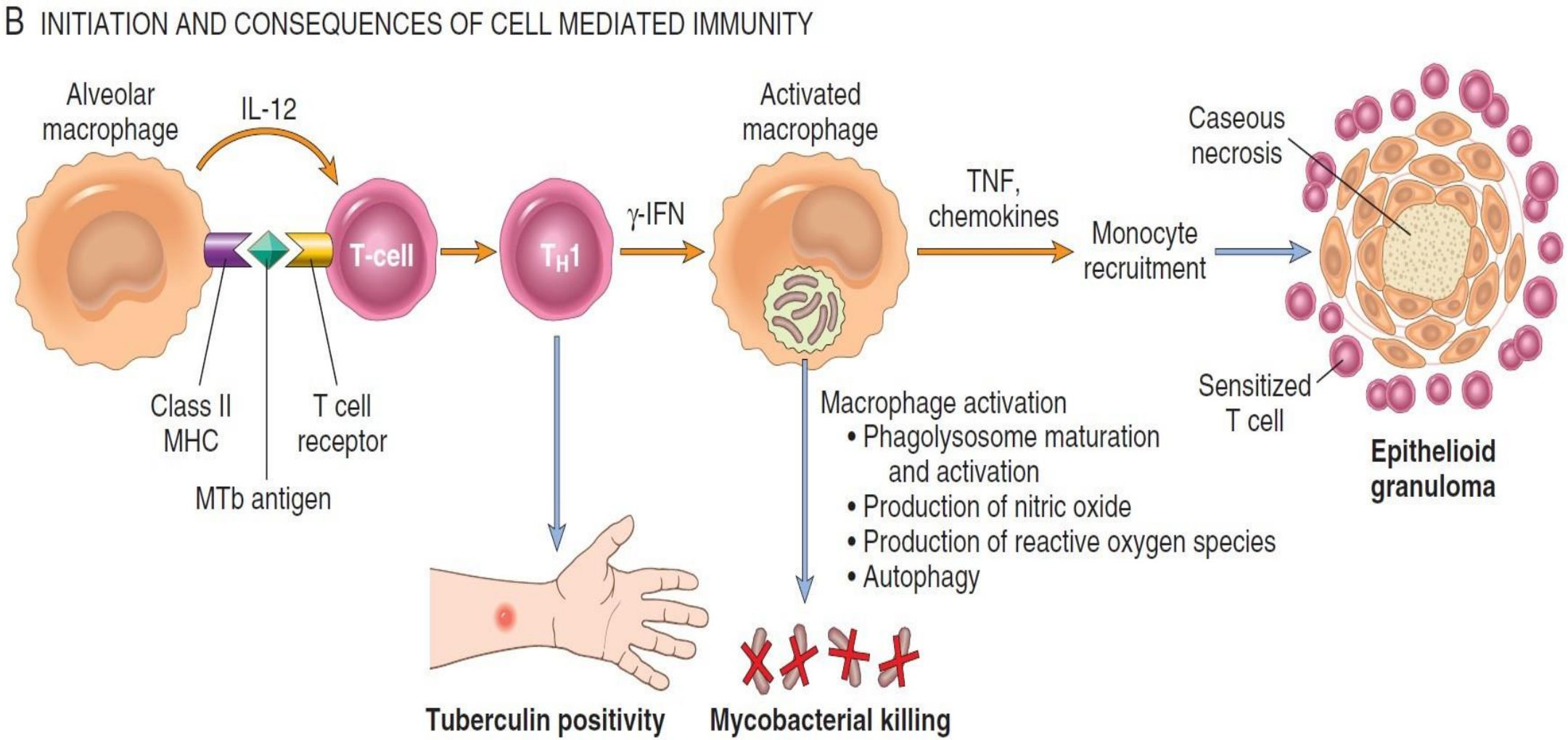
- The sequence begins with inhalation of virulent strains of Mycobacterium tuberculosis. Within approximately three weeks after exposure, the next steps of infection occur.

- The first step is the entry of virulent mycobacteria into macrophage endosomes. This process is mediated by several macrophage receptors, including the macrophage mannose receptor and complement receptors, which recognize components of the mycobacterial cell wall.

- After entry, the organisms inhibit normal microbicidal responses by preventing the fusion of lysosomes with phagocytic vacuoles. This allows the mycobacteria to persist and proliferate within macrophages. During the earliest phase of primary tuberculosis, which occurs in the first three weeks in nonsensitized individuals, bacillary proliferation takes place within pulmonary alveolar macrophages and alveolar spaces. This leads to bacteremia and **dissemination of the organisms to multiple sites**.

- Despite this bacteremia, most individuals at this stage are asymptomatic or experience only mild, flu-like symptoms.

Natural history of primary pulmonary tuberculosis



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- The previous figure illustrates the sequence of events leading to the development of resistance to the organism and conversion to a positive tuberculin skin test.

- Approximately three weeks after exposure, cell-mediated immunity develops under the influence of interleukin-12 secreted by macrophages. This promotes the differentiation of type 1 T-helper (Th1) lymphocytes, which begin secreting interferon-γ.

- Interferon-γ is crucial for macrophage activation. Activated macrophages then release a variety of mediators and upregulate the expression of genes with important downstream effects, including tumor necrosis factor (TNF), inducible nitric oxide synthase (iNOS), and antimicrobial peptides such as defensins.

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.

- **The fourth step consists of granulomatous inflammation and tissue damage.**
  Type 1 T cells aid in the formation of granulomas and caseous necrosis through the following steps:
  After activation by interferon-γ (IFN-γ), macrophages differentiate into epithelioid histiocytes that aggregate to form granulomas. Some epithelioid cells may fuse to form multinucleated giant cells.
  In many individuals, this immune response contains the infection before significant tissue destruction or clinical illness occurs. In other individuals with immune deficiency due to aging or immunosuppression, the infection progresses, and the ongoing immune response results in caseation and necrosis.
  Furthermore, activated macrophages produce increased amounts of tumor necrosis factor (TNF) and chemokines, which promote and recruit additional monocytes.

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.

- Individuals with inherited mutations in any component of TH1 pathway are extremely susceptible to mycobacteria infections.

- 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

- self-limited asymptomatic.
- 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

- 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.

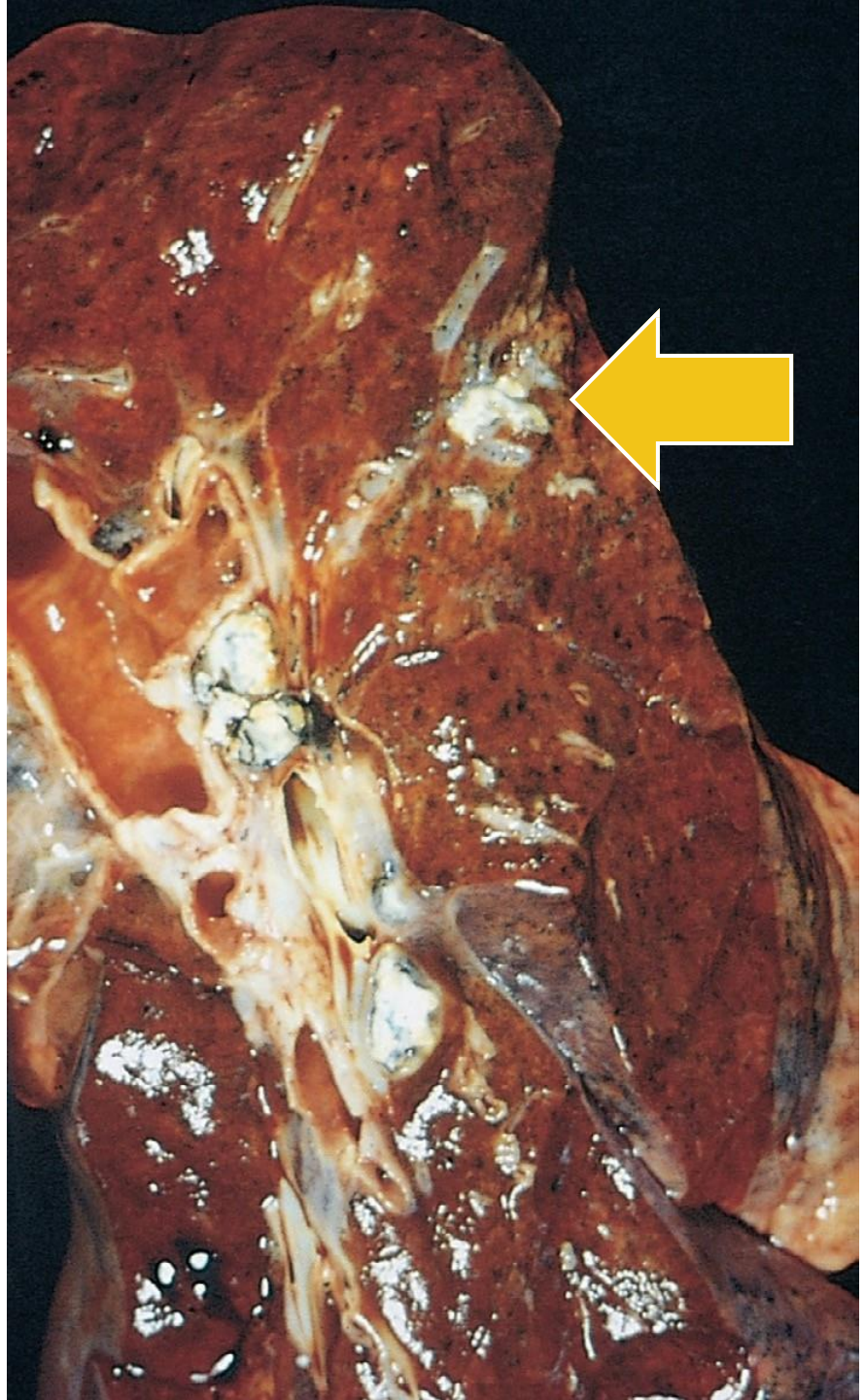
- The inhaled bacilli usually implant close to the pleura in the distal air spaces
  - in the lower part of the upper lobe.
  - in the upper part of the lower lobe.

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 in the center of the focus.

As shown in the figure.



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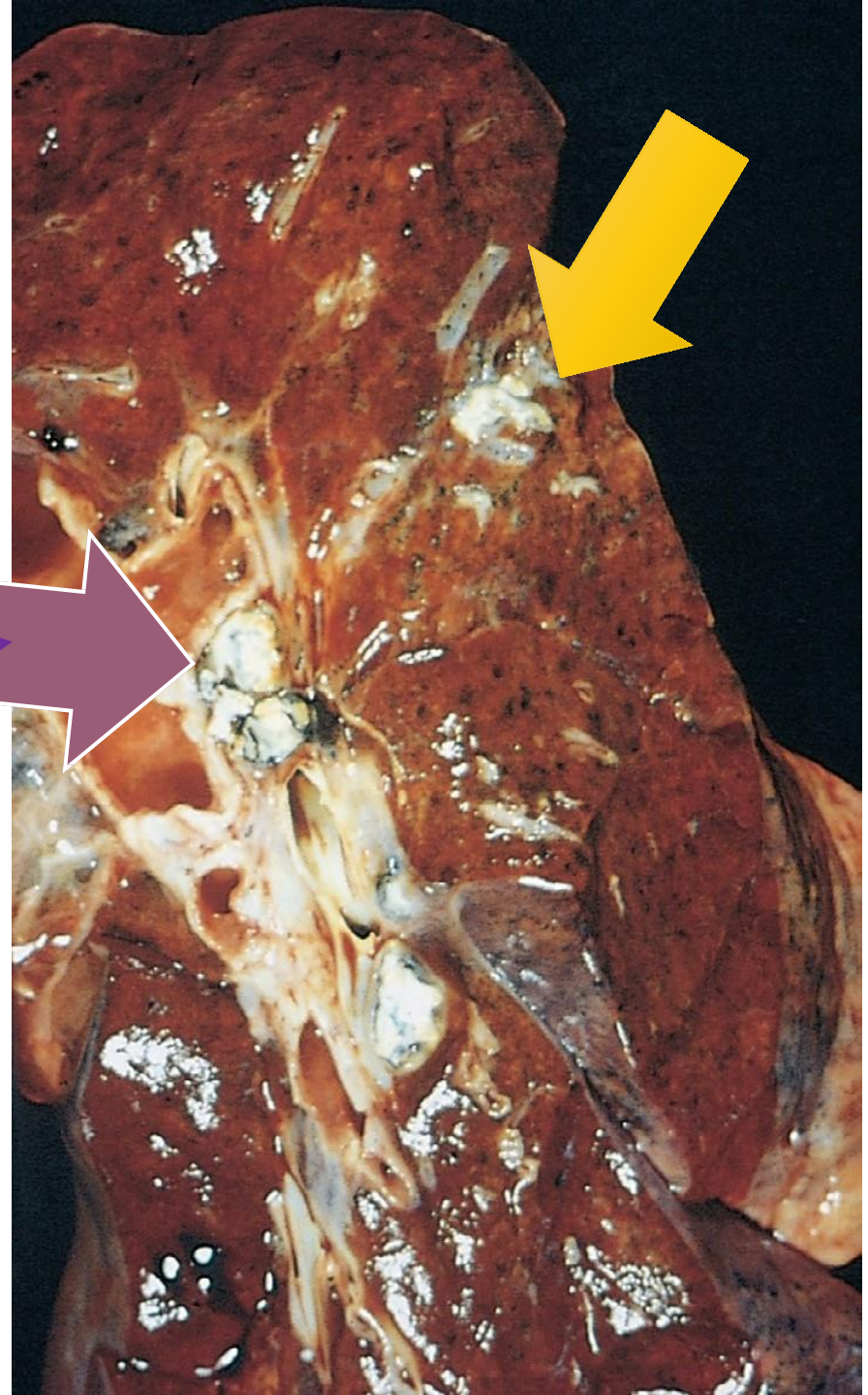
MORPHOLOGY, grossly:

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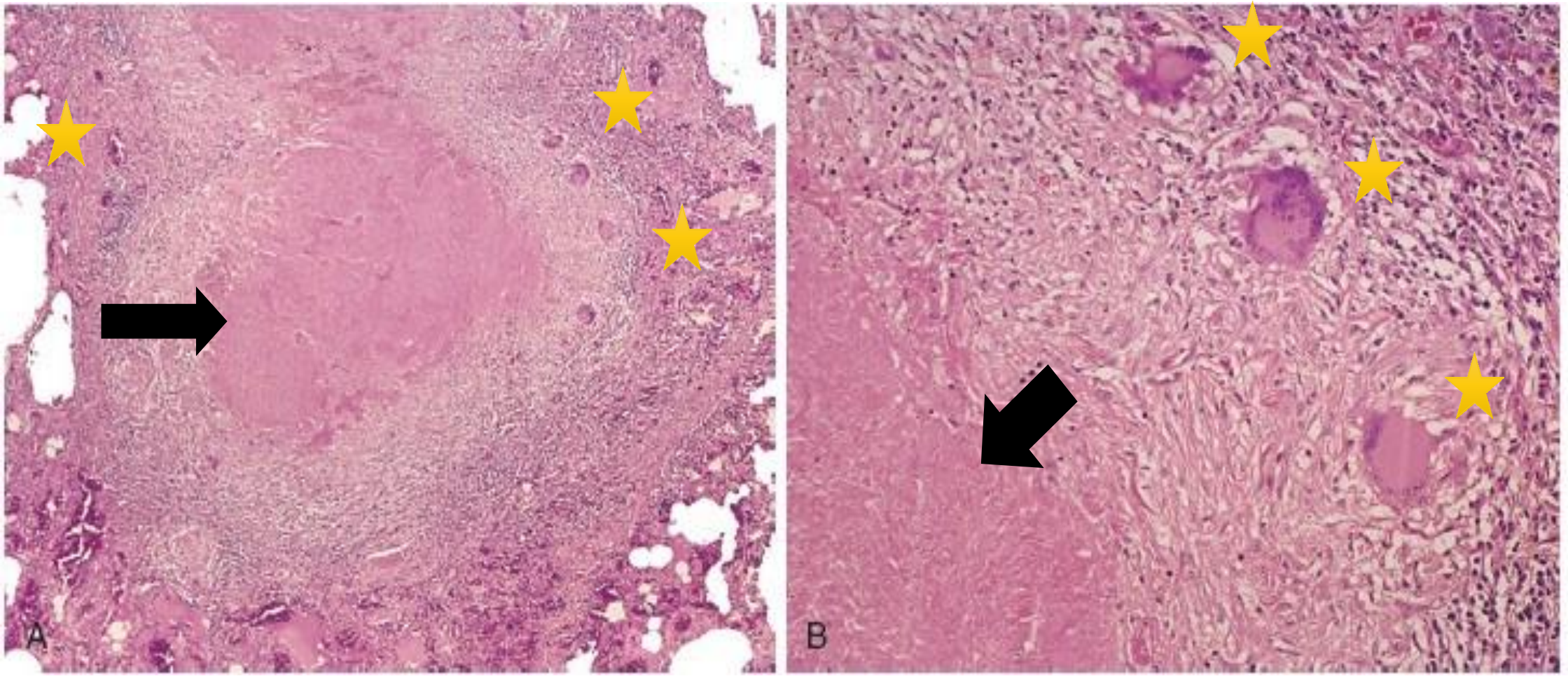
- In the first few weeks, Lymphatic and hematogenous dissemination
- In 95% cell-mediated immunity controls the infection.
- Ghon complex undergoes progressive fibrosis and calcification
- Despite seeding of other organs, no lesions develop.

MORPHOLOGY, microscopic:



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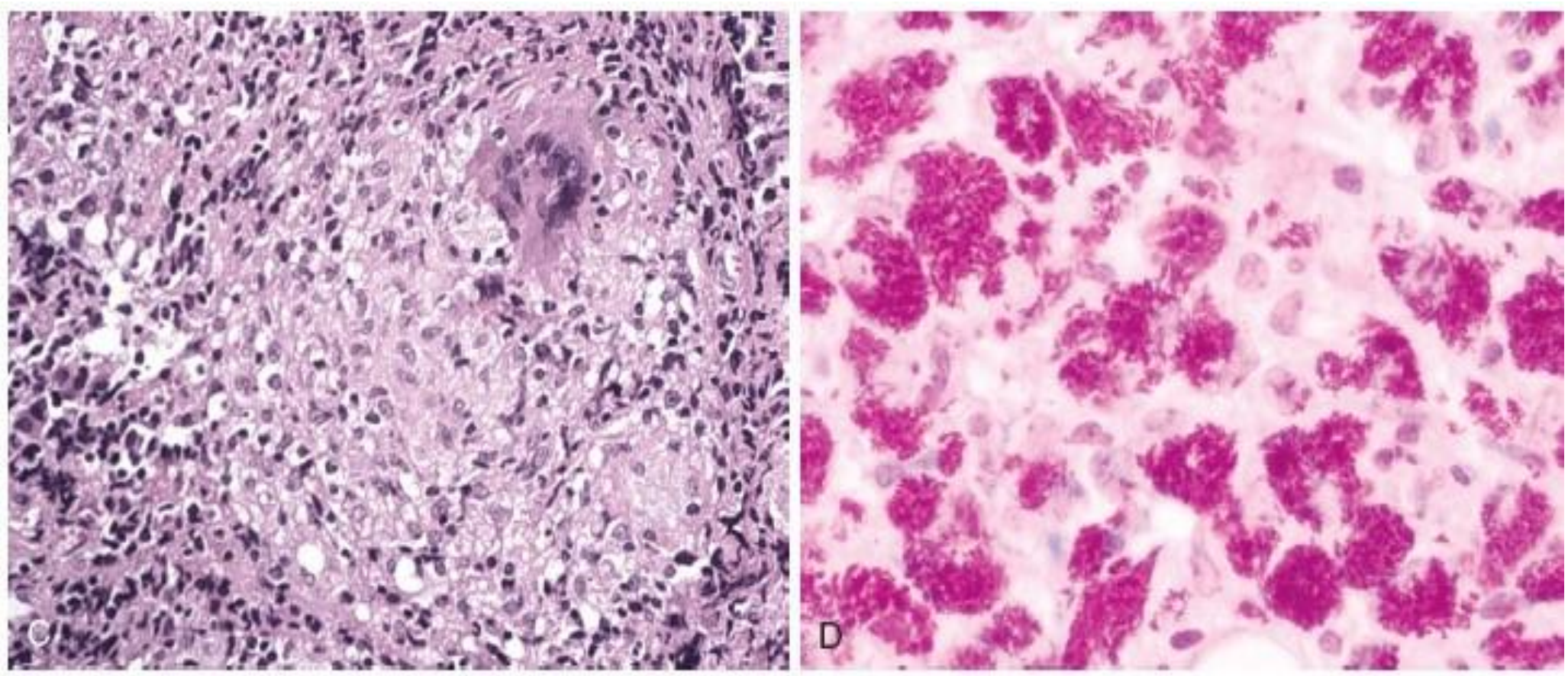
- Histologically, the sites of infection are characterized by a distinctive inflammatory reaction marked by caseating and non-caseating granulomas. These granulomas are composed of epithelioid histiocytes and multinucleated giant cells.

- Figure A demonstrates the characteristic appearance of tuberculosis at low magnification, showing well-formed granulomas.
  Figure B shows the same lesion at higher magnification.

- The black arrow indicates central granular caseous necrosis, which is surrounded by epithelioid cells and multinucleated giant cells, highlighted by the yellow stars.

- This granulomatous reaction represents the typical host response in individuals who develop effective cell-mediated immunity against Mycobacterium tuberculosis.

Occasionally, even in immunocompetent patients, TB granulomas may not show central caseation, as in Figure B.
However, irrespective of the presence or absence of caseous necrosis, special stains for acid-fast organisms are always reliable.
Figure D shows an acid-fast stain decorating sheets of macrophages packed with mycobacteria; this specimen is from immunocompromised patients.



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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 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:

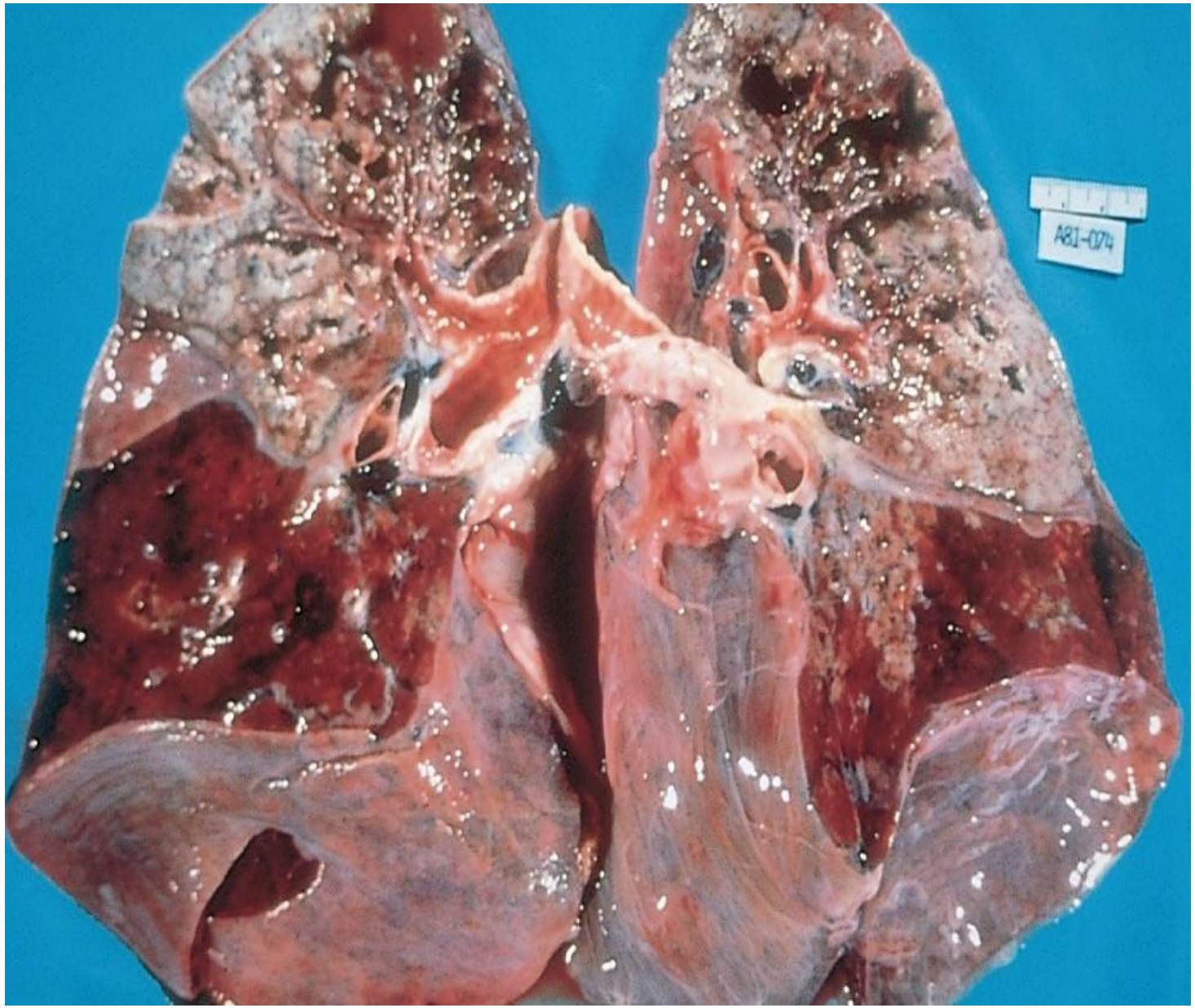
- **active lesions:** coalescent tubercles with central caseation.

- **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** that's poorly walled off by fibrous tissue.
- Erosion of blood vessels results in hemoptysis.
- **With adequate treatment**, the process may be arrested. However,healing by fibrosis often result in distortion of the pulmonary architecture.
- **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 the upper parts of both lungs by gray-white areas of caseation, along with multiple areas of softening and cavitation in a patient with secondary pulmonary tuberculosis.

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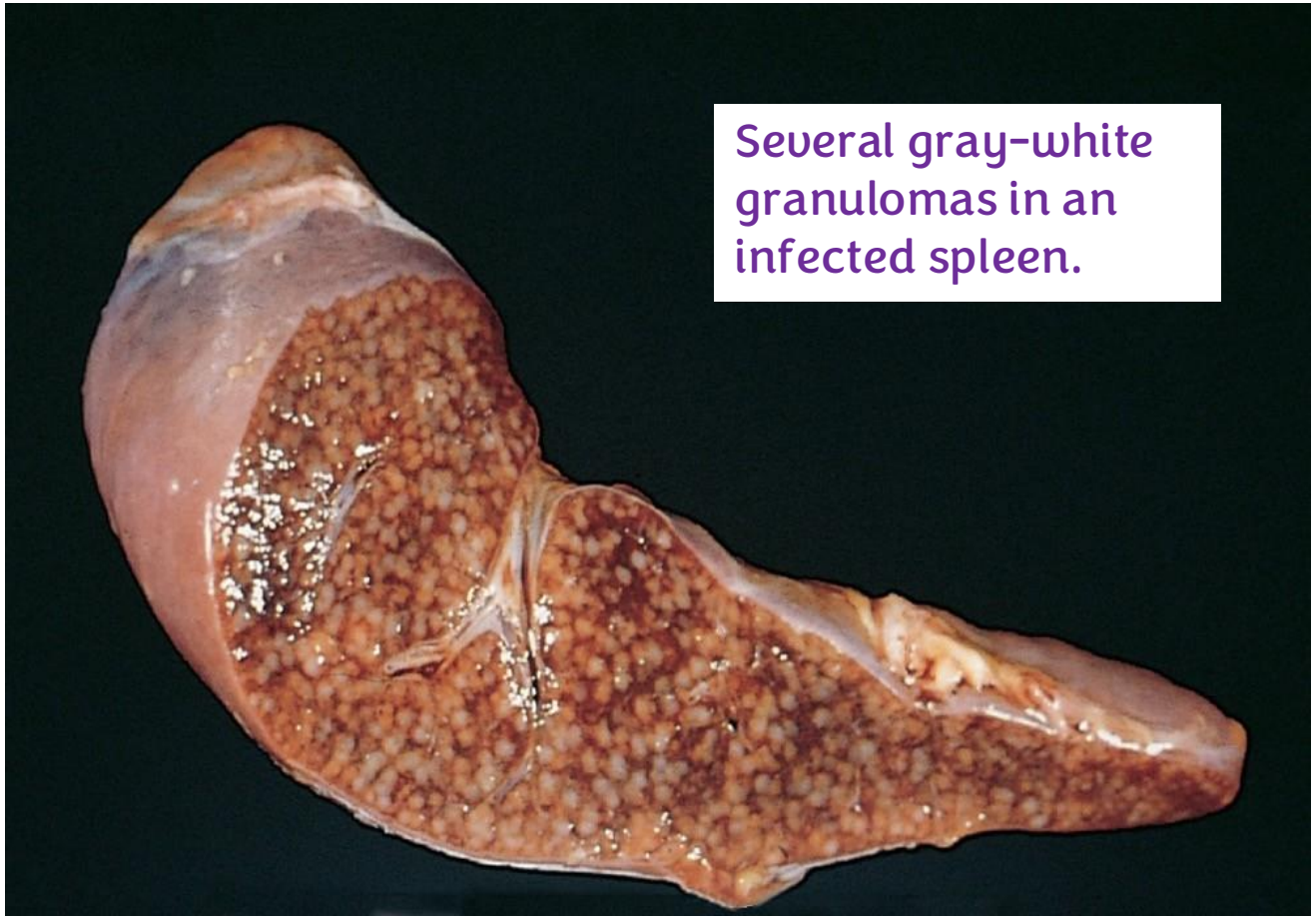
- **Miliary pulmonary disease :**
- when organisms reach the bloodstream through lymphatic vessels and then recirculate to the lung via the pulmonary arteries.

- The lesions are 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** may developed when the the infective material is spread either through the lymphatic channels or from expectorated infectious material.
- The mucosal lining may show 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.



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- **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.

- Usually involving the cervical region.

- Tends to be 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.** 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. Result from the extension of the infection to the plural surfaces.

Extrapulmonary manifestations:

- Infertility (when fallopian tube is involved),
- headache , neurologic deficits, (meninges).
- 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 by**:

➢ 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),**

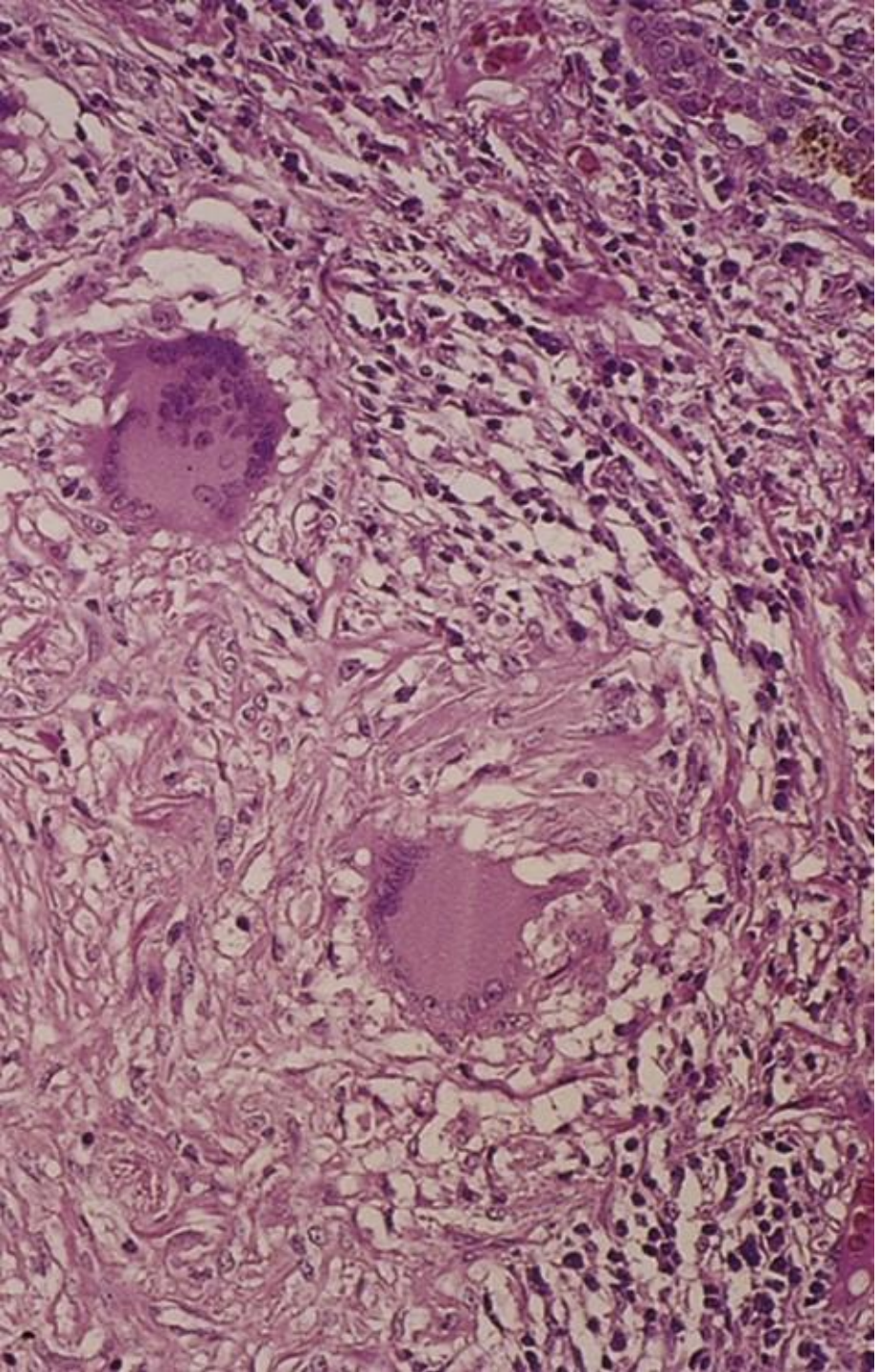
➢ **liquid media–based radiometric assays (2 weeks).**

➢ **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.



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

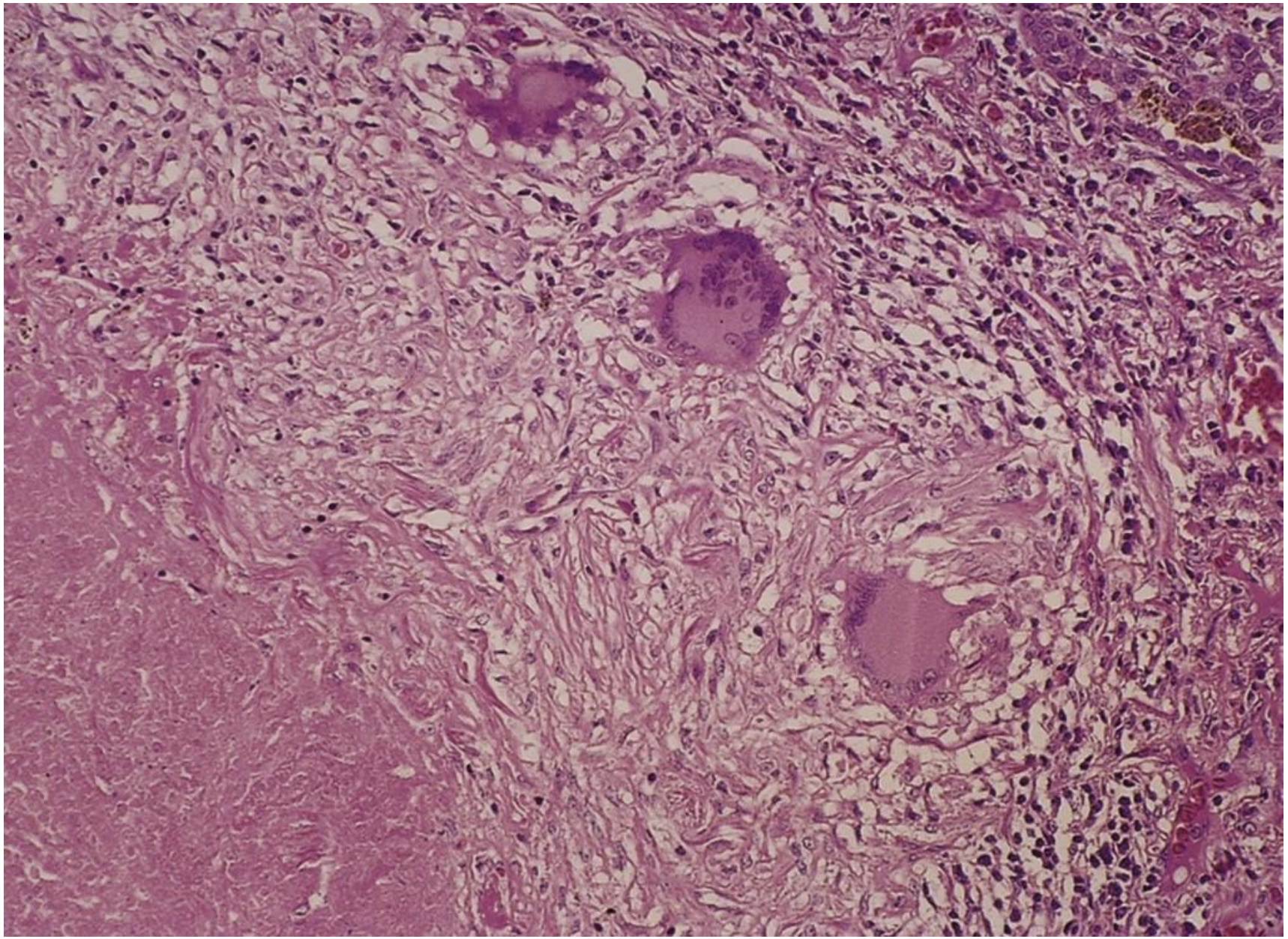
B Necrotizing granulomatous vasculitis

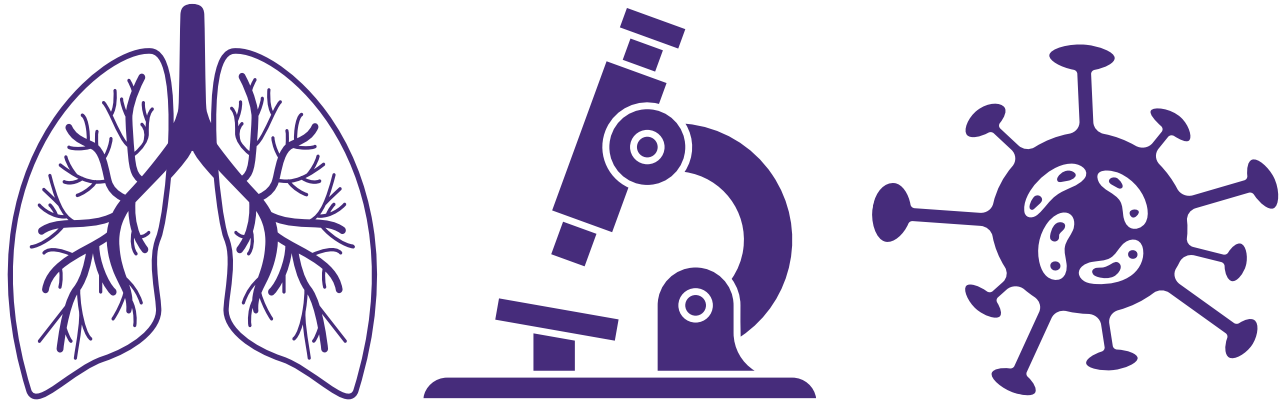
C Poorly differentiated adenocarcinoma

D Staphylococcus aureus abscess

E Thromboembolism with infarction

The answer is A





PATHOLOGY

QUIZ

LECTURE 6

External Resources

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