



Tuberculosis

- **Infectious disease** or infection (from Lat. Infectum - infect) - introduction and multiplication of microorganisms in the development macroorganism various forms of interaction: from carrier of pathogens to severe disease.
Susceptibility to infection - the ability of a person or animal to respond to the introduction of the pathogen, disease progression or carrier.

Depending on the etiology of the infectious disease is divided into:

- viral,
- mycoplasma,
- rickettsial,
- bacterial,
- fungal,
- protozoal,
- parasitic.

Mechanisms of transmission:

- fecal-oral,
- alimentary, water;
- airborne, or aspiration;
- transmissive (transmission of microorganisms through the blood);
- pin;
- mixed mechanism of transmission

Depending on the clinical and morphological features groups of infectious diseases distinguished

- ● Infections with a primary lesion of the skin (pyoderma , erysipelas , smallpox, fungal , etc.).
- Respiratory tract infections (pneumonia , influenza, tracheitis, bronchitis) .
- Infections of the digestive tract (typhoid fever , paratyphoid , amebiasis intestinal , dysentery, salmonellosis , etc.).
- Infectious diseases of the nervous system (polio , cerebrospinal meningitis abscess , encephalitis , etc.).
- transmissible infections associated with blood system (relapsing fever , malaria, hemorrhagic fevers , etc.).
- Infections with a primary lesion of the cardiovascular system (syphilis, brucellosis) .
- urogenital infections (gonorrhea, proctitis , pyelonephritis) .

Periods (stages) of the infectious disease

- **The incubation (latent) period** - the time when the infection enters the body and goes through a cycle of development, including reproduction. No subjective feeling of illness, but there are reactions between infection and body, mobilizing the body's defenses.
- **Prodromal, or initial period of illness.** Characterized by the first vague symptoms: malaise, frequent chills, headache, minor muscle and joint pain. In the area of the entrance gate often occur inflammatory changes, moderate hyperplasia of the lymph nodes and spleen.
- **The period of main manifestations of disease.** Clearly expressed symptoms of a specific infectious disease and characteristic morphological changes. This period includes the following steps: rise of manifestations of disease; stage of maximal symptoms; fading of clinical features of disease. During this period, the disease can proceed without complications, or complications can occur and the death of the patient.
- **The period of disease extinction** - the gradual disappearance of clinical symptoms, normalization of temperature and the beginning of reparative processes.
- **The period of convalescence, (recovery period)** may have different duration depending on the form of disease, its progress, the patient's condition.

Bacterial infections

- To survive in the body, bacteria must first be able to adhere to the cell membrane. Then they must deceive the body's immune mechanisms (virus "virulence") or use toxins to neutralize them so that the bacteria can thrive in this new environment (referred to as colonization). Depending on their specific survival strategy, the bacteria will produce certain inflammatory tissue reactions:
 - Invasive bacteria enter the blood stream and can cause sepsis.
 - Noninvasive bacteria destroy tissue with their toxins and exotoxins.
 - Intracellular bacteria (phagocyte parasites) trigger granulomatous inflammations.

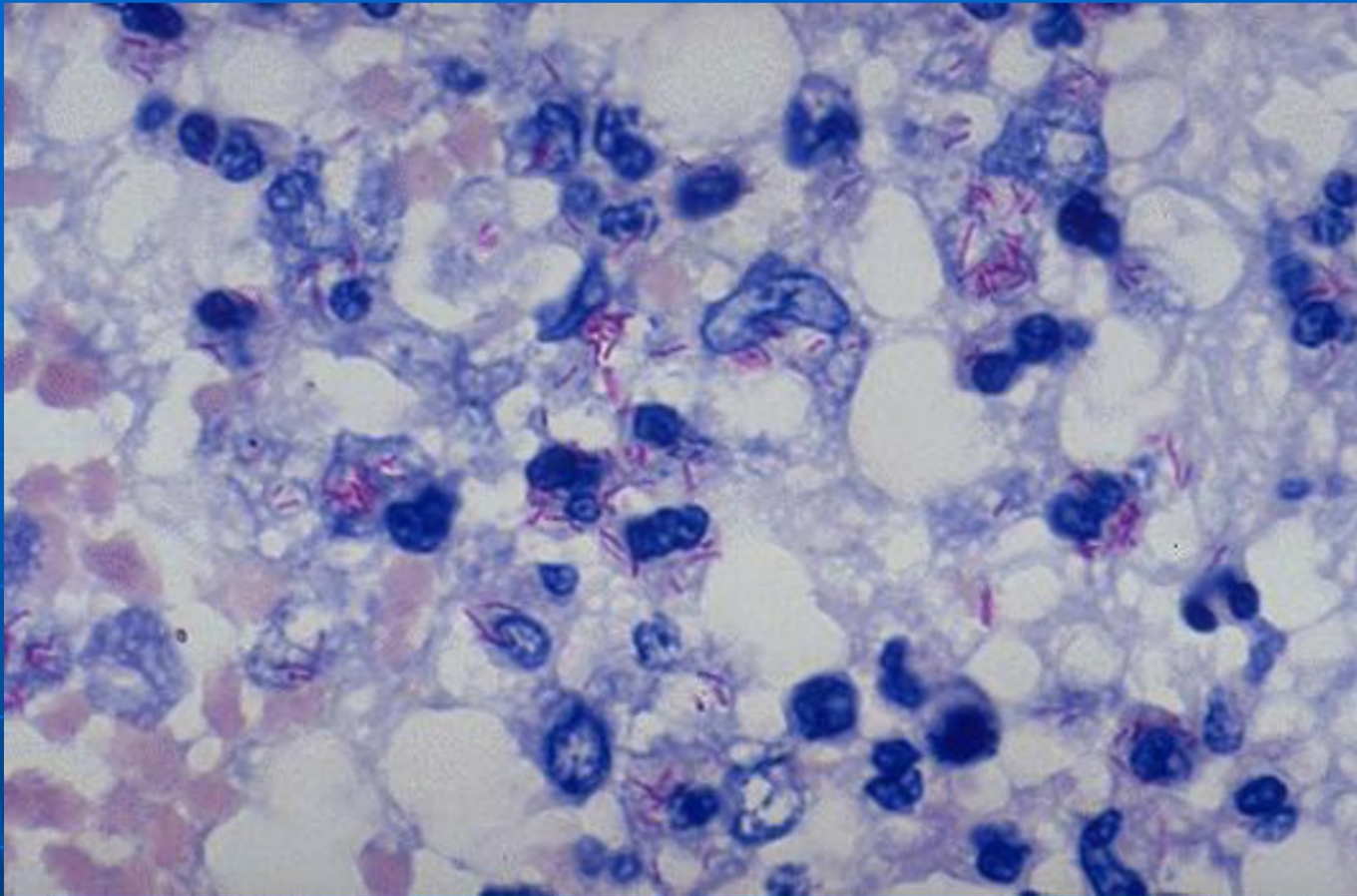
Tuberculosis

- Tuberculosis is a disease of great antiquity, having been identified in mummies from the fourth millennium BC. Tuberculosis remains a major public health problem in the developing nations of Asia, Africa, and South America. Even in technically advanced countries tuberculosis remains a public health problem in certain populations.

Tuberculosis

- WHO: 8-10 billion new cases of tuberculosis are found in the world per year.

- Two principal species responsible for tuberculosis in humans are *M. tuberculosis* and *M. bovis*. A species isolated from patients in East Africa, *M. africanus*, has properties intermediate between the human and bovine strains.



- In order to find the mycobacteria in a tissue section, a stain for acid fast bacilli is done (AFB stain). The mycobacteria stain as red rods, as seen here at high magnification.

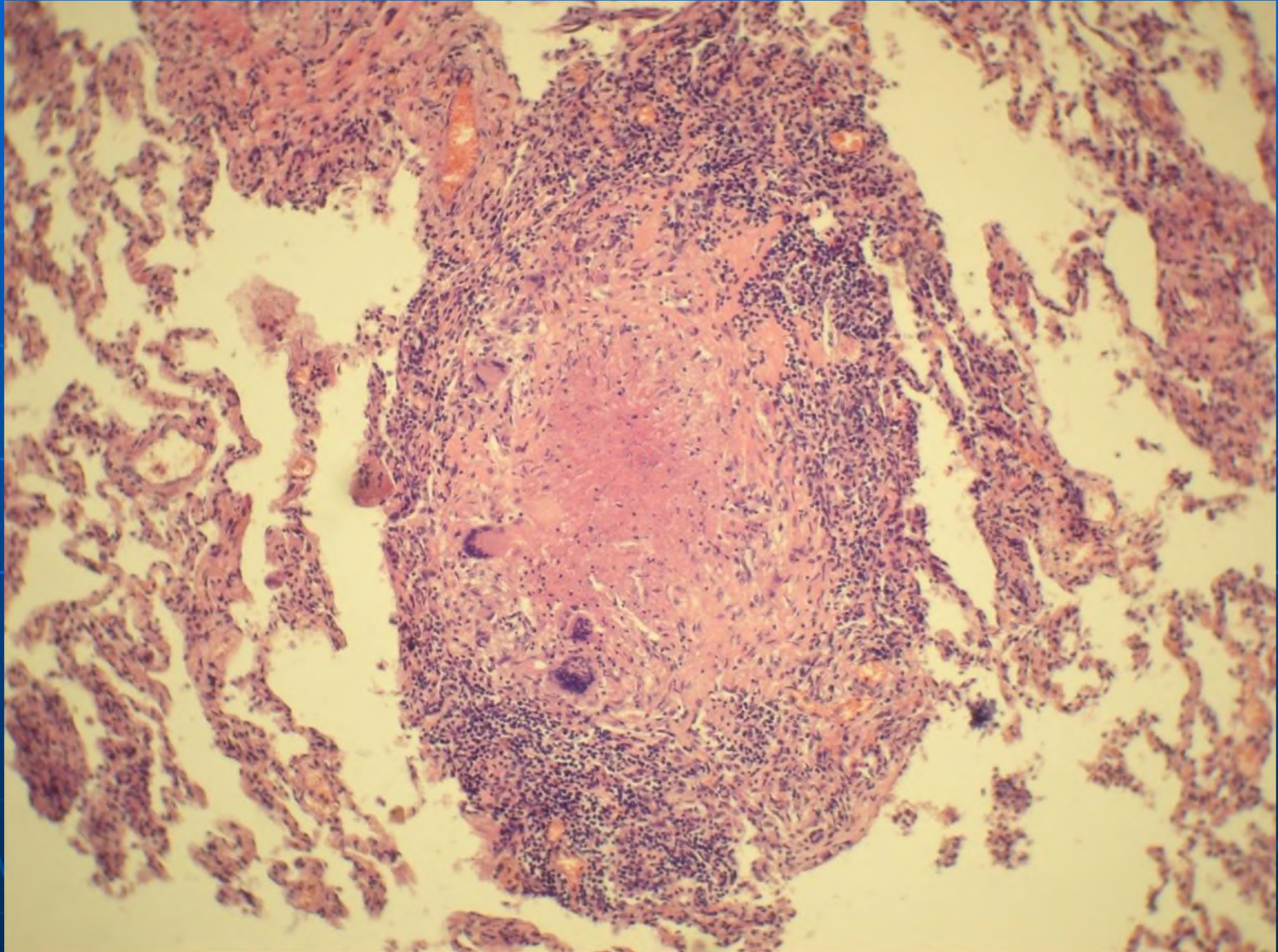
- The organism may be transmitted by inhalation, by ingestion, or rarely by direct implantation. A fetus can be affected uterotransplacentally. Patients with active pulmonary disease are the major source of human infection, and inhalation is overwhelmingly the most frequent route.
- Tuberculosis is a disease of the economically disadvantaged. Crowded living conditions and poor nutrition are predisposing factors.

- *M. tuberculosis* produces no known toxins.
- The tissue changes caused by infection result in the host response to the organisms.
- NRAMP1 — natural resistance — associated macrophage protein 1.
- It has been known since the time of Koch that the tissue response varies in its severity and tempo of development between an animal with no prior contact with tubercle bacilli and an animal that was previously infected.
- On the other hand, growth of organisms is restrained, and the spread of infection is prevented.

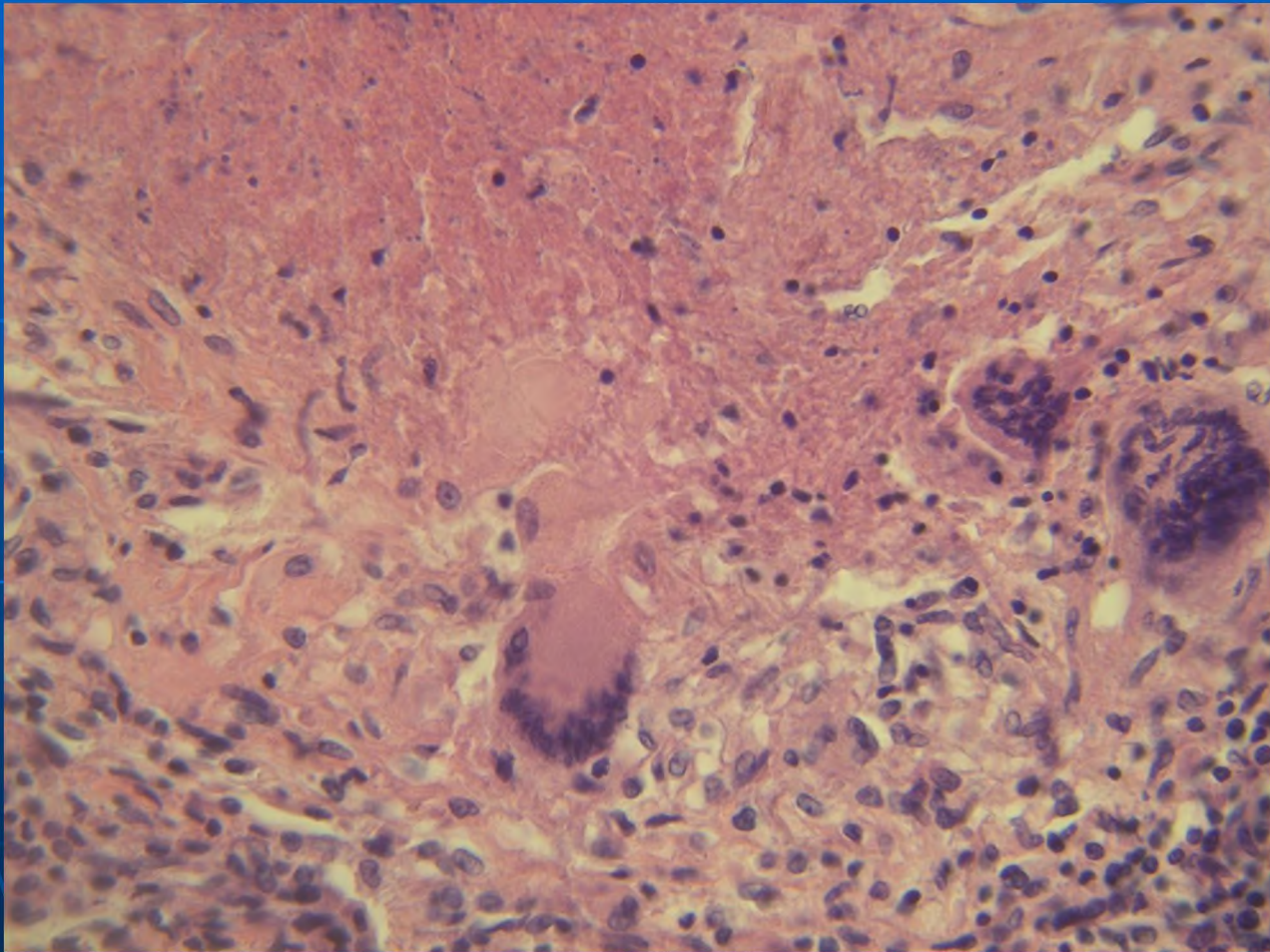
Granuloma

- The characteristic tissue response to tuberculosis is the granuloma, a compact organized collection of macrophages. In a previously uninfected animal or human the earliest response to the presence of bacilli in the tissue is an influx of inflammatory cells. The organisms are resistant to killing by the phagocytes, attributable in part to their ability to inhibit lysosome-phagosome fusion. They proliferate intracellularly, eventually killing the phagocytes.

Granuloma

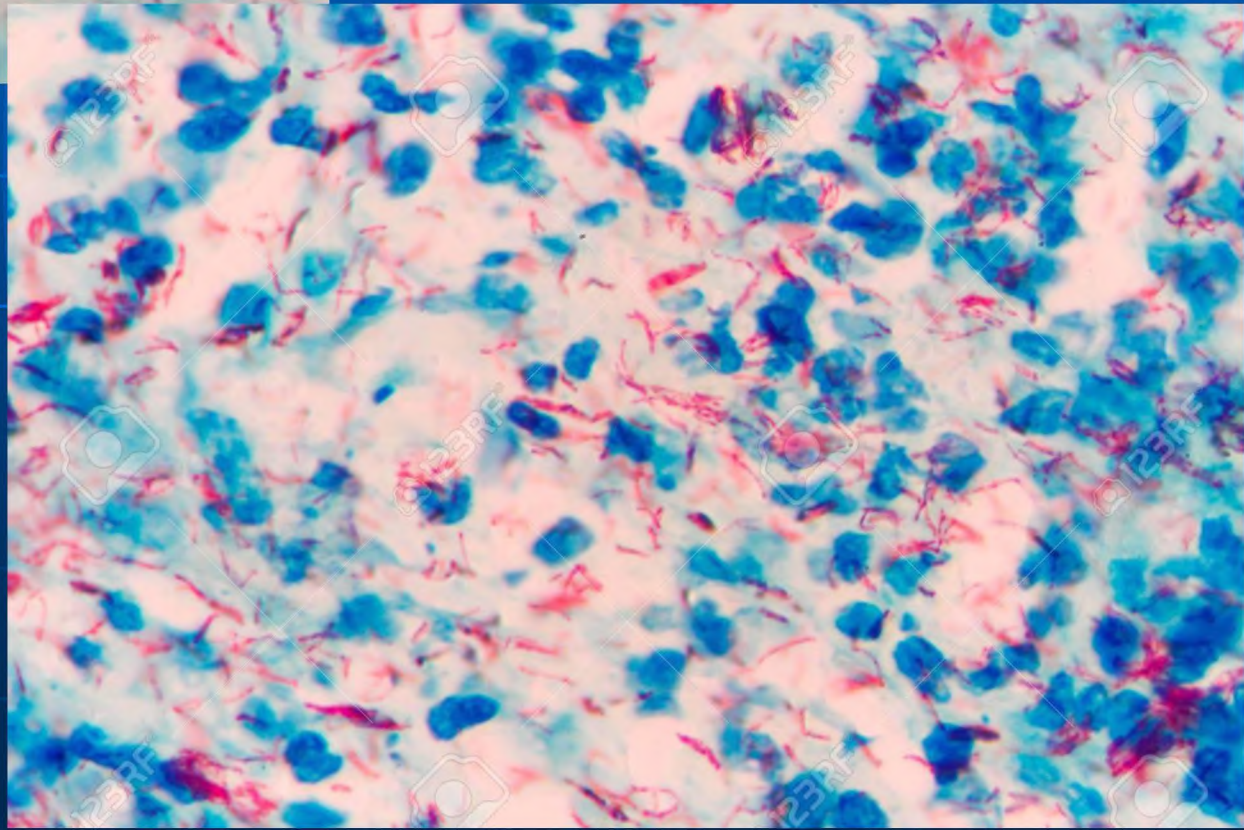
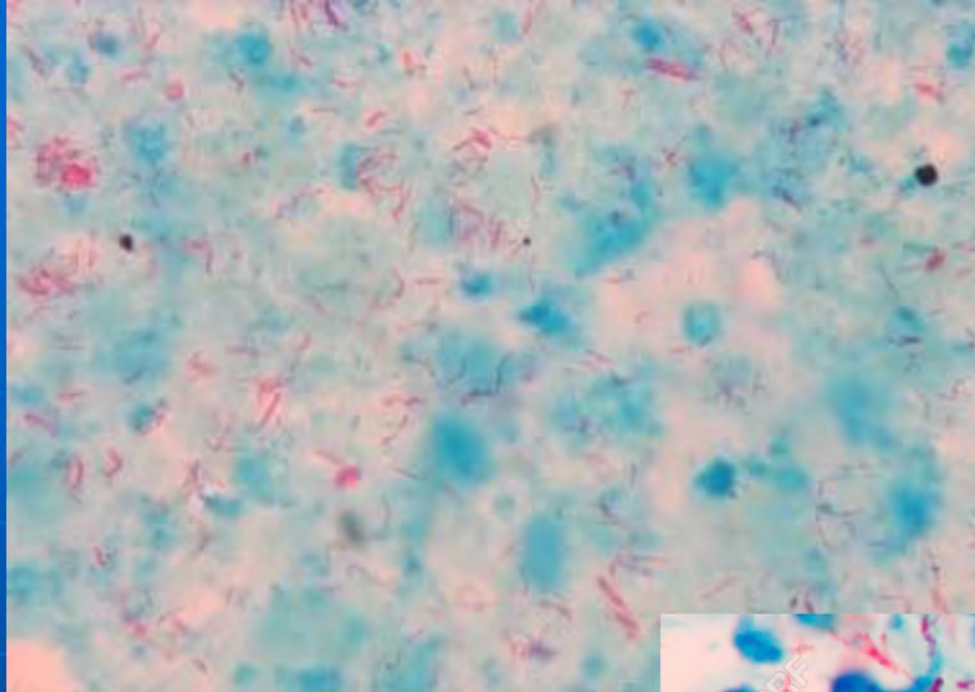


Granuloma



- The monocytes enlarge, their nucleus becomes eccentric, their cytoplasm more abundant, and they tend to aggregate first into loose sheets of cells and then more tightly into spherical aggregates. Although the cells initially remain distinct, later their cytoplasm bodies become indistinct when viewed with the light microscope; with the electron microscope this is seen to be attributable to the close interlocking of the pseudopodia of neighboring cells. These characteristic mononuclear cells are called epithelioid cells because they are closely packed like epithelium without interposed connective tissue.

- *M. tuberculosis*. Ziehl-Neelsen staining.



Tuberculosis

Tuberculosis, which is caused by infection with *Mycobacterium tuberculosis*, is divided into primary and secondary (or reactivation) tuberculosis.

Tuberculosis

Primary Tuberculosis

The disease is acquired from the initial exposure to *M. tuberculosis*, most commonly as a result of inhaling infected aerosols produced by the coughing of a person with cavitory tuberculosis. The inhaled organisms multiply in the alveoli, because the alveolar macrophages cannot readily kill the bacteria.

- A striking feature of the granulomas of tuberculosis and many other granulomas is the presence of multinucleated cells. Some multinucleated cells have their nuclei evenly dispersed in the cytoplasm. These cells are called foreign body giant cells, since they are similar in appearance to the giant cells that frequently enclose foreign material in tissues. Other giant cells called Langhans' giant cells have their nuclei disposed in a ring surrounding an eosinophilic cytocenter. Both types of giant cells, formed in the fusion of several epithelioid cells, are commonly found in epithelioid granulomas irrespective of their cause.

- As the granuloma matures, it becomes surrounded by the lymphocytes, plasma cells, capillaries, and fibroblasts. Between 4 and 6 weeks after the infection, necrosis begins to appear in the granulomas, the surrounding tissue may become edematous, and the number of organisms begins to diminish.
- The necrosis is termed caseation because its dry crumbly appearance resembles proceed cheese.

Tuberculosis

Primary Tuberculosis

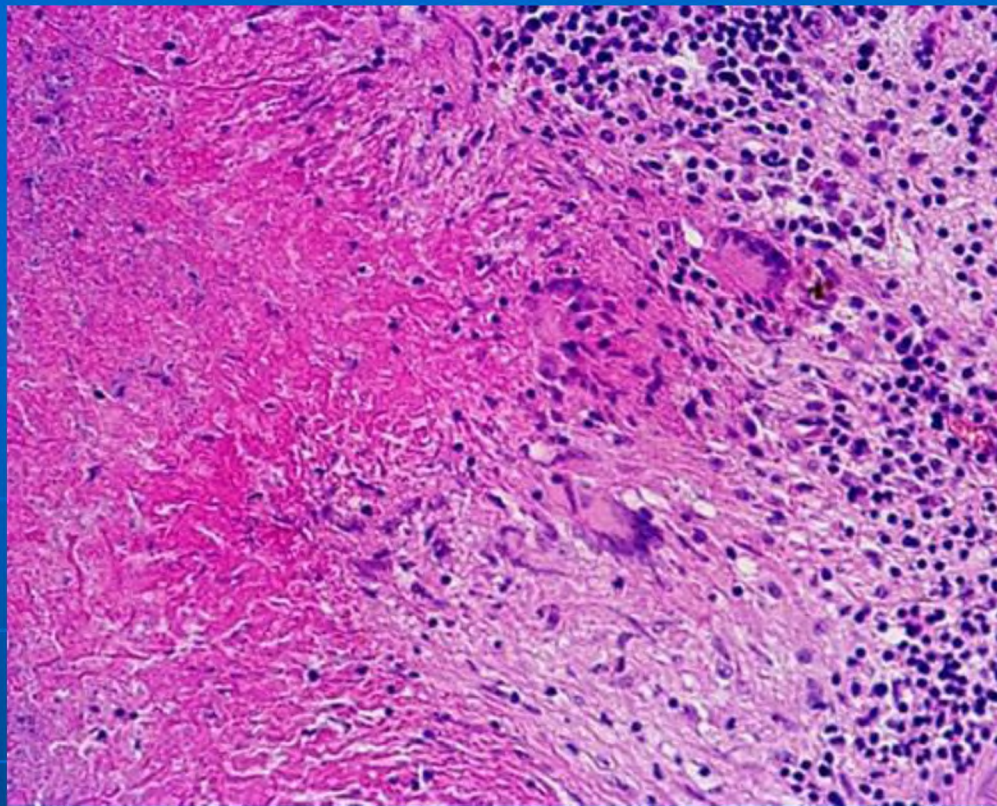


Primary tuberculosis. A healed Ghon complex is represented by a subpleural nodule and involved hilar lymph nodes.

Tuberculosis

Primary Tuberculosis

The Ghon complex is the first lesion of primary tuberculosis, consisting of a peripheral parenchymal granuloma, often in the lower lobes, and a prominent, infected mediastinal lymph node.



- lesion of primary tuberculosis, consisting of a peripheral parenchymal granuloma.
- **H&E (x240).**

- There is a small tan-yellow subpleural granuloma in the mid-lung field on the right. In the hilum is a small yellow tan granuloma in a hilar lymph node next to a bronchus. This is the "Ghon complex" that is the characteristic gross appearance with primary tuberculosis. In most persons, the granulomatous disease will not progress. Over time, the granulomas decrease in size and can calcify, leaving a focal calcified spot on a chest radiograph that suggests remote granulomatous disease.



Tuberculosis

Primary Tuberculosis

On gross examination, the healed, subpleural Ghon nodule is 1 to 2 cm in diameter, well circumscribed, and centrally necrotic. In later stages, the lesion is fibrotic and calcified.

Tuberculosis

Primary Tuberculosis

Microscopically, a granuloma with central, caseous necrosis shows varying degrees of fibrosis. The microscopic features of the draining hilar lymph nodes are similar to those of the peripheral parenchymal lesion.

Tuberculosis

Primary Tuberculosis

The large majority (>90%) of primary infections are asymptomatic, and the lesions remain localized and heal.

However, less commonly, primary tuberculosis does not remain limited but, rather, spreads to other parts of the lung (**progressive primary tuberculosis**).

Tuberculosis

Primary Tuberculosis

This condition is usually seen in early childhood or in immunosuppressed adults. The initial lesion enlarges, producing necrotic areas as large as 6 cm or more in the greatest dimension. Central liquefaction results in cavities, which may expand to occupy most of the lower lobe. At the same time, the draining lymph nodes display similar histologic changes.

Tuberculosis

Secondary Tuberculosis

This stage represents either reactivation of primary pulmonary tuberculosis or new infection in a host previously sensitized by primary tuberculosis. The initial reaction to *M. tuberculosis* is different in patients with secondary tuberculosis.

Tuberculosis

Secondary Tuberculosis

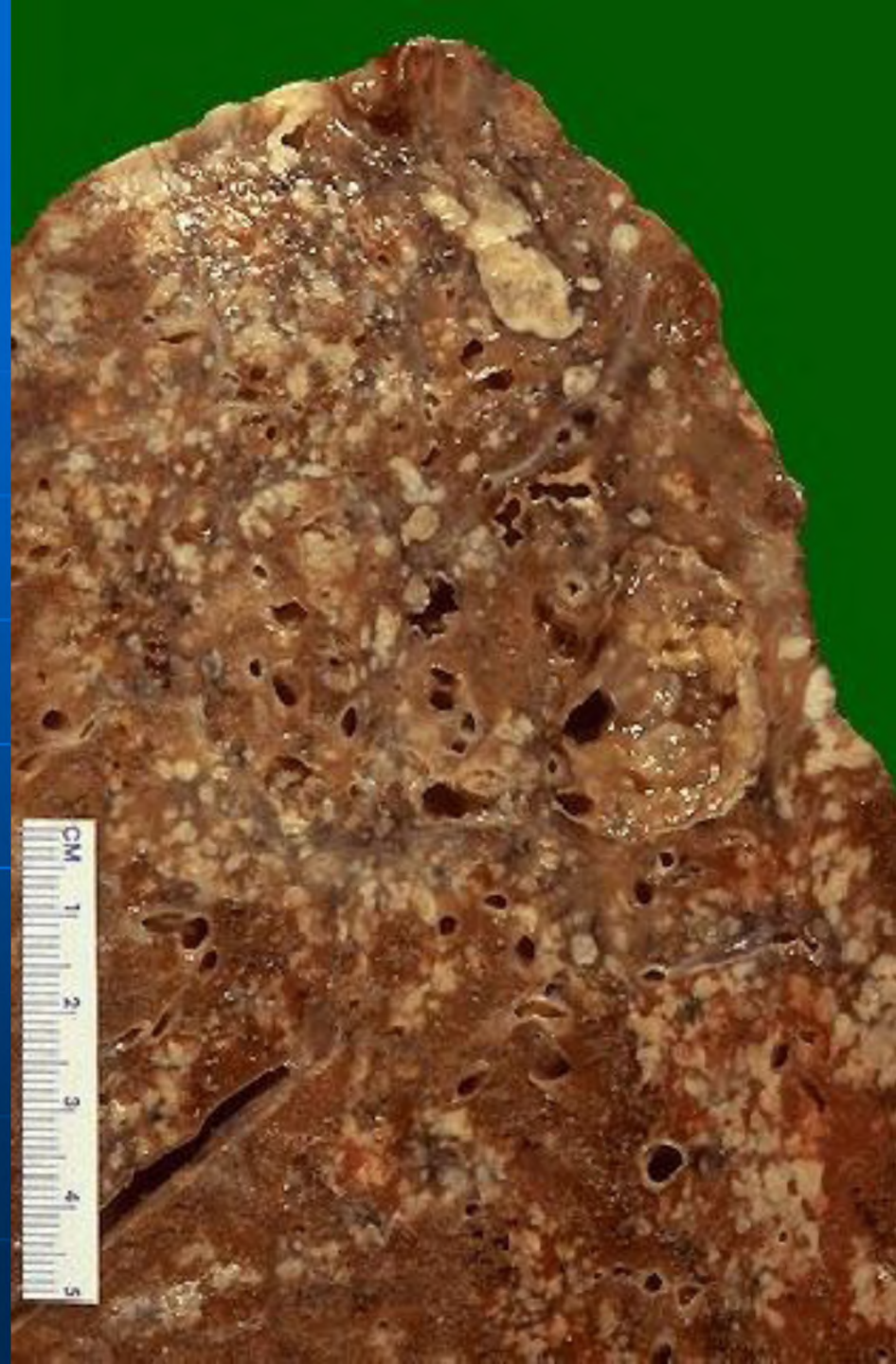
A cellular immune response occurs after a latent interval and leads to formation of many granulomas and extensive tissue necrosis. The apical and posterior segments of the upper lobes are most commonly involved.

Tuberculosis

Secondary Tuberculosis

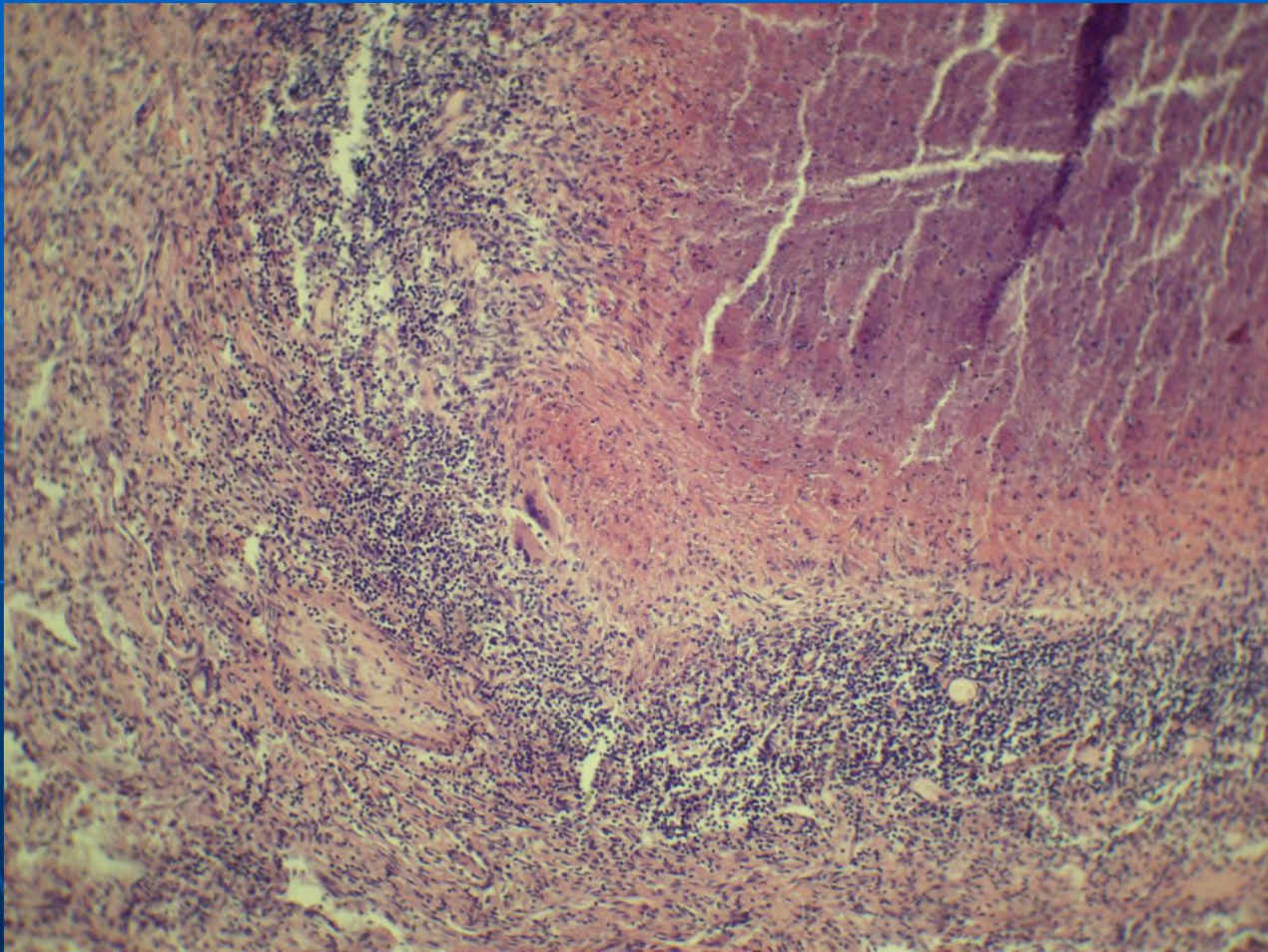
- Acute Focal Tuberculosis
- Fibrous Focal Tuberculosis
- Infiltrative Tuberculosis
- Caseous Pneumonia
- Tuberculoma
- Acute Cavernous Tuberculosis
- Fibrous Cavernous Tuberculosis
- Cirrhotic Tuberculosis

- On closer inspection, the granulomas have areas of caseous necrosis. This is very extensive granulomatous disease. This pattern of multiple caseating granulomas primarily in the upper lobes is most characteristic of secondary (reactivation) tuberculosis. However, fungal granulomas (histoplasmosis, cryptococcosis, coccidioidomycosis) can mimic this pattern as well.



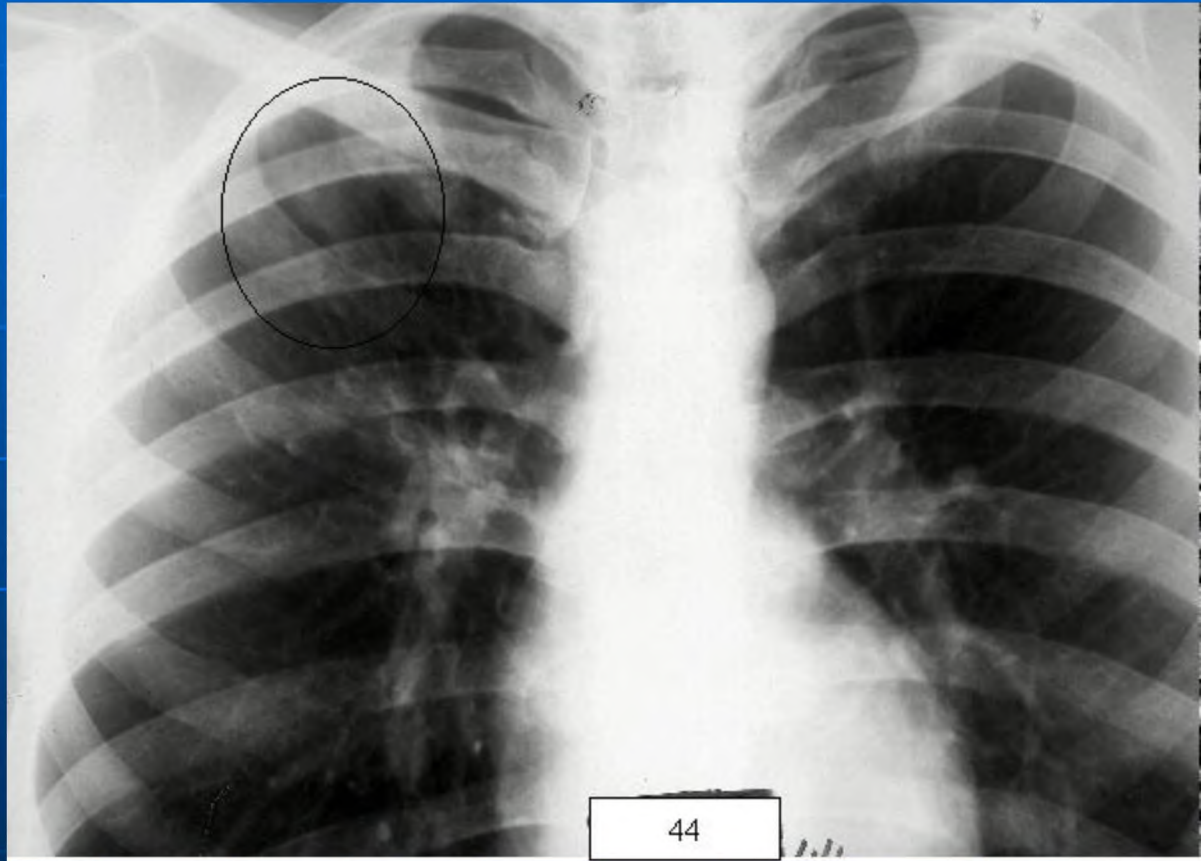
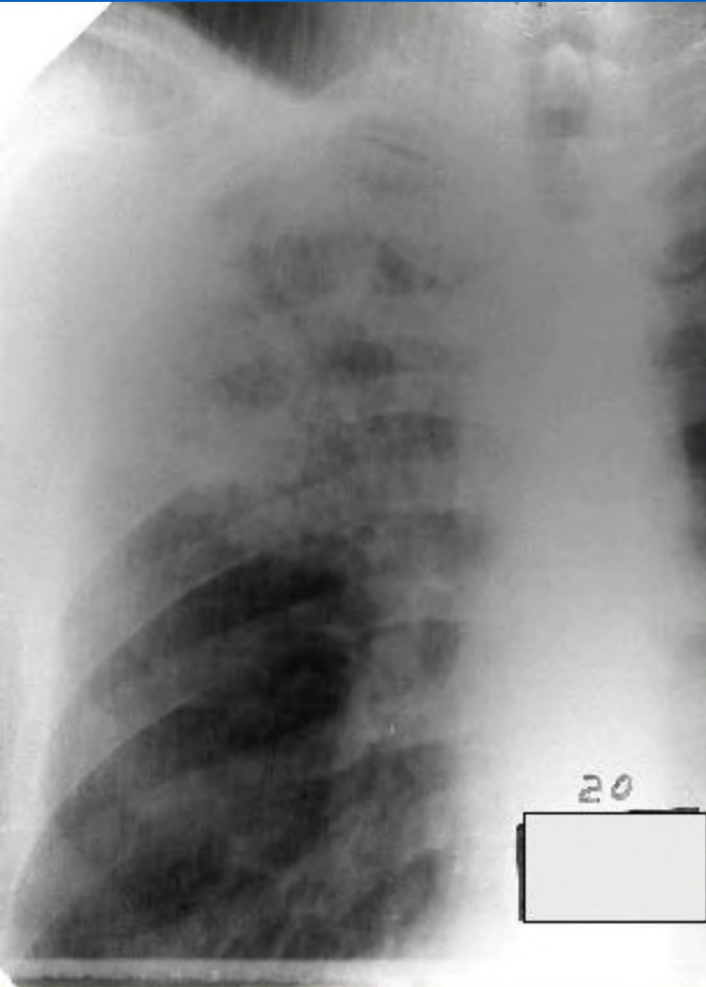
Tuberculosis

Secondary Tuberculosis, Acute Focal Tuberculosis



Tuberculosis

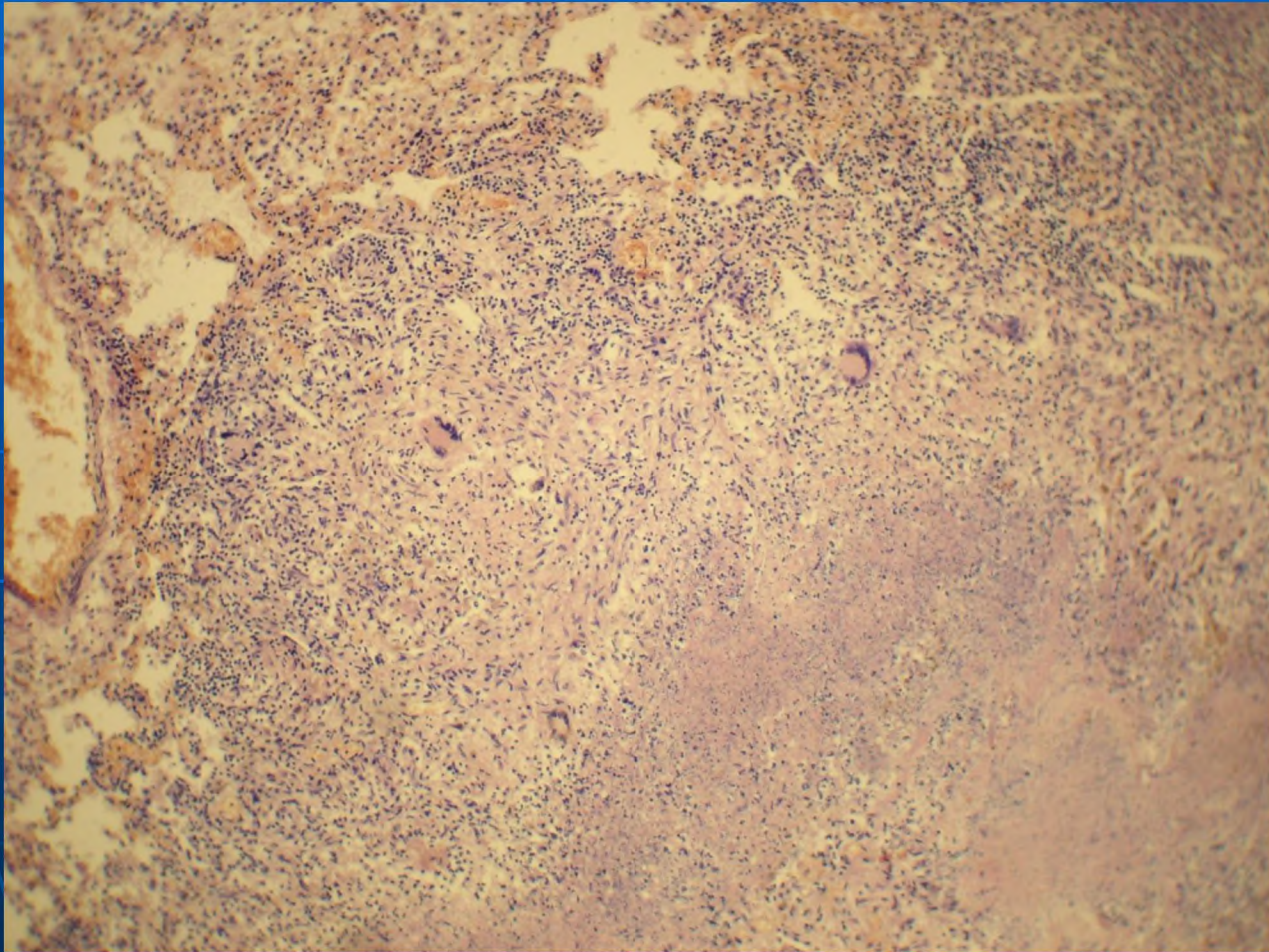
Secondary Infiltrative Tuberculosis



Infiltrate in the upper lobe of right lung.

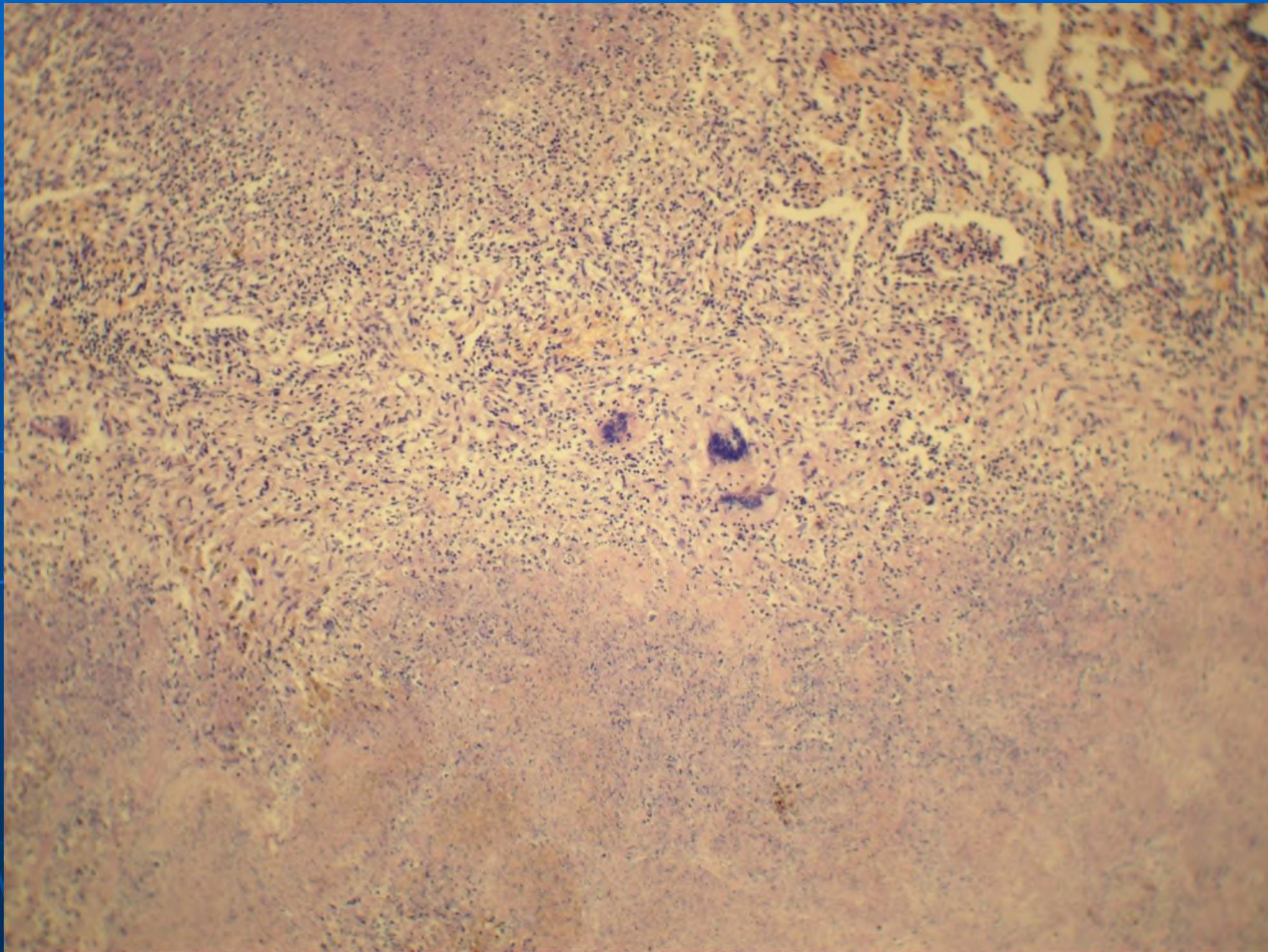
Tuberculosis

Secondary Infiltrative Tuberculosis



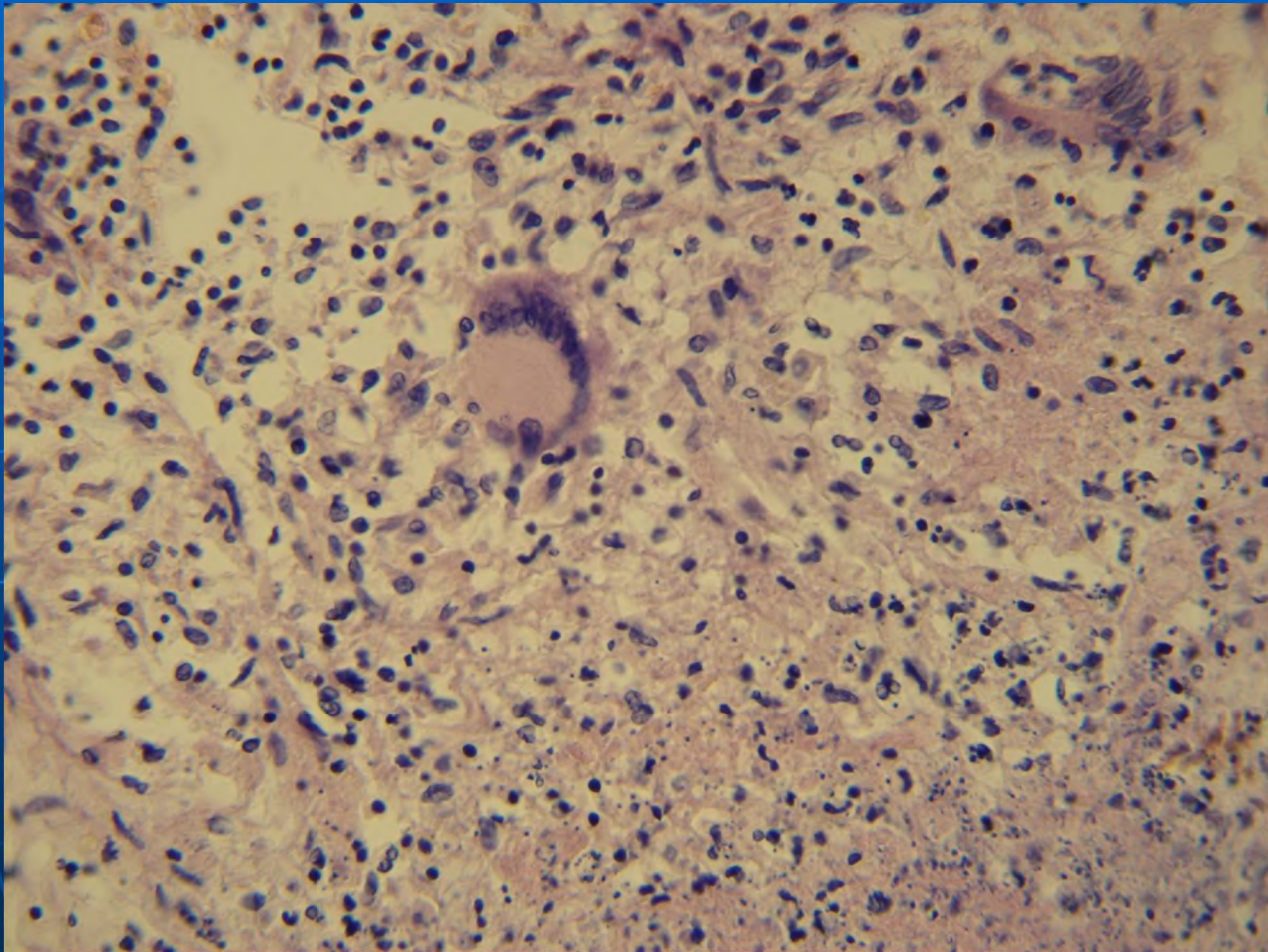
Tuberculosis

Secondary Infiltrative Tuberculosis



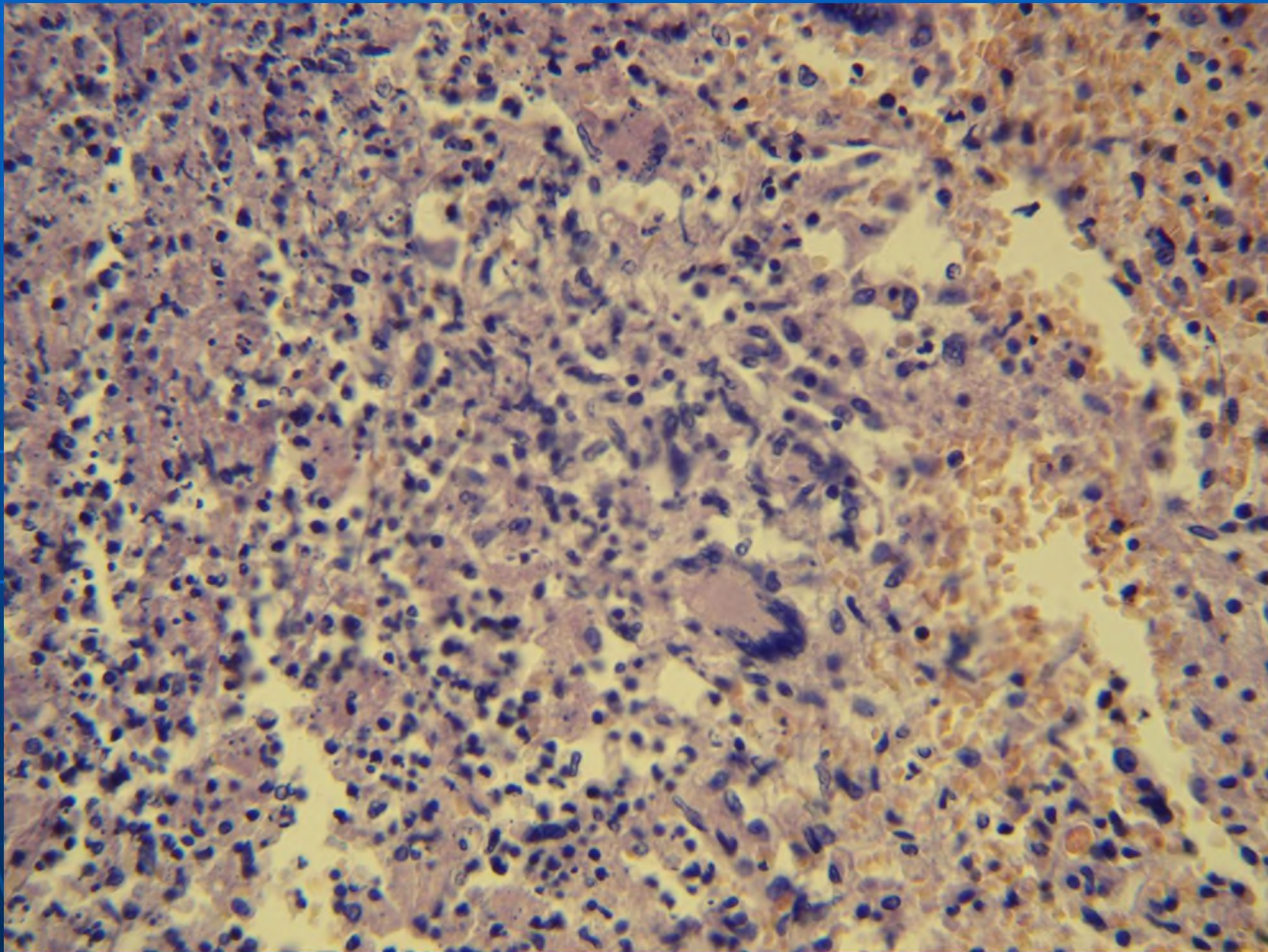
Tuberculosis

Secondary Infiltrative Tuberculosis



Tuberculosis

Secondary Infiltrative Tuberculosis



Tuberculosis

Secondary Tuberculosis

A diffuse, fibrotic, and poorly defined lesion develops that displays focal areas of caseous necrosis. Often, these foci heal and calcify, but some erode into a bronchus, after which drainage of infectious material creates a tuberculous cavity.

Tuberculosis

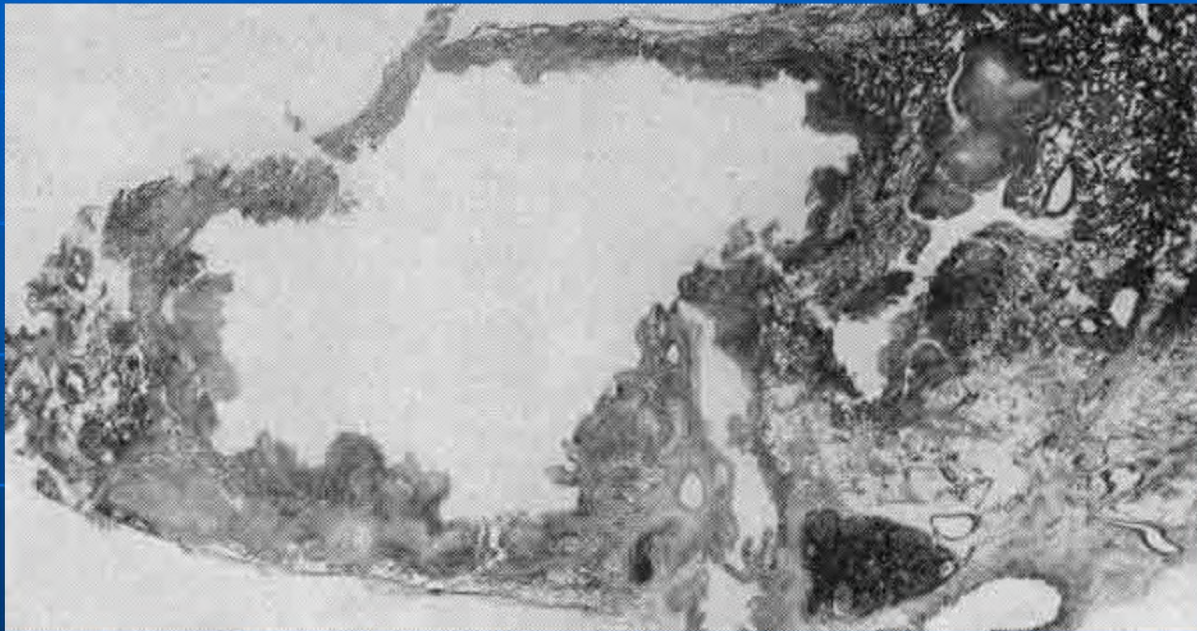
Secondary Tuberculosis

Tuberculous cavities range in size from less than 1 cm in diameter to large, cystic areas that occupy almost the entire lung. Most cavities measure from 3 to 10 cm in diameter, however, and tend to be situated in the apices of the upper lobes, although they may occur anywhere in the lung.

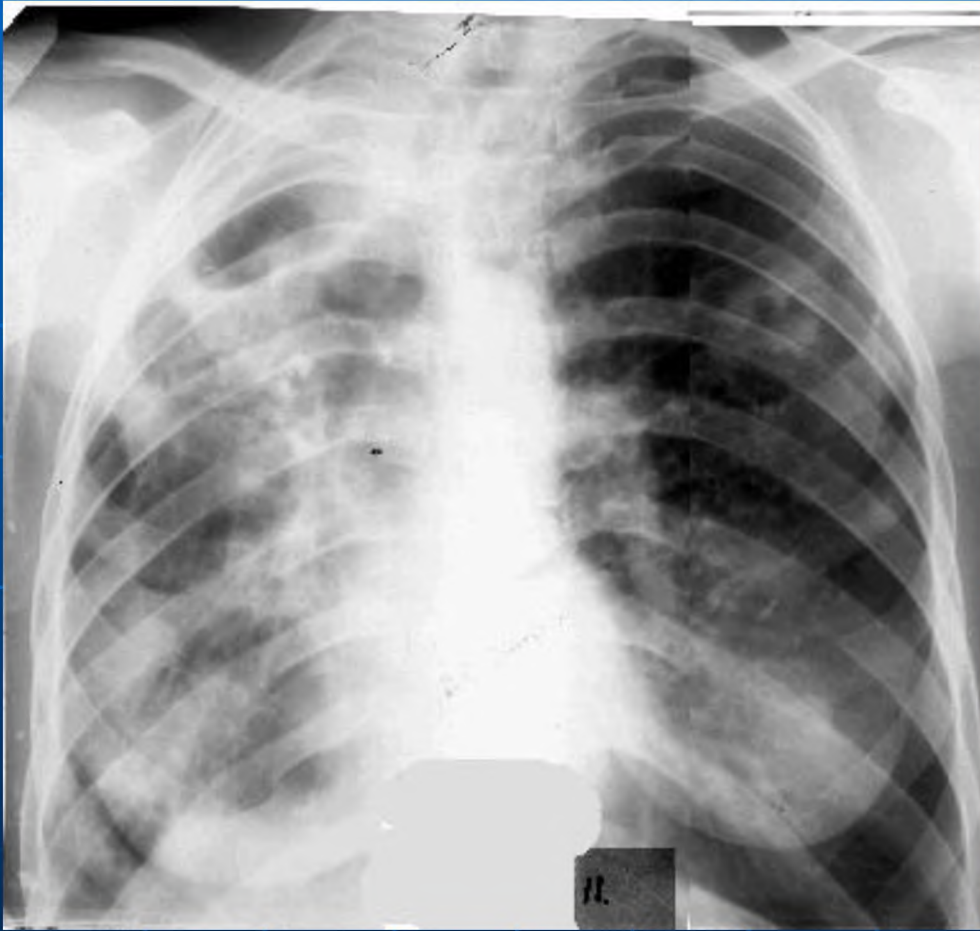
Acute Cavernous Tuberculosis



Acute Cavernous Tuberculosis

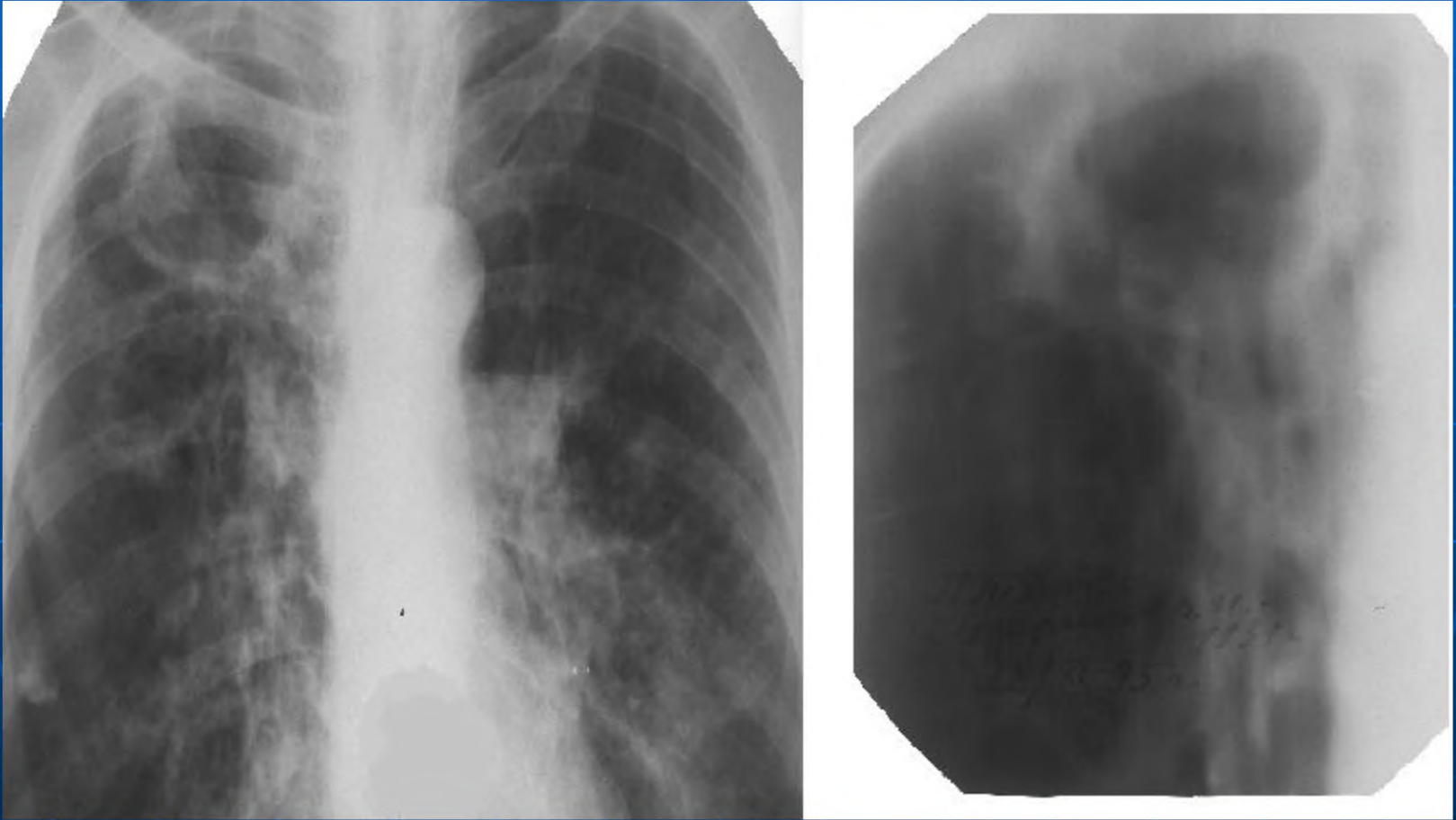


Fibrous Cavernous Tuberculosis



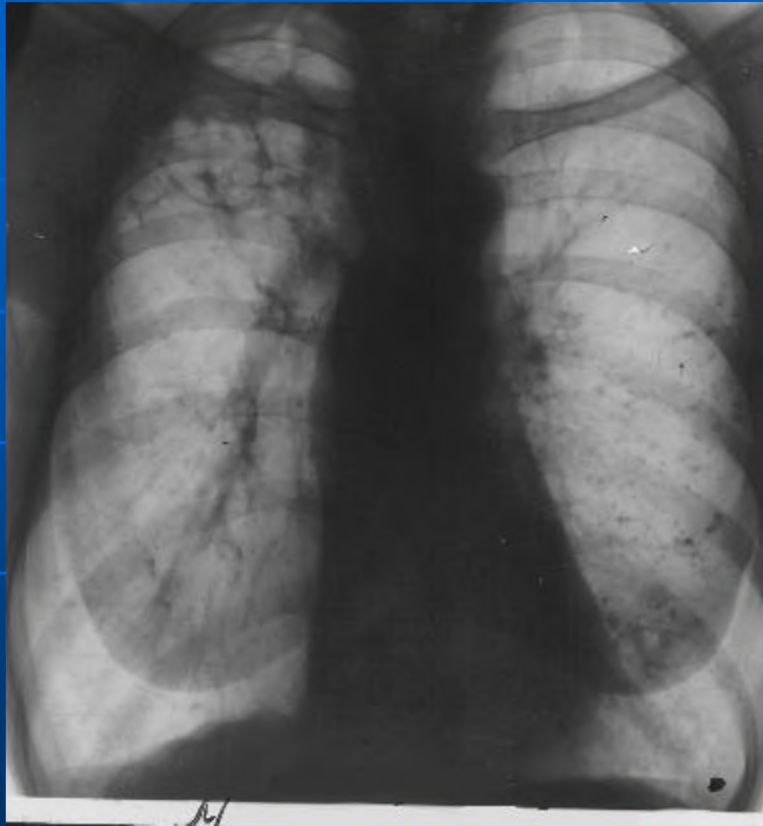
Fibrous Cavernous
Tuberculosis
Destruction of right lung.

Fibrous Cavernous Tuberculosis



Giant caverna.

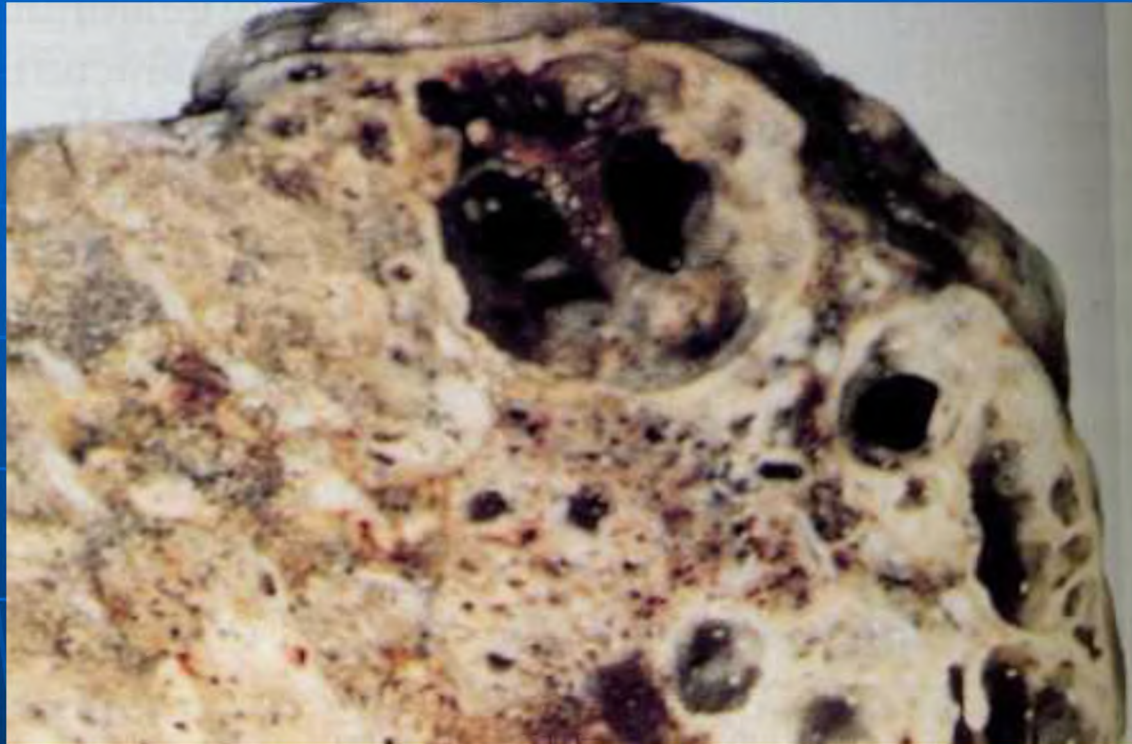
Fibrous Cavernous Tuberculosis



In the upper lobe of the right lung the ring-shaped, thin-walled shade with accurate contours, the sizes 6 x 5 is defined see the dense centers and фиброз in an adjoining part of a lung Come to light. The share in sizes isn't reduced.

Tuberculosis

Secondary Tuberculosis



Cavitory tuberculosis. The apex of the left upper lobe shows tuberculous cavities surrounded by a consolidated and fibrosed pulmonary parenchyma, which contains small tubercles.

Tuberculosis

Secondary Tuberculosis

The wall of the cavity is composed of an inner, thin, gray membrane encompassing soft necrotic nodules, a middle zone of granulation tissue, and an outer collagenous border. The lumen is filled with caseous material containing acid-fast bacilli.

Tuberculosis

Secondary Tuberculosis

The tuberculous cavity often communicates freely with a bronchus, and release of infectious material into the airways serves to disseminate the infection within the lung. The walls of healed tuberculous cavities eventually become fibrotic and calcified.

CAVITARY
TUBERCULOSIS:
Extensive necrosis
with cavitation,
usually occurring in
the upper lung or
apex, is a
characteristic
feature of
"secondary" or
"adult type"
tuberculosis.



Tuberculosis

Secondary Tuberculosis, Caseous Pneumonia



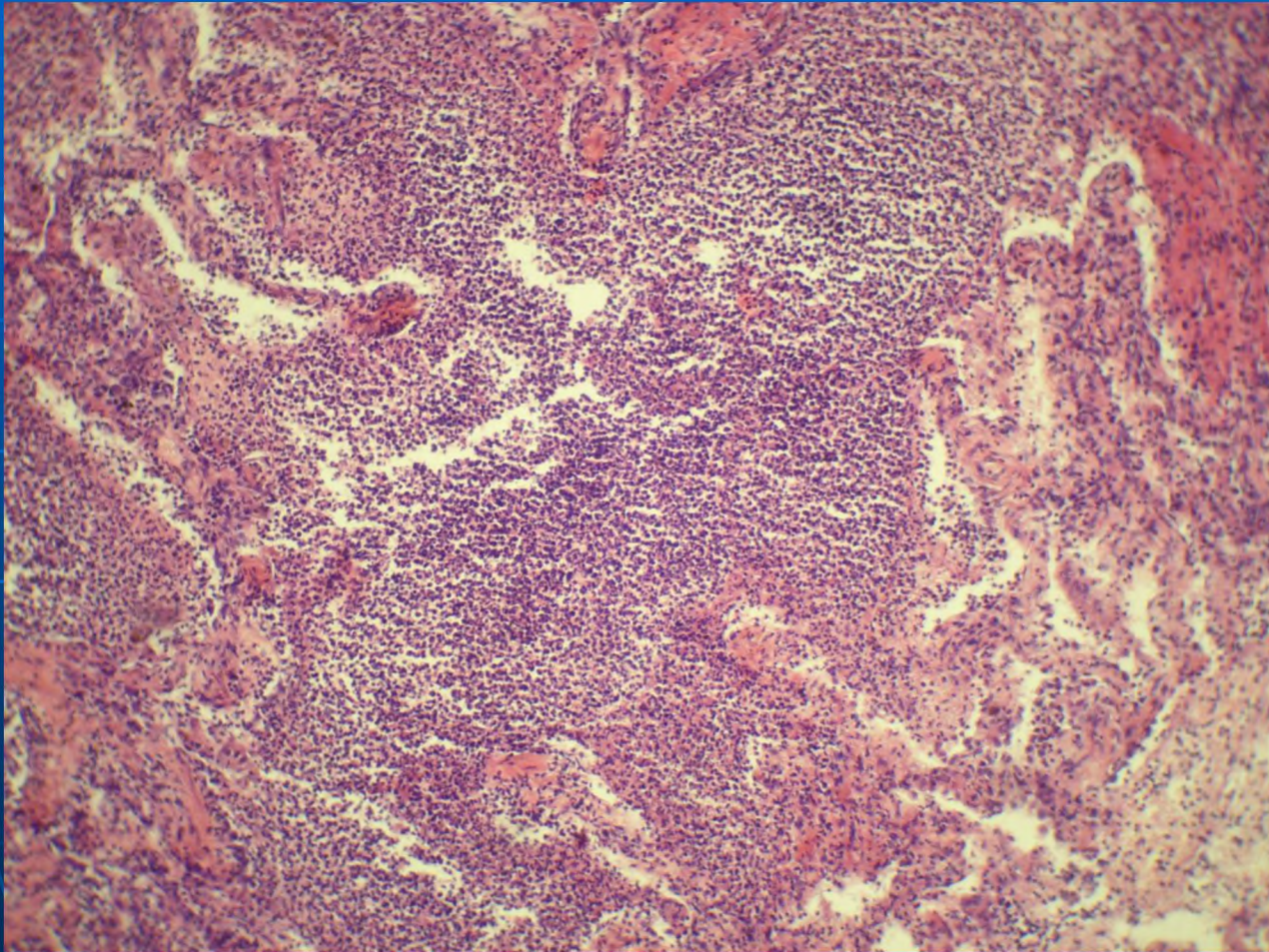
Patient M, 41 year. Caseous Pneumonia of the upper lobe of right lung and plural centers of disintegration.

- Cavitation and extensive tuberculous bronchopneumonia



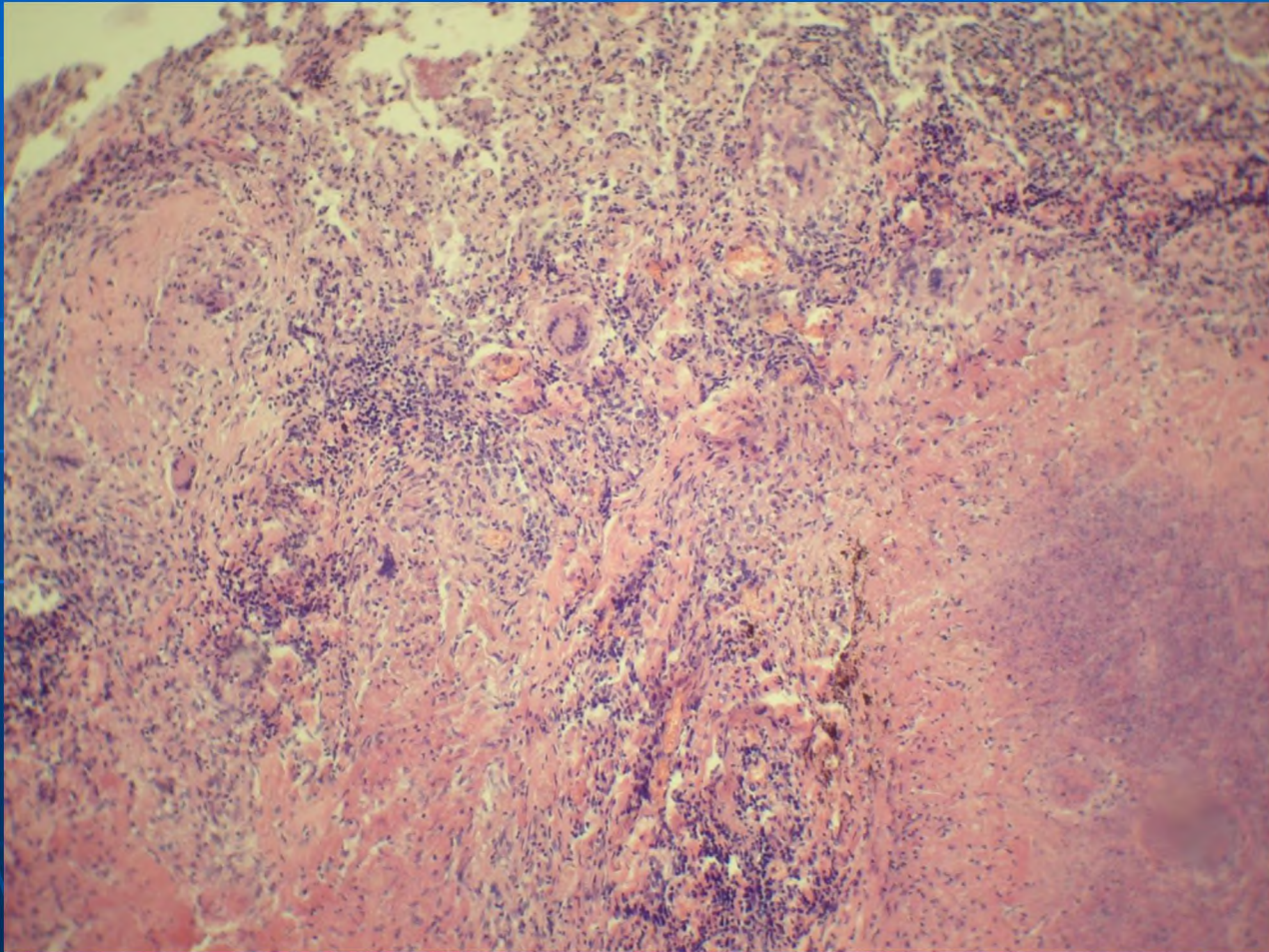
Tuberculosis

Secondary Tuberculosis, Caseous Pneumonia



Tuberculosis

Secondary Tuberculosis, Caseous Pneumonia

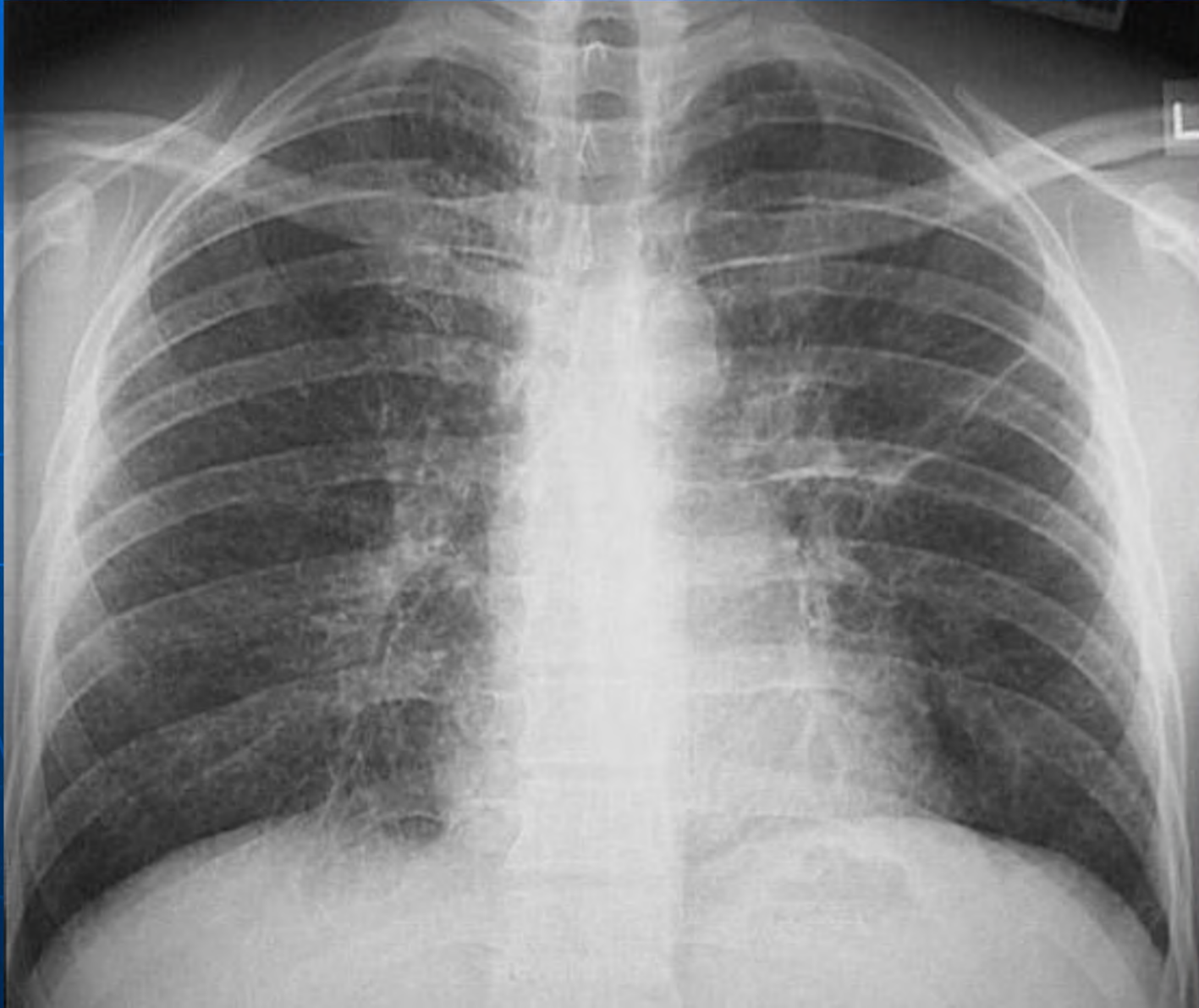


Tuberculosis

Hematogenic Tuberculosis

- **Miliary tuberculosis** refers to the presence of multiple, small (size of millet seeds), tuberculous granulomas in many organs. It results from hematogenous dissemination of the organisms, usually from secondary pulmonary tuberculosis but occasionally from primary pulmonary tuberculosis or from other sites.
- **Hemoptysis** results from the erosion of small pulmonary arteries in the wall of a cavity. It may be severe enough to drown patients in their own blood.
- **Bronchopleural fistula** occurs when a subpleural cavity ruptures into the pleural space. In turn, **tuberculous empyema** and **pneumothorax** result.
- **Intestinal tuberculosis** may follow swallowing of the tuberculous material.

This chest radiograph reveals a miliary pattern in all lung fields. Note the stippled appearance throughout.



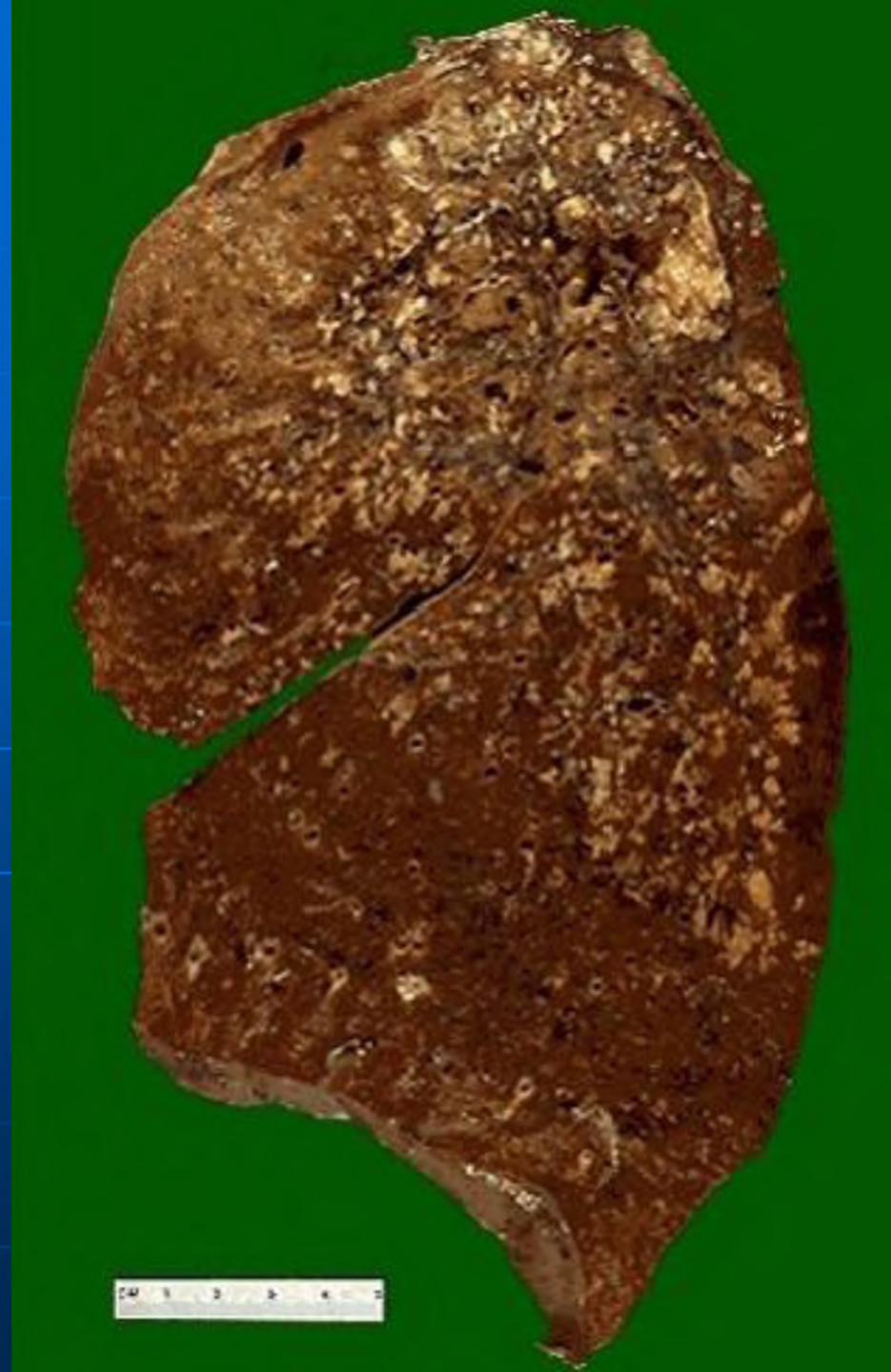
- When the immune response is poor or is overwhelmed by an extensive infection, then it is possible to see the gross pattern of granulomatous disease seen here. This is a "miliary" pattern of granulomas because there are a multitude of small tan granulomas, about 2 to 4 mm in size, scattered throughout the lung parenchyma. The miliary pattern gets its name from the resemblance of the granulomas to millet seeds.

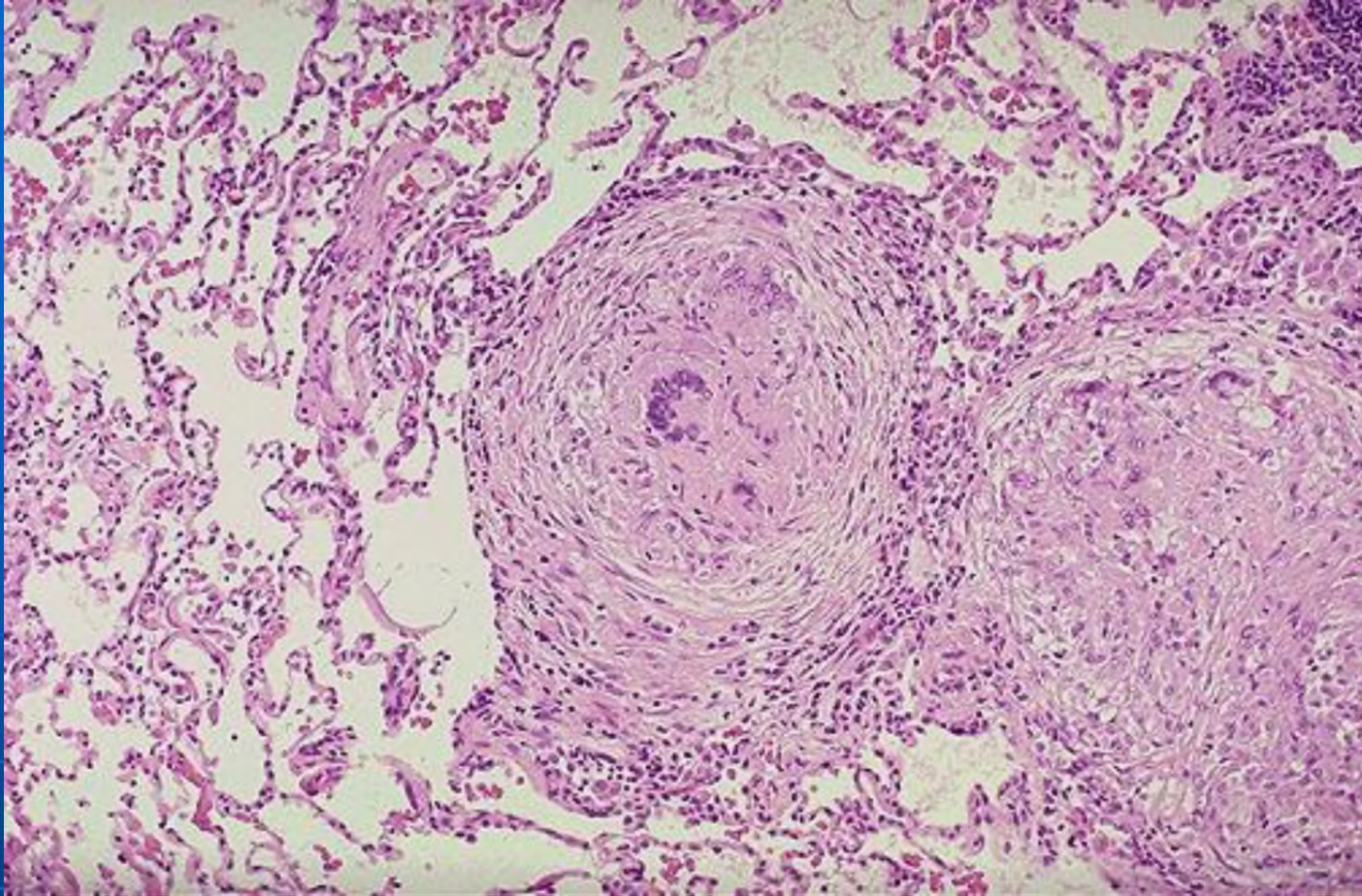


- Here is the gross appearance of a lung with tuberculosis. Scattered tan granulomas are present, mostly in the upper lung fields. Some of the larger granulomas have central caseation. Granulomatous disease of the lung grossly appears as irregularly sized rounded nodules that are firm and tan. Larger nodules may have central necrosis known as caseation).

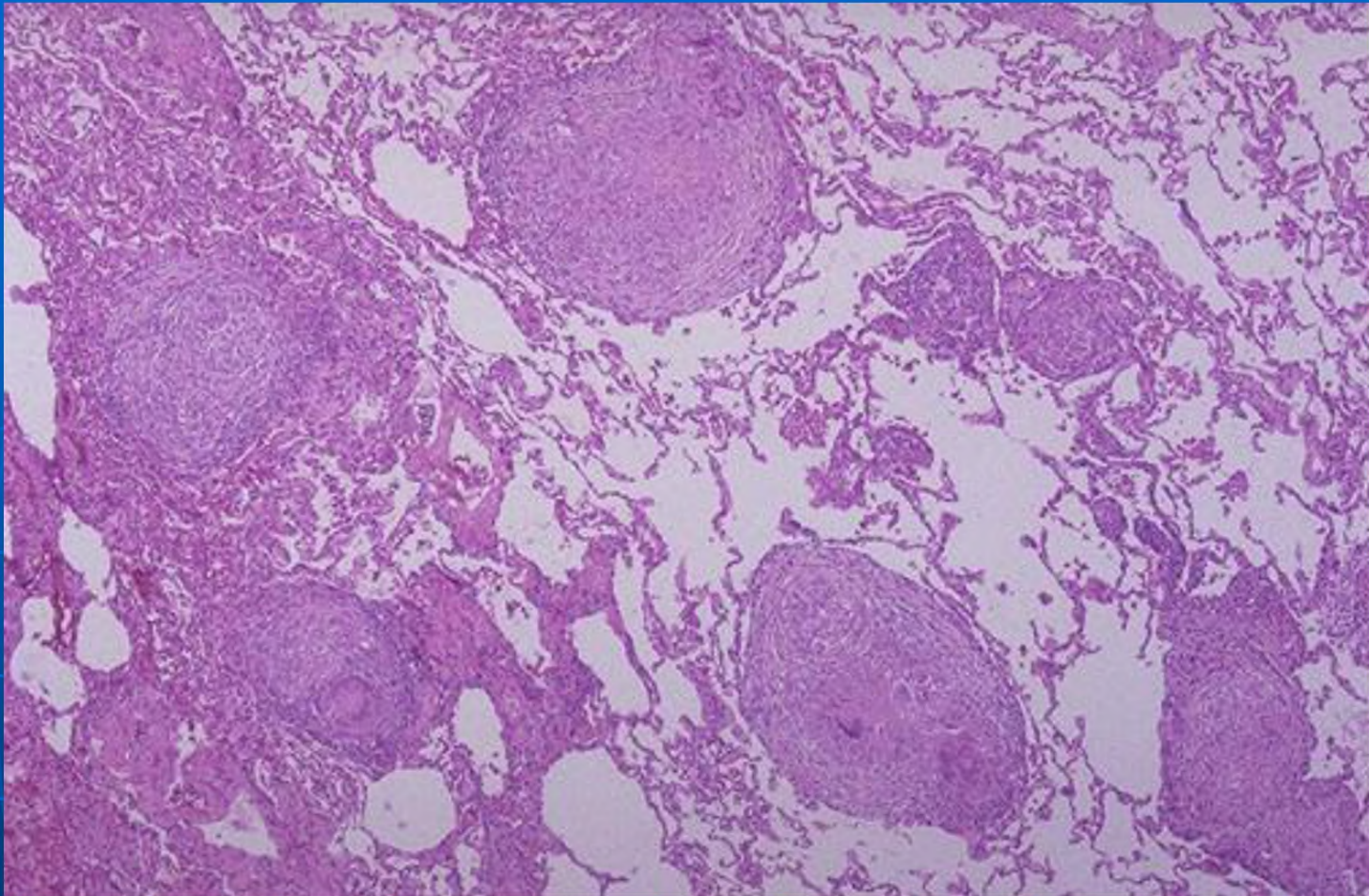


- This is another example of granulomatous disease of the lung. The pattern of smaller nodules which have a propensity for upper lobe involvement suggests a granulomatous process rather than metastatic disease.



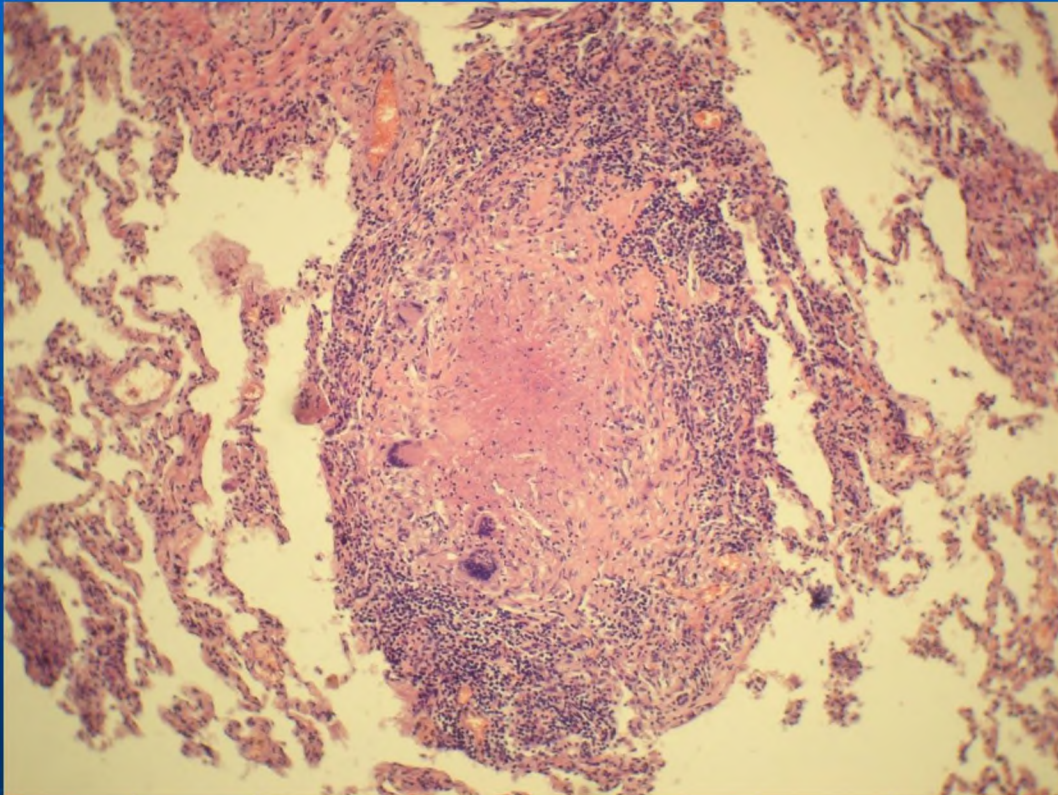


- Well-defined granulomas are seen here. They have rounded outlines. The one toward the center of the photograph contains several Langhans giant cells. Granulomas are composed of transformed macrophages called epithelioid cells along with lymphocytes, occasional PMN's, plasma cells, and fibroblasts. The localized, small appearance of these granulomas suggests that the immune response is fairly good.



- At low magnification, this photomicrograph reveals multiple granulomas. Granulomatous disease by chest radiograph can appear as reticulonodular densities.

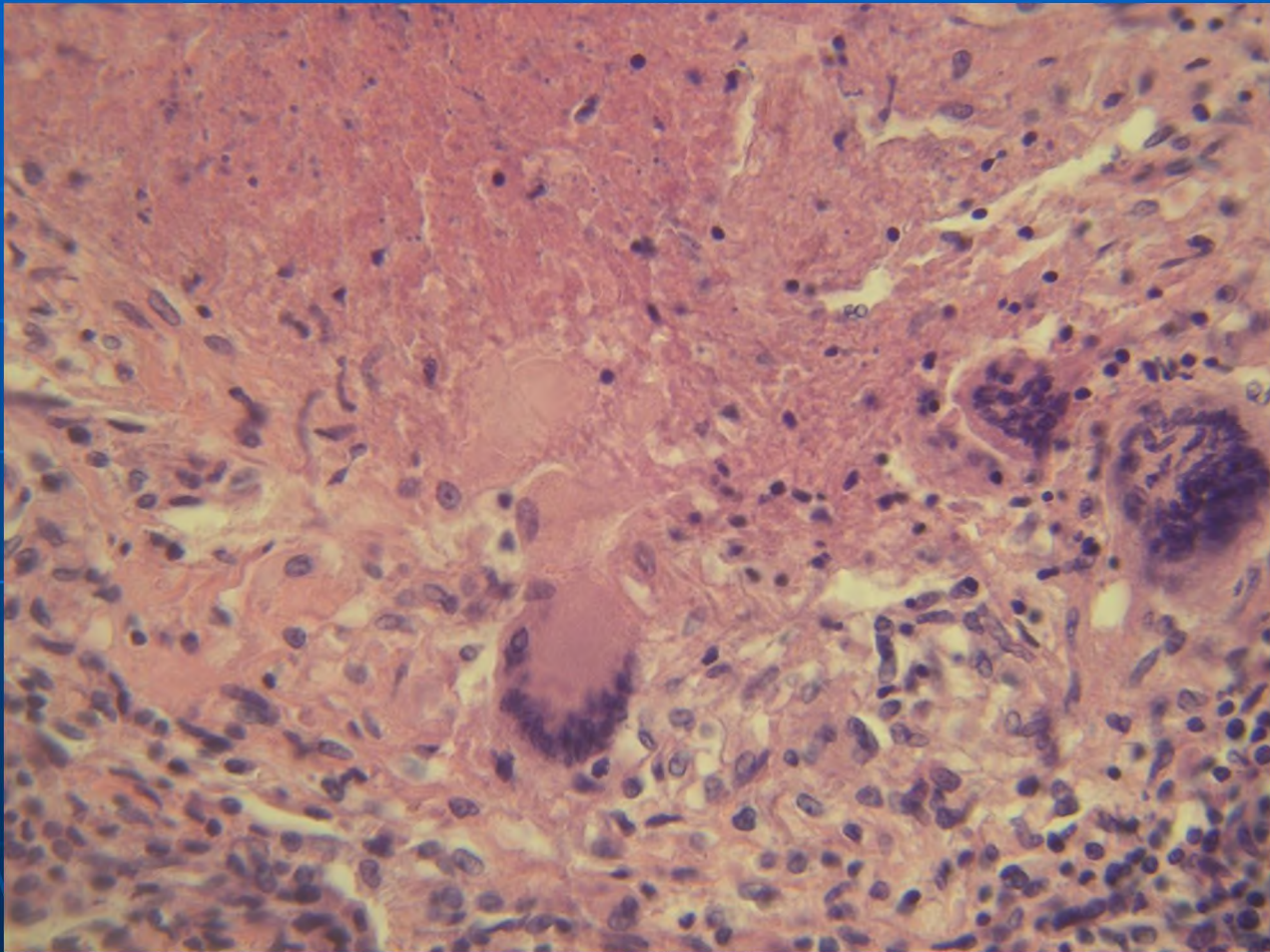
Tuberculosis

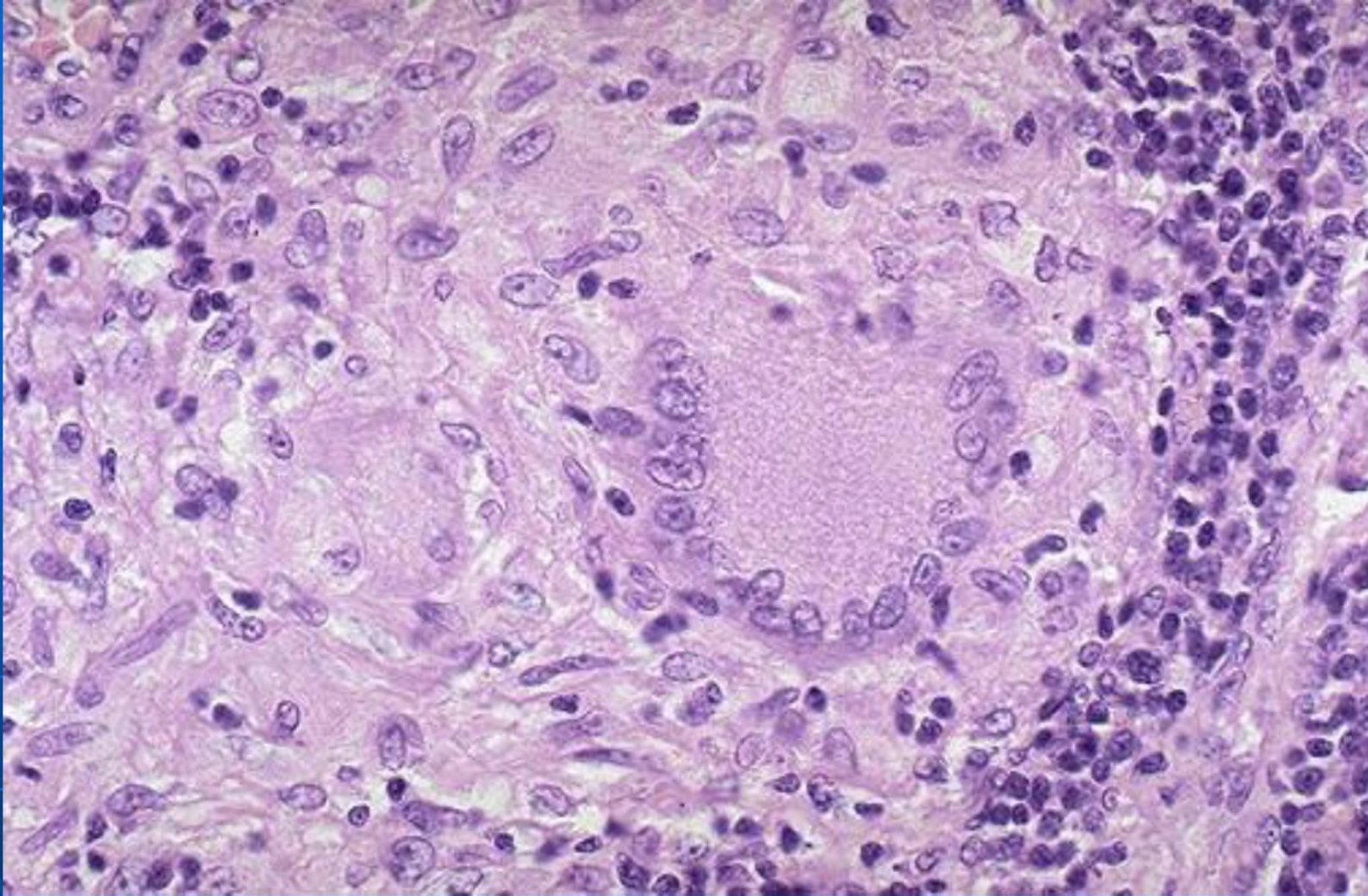


Miliary tuberculosis.
A small tuberculous granuloma with conspicuous central caseation is present in the pulmonary parenchyma.

Tuberculosis

Miliary Tuberculosis





- At high magnification, the granuloma demonstrates that the epithelioid macrophages are elongated with long, pale nuclei and pink cytoplasm. The macrophages organize into committees called giant cells. The typical giant cell for infectious granulomas is called a Langhans giant cell and has the nuclei lined up along one edge of the cell. The process of granulomatous inflammation takes place over months to years.

Tuberculosis

Tuberculosis is associated with a number of complications:

- It results from hematogenous dissemination of the organisms, usually from secondary pulmonary tuberculosis but occasionally from primary pulmonary tuberculosis or from other sites.
- Tuberculous meningitis.
- **Hemoptysis** results from the erosion of small pulmonary arteries in the wall of a cavity. It may be severe enough to drown patients in their own blood.
- **Pulmonary bleeding.**
- **Bronchopleural fistula** occurs when a subpleural cavity ruptures into the pleural space. In turn, **tuberculous empyema** and **pneumothorax** result.
- **Intestinal tuberculosis** may follow swallowing of the tuberculous material.

Pathology of Lung Infection

Fungal Infections

Aspergillosis

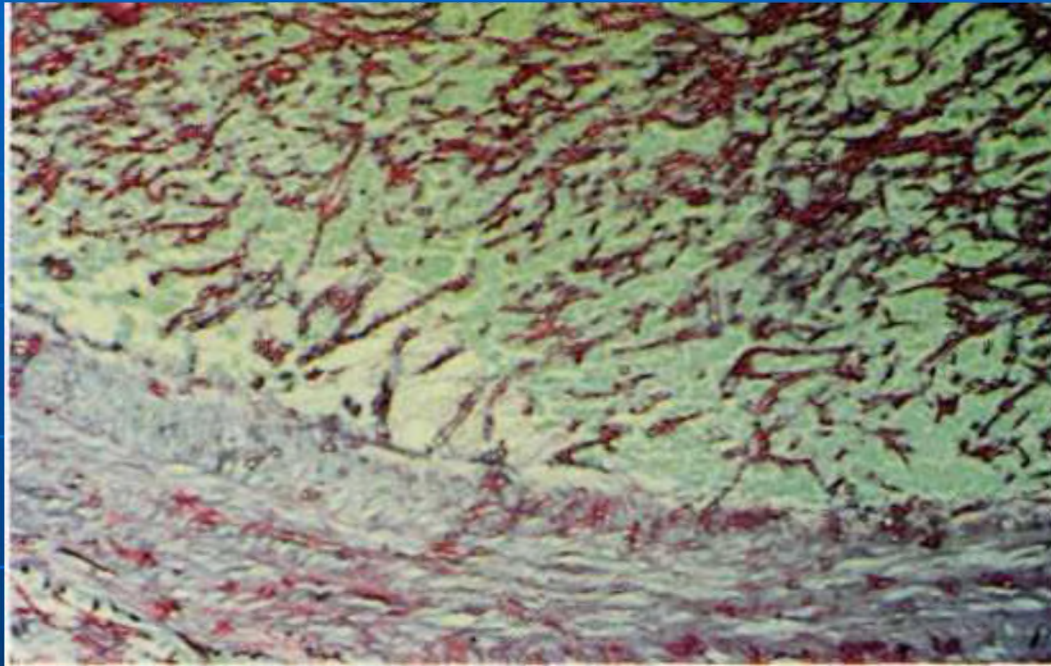
Infection of the lungs by *Aspergillus* species, usually *A. niger* or *A. fumigatus*, can occur in a number of circumstances:

- **Invasive Pulmonary Aspergillosis.**
- **Aspergilloma.**
- **Allergic Bronchopulmonary Aspergillosis.**

Pathology of Lung Infection

Fungal Infections

Aspergillosis



Invasive pulmonary aspergillosis. A branch of the pulmonary artery shows fungal hyphae in the wall and within the lumen.

Pathology of Lung Infection

Fungal Infections

Aspergillosis

Invasive Pulmonary Aspergillosis. This is the most serious manifestation of *Aspergillus* infection, occurring almost exclusively as an opportunistic infection in persons with compromised immunity, usually because of cytotoxic therapy or acquired immunodeficiency syndrome (AIDS). The lungs exhibit patchy, multifocal areas of consolidation and, occasionally, cavities. **Extensive blood vessel invasion** (usually arterial results in occlusion, thrombosis, and infarction of lung tissue. Invasive aspergillosis is a fulminant pulmonary infection that is not amenable to therapy.

Pathology of Lung Infection

Fungal Infections

Aspergillosis

Aspergilloma. *Aspergillus* species may grow in preexisting cavities, such as those caused by tuberculosis or bronchiectasis. They proliferate to form an aspergilloma ("fungus ball" or mycetoma) within the cavities.

Pathology of Lung Infection

Fungal Infections

Aspergillosis

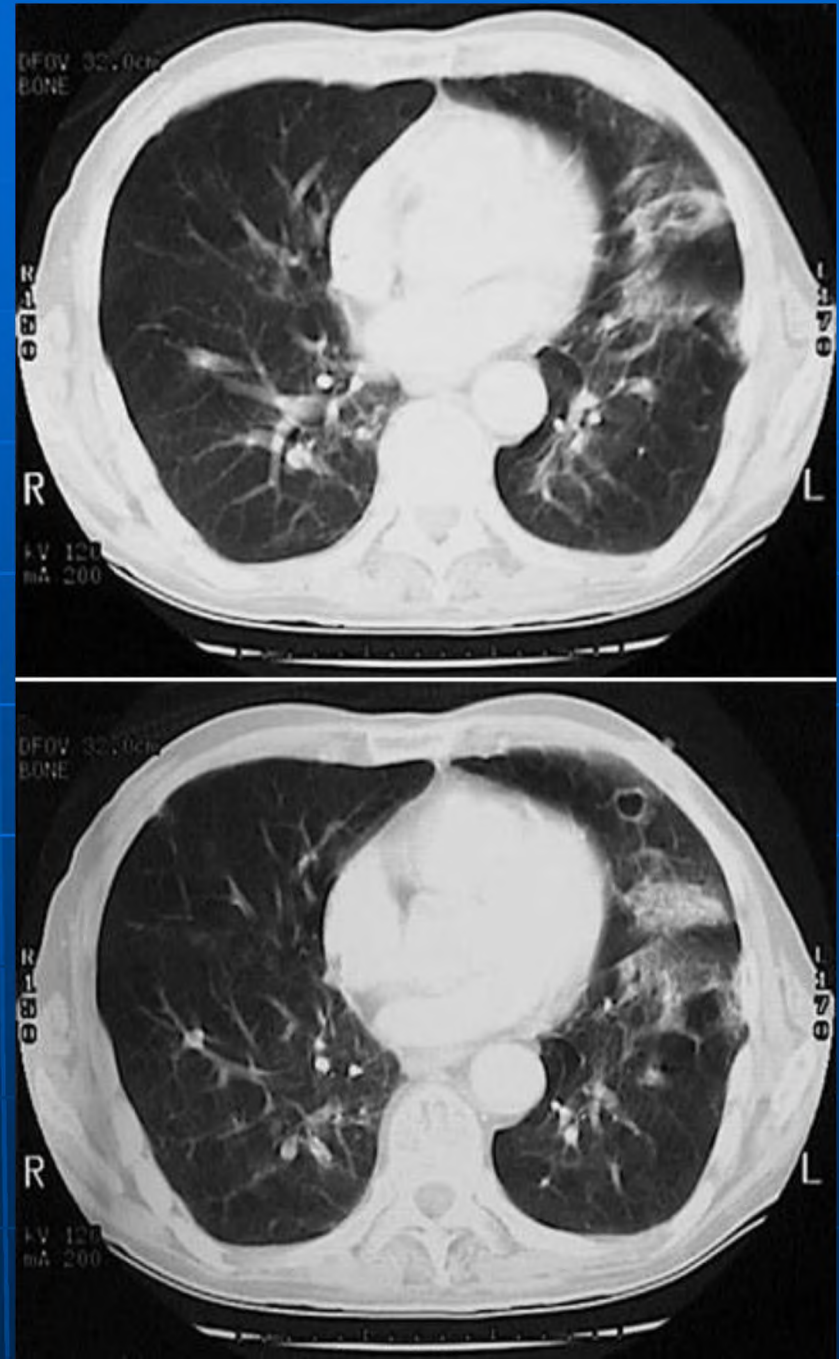
Allergic Bronchopulmonary Aspergillosis.

Certain persons with asthma demonstrate an unusual immunologic reaction to *Aspergillus* infection, which is characterized by (1) transient pulmonary infiltrates on chest radiographs, (2) eosinophilia of blood and sputum, (3) skin sensitivity and serum precipitins to *A.fumigatus*, and (4) elevated levels of serum IgE. The administration of systemic corticosteroids usually controls the acute episode.

- This is a fungal granuloma produced by *Aspergillus*. An infectious process is suggested by the fact that the lesion has crossed the fissure as though it weren't there. A neoplasm usually is initially impeded by an anatomical barrier. This granuloma has an irregular, red margin and a firm, tan-orange center.



- The chest CT scan seen here displays two panels, each with nodular densities in an immunocompromised patient with neutropenia and pulmonary aspergillosis.

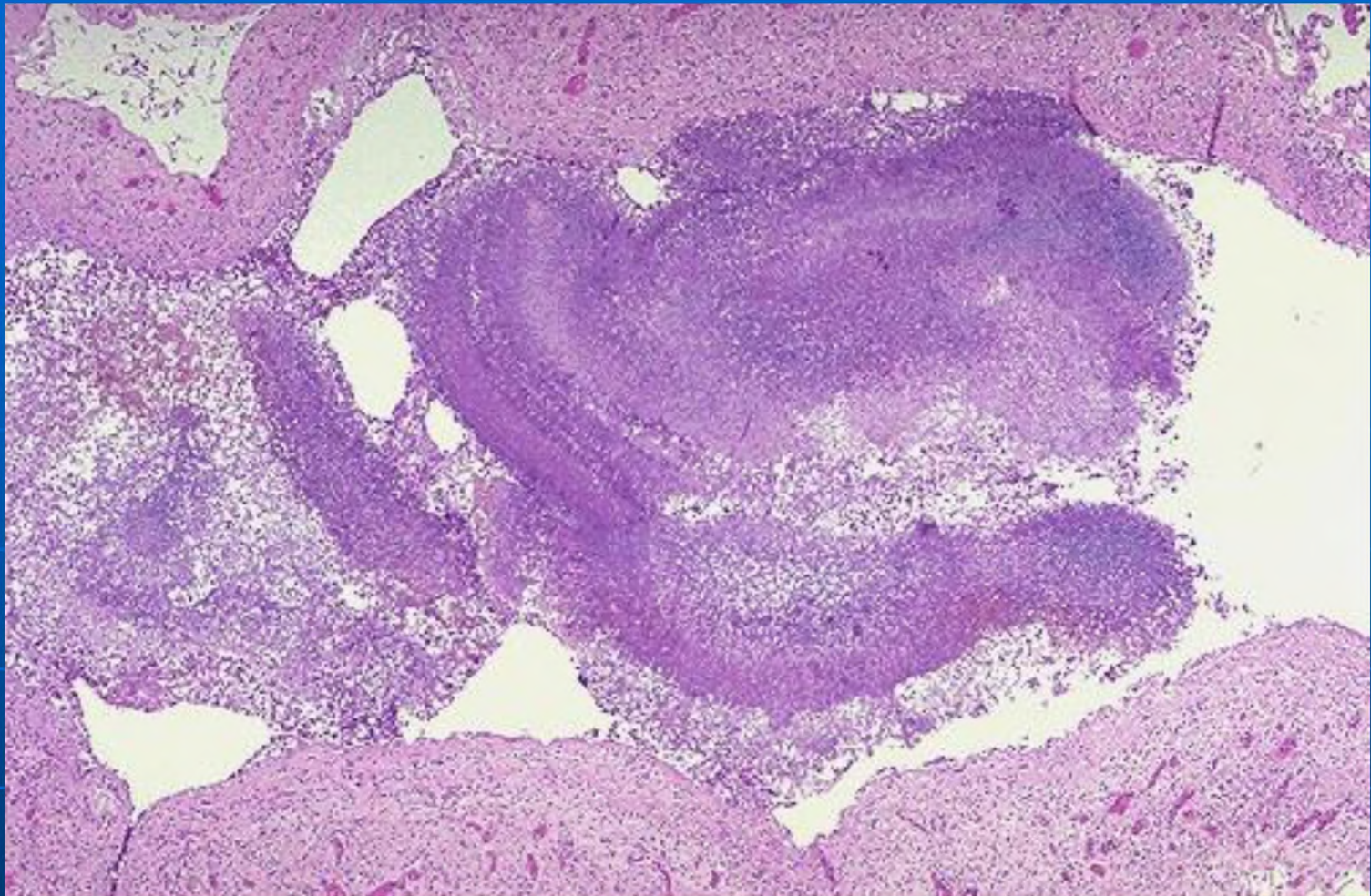




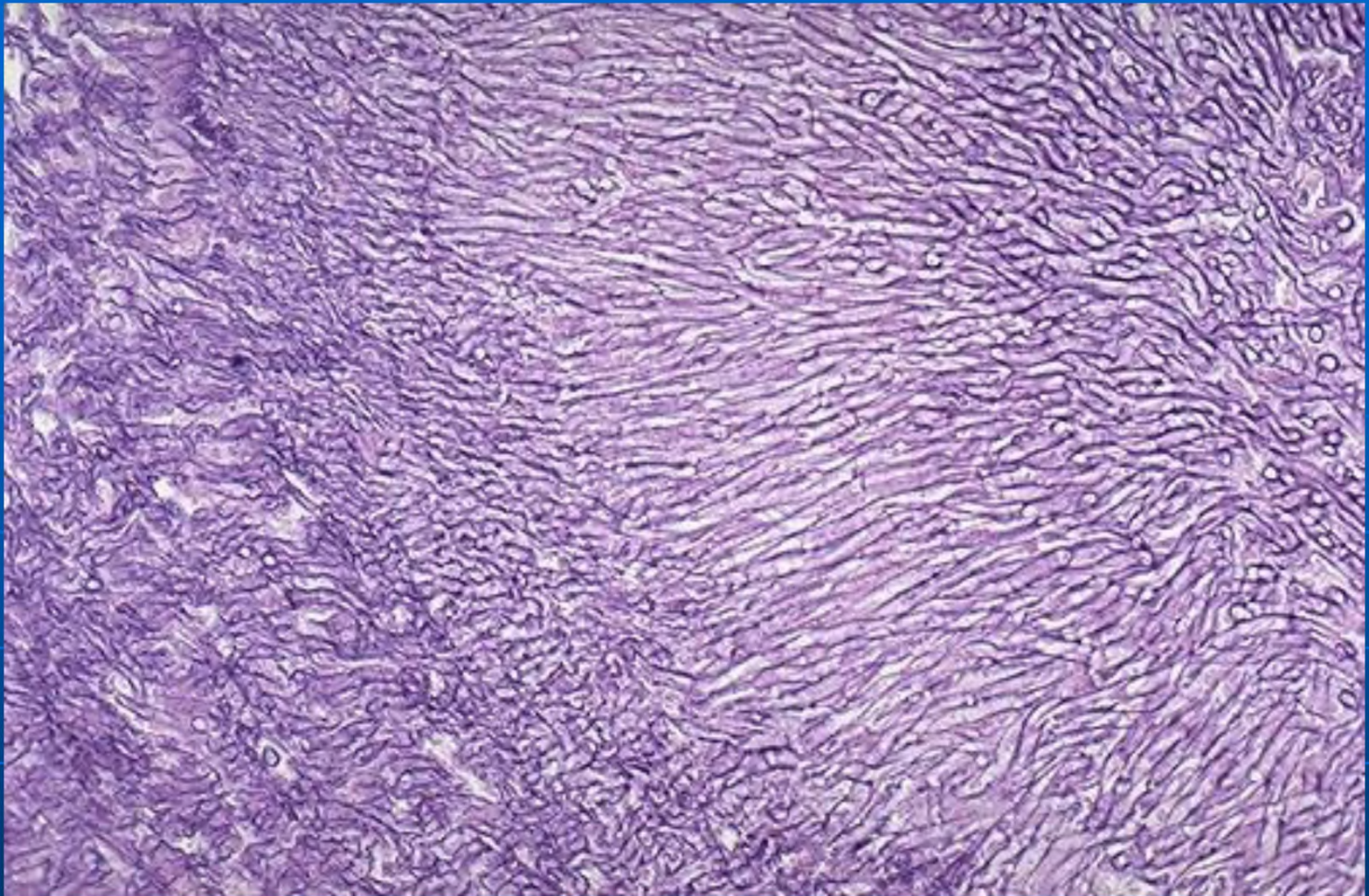
- Aspergillus has a tendency to invade vessels, even large pulmonary arterial branches as seen here, with a thrombus formed of fungal hyphae as well as blood clot filling the lumen. This can result in dissemination to other organs, as well as pulmonary infarction.

- Here is another fungal granuloma. Note the sharp outlines.

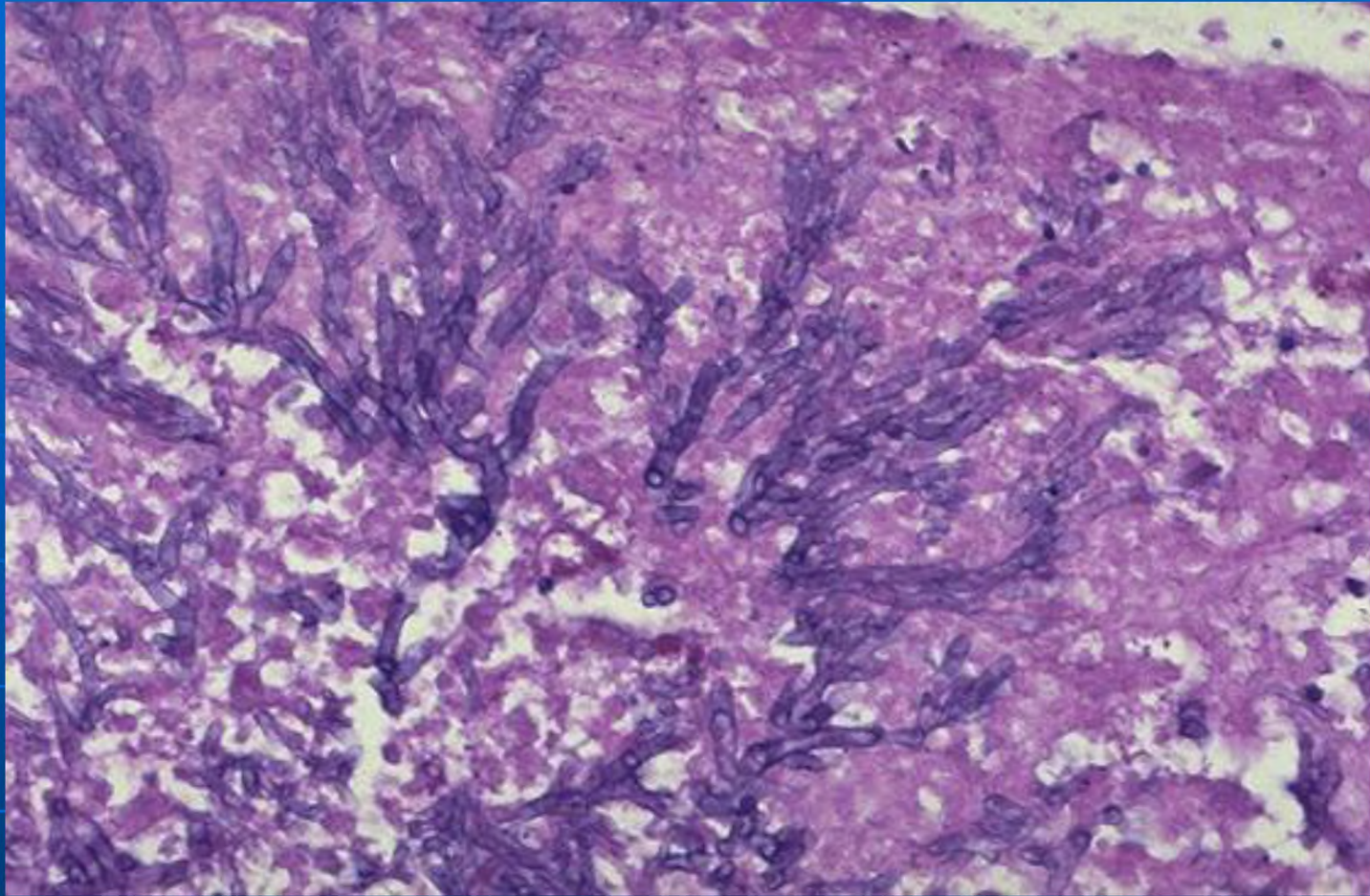




- A fungus ball composed of blue-staining hyphal elements of Aspergillus is seen here in a bronchus. Fungus balls may also form when fungi colonize cavitary lesions of tuberculosis.



- Branching, septate hyphae are close-packed here and radiating outward in this aspergilloma.

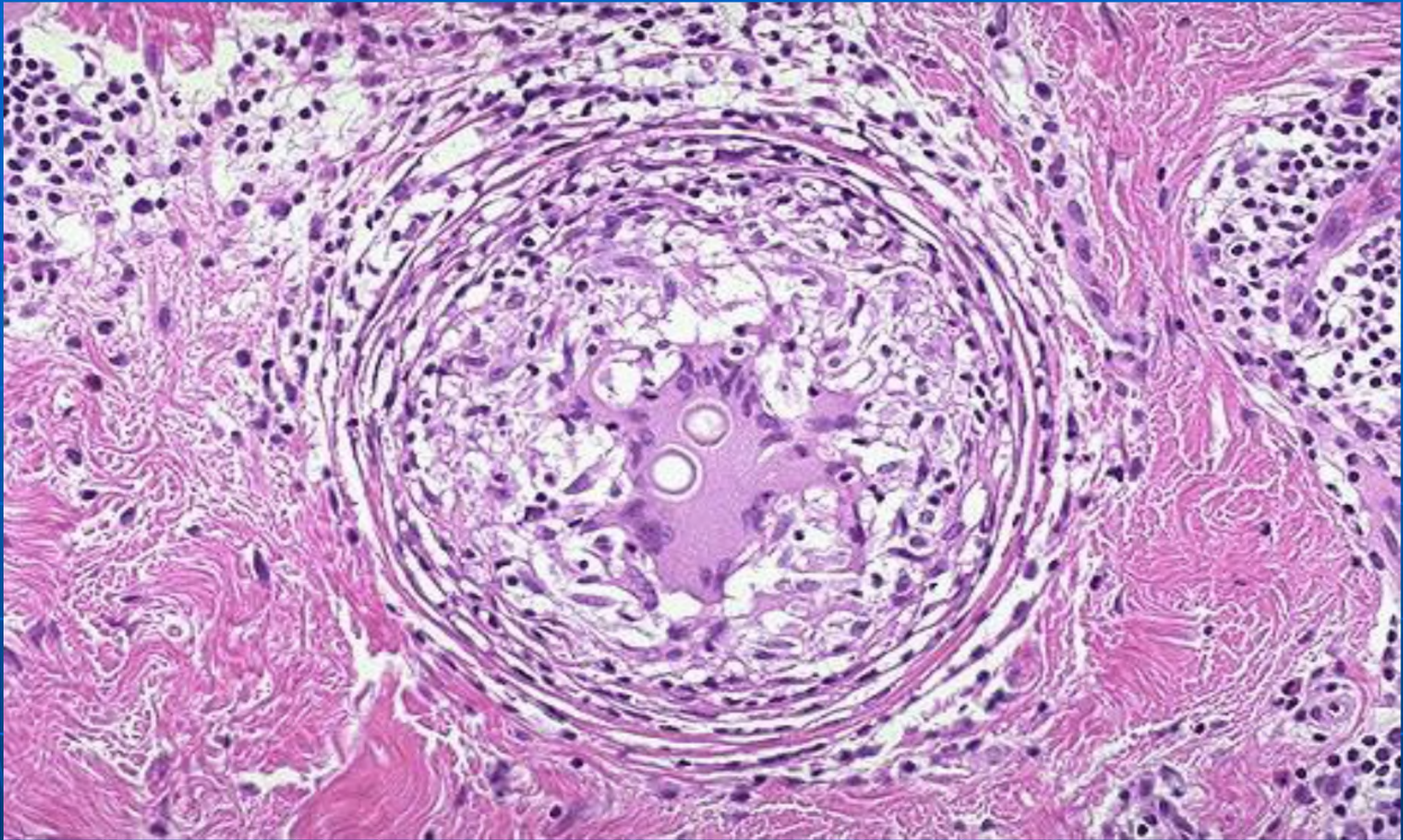


- The hyphae of *Aspergillus* are seen more clearly here. *Aspergillus* has a propensity to invade into blood vessels.

Fungal Infections

Coccidioidomycosis

Coccidioidomycosis, which is caused by inhalation of the spores of *Coccidioides immitis*, is widely spread through the southwestern part of the United States, sharing many of the clinical and pathologic features of histoplasmosis and tuberculosis.

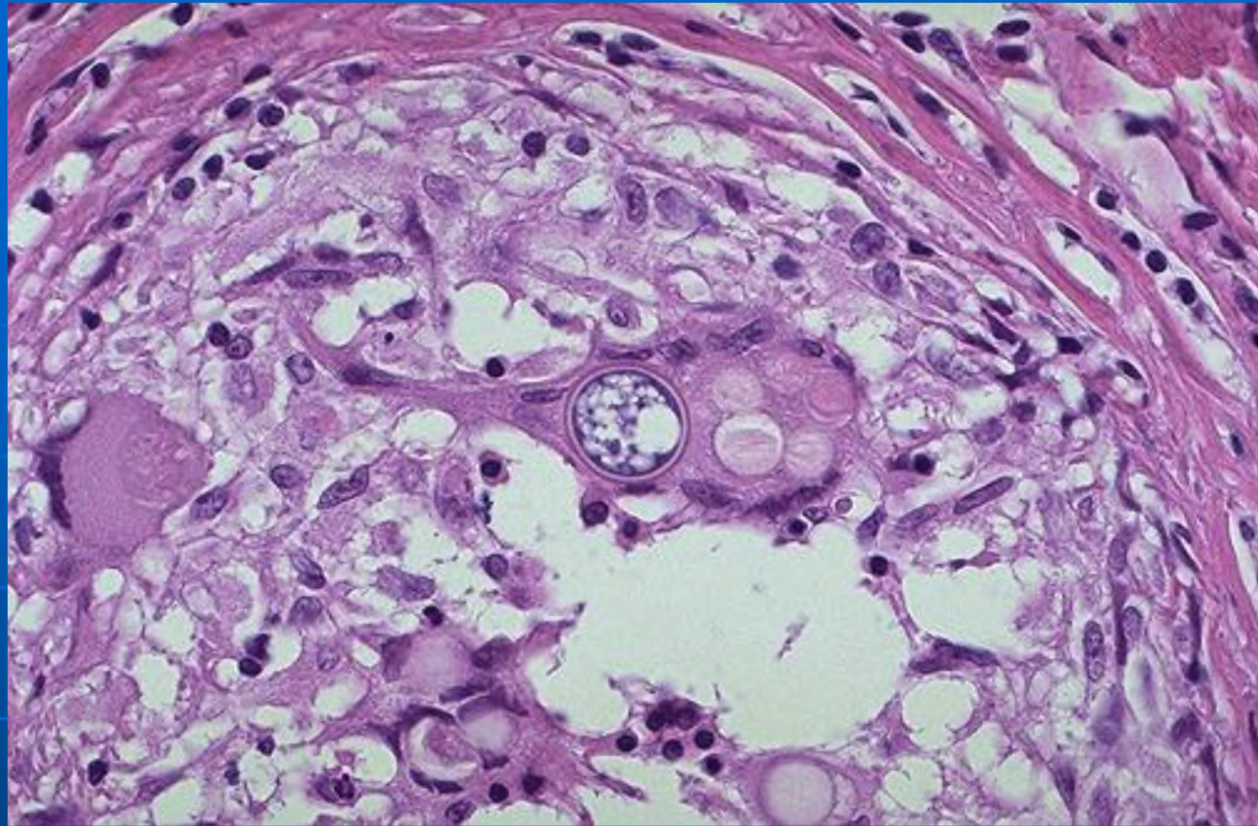


- This well-formed granuloma has a large Langhans giant cell in the center. Two small spherules of *Coccidioides immitis* are seen in the giant cell.

Fungal Infections

Coccidioidomycosis

In most instances, the lesions are limited to a peripheral parenchymal granuloma, with or without lymph node granulomas. In a few instances, however, the lesion is progressive, although the rate of progression is slow. Immunocompromised patients may experience rapid progression of the disease.



- At higher magnification, the thick wall of the *C. immitis* spherule is seen in a giant cell in the center of the photomicrograph. The spherule contains endospores. In the United States, *C. immitis* is endemic to the southwest.

Fungal Infections

Histoplasmosis

Histoplasmosis is a disease of the midwestern and southeastern regions of the United States, particularly the Mississippi and Ohio river valleys. The disease is caused by inhalation of *Histoplasma capsulatum* in infected dust, commonly from bird droppings.

Pathology of Lung Infection

Fungal Infections

Histoplasmosis

Pathology: Histoplasmosis has many clinical and pathologic similarities with tuberculosis. The great majority of infections are asymptomatic and result in lesions similar to the Ghon complex, including a parenchymal granuloma and similar lesions in the draining lymph nodes.

Pathology of Lung Infection

Fungal Infections

Histoplasmosis

The granulomas are particularly prone to calcify, often with a concentric, laminar pattern. In a few cases, the pulmonary lesion progresses or reactivates, which leads to a progressive fibrotic and necrotic lesion that closely resembles reactivation tuberculosis.

Pathology of Lung Infection

Fungal Infections

Cryptococcosis

Cryptococcosis results from inhalation of the spores of *Cryptococcus neoformans*, an organism that is frequently encountered in pigeon droppings. The pulmonary lesions range from small parenchymal granulomas to several large, granulomatous nodules, pneumonic consolidation, and even cavitation. Most serious cases of pulmonary cryptococcosis occur in those who are immunocompromised.

Pathology of Lung Infection

Fungal Infections

North American Blastomycosis

Blastomycosis is an uncommon condition caused by *Blastomyces dermatitidis*. It is concentrated in the basins of the Missouri, Mississippi, and Ohio rivers in the United States. The clinical and pathologic features resemble those associated with the fungi mentioned earlier. They may present as a lesion resembling a Ghon complex or as a progressive pneumonic condition.



HUMAN IMMUNODEFICIENCY VIRUS DISEASE AND AIDS

Human immunodeficiency virus (HIV)

- There are about 33.2 million (estimate range: 30.6 million - 36.1 million) HIV-infected people in the world of whom about 22.5 million (range: 20.9 million - 24.3 million) are in sub-Saharan Africa where the adult infection prevalence is about 6%.

Human immunodeficiency virus (HIV)

- In October 2008, CDC released new estimates of the extent of the HIV/AIDS epidemic. These showed that 1,106,400 adults and adolescents were living with HIV infection in the United States at the end of 2006 (95% Confidence Interval: 1,056,400–1,156,400).

Asia/Pacific region

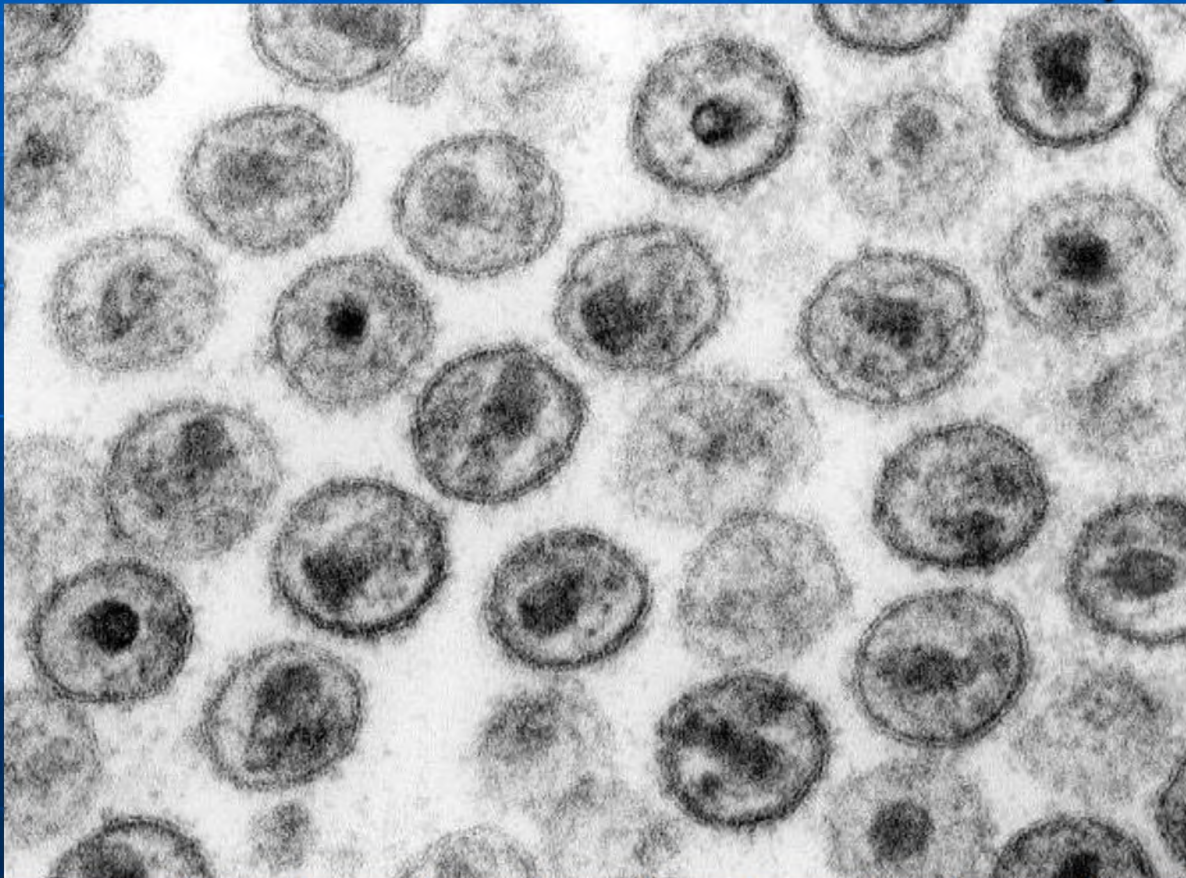
- HIV continues to be a major global public health issue, having claimed more than 39 million lives so far. **In 2013, 1.5 [1.4–1.7] million people died** from HIV-related causes globally.
- In 2006, about 1 million people in the Asia/Pacific region became infected by HIV and 630,000 people died. The total infected population in this region is an estimated 4.9 million (range 3.7 million - 6.7 million) people; of these, 2.1 million are age 15 to 24 years and 2.4 million are women (up 21% since 2004). In this region, HIV is increasing at a rate of 10% per year.

In sub-Saharan Africa

- There were approximately **35.0 [33.2–37.2] million people living with HIV** at the end of 2013 with 2.1 [1.9–2.4] million people becoming newly infected with HIV in 2013 globally.
- Sub-Saharan Africa is the most affected region, with 24.7 [23.5–26.1] million people living with HIV in 2013. Also sub-Saharan Africa accounts for almost 70% of the global total of new HIV infections.
- There are an estimated 22.5 million (range: 20.9 million–24.3 million) people infected by HIV with over 2.8 million new infections in 2006. In this region, there were 2.1 million deaths. Ten million young Africans between the ages of 15 and 24 and 3 million children are infected.

HIV

- It is likely that HIV first appeared in humans in Africa near the beginning of the twentieth century



Electron
microscopy of
human
immunodeficiency
virus (HIV)-1
virions.

Courtesy of
CDC/Dr. Edwin P.
Ewing, Jr.

- Human immunodeficiency virus (HIV) is a blood-borne virus typically transmitted via sexual intercourse, shared intravenous drug paraphernalia, and mother-to-child transmission (MTCT), which can occur during the birth process or during breastfeeding. HIV disease is caused by infection with HIV-1 or HIV-2, which are retroviruses in the Retroviridae family, Lentivirus genus.

- The human immunodeficiency virus (HIV) is a retrovirus that infects cells of the immune system, destroying or impairing their function. As the infection progresses, the immune system becomes weaker, and the person becomes more susceptible to infections. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS). It can take 10-15 years for an HIV-infected person to develop AIDS; antiretroviral drugs can slow down the process even further.

- HIV is transmitted through unprotected sexual intercourse (anal or vaginal), transfusion of contaminated blood, sharing of contaminated needles, and between a mother and her infant during pregnancy, childbirth and breastfeeding.

STRUCTURE OF THE VIRUS

COMPONENTS OF HIV

- HIV is a retrovirus with a similar structure to other retroviruses.
- **SURFACE STRUCTURES**
- **Viral membrane**
- The membrane is host-derived as a result of budding from the cell surface. Some host proteins become incorporated into the viral membrane. This lipid envelope make the virus susceptible to organic solvents.

Surface glycoprotein

- Gp160 is encoded by the env (envelope) gene. Gp160 is cleaved after translation by host enzymes in the Golgi Body to form Gp120 (SU) and Gp41 (TM). Gp 41 is embedded in the membrane, Gp120 is not but is held to Gp41 by non-covalent interactions. It is easily shed from the virus particle. There is a large number of sugar chains on gp120 (which may pose a problem for a vaccine). Gp120 is the protein that interacts with a receptor on the cell to be infected. Gp41 is the fusogen that is exposed after Gp120 has bound to the cell.

Signs and symptoms

The patient with HIV may present with signs and symptoms of any of the stages of HIV infection. No physical findings are specific to HIV infection; the physical findings are those of the presenting infection or illness. Manifestations include the following:

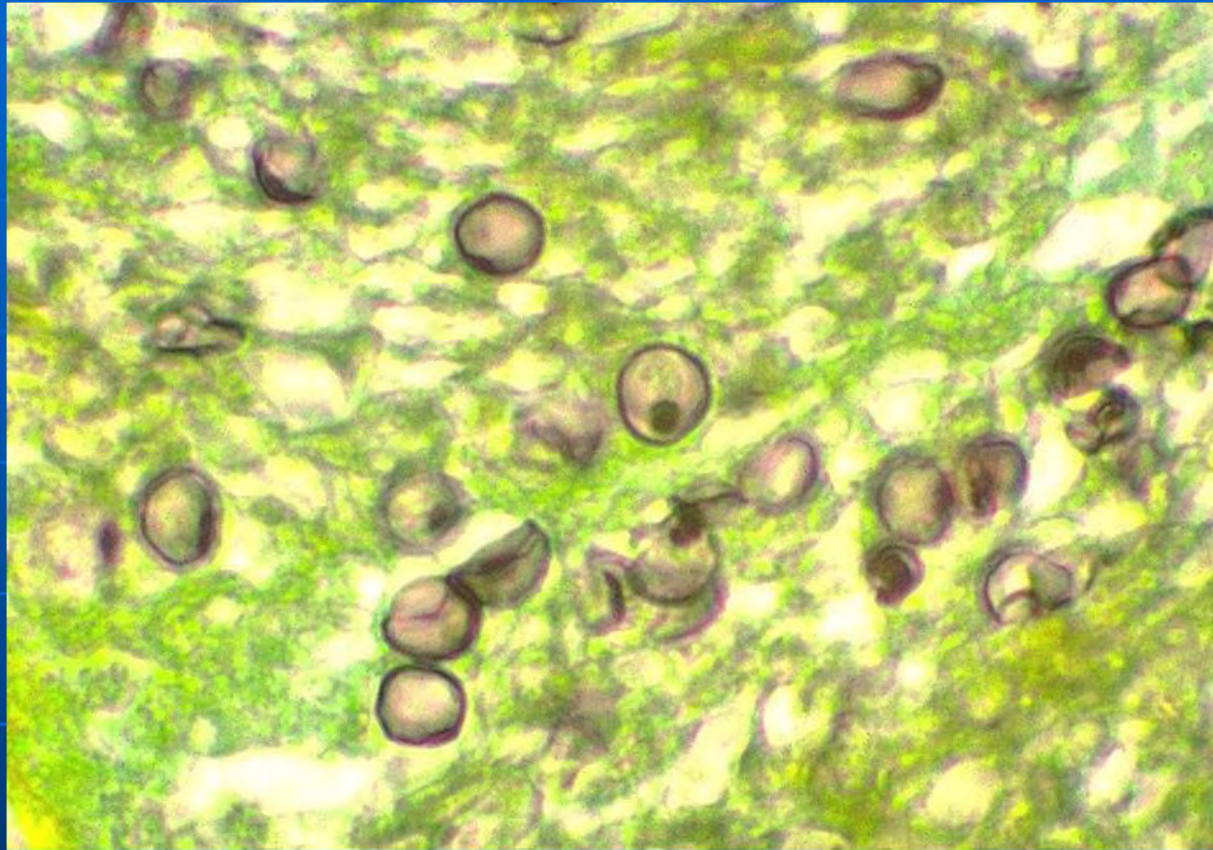
- Acute seroconversion manifests as a flulike illness, consisting of fever, malaise, and a generalized rash
- The asymptomatic phase is generally benign
- Generalized lymphadenopathy is common and may be a presenting symptom
- AIDS manifests as recurrent, severe, and occasionally life-threatening infections or opportunistic malignancies
- HIV infection can cause some sequelae, including AIDS-associated dementia/encephalopathy and HIV wasting syndrome (chronic diarrhea and weight loss with no identifiable cause)

HIV

- Kaposi's sarcoma



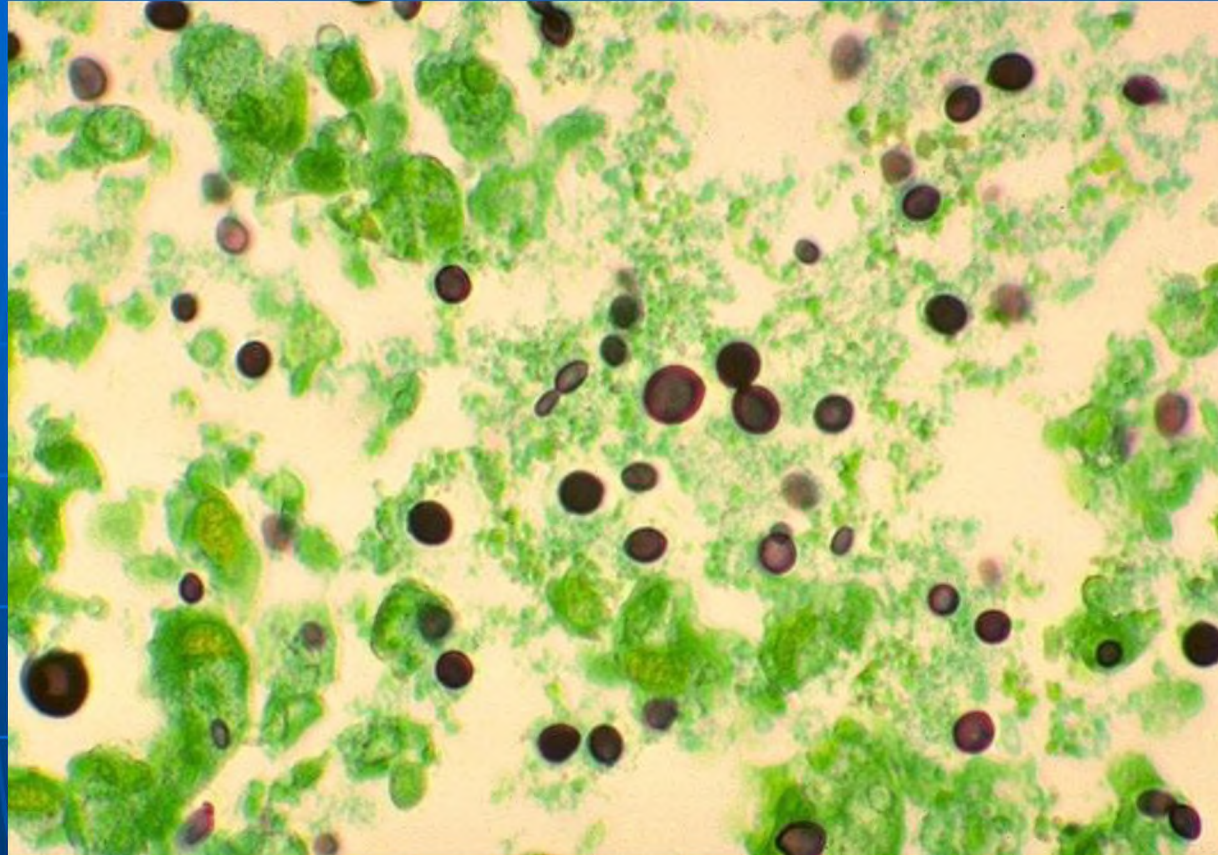
Cysts of *Pneumocystis carinii* in AIDS.



- Histopathology of lung shows characteristic cysts with cup forms and dot-like cyst wall thickenings.

Methenamine silver stain. Dr. Edwin P. Ewing, Jr.

Cryptococcosis of lung in patient with AIDS.



- Methenamine silver stain. Histopathology of lung shows numerous extracellular yeasts of *Cryptococcus neoformans* within an alveolar space. Yeasts show narrow-base budding and characteristic variation in size. CDC/Dr. Edwin P. Ewing, Jr. epe1@cdc.gov

- No cases of diffuse, undifferentiated non-Hodgkins lymphoma were reported in the young male (20 - 39 years old) population of the San Francisco area during the period 1977-1980. However, from March 1981 to January 1982, the unusual occurrence of four cases within 10 months was observed; again, these were in the homosexual male population.

Human immunodeficiency virus (HIV)

- The virus was isolated in 1984 by Luc Montanier (Pasteur Institute, Paris), who shared the Nobel Prize for his discovery in 2008, and Robert Gallo (NIH, Bethesda, USA).

Human immunodeficiency virus (HIV)

- From the original infection, there is usually a period of 8 to 10 years before the clinical manifestations of AIDS occur; however, this period may be two years or less. Approximately 10% of patients succumb to AIDS within 2 to 3 years.

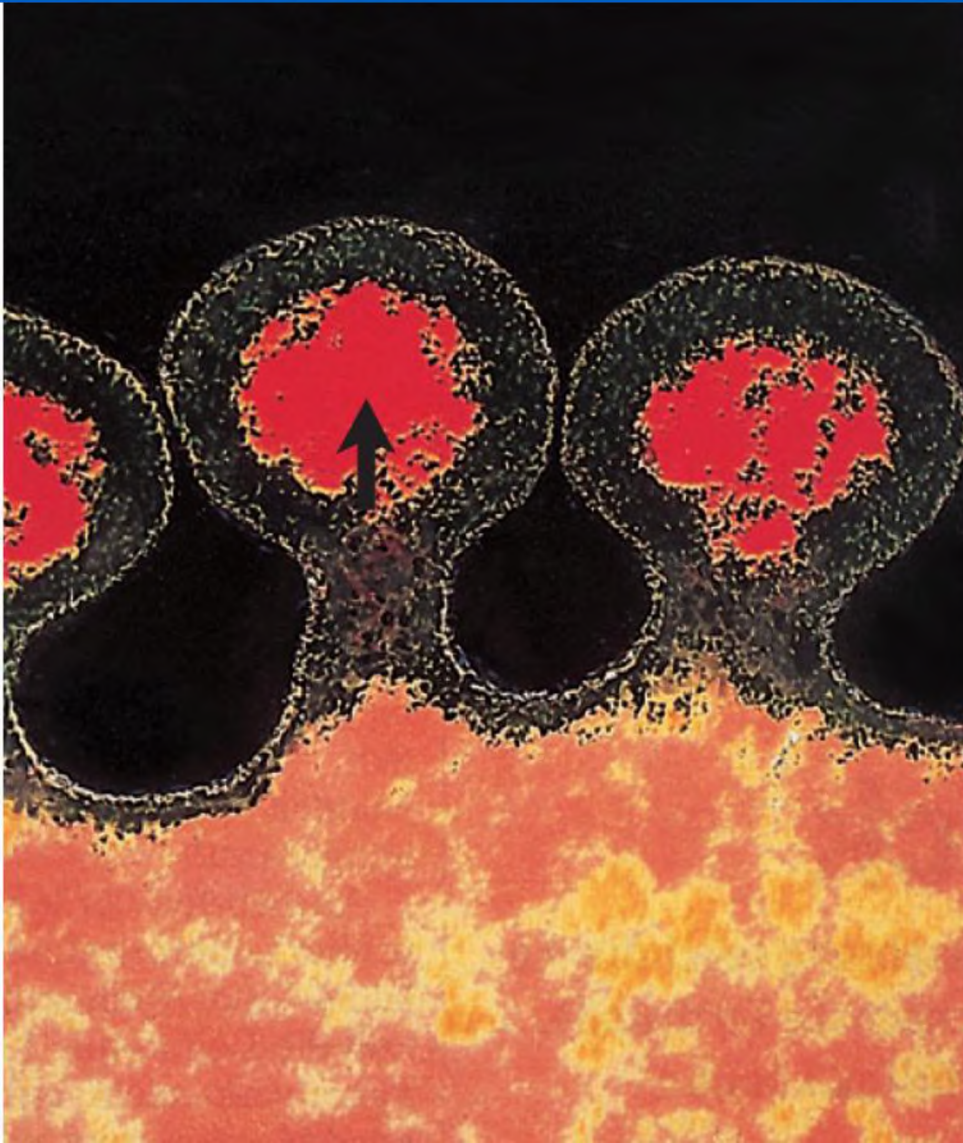
Human immunodeficiency virus (HIV)



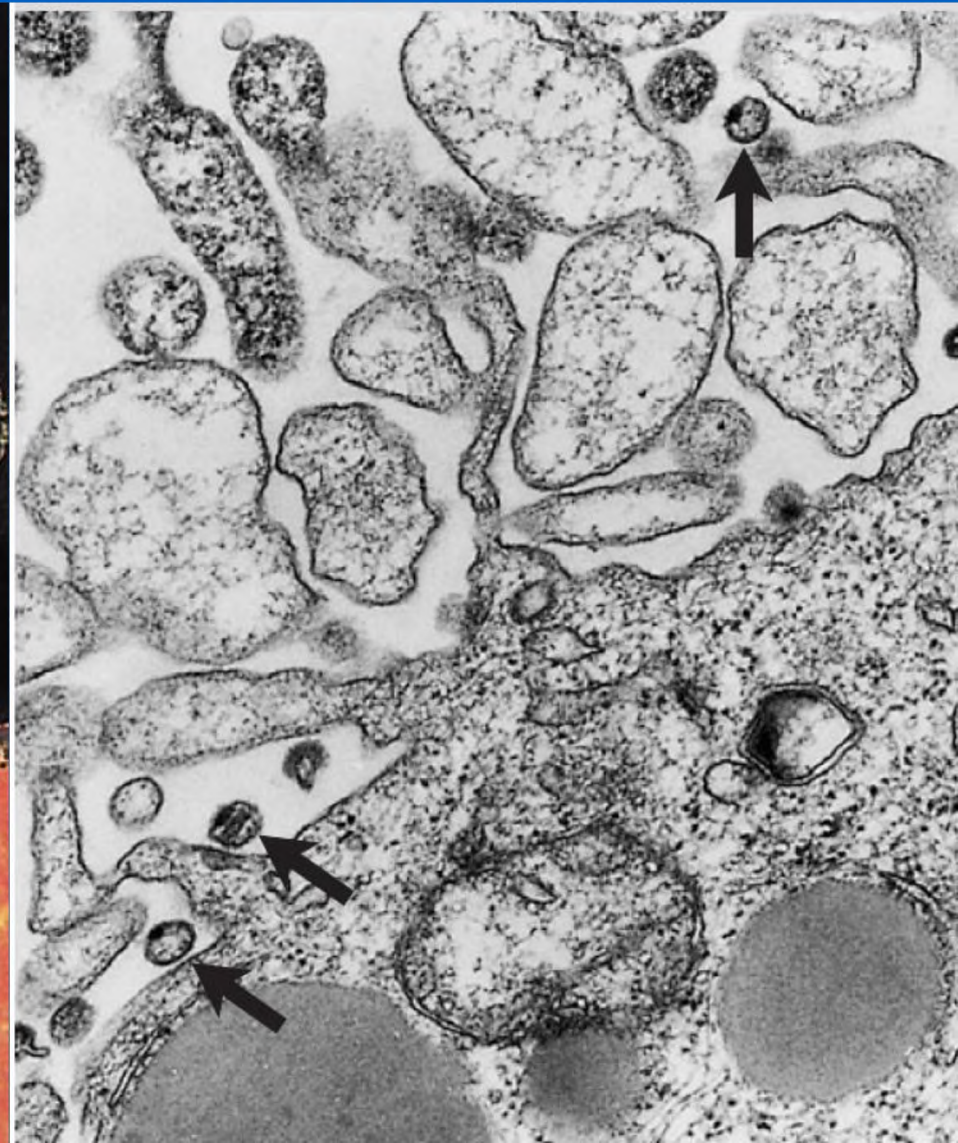
HIV-1 budding from cultured lymphocyte.
Transmission electron micrograph.

- Dendritic cells in the mucosal linings bind the virus shed by macrophages and carry it to the lymph nodes where CD4+ T4 cells become infected.

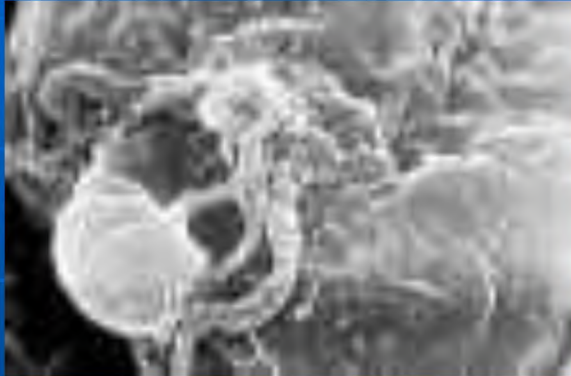
**HIV budding,
TEM x 50 000**



**HIV budding,
TEM x 20 000**



Human immunodeficiency virus (HIV)



Scanning electron micrograph of HIV-1 budding from cultured lymphocyte. Multiple round bumps on cell surface represent sites of assembly and budding of virions (CDC)

- There is a "window period" of seronegativity during which an infected person does not give a positive western blot HIV test or ELISA, even though the viral load is high and the patient may exhibit some symptoms. This seronegative period can last for six months before seroconversion although the latter usually occurs between one and four weeks after infection.

During the course of infection, there is a profound loss of the specific immune response to HIV because:

- responding CD4+ cells become infected. Thus, there is clonal deletion leading to tolerance. The cells that proliferate to respond to the virus are infected and killed by it epitope variation can lead to escape of HIV from the immune response
- activated T cells are susceptible to apoptosis. Spontaneous apoptosis of uninfected CD4+ and CD8+ T cells occurs in HIV-infected patients. Also there appears to be specific apoptosis of HIV-specific CD8+ cells
- the number of follicular dendritic cells falls over time, resulting in diminished capacity to stimulate CD4+ cells

Onset of disease - AIDS

- The period of clinical latency varies in length from as little as 1 to 2 years to more than 15 years.
- It is the onset of HIV-associated cancers and opportunistic infections that defines AIDS proper.

AIDS

- AIDS is currently defined in persons older than 13 years as the presence of one of 25 conditions indicative of severe immunosuppression or HIV infection in an individual with a CD4+ cell count of less than 200 cells per cubic mm of blood.

AIDS.



- Candida and herpes simplex in AIDS

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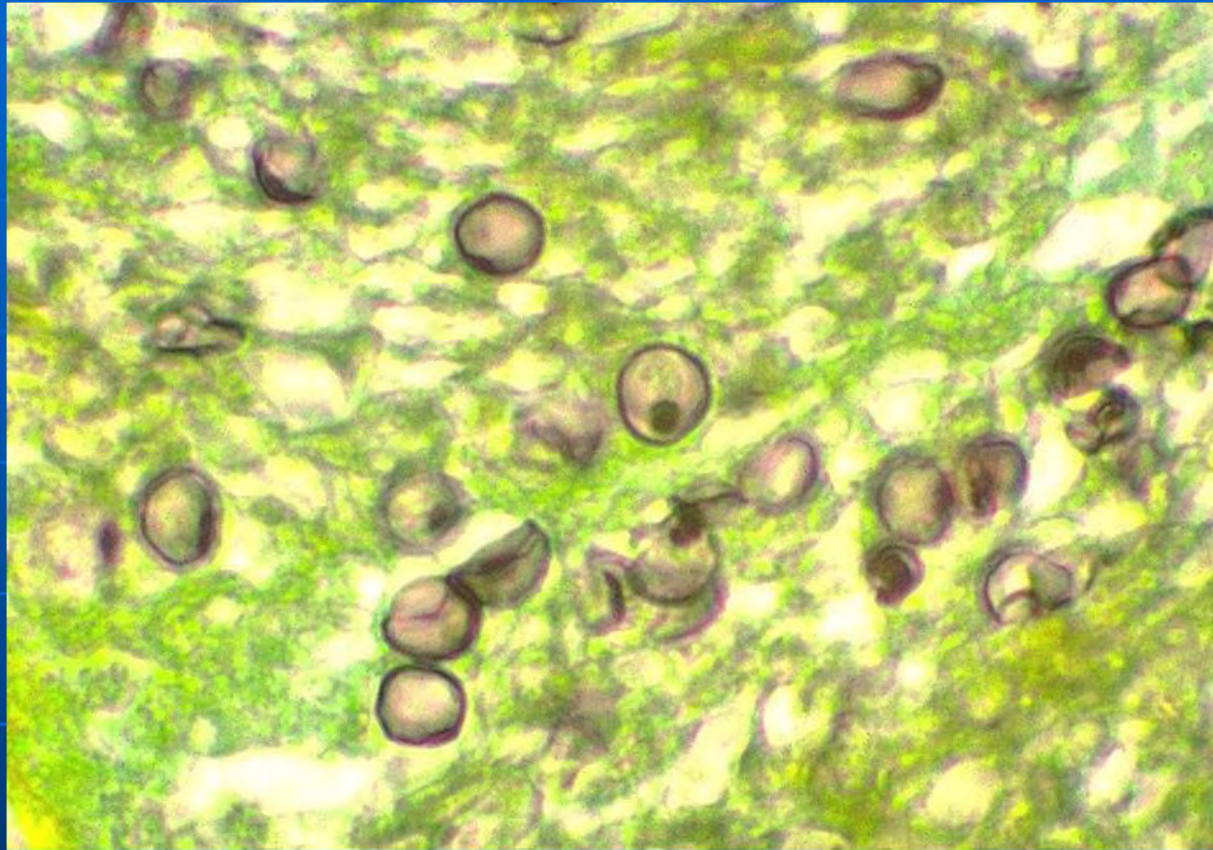
AIDS.



- Hairy leukoplakia of tongue in AIDS

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Cysts of *Pneumocystis carinii* in AIDS.

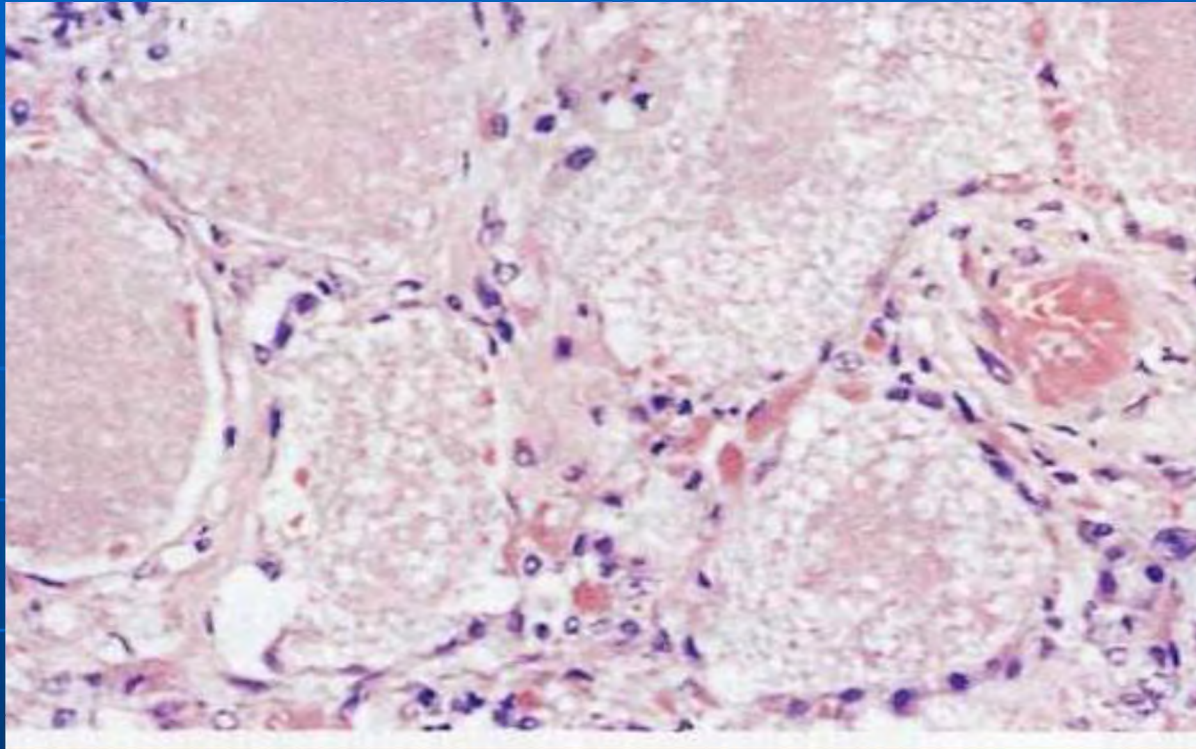


- Histopathology of lung shows characteristic cysts with cup forms and dot-like cyst wall thickenings.

Methenamine silver stain. Dr. Edwin P. Ewing, Jr.

Pathology of Lung Infection

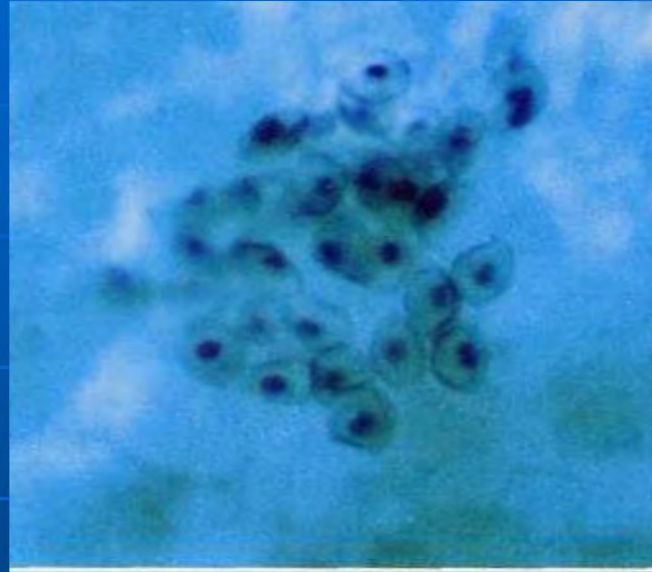
Pneumocystis carinii Pneumonia



Pneumocystis carinii pneumonia. The alveoli are filled with a foamy exudate, and the interstitium is thickened and contains a chronic inflammatory infiltrate.

Pathology of Lung Infection

Pneumocystis carinii Pneumonia



A centrifuged bronchoalveolar lavage specimen impregnated with silver shows a cluster of *Pneumocystis* cysts.

PNEUMOCYSTIS CARINII

Pneumonia

Pneumocystis carinii causes progressive, often fatal pneumonias in persons with severely impaired cell-mediated immunity and is the most common serious opportunistic pathogen in persons with AIDS.

PNEUMOCYSTIS CARINII Pneumonia

P. carinii is distributed worldwide, and because 75% of the population have acquired antibodies by 5 years of age, it is reasonable to assume the organisms are inhaled regularly by all. In persons with intact cell-mediated immunity, *P. carinii* infection is rapidly contained, without producing symptoms.

PNEUMOCYSTIS CARINII Pneumonia

However, 80% of all patients with AIDS develop *P. carinii* pneumonia during the course of their illness.

PNEUMOCYSTIS CARINII

Pneumonia

Pathogenesis: *P. carinii* reproduces in intimate association with alveolar type 1 lining cells, and active disease is confined to the lungs. Infection begins with attachment of the *Pneumocystis* trophozoite to the alveolar lining cell.

The trophozoite feeds on the host cell, enlarges, and transforms into the cyst form, which contains daughter organisms. The cyst then ruptures to release new trophozoites, which, in turn, attach to additional alveolar lining cells. If the process is not checked by the host immune system or antibiotic therapy, the infected alveoli eventually fill with organisms and proteinaceous fluid.

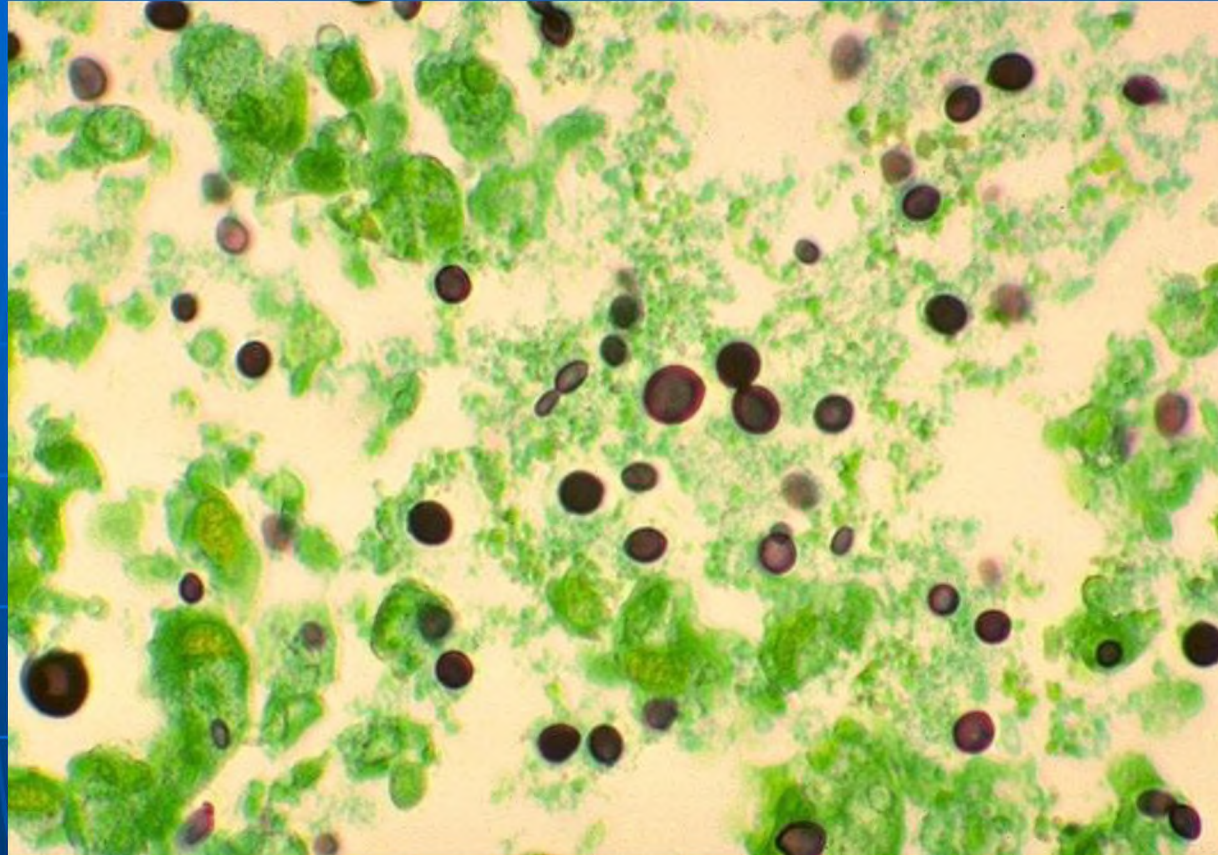
The progressive filling of alveoli prevents adequate gas exchange, and the patient slowly suffocates. The pathology of *P. carinii* pneumonia is discussed.

Pathology of Lung Infection

Pneumocystis carinii Pneumonia

Clinical Features: The presentation of Pneumocystis pneumonia is variable. At one extreme, symptoms are minimal, whereas at the other, there is rapidly progressive respiratory failure. Treatment is with trimethoprim-sulfisoxazole or pentamidine.

Cryptococcosis of lung in patient with AIDS.



- Methenamine silver stain. Histopathology of lung shows numerous extracellular yeasts of *Cryptococcus neoformans* within an alveolar space. Yeasts show narrow-base budding and characteristic variation in size. CDC/Dr. Edwin P. Ewing, Jr. epe1@cdc.gov

Pathology of Lung Infection

Fungal Infections

Cryptococcosis

Cryptococcosis results from inhalation of the spores of *Cryptococcus neoformans*, an organism that is frequently encountered in pigeon droppings. The pulmonary lesions range from small parenchymal granulomas to several large, granulomatous nodules, pneumonic consolidation, and even cavitation. Most serious cases of pulmonary cryptococcosis occur in those who are immunocompromised.

HIV. Kaposi's sarcoma.



- Kaposi's sarcoma (skin).

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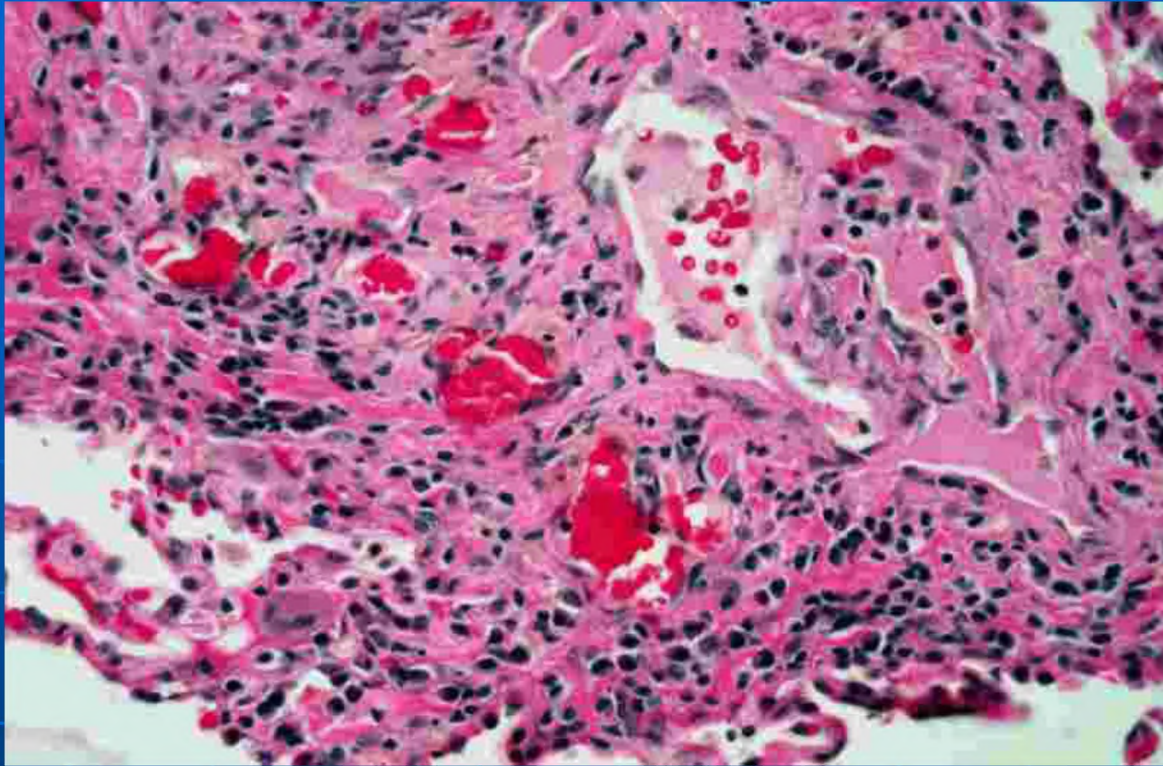
HIV. Kaposi's sarcoma.



- Skin showing AIDS-associated Kaposi's sarcoma

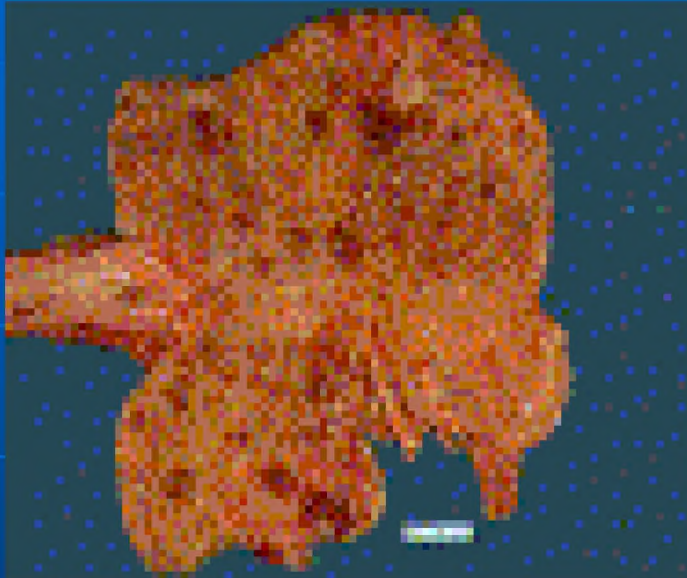
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HIV. Kaposi's sarcoma.

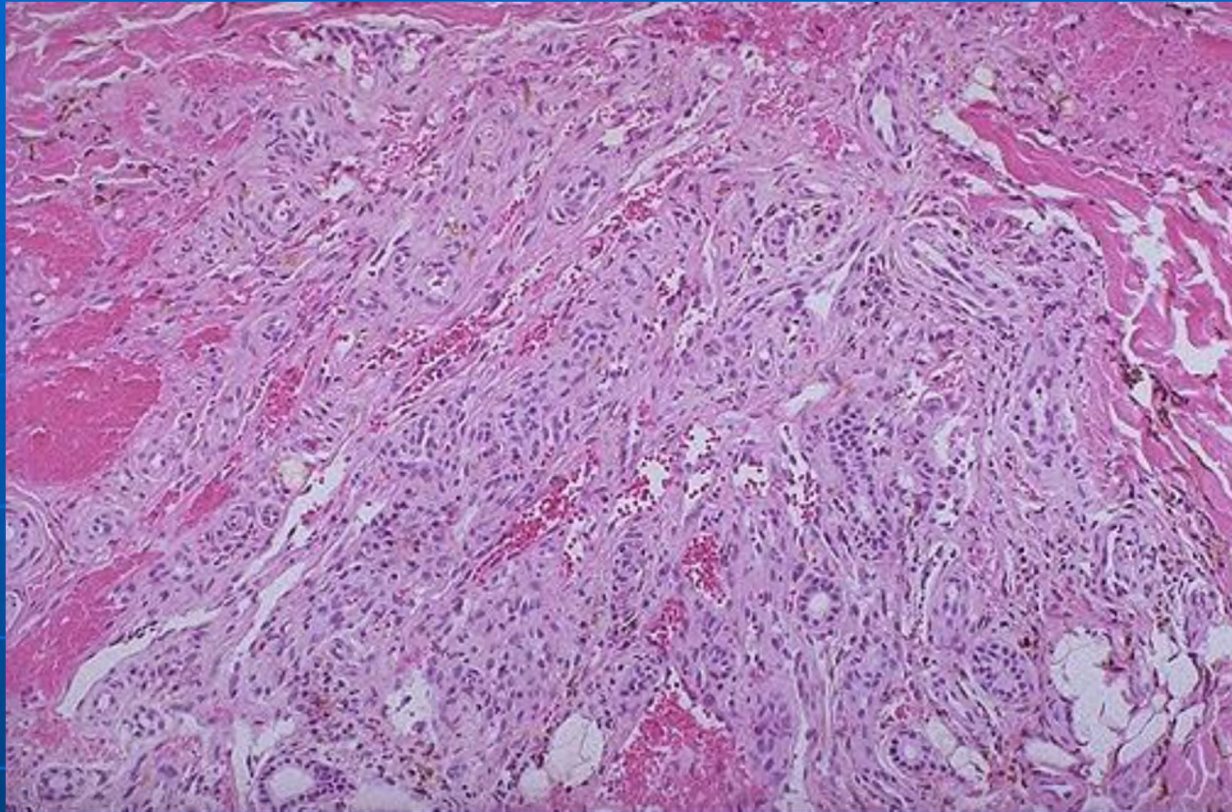


- The perivenular infiltrate of Kaposi sarcoma shows a mixture of spindle cells, inflammatory cells, and ectatic vascular spaces. *The Johns Hopkins Autopsy Resource (JHAR). Image Archive.*

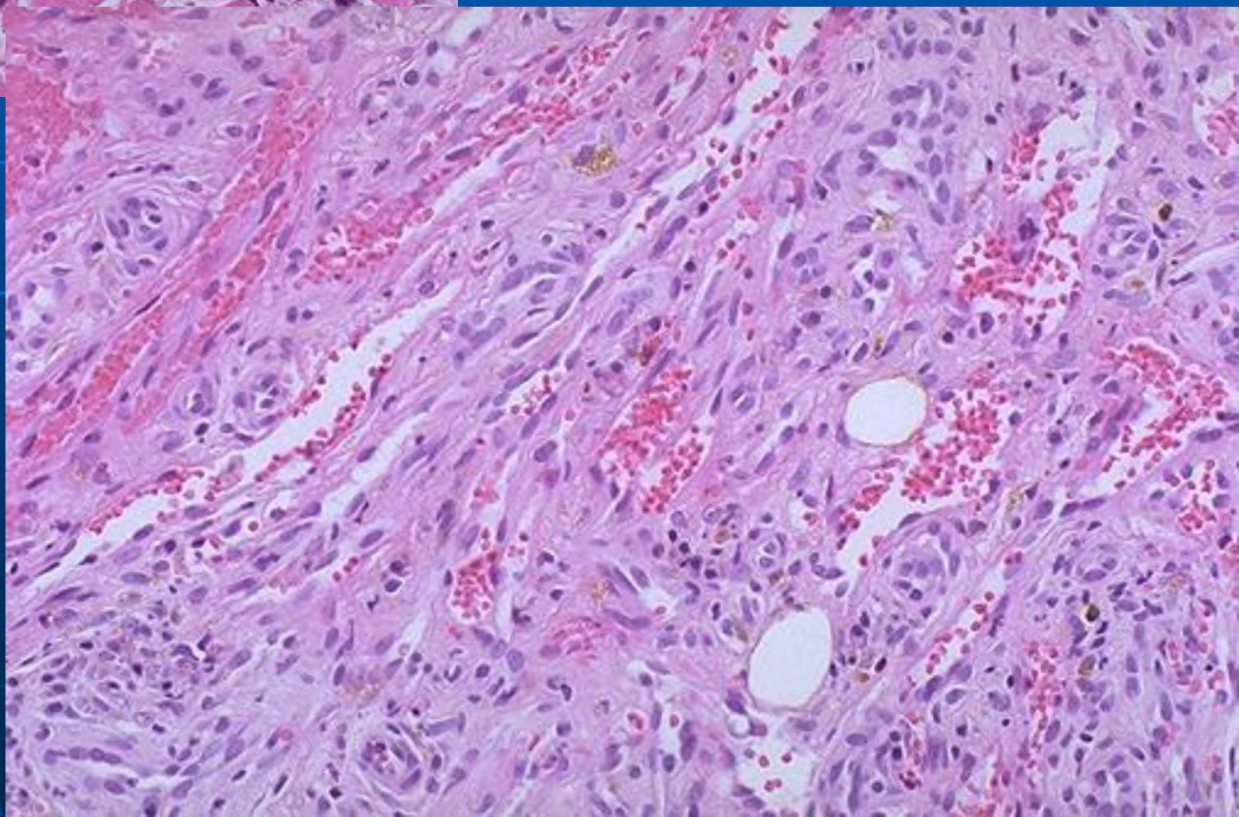
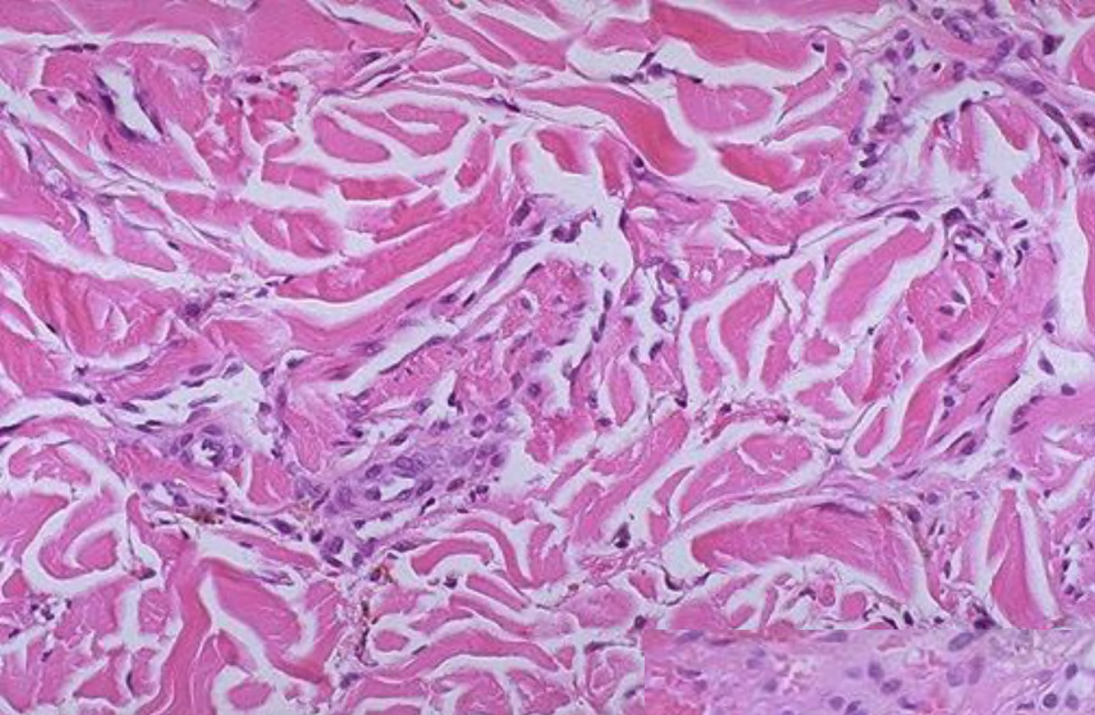
HIV. Kaposi's sarcoma.

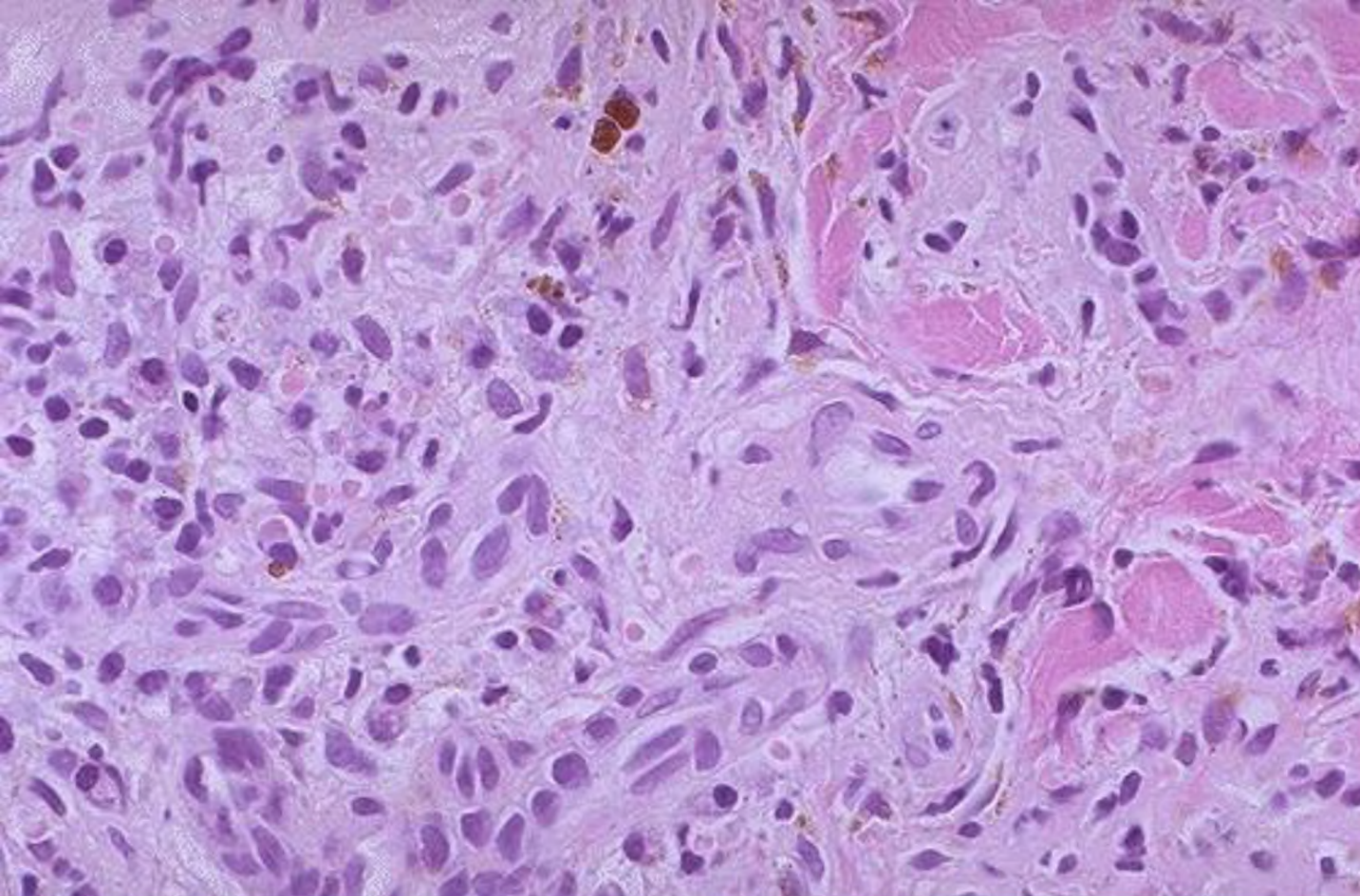


- Lesions on the stomach of a patient with Kaposi's sarcoma



- Kaposi's sarcoma microscopically produces slit-like vascular spaces in the dermis of the skin, seen here as a nodule.





- Kaposi's sarcoma characteristically has deposits of hemosiderin granules and faint, pale pink hyaline globules, as seen here.

AIDS.



- Candida, herpes simplex

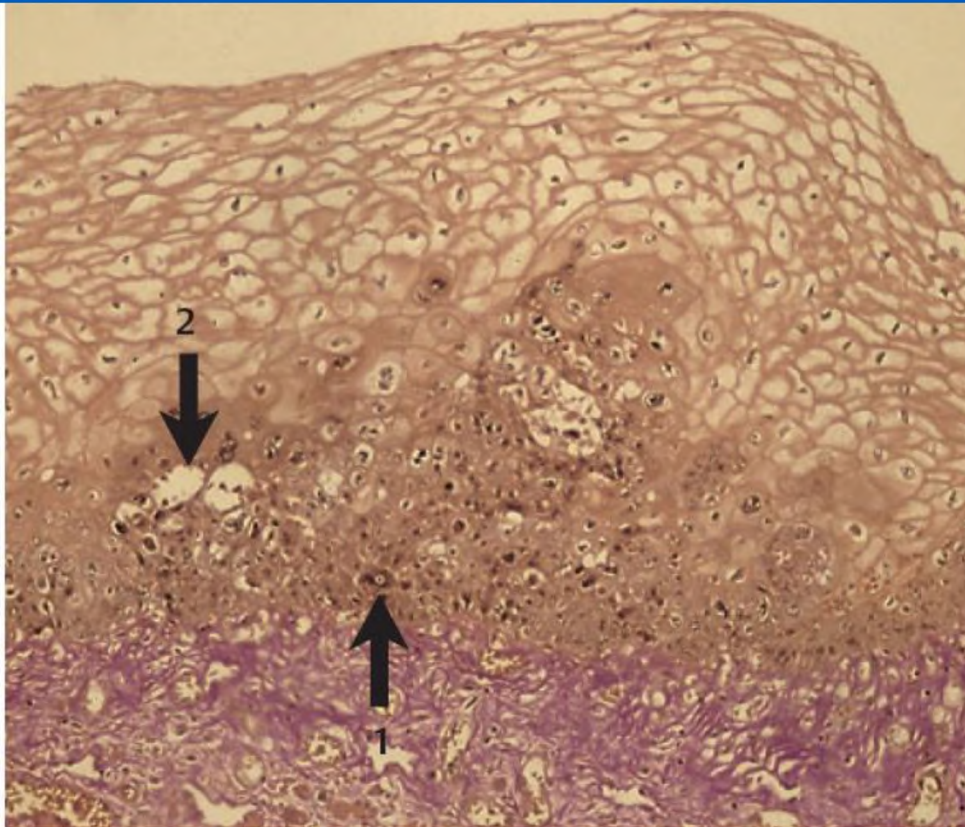
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Herpes simplex



Labial herpes (van Gieson's stain) x 50

Labial herpes







AIDS.



- Hairy leukoplakia of tongue in AIDS

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Leukoplakia of tongue

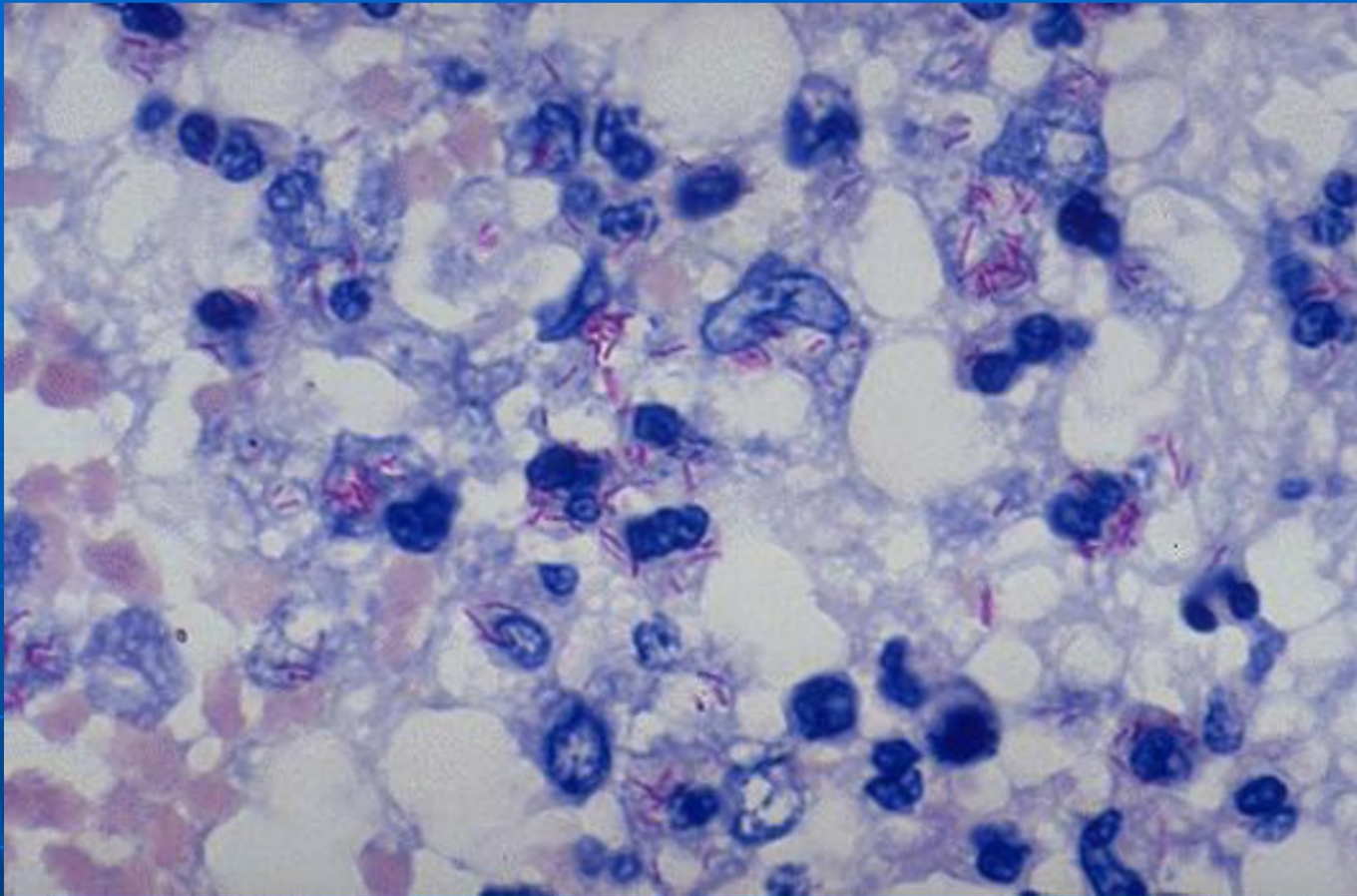


Patients with AIDS

- In 2006, the estimated number of persons living with AIDS (i.e. overt disease rather than infection by the virus) in the United States and dependent areas was 448,871. In the 50 states and the District of Columbia, this included 432,915 adults and adolescents, and 3,775 children under age 13 years.

- Note: As more and more people survive with an HIV infection because of successful chemotherapeutic intervention, the number of infectious people in the population is rising even though fewer people are dying of AIDS

- CD8+ cells are only infected by HIV in small numbers and their levels remain high during the course of the disease for many years. And then, until recently inexplicably, they rapidly die off. It appears that some of the HIV subtypes that occur late in infection prompt a mass apoptosis of CD8 cells.



- In order to find the mycobacteria in a tissue section, a stain for acid fast bacilli is done (AFB stain). The mycobacteria stain as red rods, as seen here at high magnification.

Granuloma

- The characteristic tissue response to tuberculosis is the granuloma. Cellular reactions are not so prominent.

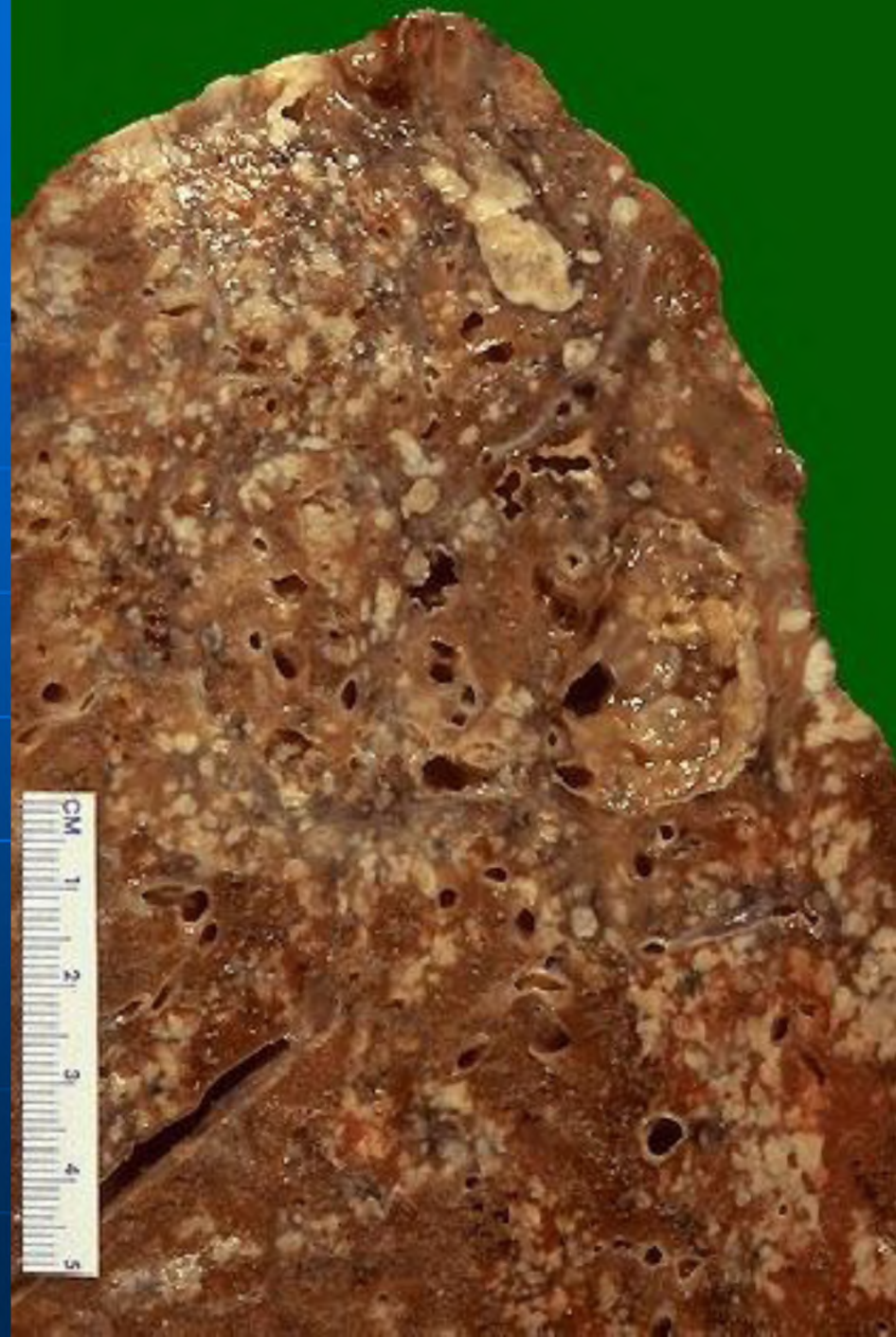
Tuberculosis

Primary Tuberculosis



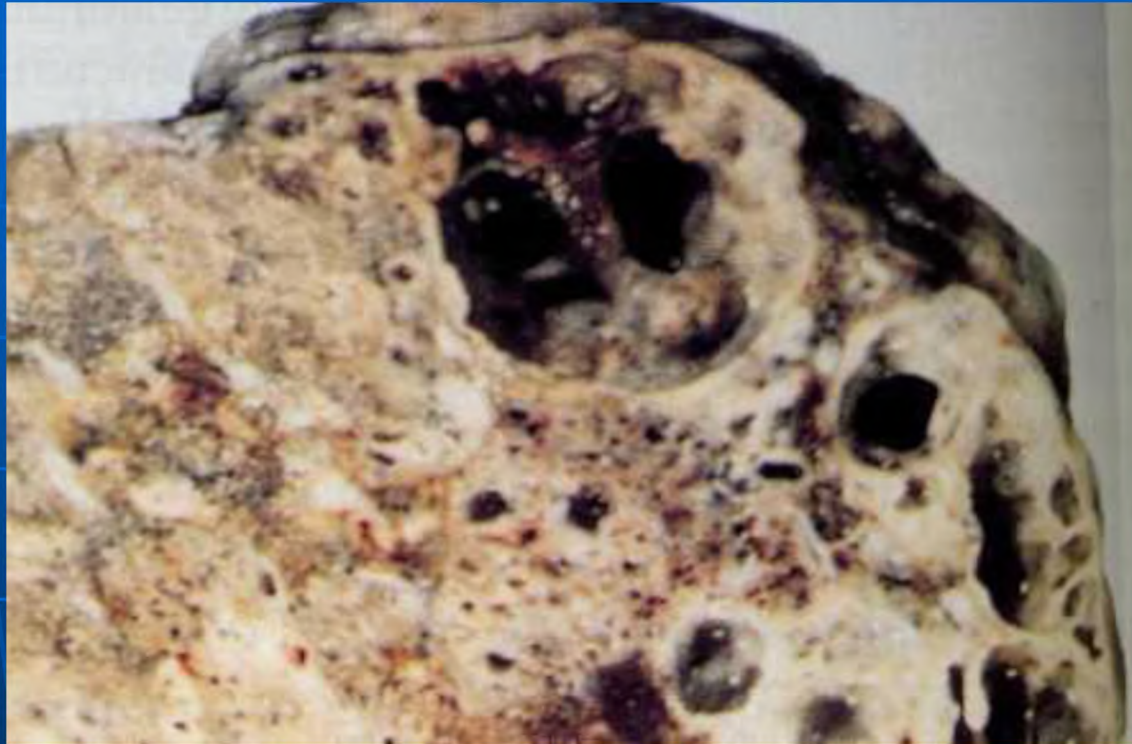
Primary tuberculosis. A healed Ghon complex is represented by a subpleural nodule and involved hilar lymph nodes.

- On closer inspection, the granulomas have areas of caseous necrosis. This is very extensive granulomatous disease. This pattern of multiple caseating granulomas primarily in the upper lobes is most characteristic of secondary (reactivation) tuberculosis. However, fungal granulomas (histoplasmosis, cryptococcosis, coccidioidomycosis) can mimic this pattern as well.



Tuberculosis

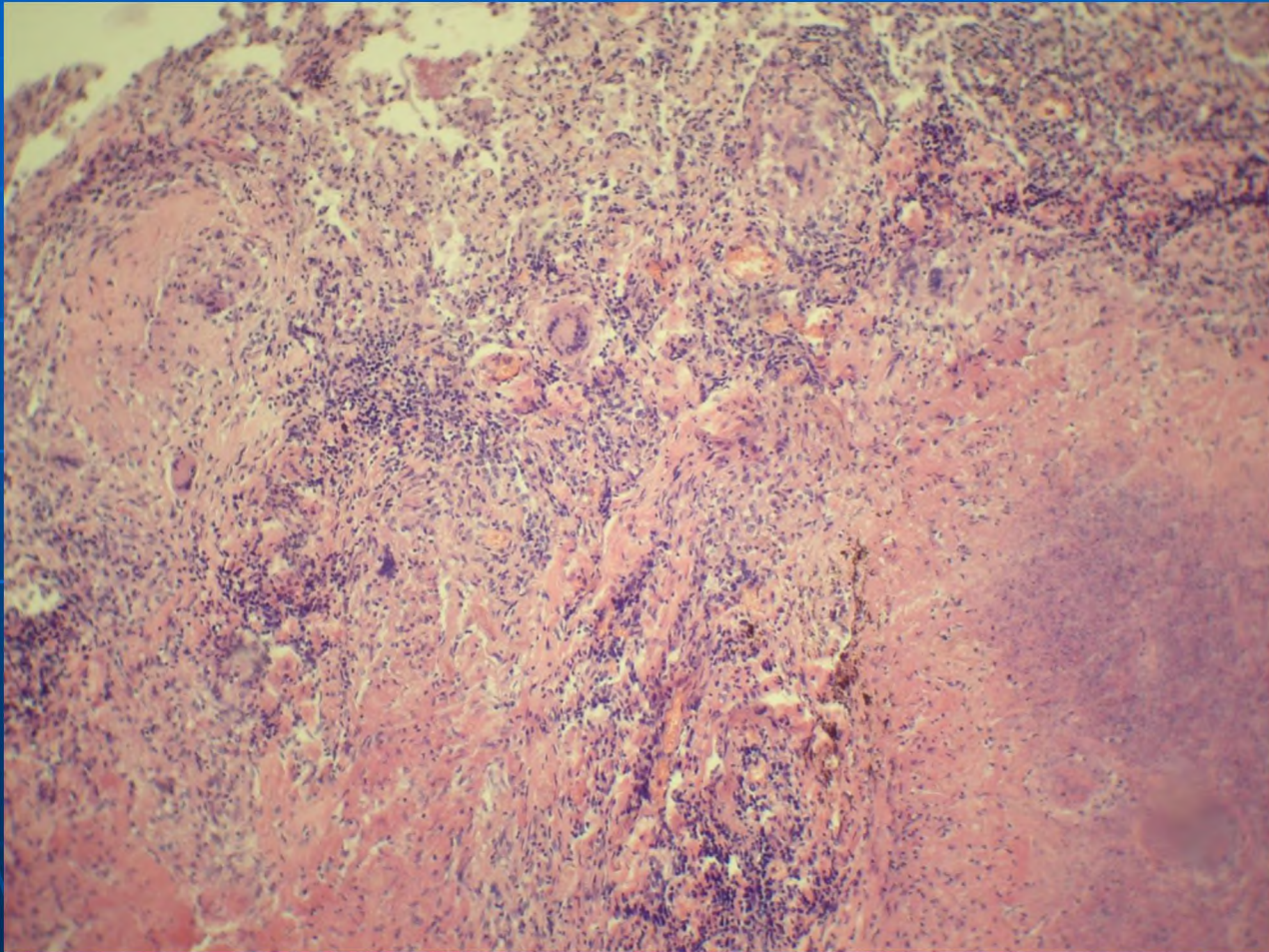
Secondary Tuberculosis



Cavitory tuberculosis. The apex of the left upper lobe shows tuberculous cavities surrounded by a consolidated and fibrosed pulmonary parenchyma, which contains small tubercles.

Tuberculosis

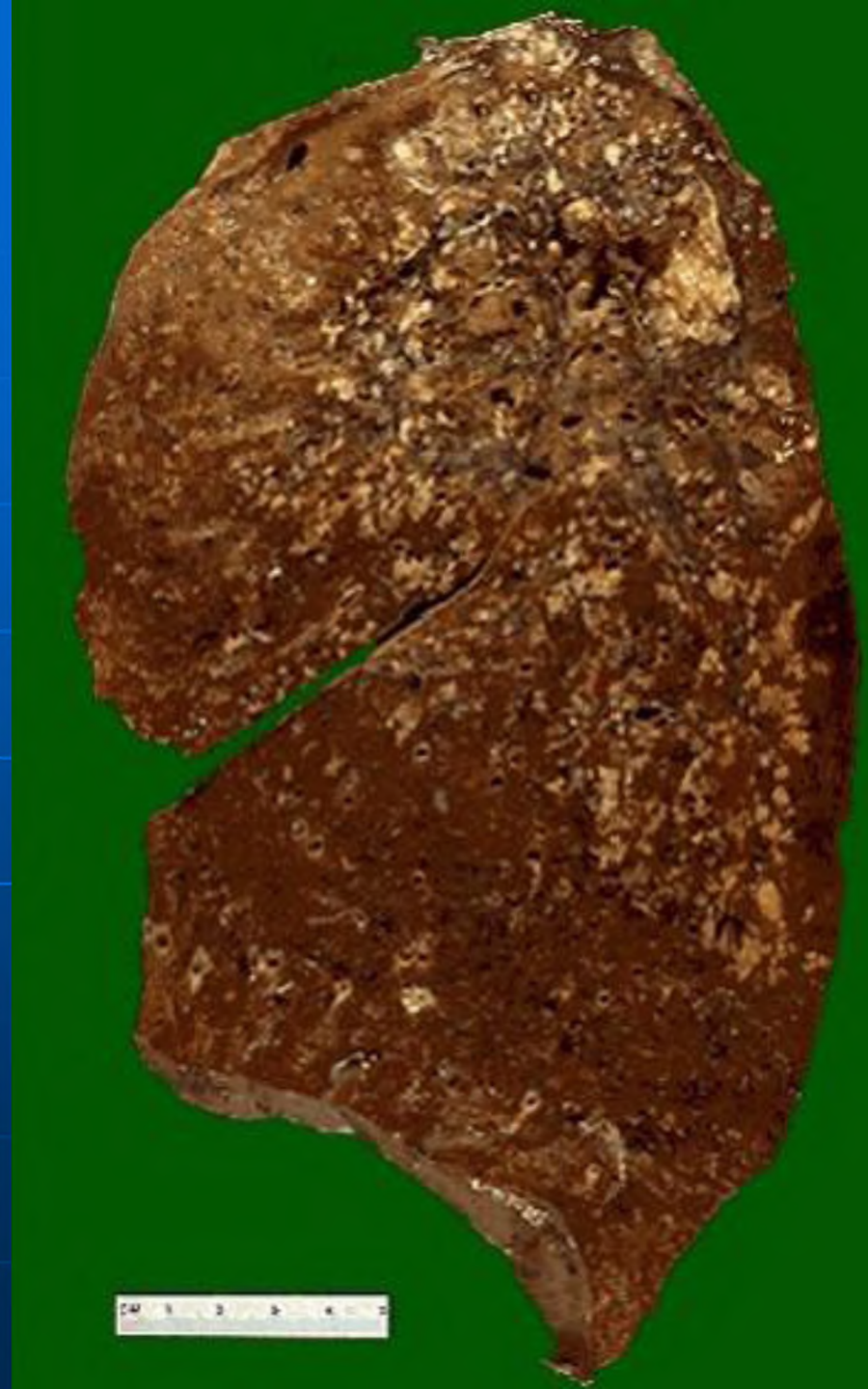
Secondary Tuberculosis, Caseous Pneumonia



- Here is the gross appearance of a lung with tuberculosis. Scattered tan granulomas are present, mostly in the upper lung fields. Some of the larger granulomas have central caseation. Granulomatous disease of the lung grossly appears as irregularly sized rounded nodules that are firm and tan. Larger nodules may have central necrosis known as caseation).

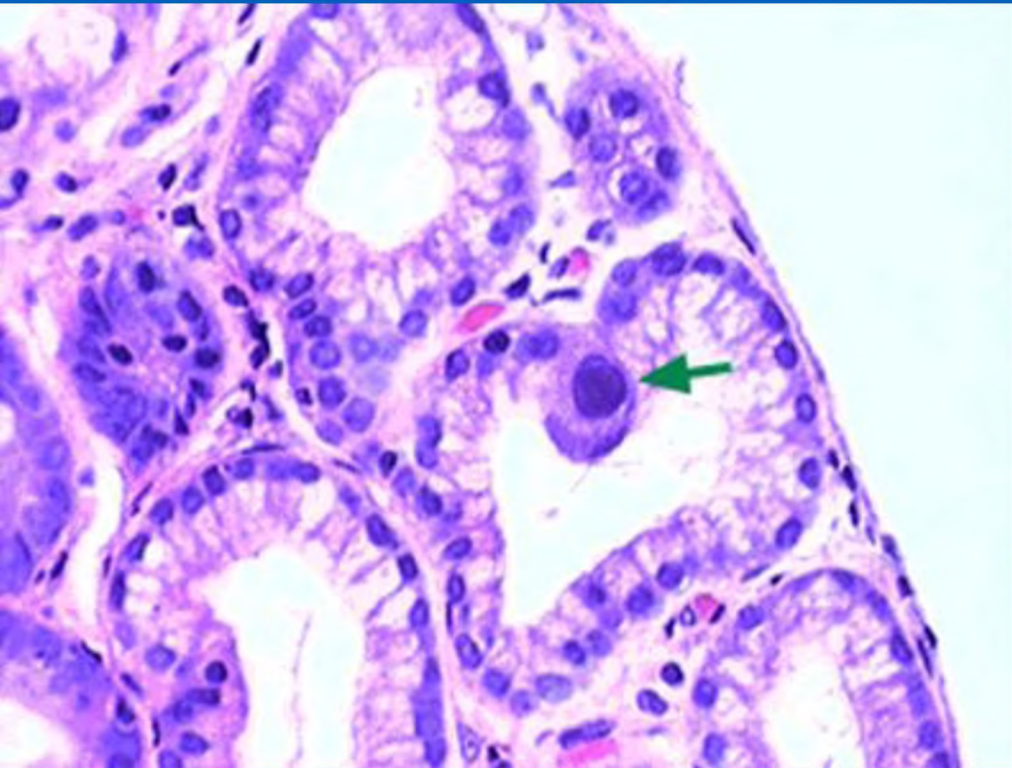


- This is another example of granulomatous disease of the lung. The pattern of smaller nodules which have a propensity for upper lobe involvement suggests a granulomatous process rather than metastatic disease.



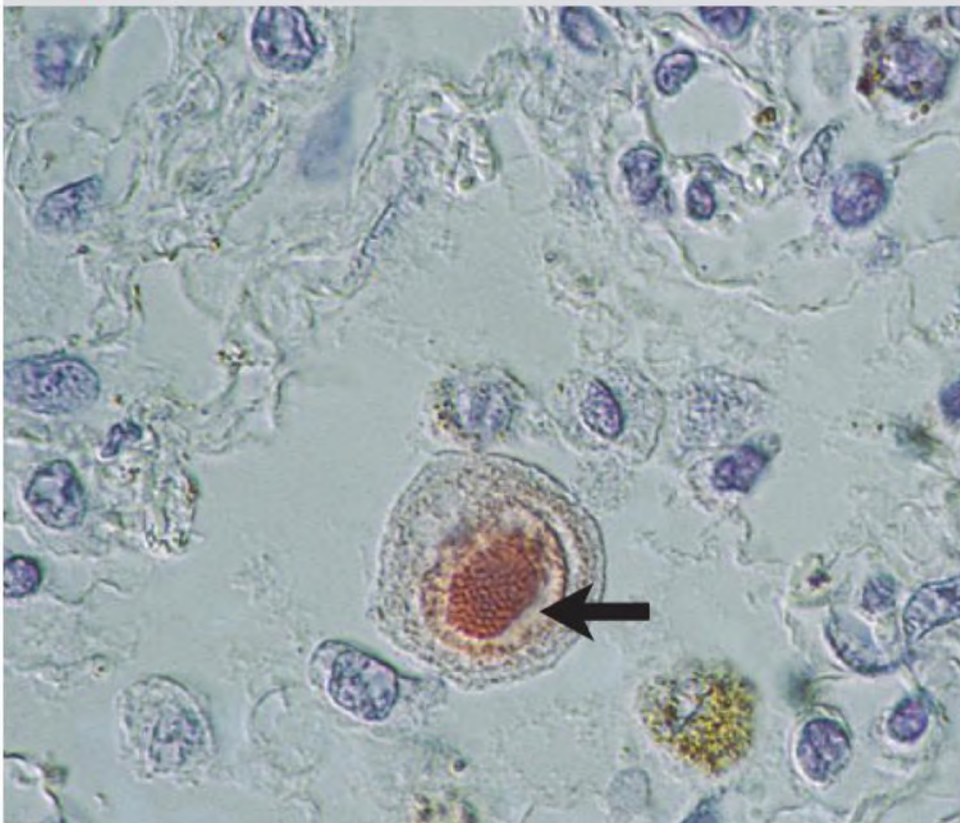
Viral Pneumonia

Cytomegalovirus produces a characteristic interstitial pneumonia. Initially described in infants, it is now well recognized in immunocompromised persons. This viral pneumonia features an intense, interstitial infiltrate of lymphocytes. The alveoli are lined by type II cells that have regenerated to cover the epithelial defect left by the necrosis of type I cells. The infected alveolar cells are very large and display the typical dark-blue nuclear inclusions.

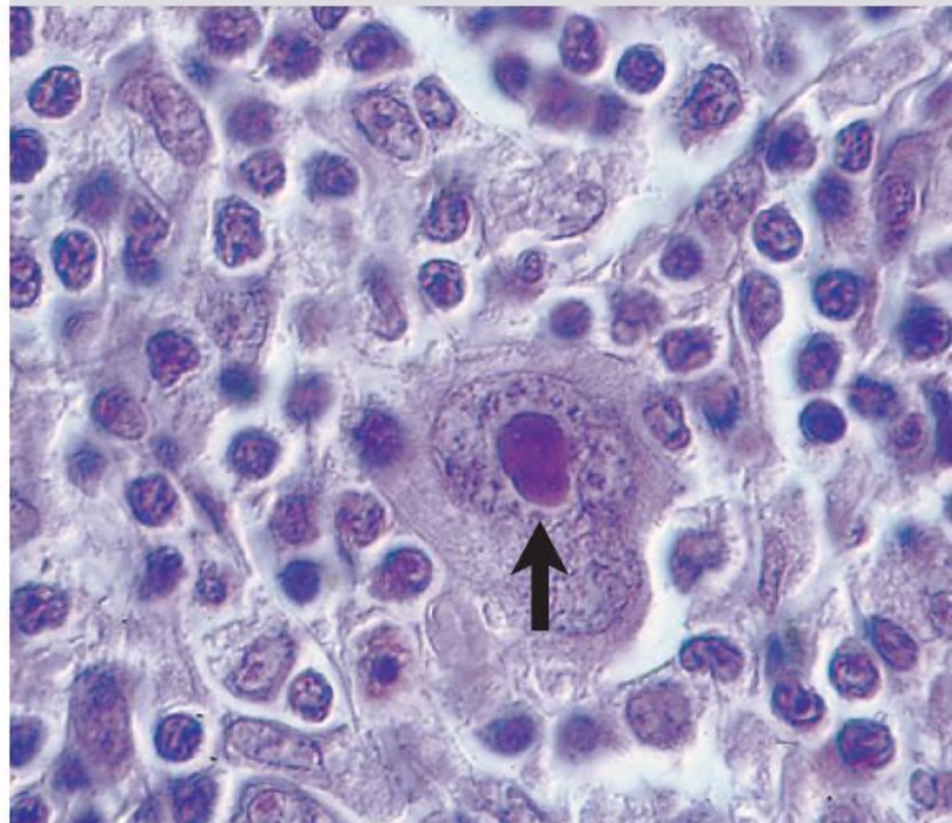


- Cytomegalovirus x400
 - Classic CMV intranuclear inclusions are deep purple, occupy >50% of the nuclear diameter, have a clear perinuclear zone and a rim of condensed nuclear chromatin
 - In this case the perinuclear clear zone is obliterated by the large size of the CMV inclusion
 - Intracytoplasmic CMV inclusions can be present as small punctate dots (nicely seen in this case)
- (Description By: Martin Nadel, M.D.)
- (Image Contrib. by: Martin Nadel, M.D. UCHC)

E Cytomegaly giant cell nucleoli
(IF; CMv) x 600



F Tumor cell giant nucleoli
(HE) x 600



Influenza

- Influenza is an acute highly contagious disease caused by an RNA virus (family Orthomyxoviridae), having an affinity to the epithelium of the respiratory tract. The disease usually occurs in the cold season.

Epidemiology.

- The disease can be caused by one of the three influenza viruses: A, B, C. Serotype A is the most epidemically dangerous, it infects the human, swine, horses and birds. Serotype B causes sporadic outbreaks and epidemics, and serotype C only leads to sporadic outbreaks of influenza, especially in children.

- A sick person is contagious for 24 hours before the onset of clinical symptoms, and for two days after clinical recovery.

Pathogenesis of influenza

- Implementation and reproduction of the virus in primary airway epithelium suitable incubation period of the disease. Duration - from several hours to 2-4 days.
- Viremia is accompanied by a prodrome and corresponds to the prodromal stage of the disease.
- Secondary viral replication in epithelial cells, leading to the generalization of infection, corresponding to the height of the disease. Clinically characterized by fever, headache, catarrh rhinitis, cough, conjunctivitis, often joint and muscle pain.

Pathogenesis and morphogenesis of influenza due to the following properties of the virus:

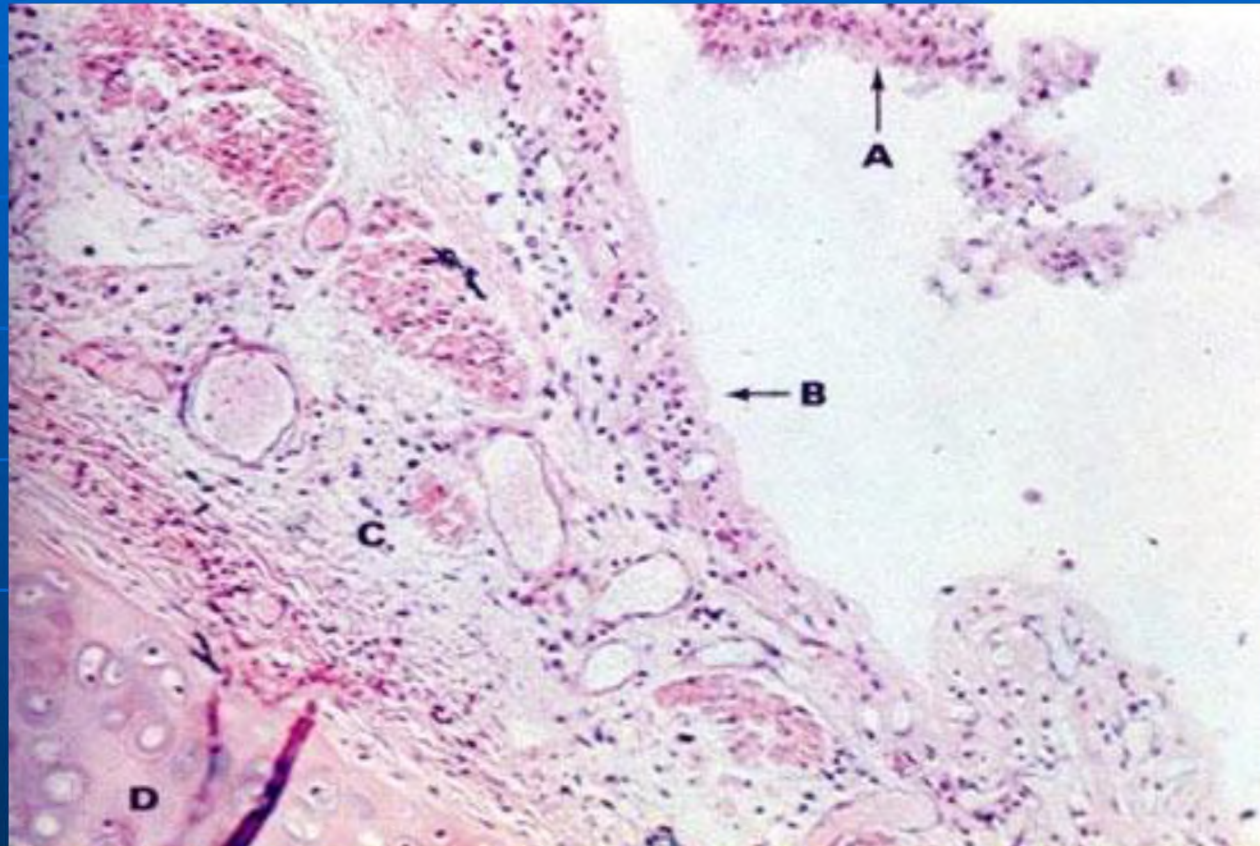
- cytopathic property leads to ballooning degeneration of the airway epithelium, desquamation and its lysis, violation of the drainage function of bronchi;
- immunosuppressive property contributes to the development of immunodeficiency (reduced chemotaxis, phagocytic activity of macrophages and neutrophils, the appearance of circulating immune complexes);
- vazopathic (vazoparalitic) property causes congestion, stasis, plasma impregnation of blood vessel walls, perivascular edema and hemorrhages.

- There are an easy, moderate and severe forms of influenza.
- Easy form of influenza is the most common. It characterized by acute catarrhal rinolaringitis or rinolaringotraheobronchitis.

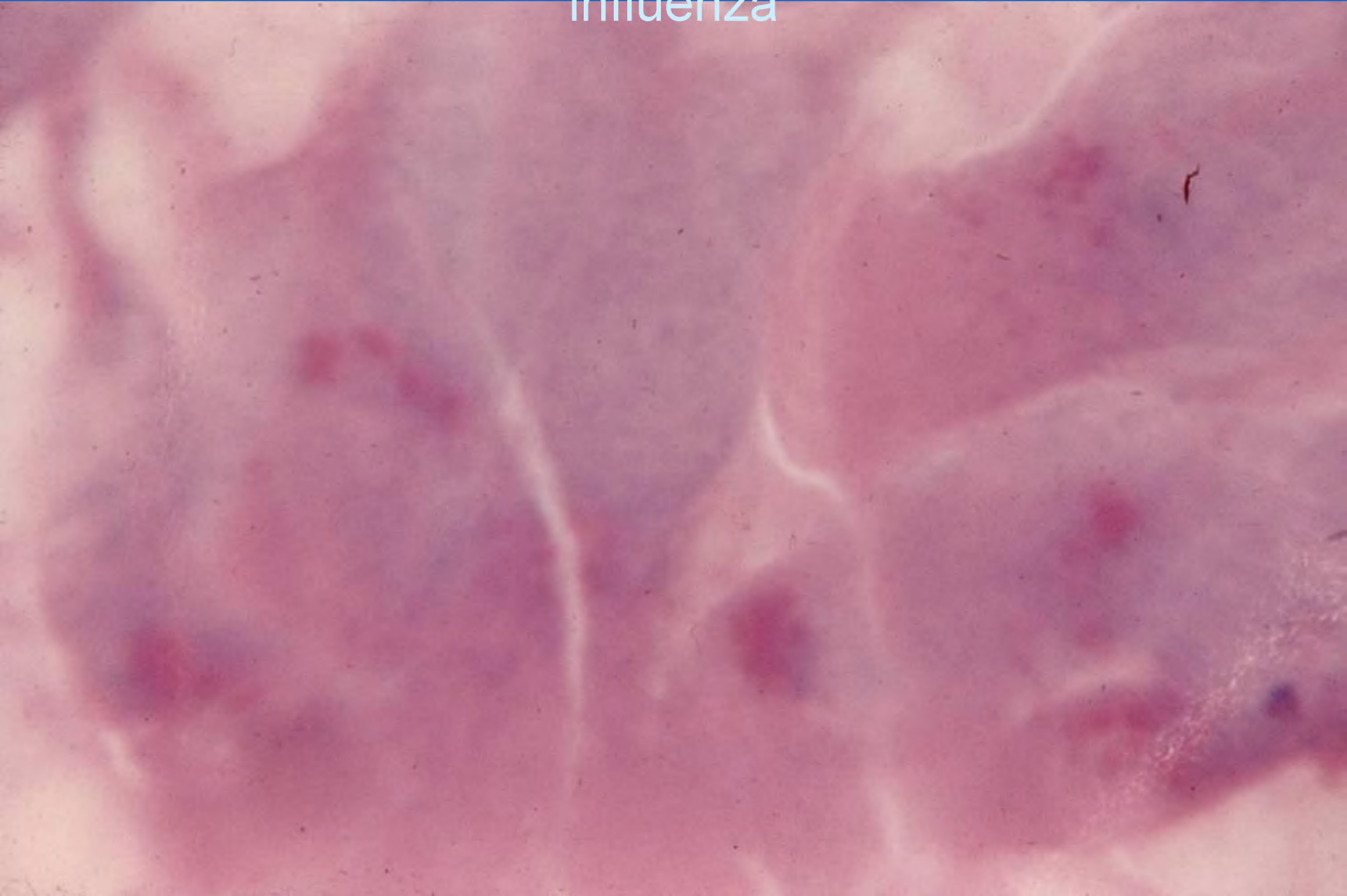
Influenza



Catarrh during influenza

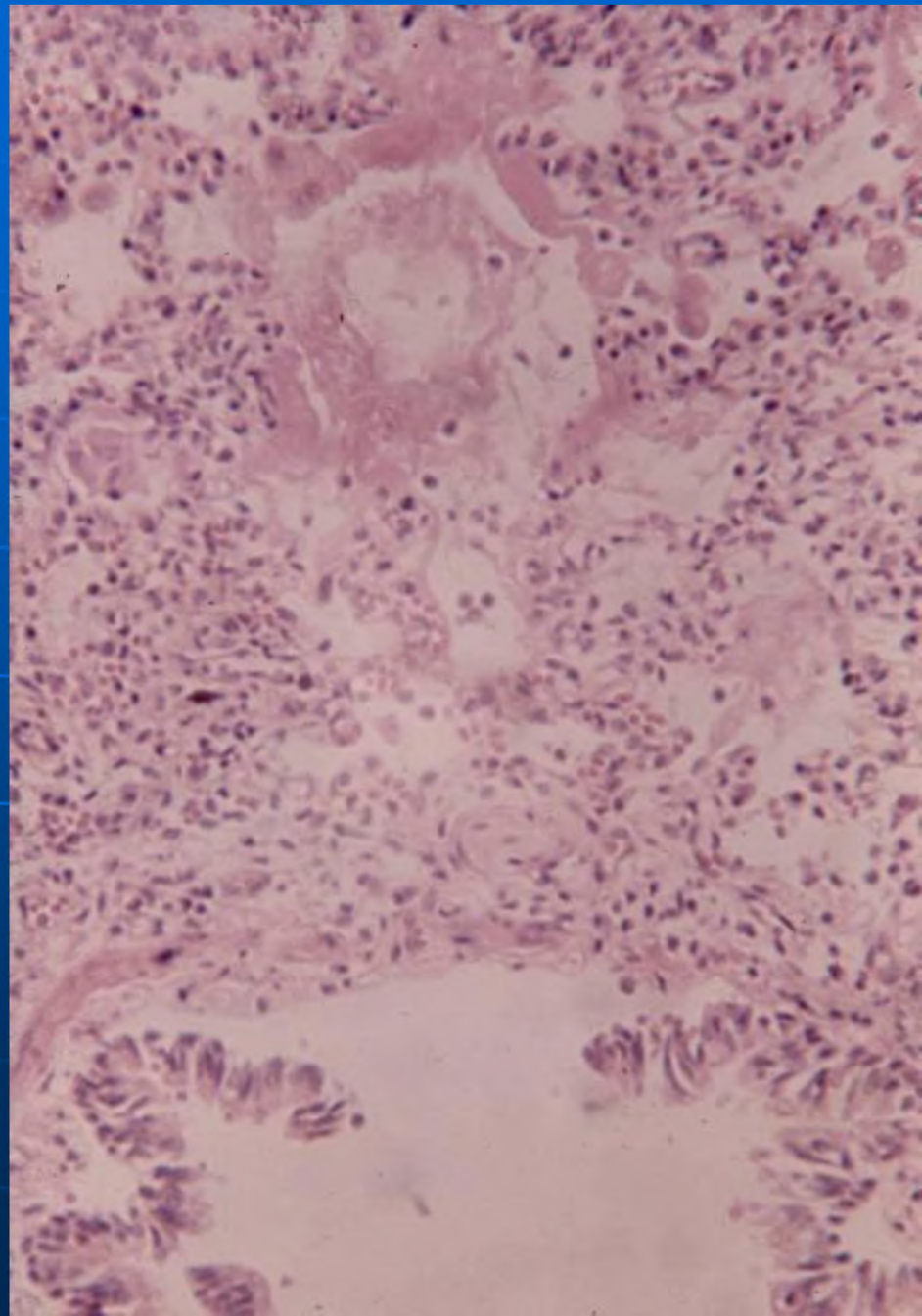
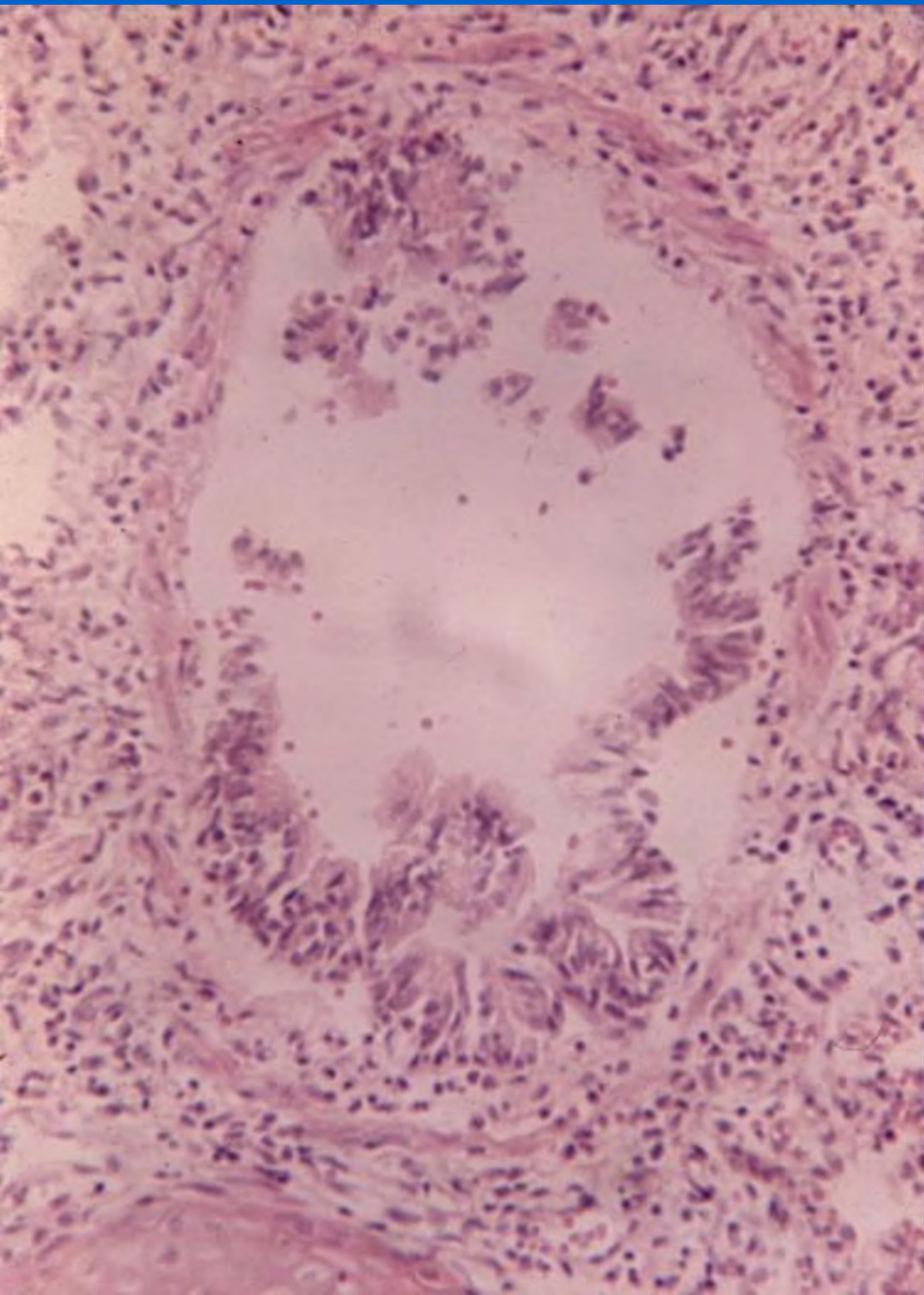


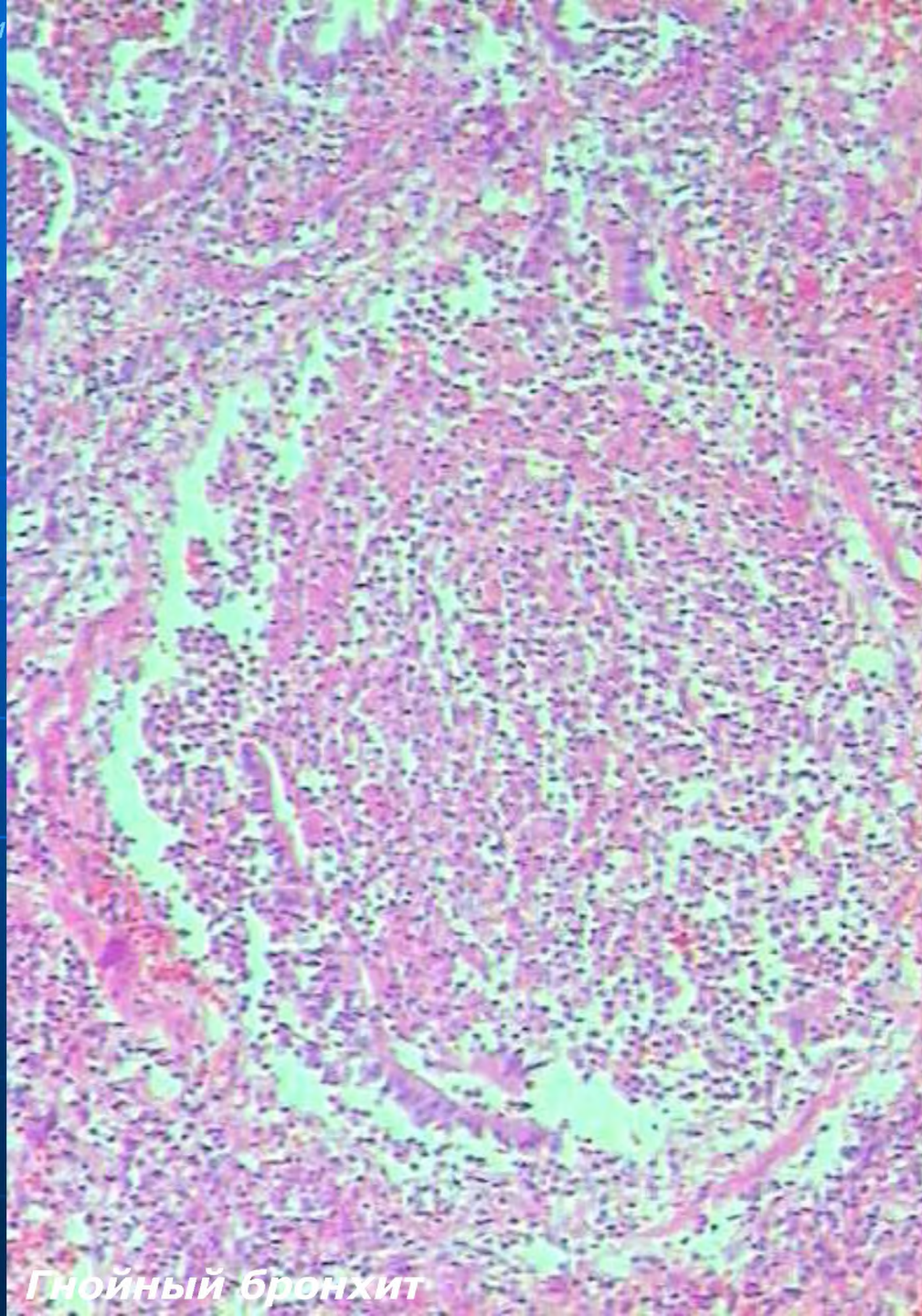
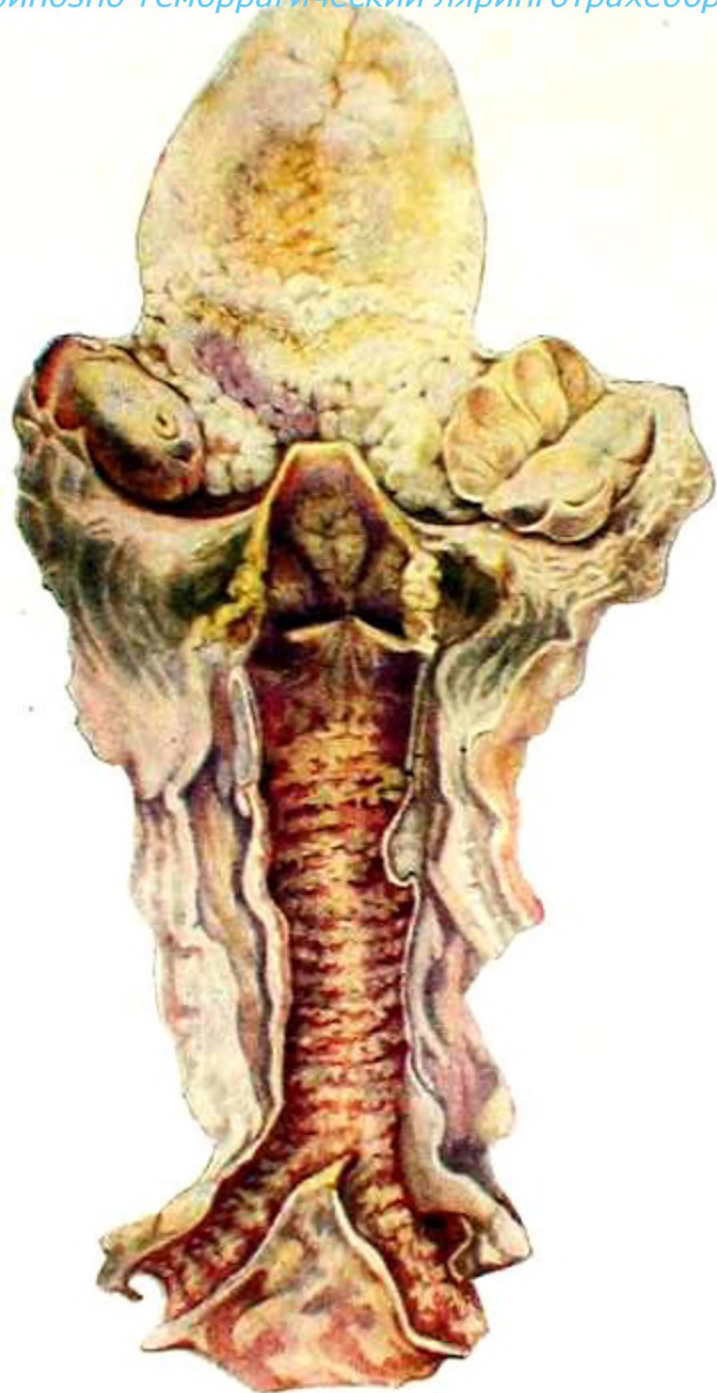
Fuksinofilic inclusions in respiratory epithelial cells with influenza



- Moderate influenza. Typically the inflammation spreads to all parts of the bronchial tree, sometimes to the alveoli. Inflammation serous or fibrinous-hemorrhagic, with infiltration by lymphocytes, macrophages, isolated neutrophilic leukocytes, with areas of necrosis.

Cytopathic effects of A2 influenza virus





Гнойный бронхит

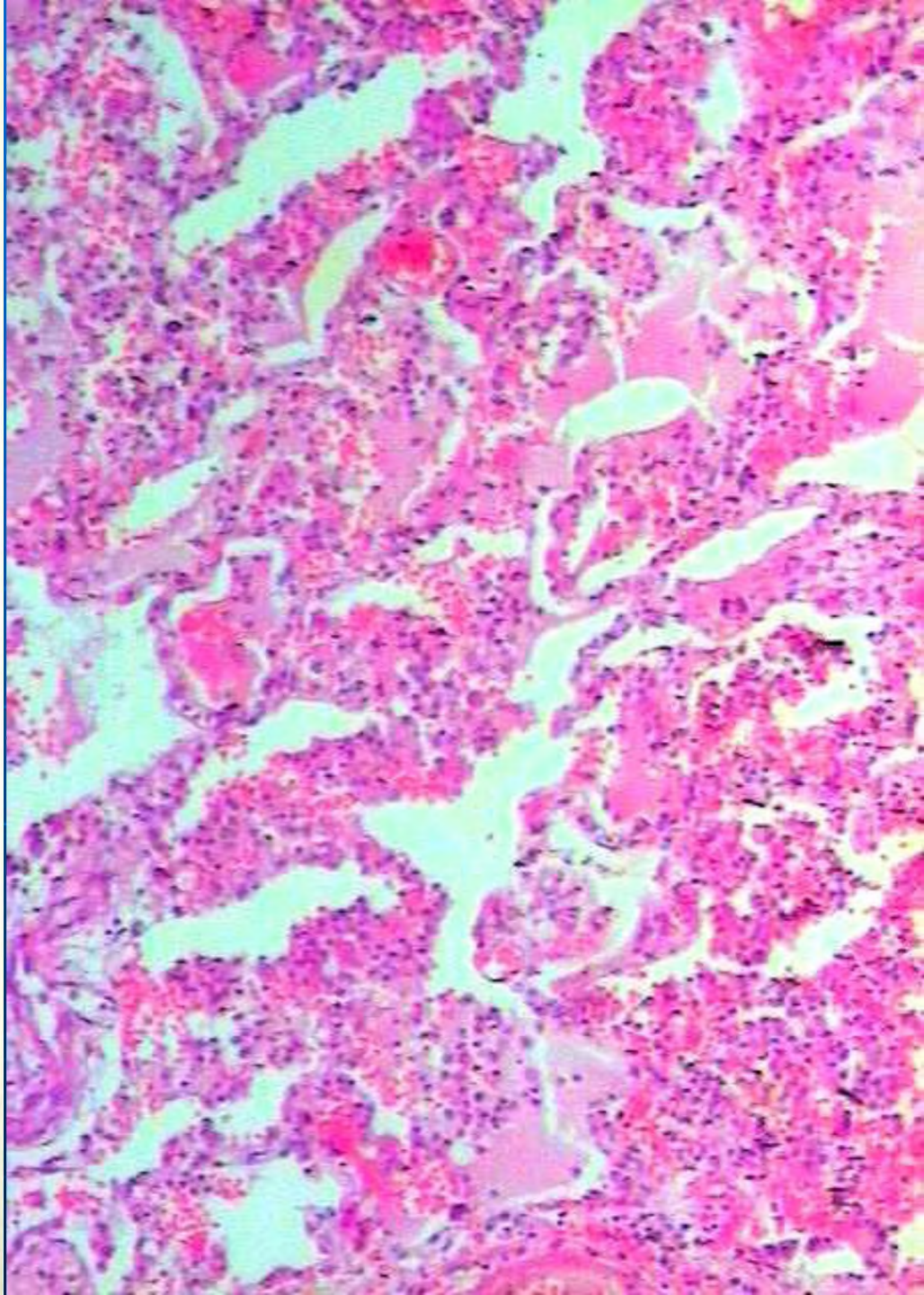
- ● Severe influenza occurs in two forms: toxic influenza and influenza with pulmonary complications.
- ◇ Toxic influenza characterized by severe general changes and increased serous-hemorrhagic inflammation with an increase in hemorrhagic and necrotic component of the inflammatory response.

Viral encephalopathy in toxic form of infection



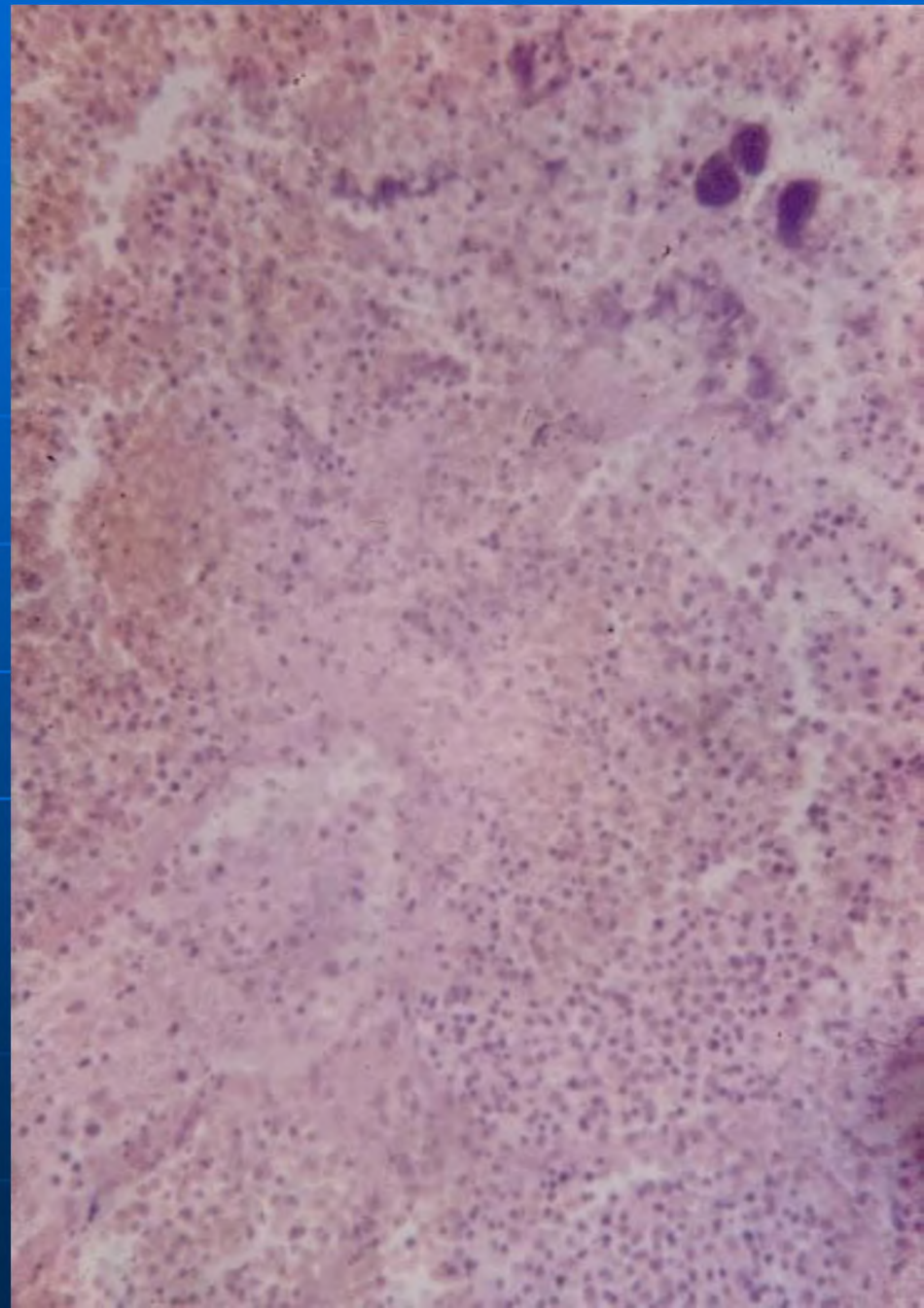
Influenza with pulmonary complications

- occurs when the secondary bacterial infections with the development of severe focal bronchopneumonia typically a week after the onset of the disease. Bacterial infection characterized by a purulent inflammation, first serous-hemorrhagic then purulent hemorrhagic necrosis of lung tissue. The larynx and trachea - fibrinous-hemorrhagic (sometimes necrotic) laryngotracheitis, bronchial – serous-purulent or hemorrhagic, purulent bronchitis involving all layers of the wall of the bronchus, often with its melting area (segmental destructive panbronhit).
- Scarred lung sharply increased, uneven lightness and density at the expense of alternating red and gray. Bulging and sink bluish or reddish-gray areas of atelectasis, swollen pale gray areas of emphysema, abscesses are dirty gray, bleedings are dark red.
- Spleen increased slightly, gives only a small scrape pulp, lymphadenitis is weak.

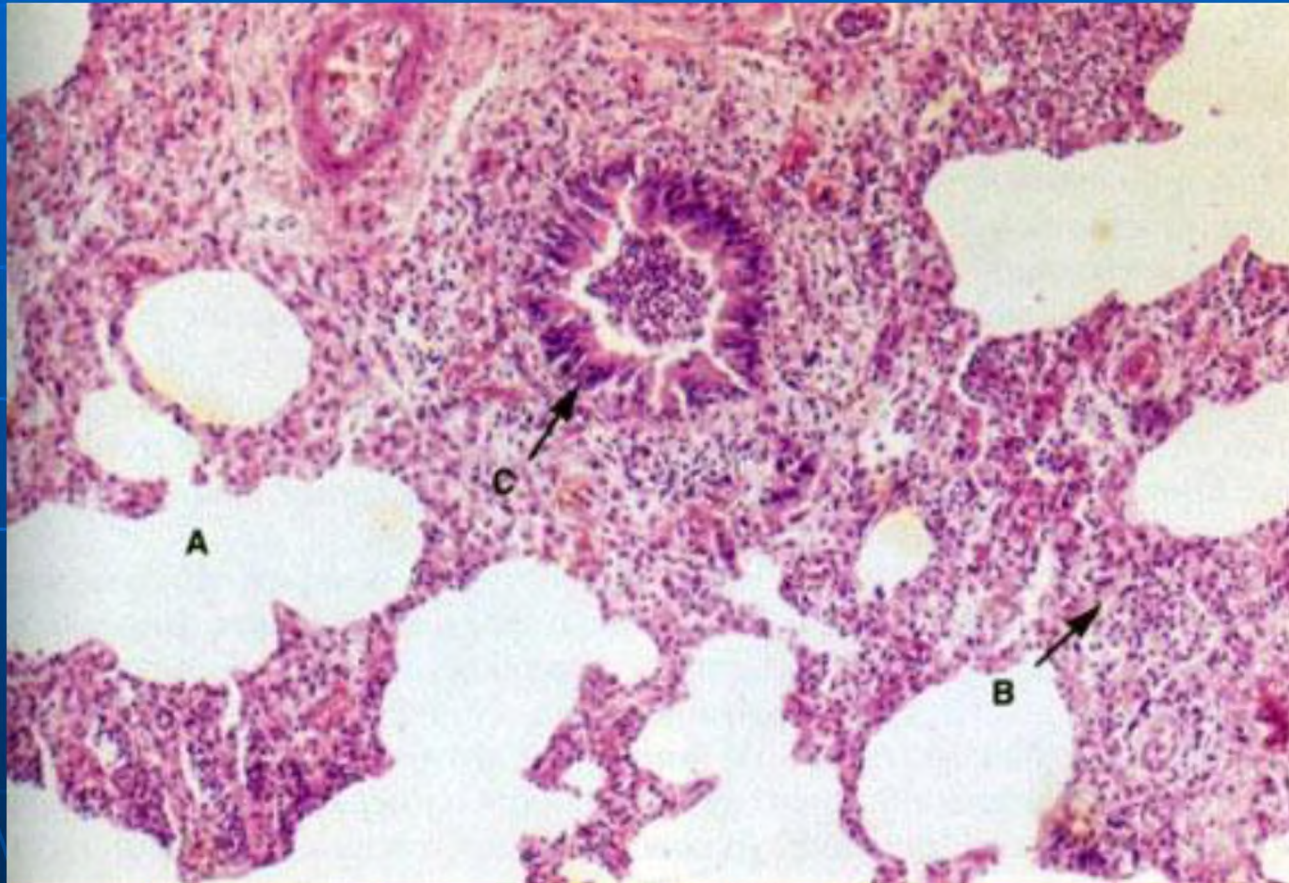


Multiple foci of hemorrhage and focal atelectasis

Pneumonia with influenza



Influenza: focal-confluent pneumonia



Outcomes.

- Influenza, mild to moderate, has favorable outcome (5-7 and 20-25 days, respectively) - a full recovery. In severe and complicated forms of influenza death is possible for 4-5 days from cardiopulmonary failure with progression of pneumonia and its complications: hemorrhage, intoxication, hemorrhagic pulmonary edema. Influenza is most dangerous for young children, elderly patients with cardiovascular disease. Children may develop a false croup and death from asphyxia, the elderly - exacerbation of chronic diseases.

Coronavirus: novel coronavirus (COVID-19) infection

- COVID-19 (coronavirus disease 2019) is a respiratory tract infection with a newly recognized coronavirus, SARS-CoV-2, thought to have originated as a zoonotic virus that has mutated or otherwise adapted in ways that allow human pathogenicity
- • Disease was provisionally called 2019-nCoV infection at start of outbreak (2019 novel coronavirus infection)

Coronavirus (COVID-19) infection

- Illness ranges in severity from asymptomatic or mild to severe; a significant proportion of patients with clinically evident infection develop severe disease, which may be complicated by acute respiratory distress syndrome and shock
- Mortality rate among diagnosed cases (case fatality rate) is generally about 2% to 3% but varies by country; true overall mortality rate is uncertain, as the total number of cases (including undiagnosed persons with milder illness) is unknown

Coronavirus (COVID-19) infection

- Pathogen is a betacoronavirus, similar to the agents of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome)
- Classified as a member of the species Severe acute respiratory syndrome-related coronavirus
- Designated as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)

DIAGNOSIS

- CLINICAL PRESENTATION
- History
 - • In symptomatic patients, illness may evolve over the course of a week or longer, beginning with mild symptoms that progress (in some cases) to the point of respiratory distress and shock
- Most common complaints are fever (more than 80%) and cough, which may or may not be productive
- Myalgia and fatigue are common

DIAGNOSIS

- CLINICAL PRESENTATION
- **Alterations in smell and taste** are increasingly reported, often as an early symptom
- Patients with moderate to severe disease complain of **dyspnea**
- Hemoptysis has been reported in a small percentage of patients
- Pleuritic chest pain has been reported
- Upper respiratory tract symptoms (eg, rhinorrhea, sneezing, sore throat) are unusual
- Headache and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) are uncommon but may occur

DIAGNOSIS

- CLINICAL PRESENTATION
- Patients may report close contact with an infected person; outside of an identified outbreak area, a history of recent travel (within 14 days) to an area with widespread infection is relevant, although community transmission including cases with no identifiable risk factor also occurs

Physical examination

- Reported case series have not detailed physical findings, but clinicians should be particularly attuned to pulmonary and hemodynamic indicators of severe disease
- Patients with severe disease may appear quite ill, with tachypnea and labored respirations. Fever is typical, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever
- Conjunctival secretions, injection, and chemosis have been reported

Physical examination

- A variety of skin changes have been described, including erythematous rashes, purpura, petechiae, and vesicles; acral lesions resembling chilblains or Janeway lesions have been seen, particularly in young patients
- Hypotension, tachycardia, and cool/clammy extremities suggest shock

Physical examination

- In children, hypotension plus 2 or more of the following criteria:
 - – Altered mental status
 - Tachycardia (heart rate more than 160 beats per minute in infants or 150 in older children) or bradycardia (heart rate less than 90 in infants or 70 in older children)
 - Prolonged capillary refill (more than 2 seconds) or warm vasodilation and bounding pulses
 - Tachypnea
 - Mottled skin, petechiae, or purpura
 - Oliguria

COMPLICATIONS

Most common complication is acute respiratory distress syndrome; other reported complications include:

- Septic shock
- Acute kidney injury
- Myocardial injury
- Secondary bacterial and fungal infections
- Multiorgan failure

Case fatality

Case fatality rates by age in the United States:

- 10% to 27% for those aged 85 years or older
- 3% to 11% for those aged 65 to 84 years
- 1% to 3% for those aged 55 to 64 years
- Less than 1% for those aged 0 to 54 years

Case fatality

Case fatality rates for disease in Chinese patients with common comorbidities:

- 10.5% for cardiovascular disease
- 7.3% for diabetes
- 6% for chronic respiratory disease
- 6% for hypertension
- 6% for cancer