Tuberculosis Part 1

Some useful truths

- Tuberculosis will be dealt with in detail in chapter 9 in a few week's time when we deal with the air borne bacterial diseases and the diseases of the lower respiratory tract.
- However, tuberculosis is much in evidence in Lab #1!

- By giving you several images in this power point, I am giving you both a Pathology lab and a Miocrobiology/ Histology/Cytology lab that clearly shows the ravages of this awful disease.
- And you don't even have to peer through a microscope or smell any formaldehyde etc! Isn't that great?
- We also have relevant Pharmacology concerning the principles of treating this disease, and to show you **how all these disciplines are married together to enhance our understanding of this worldwide problem!**
- **This presentation contains very good material.**
- **Diligent students should try to extract as much from it as they can.**
- **The slides that stress the MICROBIOLOGY have a PINK BACKGROUND.**

- Why the fuss about tuberculosis today ?
- **Because TUBERCULOSIS IS BACK WITH A BANG!**
- **So we need to take it seriously even here in the USA! Here's why?**
- **The development of antibiotics changed tuberculosis from a debilitating/fatal illness to one that was readily controlled with oral medications.**
- **The prevalence declined until the 1980s, but is now rapidly increasing, particularly among immunodeficient individuals.**
- **The organisms are increasingly resistant to multiple antimicrobials.**
- **Treatment consists of several drugs because resistance develops to single agent therapy.**
- More and more people are migrating to the USA that might be carrying the disease!

- **Mycobacteria infect mononuclear phagocytes, where they may live for years as intracellular parasites.**
- **Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction.**
- **Fulminant mycobacterial infections develop when the host's immune response is compromised.**
- **Thus patients with AIDS and alcohol addiction are particularly susceptible.**

- **Tuberculosis Is a Major Cause of Death Worldwide and can be a lifelong infection**.
- **At the turn of the 20th century, tuberculosis (TB) was the world's leading cause of death from all causes, accounting for one fatality in every seven cases.**
- **Today's statistics, though improved, are still very high**.
- In the United States, the CDC reported 14,517 cases for 2004, over half of which occurred in foreign-born persons.
- **In developing nations health officials report more deaths from TB than from any other infectious disease**.
- The WHO estimates that globally 2 million die of TB every year.
- The organization also believes one billion people globally will become infected and 36 million will die of tuberculosis by 2020, unless control measures. are strengthened.

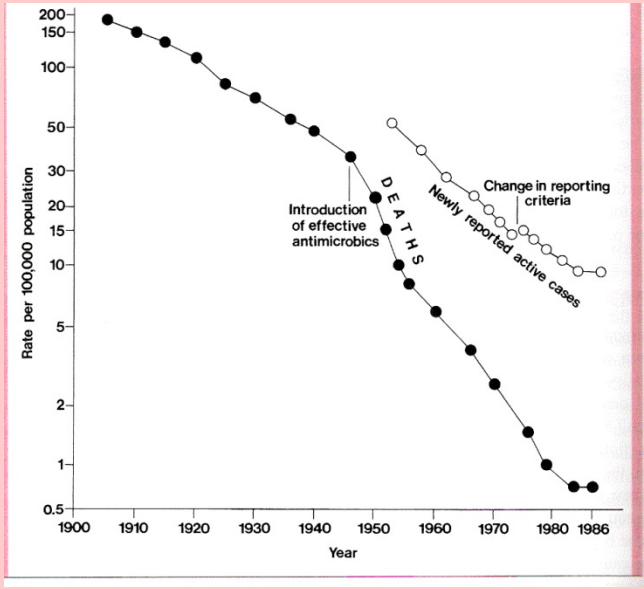
- **Tuberculosis is a particularly insidious problem to those who have AIDS. In these patients, the T lymphocytes, immune system cells that normally mount a response to M. tuberculosis, are being destroyed, and the patient cannot respond to the bacterial infection.**
- **HIV-infected patients face a mortality rate from TB of 70 to 90 percent, usually within one to four months of developing symptoms.**
- Unlike most other TB patients, those with HIV usually develop tuberculosis in the lymph nodes, bones, liver, and numerous other organs.
- **Ironically, AIDS patients often test negative for the tuberculin skin test because without T lymphocytes, they cannot produce the telltale red welt signaling exposure.**
- **Tuberculosis often is the first disease to occur in the AIDS patient, even before any of the other opportunistic illnesses appear, and it is generally more intractable than in non-AIDS patients.**
- The WHO estimates that worldwide, about 4.4 million people are coinfected with HIV and M. tuberculosis.

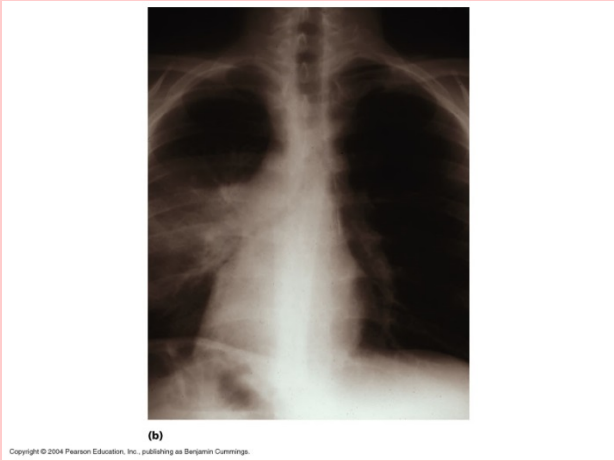
Mycobacterium tuberculosis

- “Consumption”
- ~ 2,000,000,000 cases worldwide

  Yes, that’s 2 BILLION,

  1/3 world population
- ~25-50 million new cases/year
- ~5,000,000 deaths per year
- in contrast to USA, cases are NOT DECREASING
- Highly infectious, acute to chronic



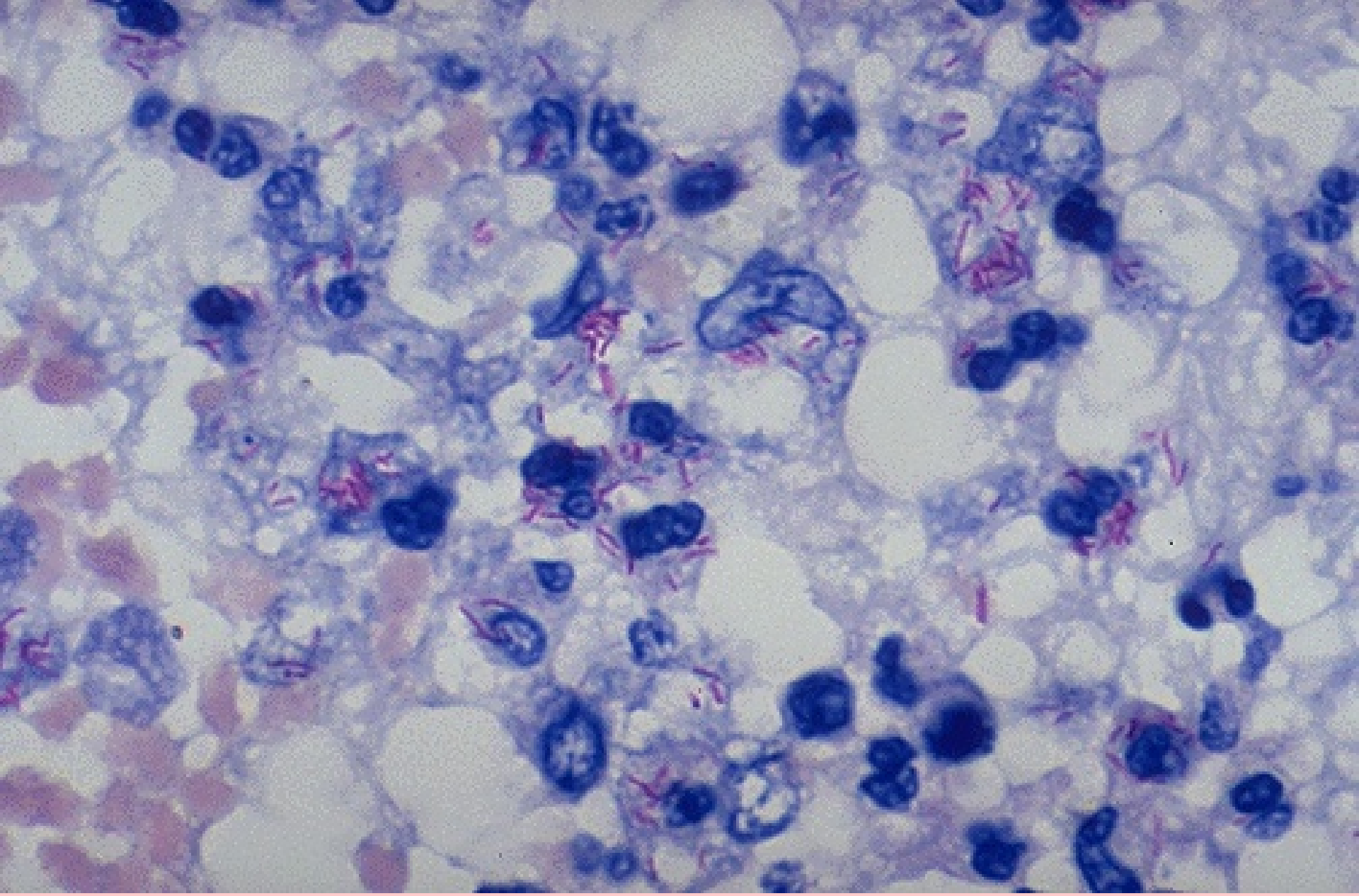


- **Tuberculosis is caused by Mycobacterium tuberculosis,** the "tubercle" bacillus first isolated by Robert Koch in 1882.
- **It is a small, aerobic nonmotile rod whose cell wall contains a layer of waxy material that greatly enhances resistance to environmental pressures.**
- **In the laboratory a sputum sample for staining must be accompanied by heat to penetrate this barrier, or a lipid dissolving material must be used.**
- **Once stained, however, the organisms resist decolorization even when subjected to a 5 percent acid-alcohol solution.**
- **Thus, the bacilli are said to be acid resistant, or acid fast.**

- Mycobacteria are **slender, rod-shaped bacilli with lipid-rich cell walls that stain stain weakly gram positive, but once stained, the walls cannot be easily decolorized by treatment with acidified organic solvents or with acid alcohol because they retain dye.**
- **Hence, they are termed "acid-fast."**
- **The most widely encountered mycobacterial infections is tuberculosis—the leading cause worldwide of death from infection.**
- **Mycobacterium tuberculosis, one of a number of mycobacteria, can lead to serious infections of the lungs, genitourinary tract, skeleton, and meninges**.

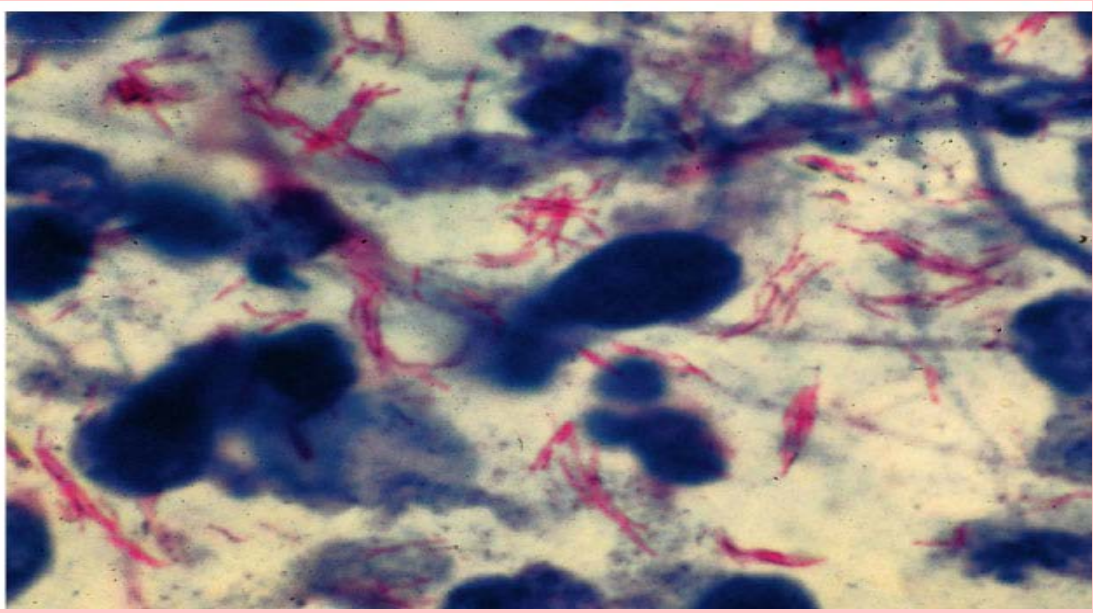
  Members of the genus Mycobacterium also cause leprosy as well as several tuberculosis-like human infections. Tuberculosis (TB) and leprosy are the best known mycobacterial diseases

  It is currently estimated that about one-third of the world's population is infected with M- tuberculosis, with thirty million people having active disease. Worldwide, eight million new cases occur, and two million people die of the disease each year.



Acid Fast Bacteria

- Mycobacterium Worldwide Distribution
  - **Slim rods, aerobic, nonmotile, slow growing**
    - **Acid Fast**
      - » **Ziehl-Neelsen**



Tuberculosis

- Mycobacterium tuberculosis
  - **Doesn't stain well with Gram (special bacterial wall)**
  - **Special stains are needed**
    - **Acid-fast stain (Ziehl-Nielsen) – AFB**
    - Auramine (Fluorescence microscope)
  - **Diagnosis**
    - **Direct microscopic exam of tissue sections (AFB stains)**
    - **Cultures (weeks)**
    - **Molecular diagnosis ~ 2 days**

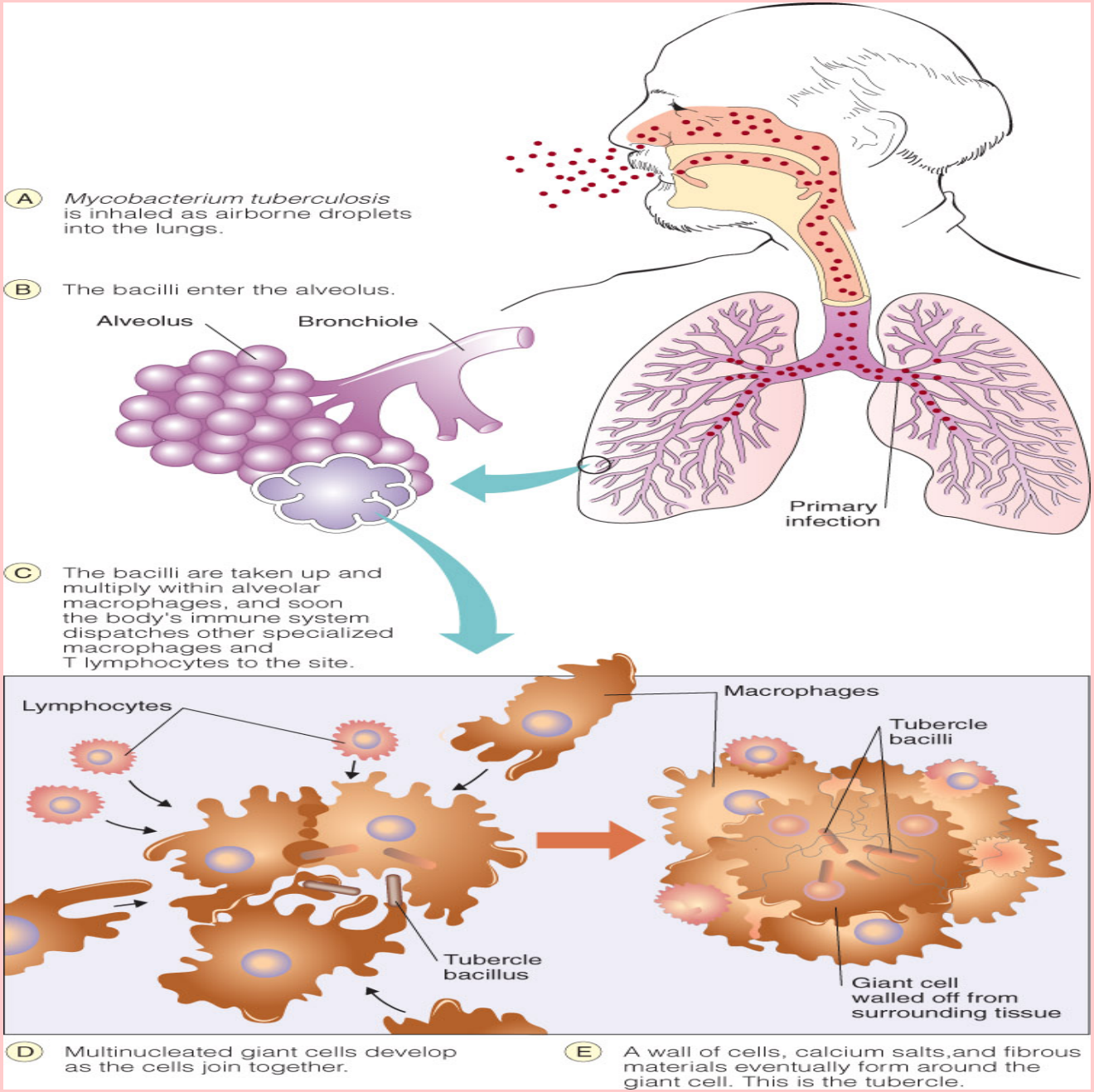
Do not confuse mycobacteria for mycosis (fungal infection)

Tuberculosis

- Worldwide distribution
- More frequent in disadvantaged groups
- Forms
- **Pulmonary**
- Spread by Inhalation of droplets containing Mtb organisms
- Tuberculosis often presents with pulmonary symptoms, but may involve lymph nodes, bones, skin, genitourinary tract and meninges.
- **Non-pulmonary**
- Spread by Ingestion of unpasteurized milk from tb cows
- Hematogenous spread from lungs

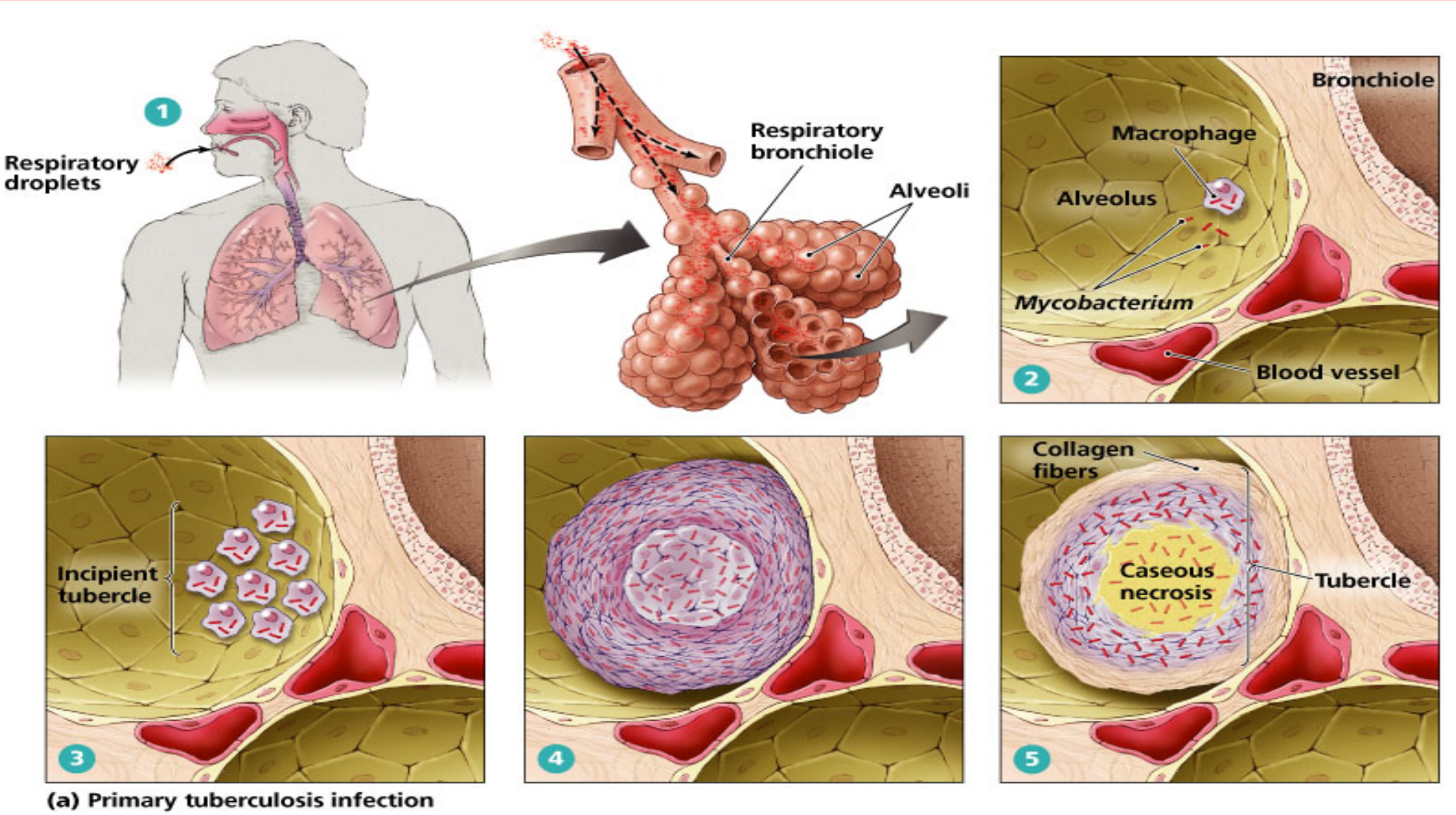
- **M. tuberculosis enters the respiratory tract in small aerosolized droplets (multiple exposures are generally necessary).**
- **Crowded conditions and poor ventilation contribute to disease spread. Thus, people who live in overcrowded urban ghettoes often contract TB.**
- **Malnutrition and a generally poor quality of life** contribute to the establishment of disease.
- **Unlike many of the other infectious diseases where the individual becomes ill within a week or two of infection, TB takes much longer.**
- **After being inhaled, the bacterial cells enter the alveoli where host -pathogen interactions occur.**
- **If the person has had no previous exposure with the pathogen, 70 percent of the individuals do not become infected.**

- The other 30 percent develop primary tuberculosis.
- **In about 90 percent of cases, the infection is arrested, lung lesions heal, and the individuals are never aware they are infected, although they may have a positive tuberculin test**
- This is referred to as latent tuberculosis and is carried by 2 billion people worldwide. Of these, 90 percent will never develop an active infection.
- However, 10 percent of people who have primary or latent TB will contract clinical TB and develop active disease that can be transmitted to others.
- **Individuals will become ill within three months, experience chronic cough, chest pain, and high fever, and they expel s**putum, the thick matter accumulating in the lower respiratory tract.
- **(Often the sputum is rust colored, indicating that blood has entered the lung cavity.)**
- **In these cases, the body responds to the disease by forming a wall of macrophages.**



- Macrophages accumulate in the lung
  - They form a tubercle that harbors *M. tuberculosis*
- If a tubercle breaks apart, bacteria spread throughout the body

Mycobacterium tuberculosis



(a) Primary tuberculosis infection

- As these materials accumulate in the lung, a hard nodule called a tubercle arises (hence the name tuberculosis) .
- This tubercle may be visible in a chest Xray.
- Surrounding tissue may be damaged, although the disease may become dormant.
- The tubercle undergoes fibrosis and calcification, and form granulomas.

- Unfortunately, the bacilli in the tubercle are not killed, and the tubercle may expand as the lung tissue progressively deteriorates.
- In many instances, the tubercle breaks apart and bacterial cells spread through the blood and lymph to other organs such as the liver, kidney, meninges, and bone.
- If active tubercles develop throughout the body, the disease is called **miliary tuberculosis** (milium = "seed;" in reference to the tiny lesions resembling the millet seeds in bird food).
- Tubercle bacilli produce no discernible toxins, but growth is so unrelenting the tissues are literally consumed, a factor that gave tuberculosis its alternate name, consumption.

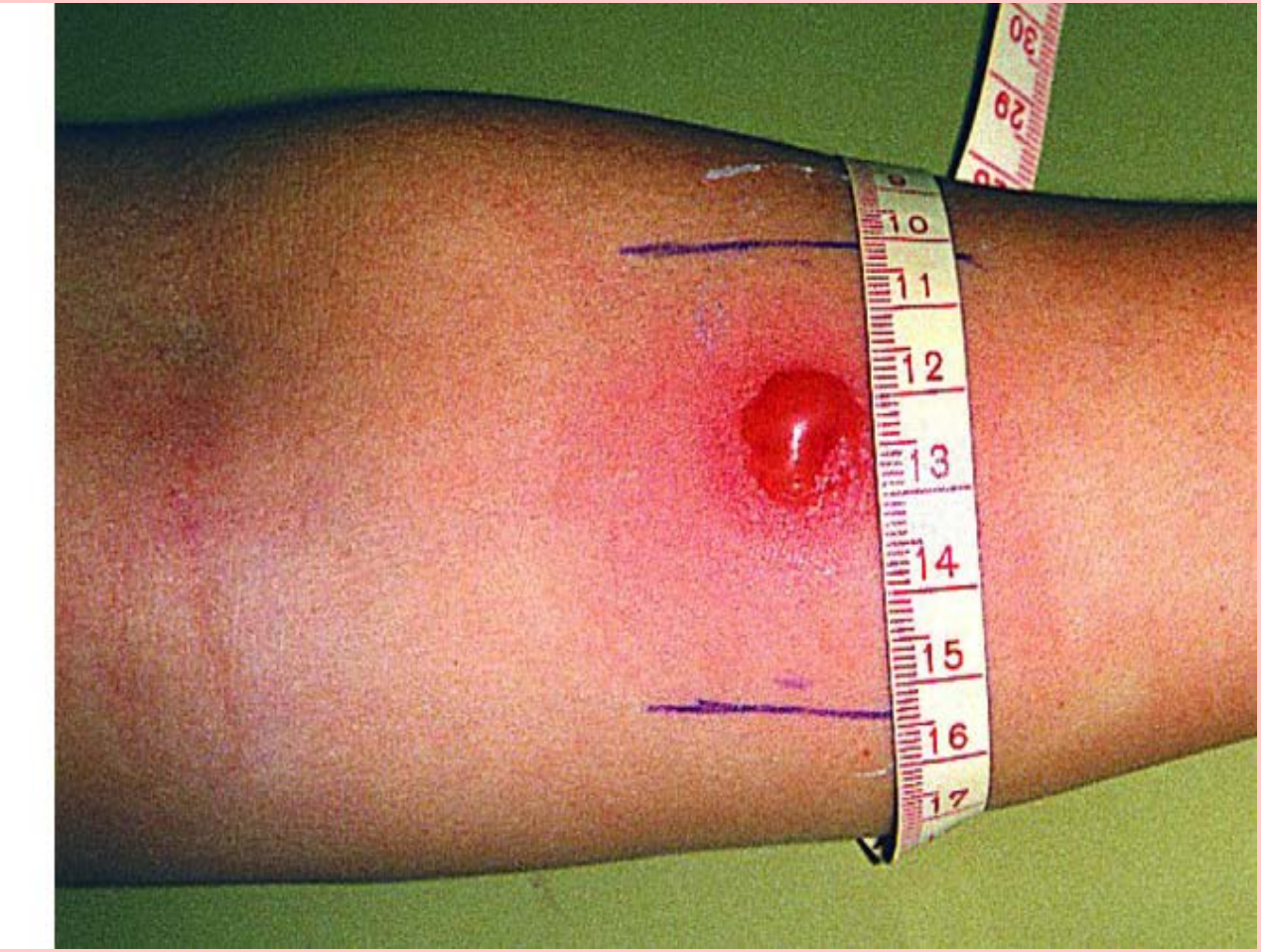
- Tuberculosis is said to be a granulomatous disease, because in the chronic sage granulomas are formed.
- **Tuberculosis is the archetype of the granulomatous diseases, but, cat-scratch disease, lymphogranuloma inguinale, leprosy, brucellosis, syphilis, some of the mycotic infections, can all cause a granulomatous inflammation.**
- **WE WILL BE STUDYING ALL THESE DISEASES IN THIS MICROBIOLOGY COURSE!**
- **So you might want to see what a granuloma looks like! And find out what a granuloma is.**

- **Early detection of tuberculosis is aided by the tuberculin reaction, a test that begins with the application of a purified protein derivative (PPD) of M. tuberculosis to the skin.**
- One method of application uses an injection of PPD intradermally into the forearm (the Mantoux test).
- Depending on the patient's risk of exposure, the skin becomes thick, and a raised, red welt of a defined diameter develops.
- **A positive test does not necessarily reflect the presence of active disease, but may indicate a recent immunization, previous tuberculin test, or past exposure to M. tuberculosis. It suggests a need for further tests.**
- **Tuberculosis is an extremely stubborn disease**.

Tuberculosis

- Testing
  - Tuberculin skin test
  - Indicates exposure to Tb
  - Type IV hypersensitivity reaction (delayed, cell-mediated)
  - Usually remains positive throughout life

T cell response
skin test +



- Immunization to tuberculosis may be rendered by injections of an attenuated strain of *Mycobacterium* bovis. This species causes tuberculosis in cows as well as humans.
- The attenuated strain is called bacille Calmette Guerin, or BCG, after Albert Calmette and Camille Guerin, the two French investigators who developed it in the 1920s
- Though the vaccine is used in parts of the world where the disease causes significant mortality and morbidity, many health officials oppose its use in the United States because they point to the success of early detection and treatment, and to the vaccine's occasional side effects.
- New vaccines consisting of sub-units, molecules of DNA, and attenuated strains of mycobacteria are currently being developed.

- Several other species of Mycobacterium deserve a brief mention. The first, **M. chelonae, is an acid-fast rod frequently found in soil and water.** During the 1980s, microbiologists first recognized this **fast-growing bacillus as a cause of lung diseases, wound infections, arthritis, and skin abscesses**.
- **M. *haemophilum*** surfaced as a pathogen in 1991 when 13 cases occurred **in immunocompromised individuals** in New York City hospitals.
- Cutaneous ulcerating lesions and respiratory symptoms were observed in the patients.
- **M. kansasii causes infections that are indistinguishable from tuberculosis**. In the United States, **infections are most common in the central states and rare in the southeast**.
- The group known as **M. avium complex (MAC) tends to cause infection only in compromised individuals.** Thus, in the United States, **MAC represents an opportunistic infection that is responsible for most cases of miliary TB in AIDS patients.**
- For all species mentioned here, there is no evidence for spread between individuals; rather, infectioin comes from contacting soil, or ingesting food water contaminated with the organism.

Mycobacterium

- **tuberculosis**
- **avium-intracellulare**

Mycobacteria of Major Clinical Importance[a]

		Characteristics					
Species	Reservoir	Virulence for Humans	Disease Caused	Case-to-Case Transmission	Growth Rate[b]	Optimum Growth Temperature	Pigment Production[c]
M. tuberculosis	Human	+++	Tuberculosis	Yes	S	37	–
M. bovis	Animals	+++	Tuberculosis	Rare	S	37	–
Bacillus Calmette–Guérin	Artificial culture	±	Local lesion	Very rare	S	37	–
M. kansasii	Environmental	+	Tuberculosis-like	No	S	37	Photochromogen
M. scrofulaceum	Environmental	+	Usually lymphadenitis	No	S	37	Scotochromogen
M. avium-intracellulare	Environmental; birds	+	Tuberculosis-like	No	S	37	±
M. fortuitum	Environmental	±	Local abscess	No	F	37	±
M. marinum	Water; fish	±	Skin granuloma	No	S	30	Photochromogen
M. ulcerans	Probably environmental; tropical	+	Severe skin ulceration	No	S	30	–
M. leprae	Human	+++	Leprosy	Yes	NG	NG	NG
M. smegmatis	Human, external urethral area	–	None	–	F	37	–

TUBERCULOSIS Part 2

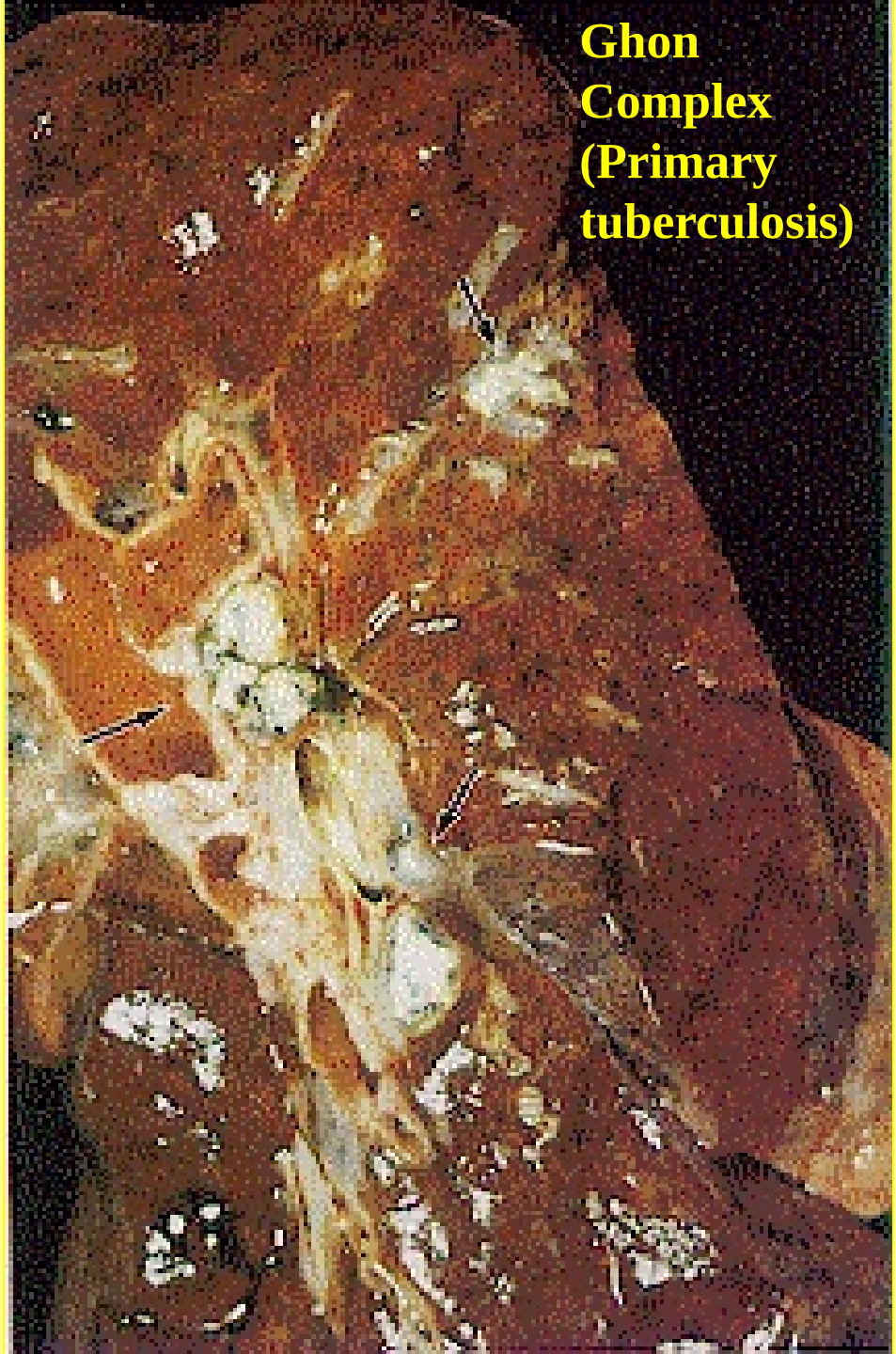
- The following slides with the blue backgrounds, contain pictures from my Pathology lectures slides.
- I share these with you as a matter of interest, and to show you the extent of the damage *Mycobacterium tuberculosis* can do!
- The pictures in this section will help you to visualize the information presented in the account of the Microbiology in the foregoing slides.
- Some of the information in these slides ought also to be merged into your lab report.
- First are some pictures of the gross anatomic features of the disease, and then some of the microscopic features (the forte of the CYTOLOGIST!)

Primary tuberculosis

- **Initial infection**
  - **Most often asymptomatic**
  - **Most often self-limited – doesn't progress to clinical disease**
  - **Path**
    - **Ghon (primary) complex**

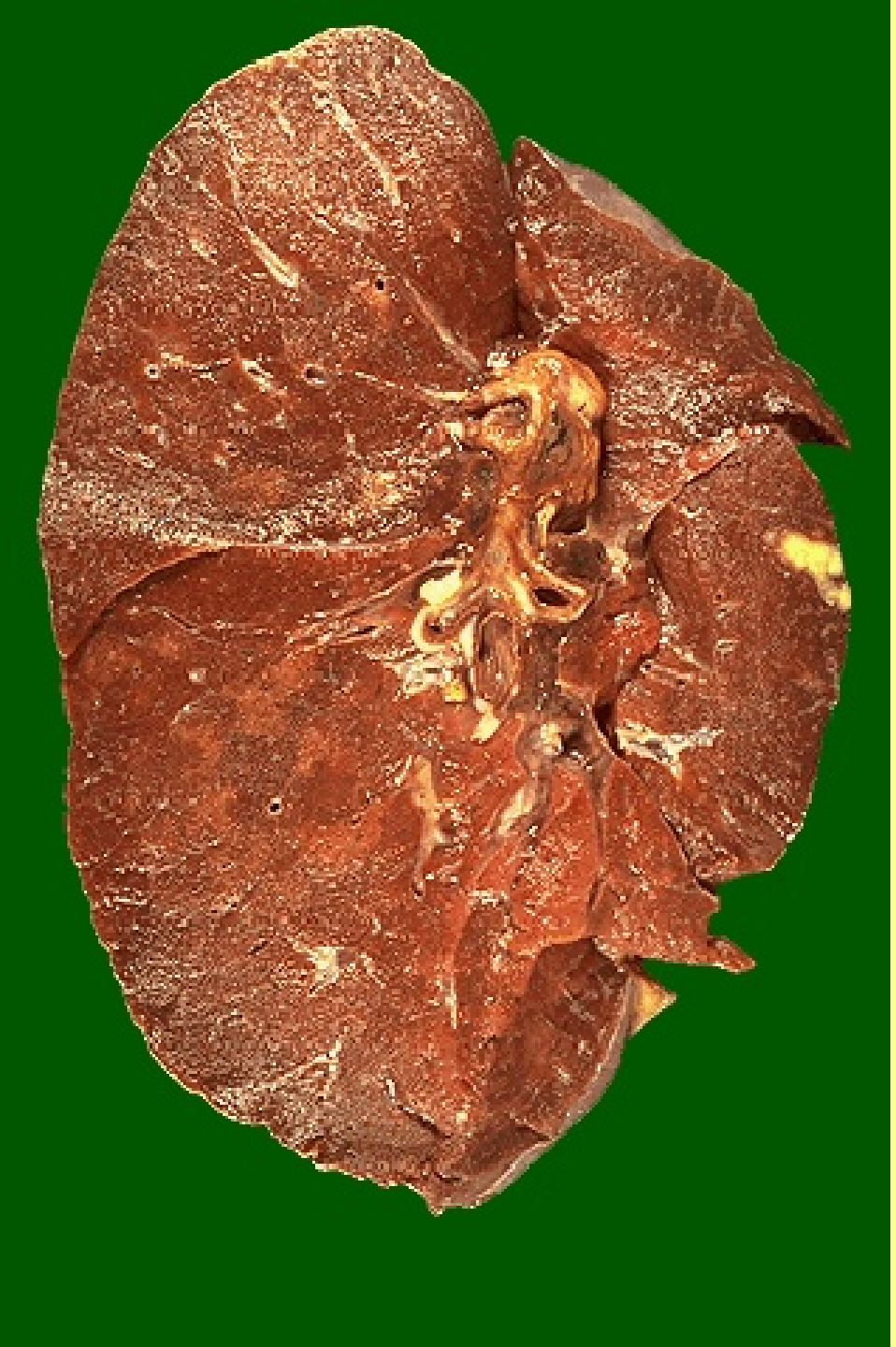
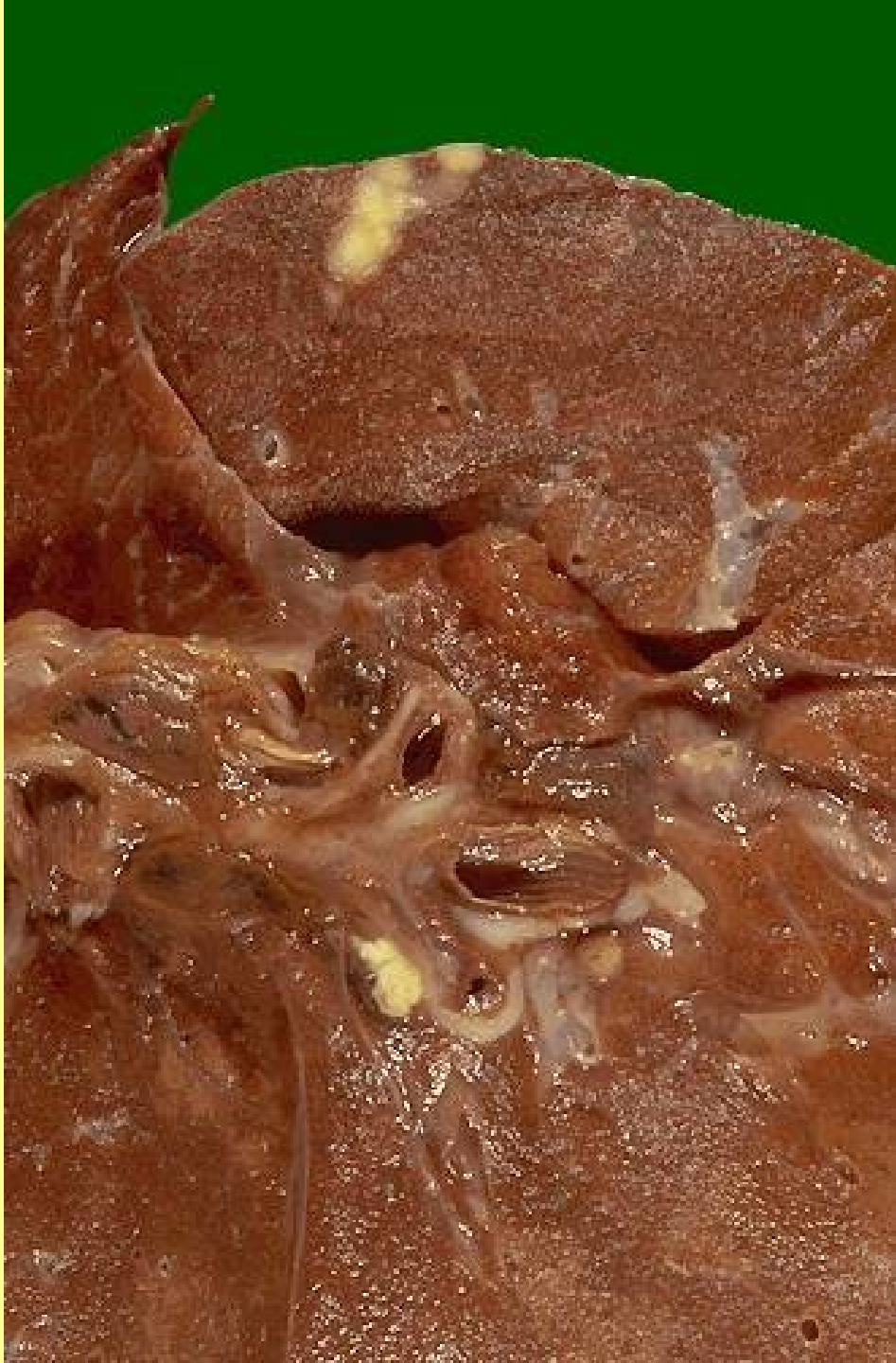
Primary tuberculosis

- **Ghon complex**
  - 2 elements
    - Subpleural parenchymal tubercle
    - Draining lymph node involvement
  - May calcify – visible on X-ray


Ghon
Complex
(Primary
tuberculosis)

Primary tuberculosis

- **Initial infection**
  - **Most often asymptomatic**
  - **Most often self-limited – doesn't progress to clinical disease**
  - **Path**
    - **Ghon (primary) complex**

Secondary tuberculosis

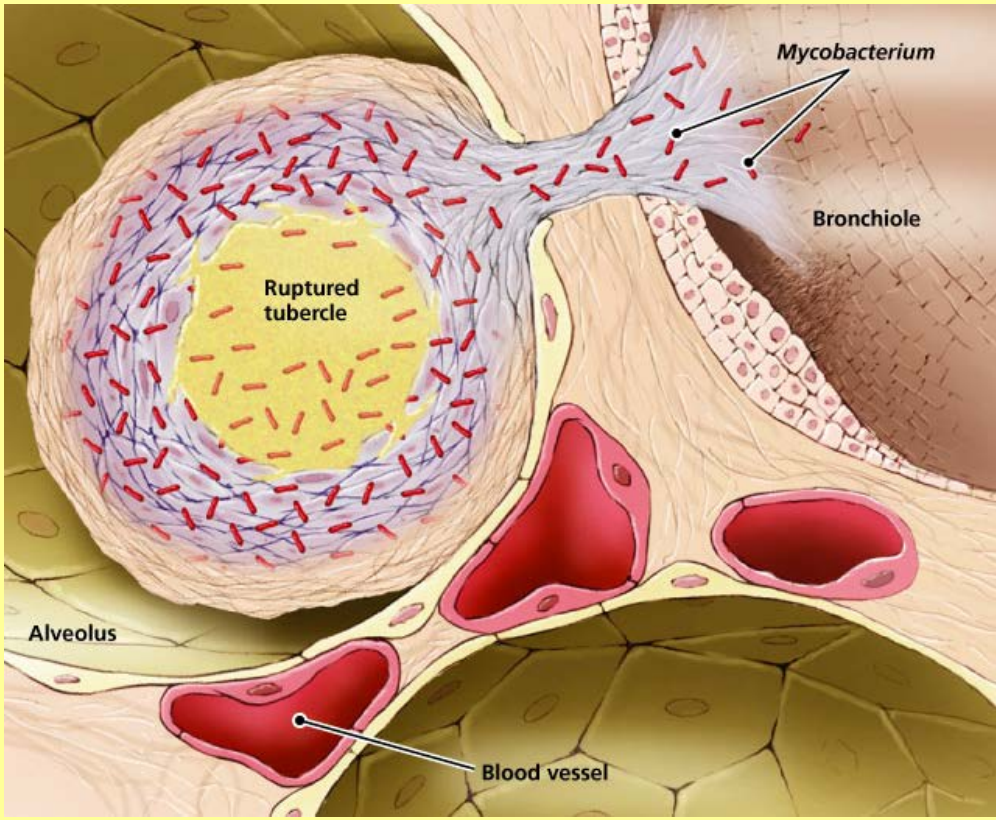
- Usually – **activation of a prior Ghon complex**
- **Spread to new pulmonary / extrapulmonary sites**
- Clinical
  - Generalized wasting
  - Low-grade fever
  - Cough
  - Hemoptysis
  - Pleural effusion (often bloody)

Secondary tuberculosis

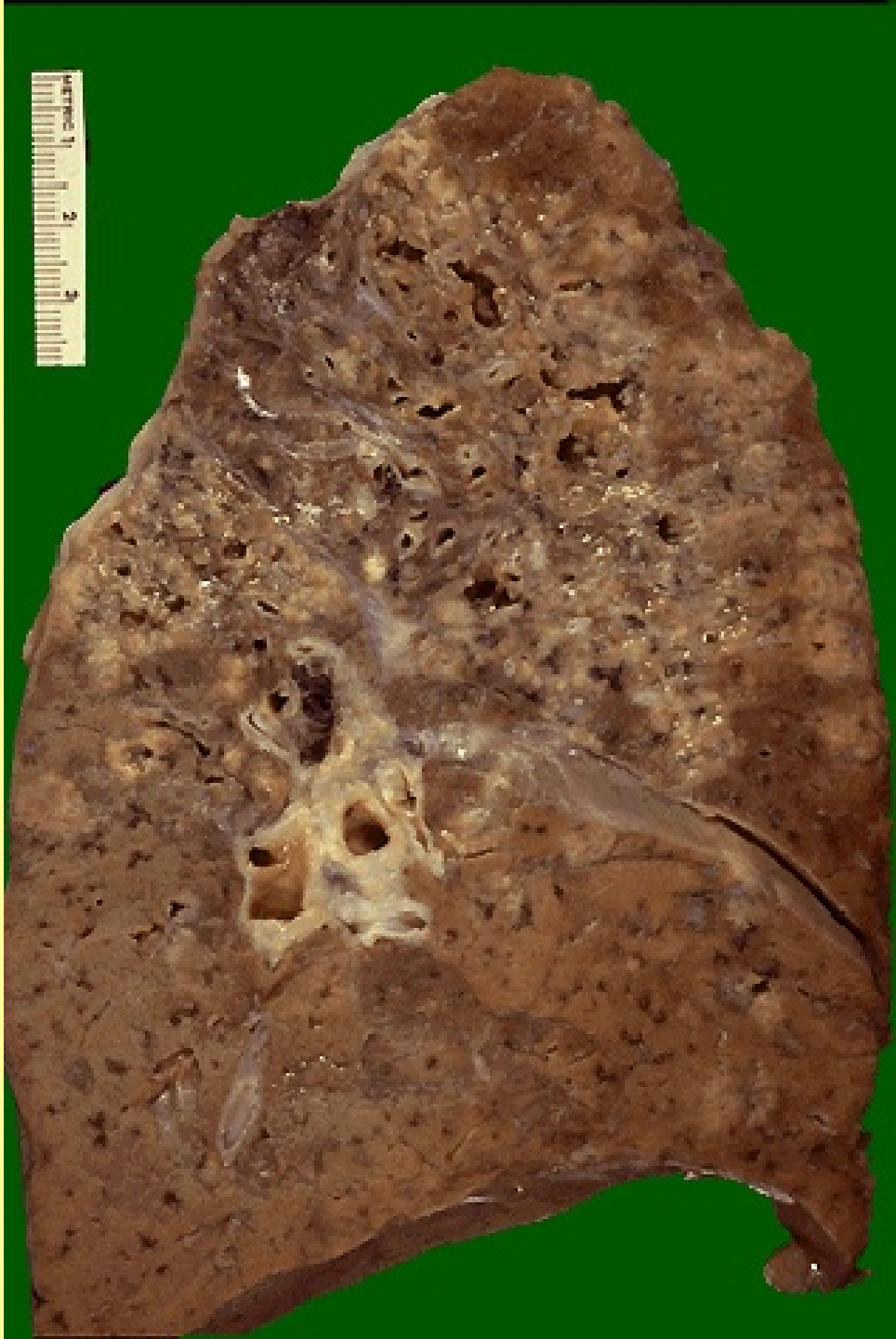
- Path
  - Patchy / nodular/ diffuse (pneumonic)
  - Necrotizing granulomatous inflammation
  - Hilar lymph nodes involvement
  - Cavitary lesions (coalescence and cavitation of lesions with evacuation of caseum – cough)
  - Scarring and calcification
  - Lymphatic / hematogenous dissemination (miliary tb) to:
    - Lungs
    - Extrapulmonary

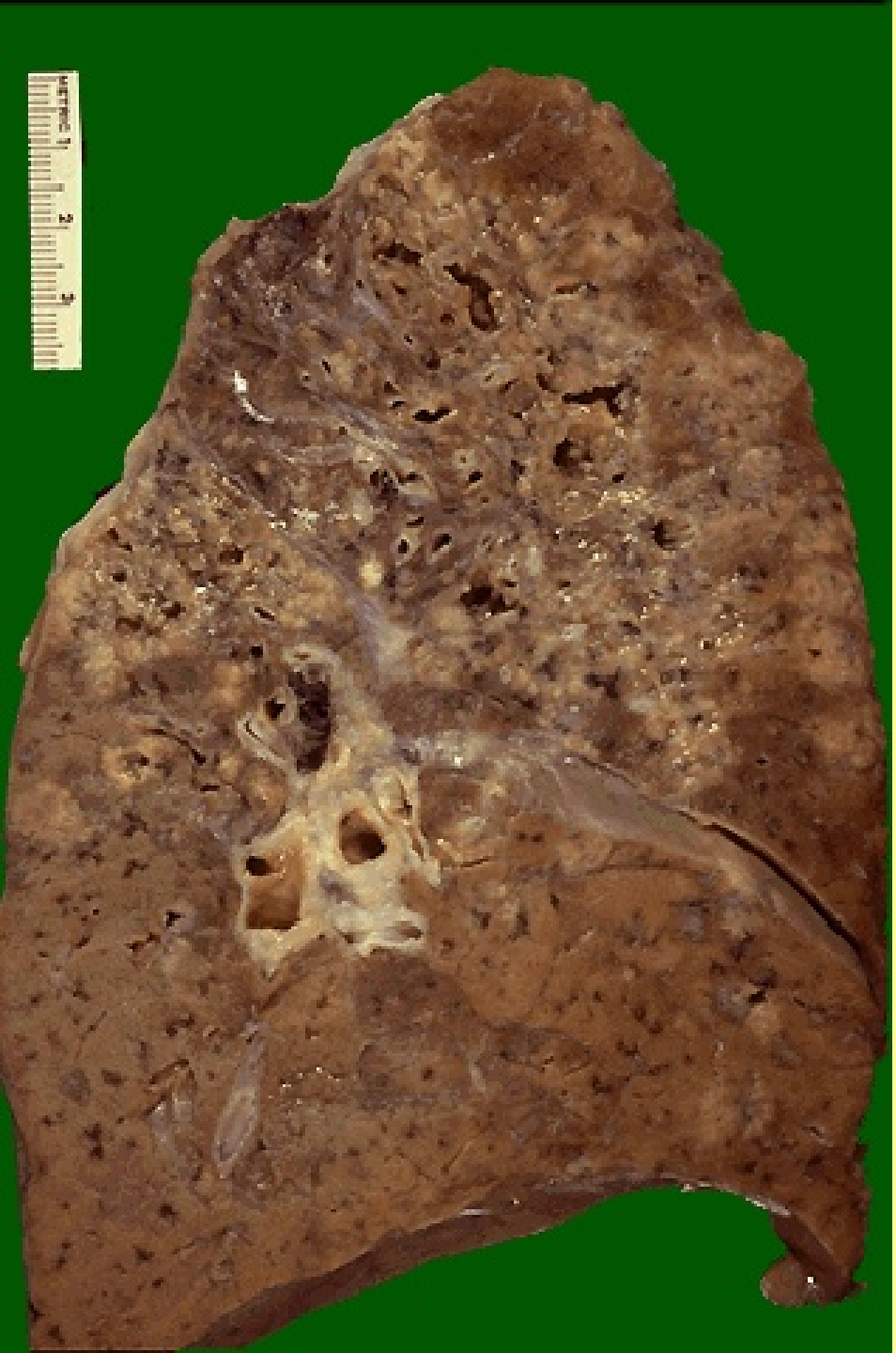
Mycobacterium tuberculosis

- **Secondary (reactivation)**
  - long term, as immune system degrades
- Disseminated
  - extension of secondary by circulation of infected macrophages
    - lowered immunity: diabetes, nutrition, stress, drug use
  - spreads through lymph system to many organs
    - kidney bone brain bowel
    - meninges bone marrow



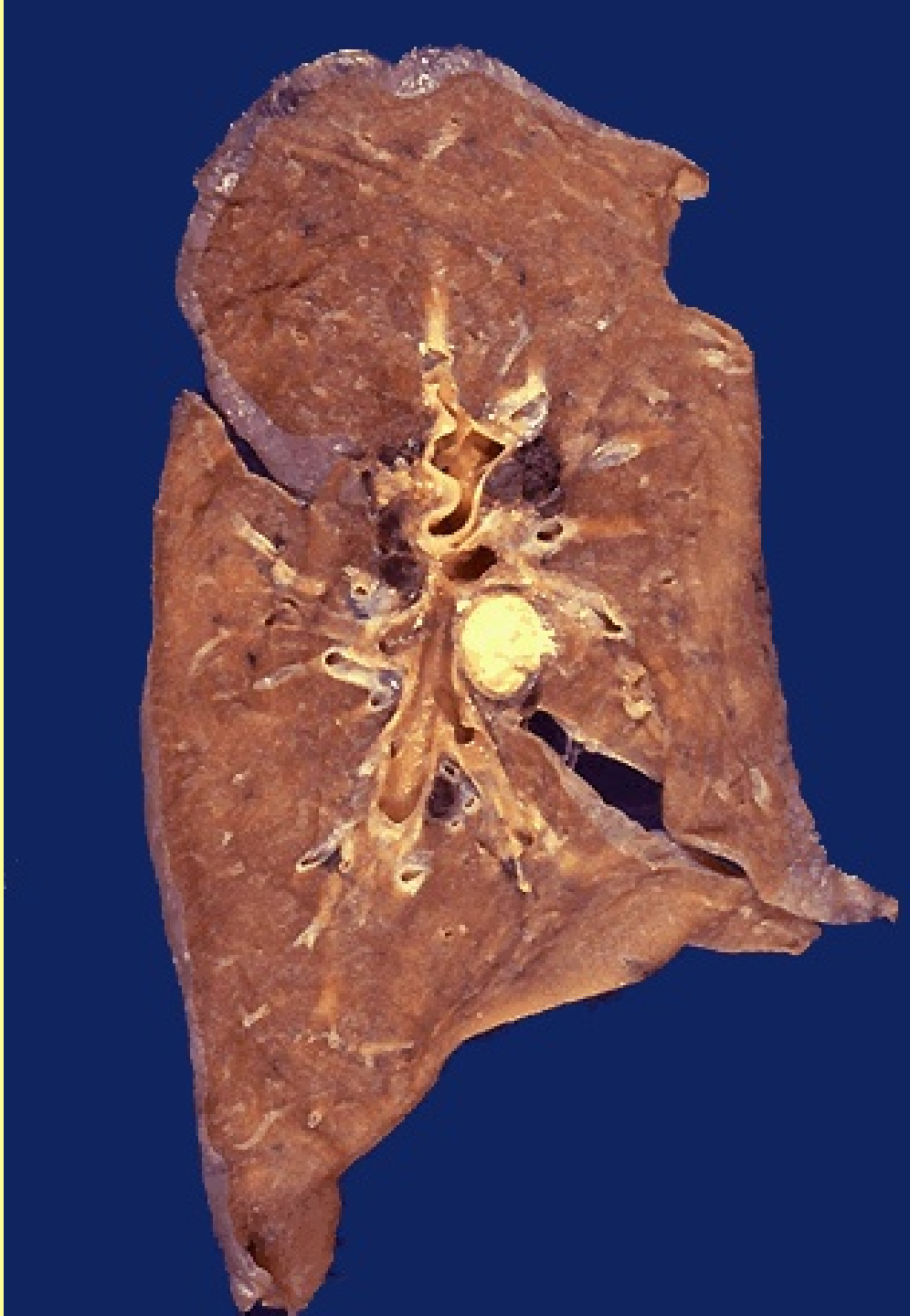
- Granulomatous disease can become quite extensive. Here are numerous confluent granulomas in upper lung fields in a case of active pulmonary tuberculosis.



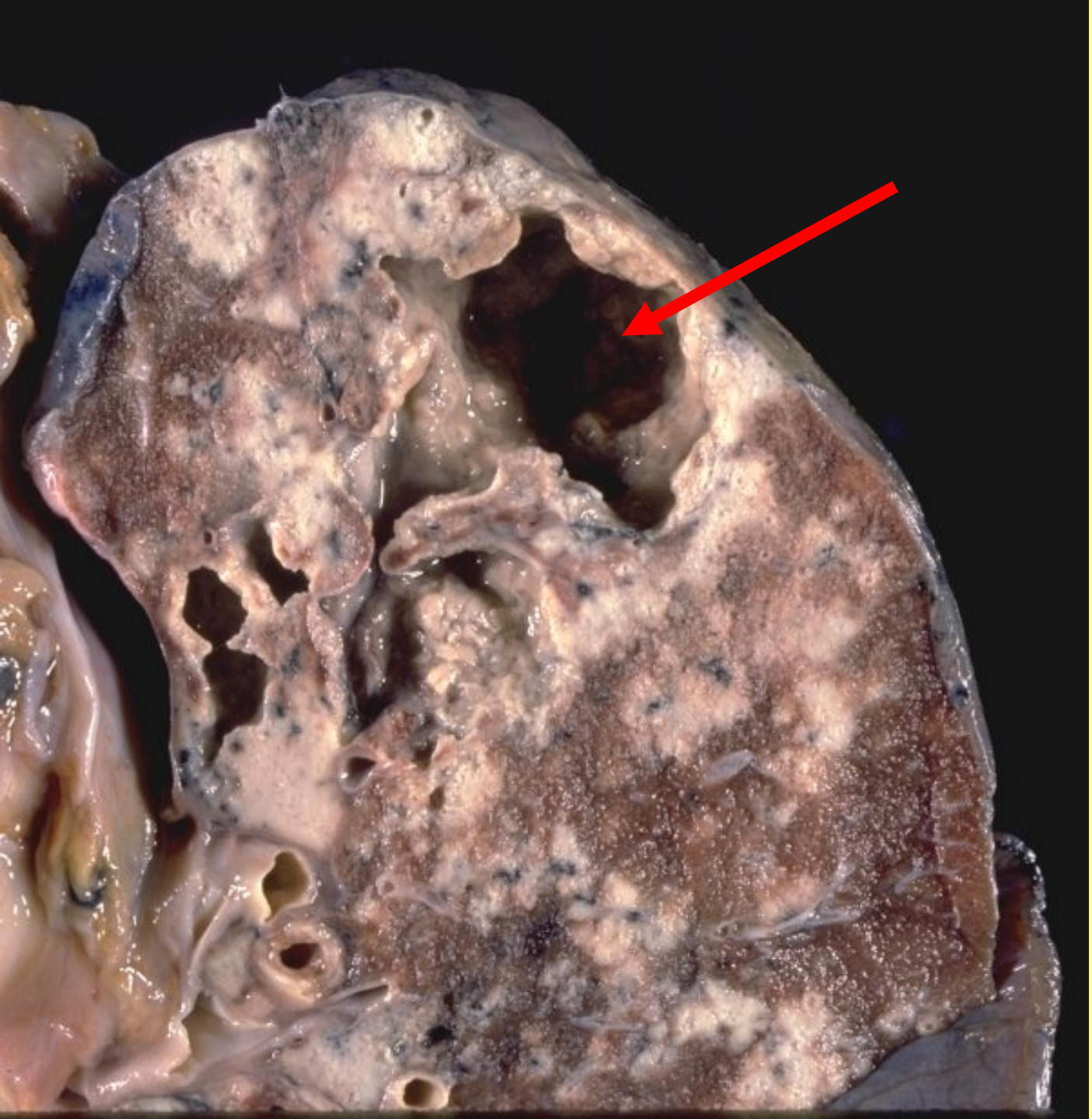


Grossly, a granuloma tends to be a focal lesion. Seen here in a hilar lymph node is a granuloma.

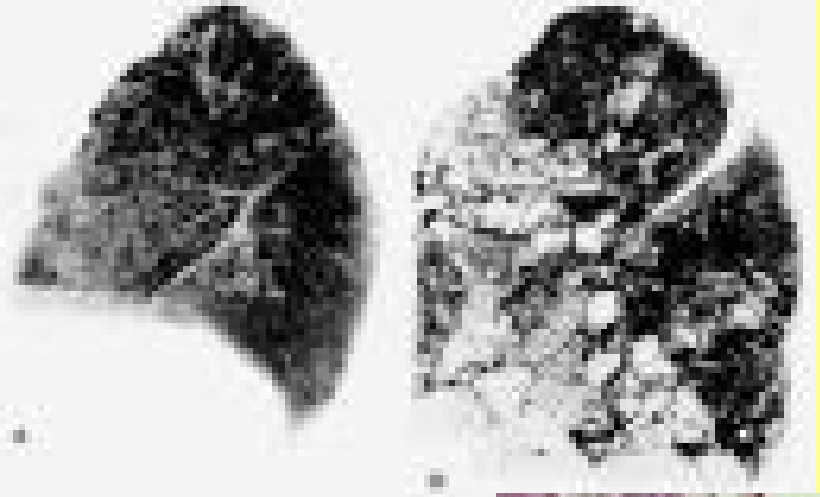
Granulomas due to infectious agents such as mycobacteria are often described as "caseating" when they have prominent caseous necrosis.



Caseous nodule in lung with severe emphysema

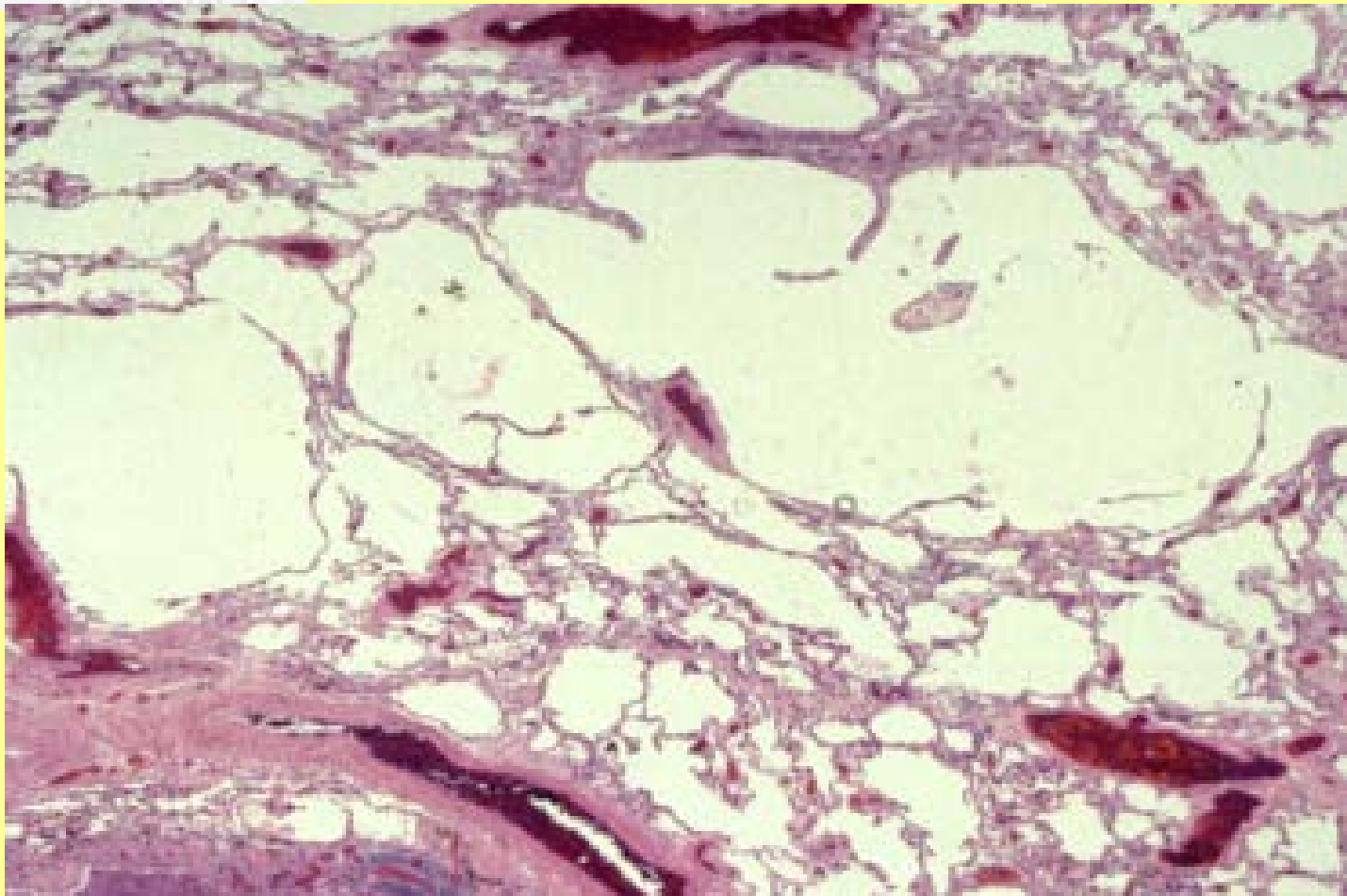


Tuberculous lung with cavity formation

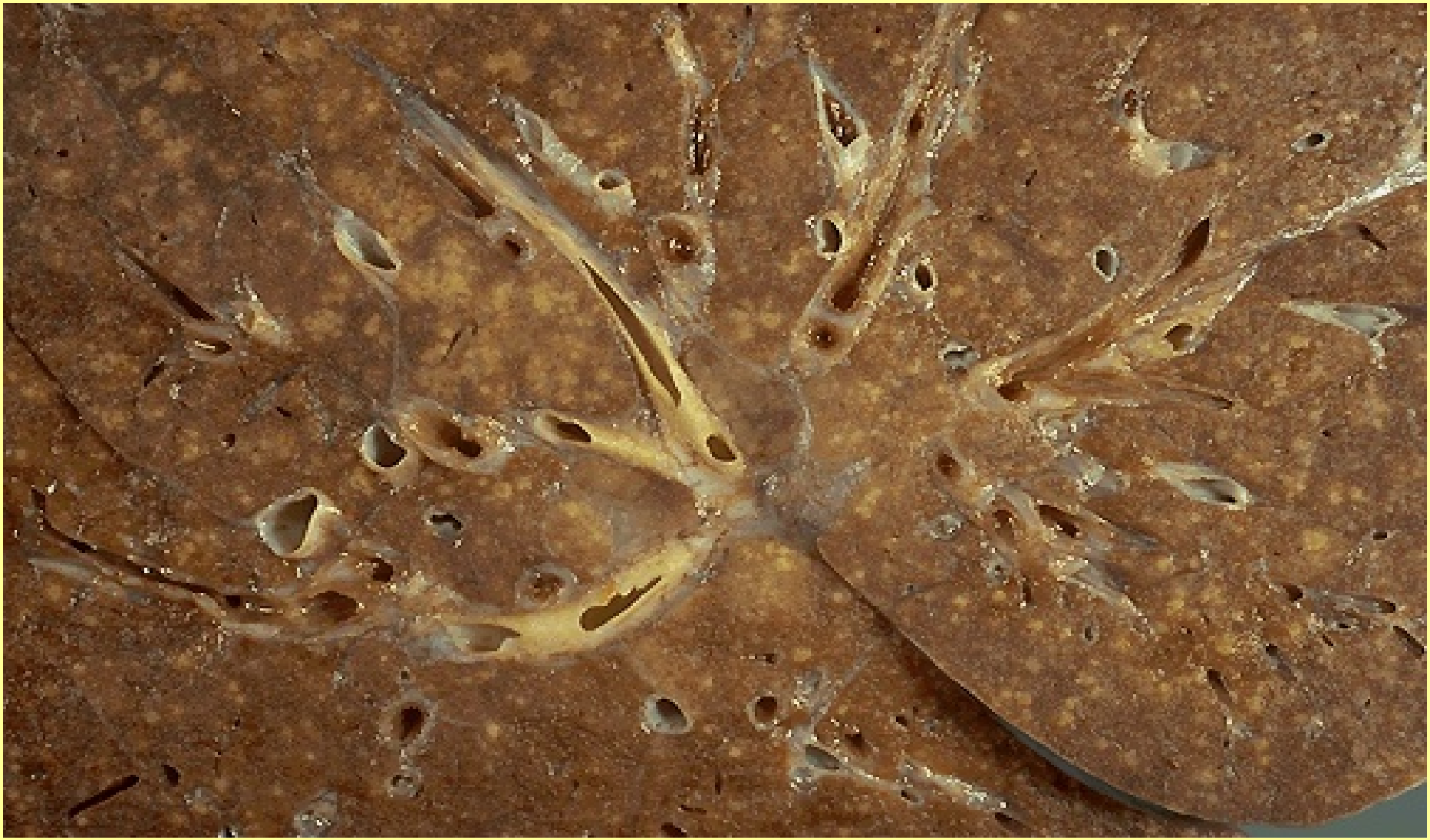


Emphysema =

breakdown of alveolar walls with formation of large spaces

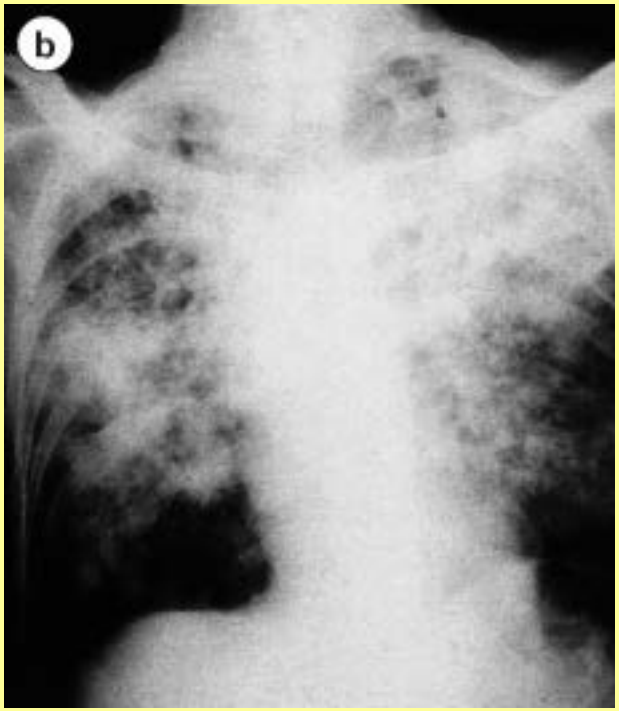


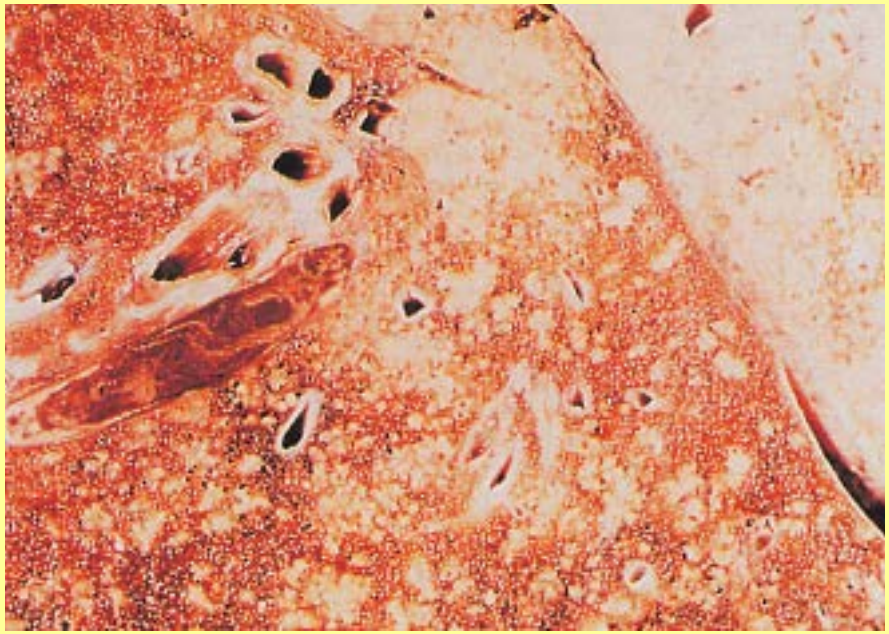
With a poor immune response to the agents producing granulomatous inflammation, there can be extensive spread of infection with the production of a "miliary" pattern of granulomas, as seen here in the lung of a patient with miliary tuberculosis. The 1 to 2 mm granulomas are scattered around like millet seeds (millet is a type of cereal grain).

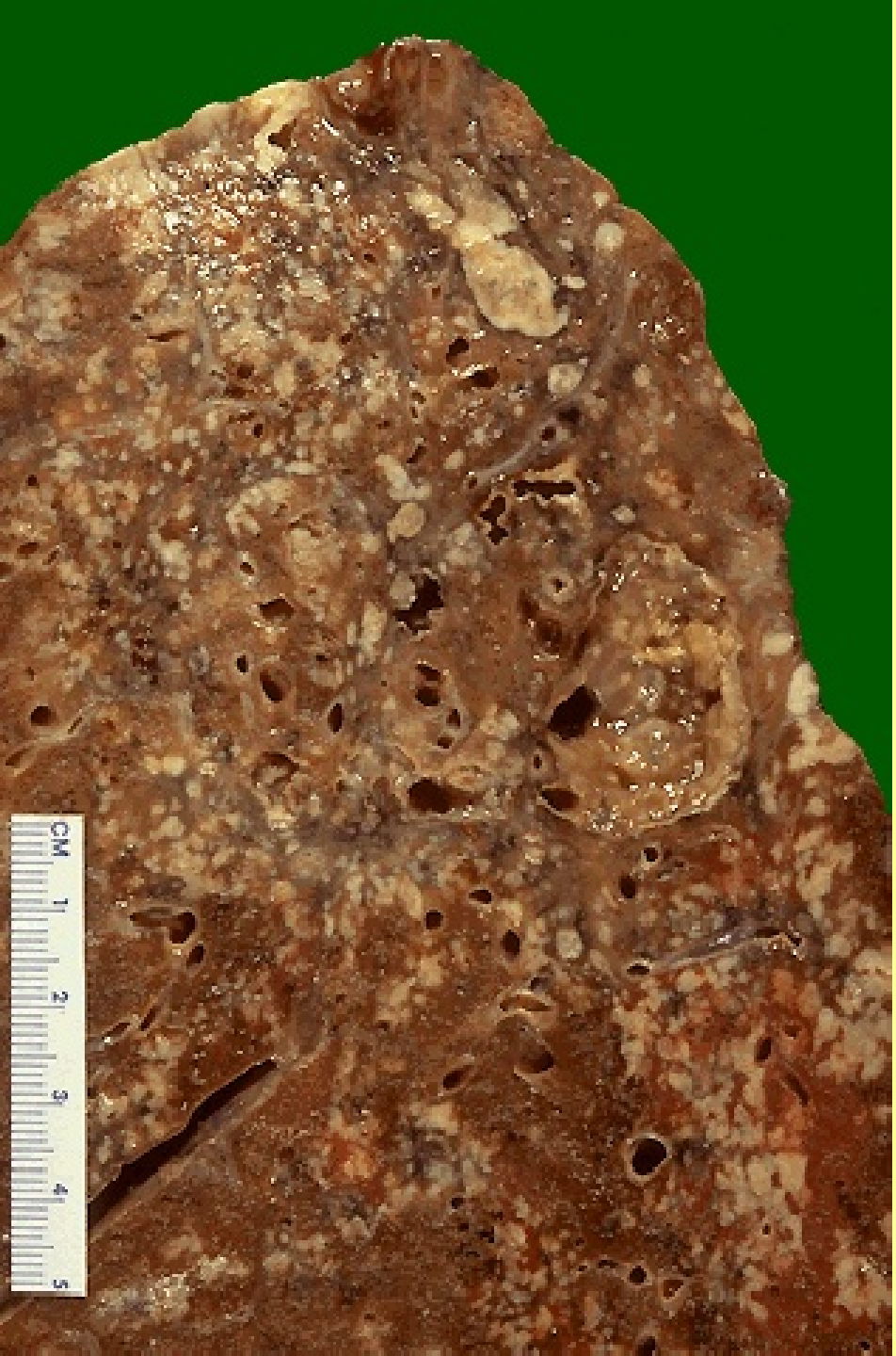


Wild Proso Millet Seeds

Miliary Tuberculosis



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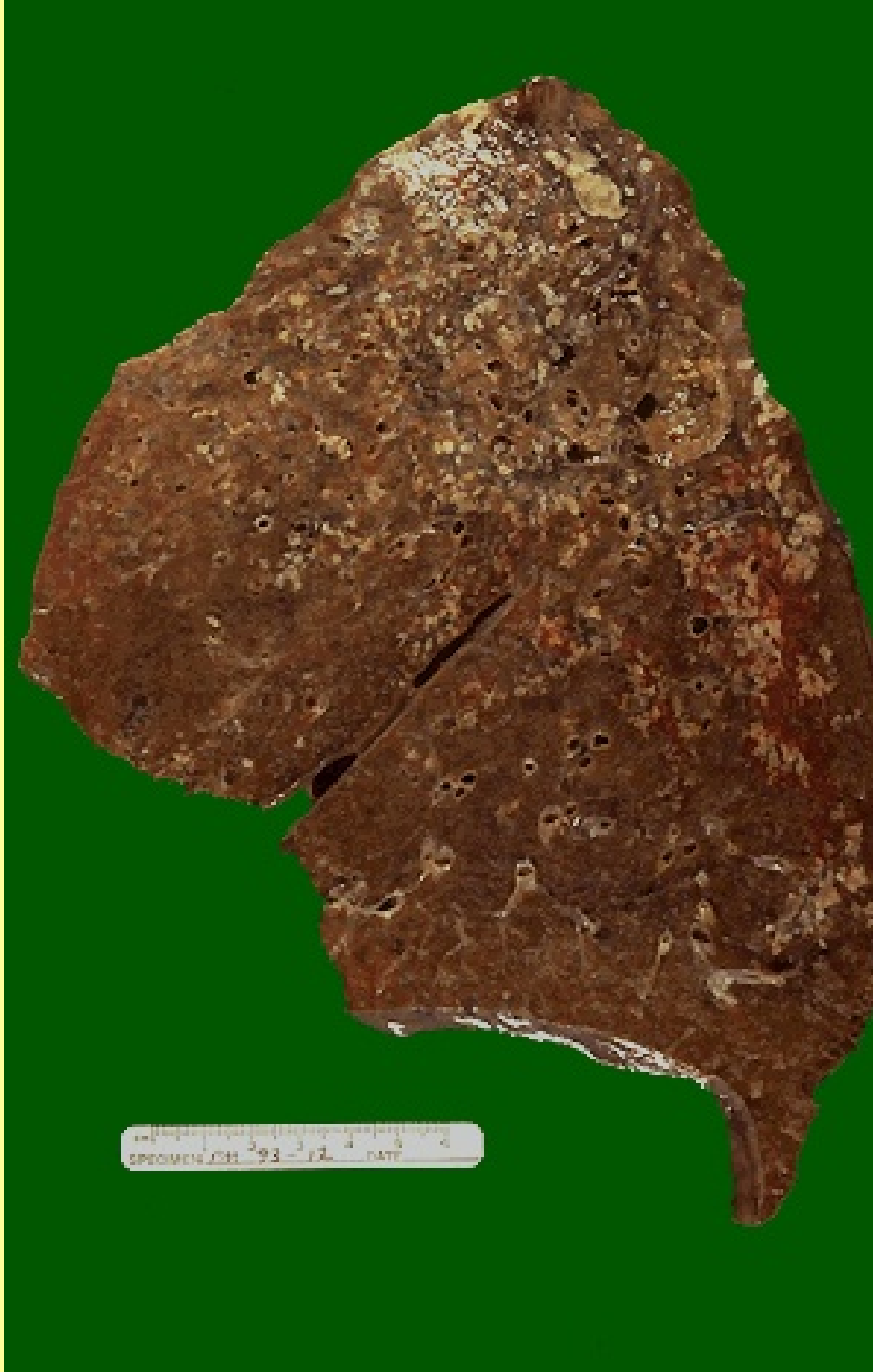
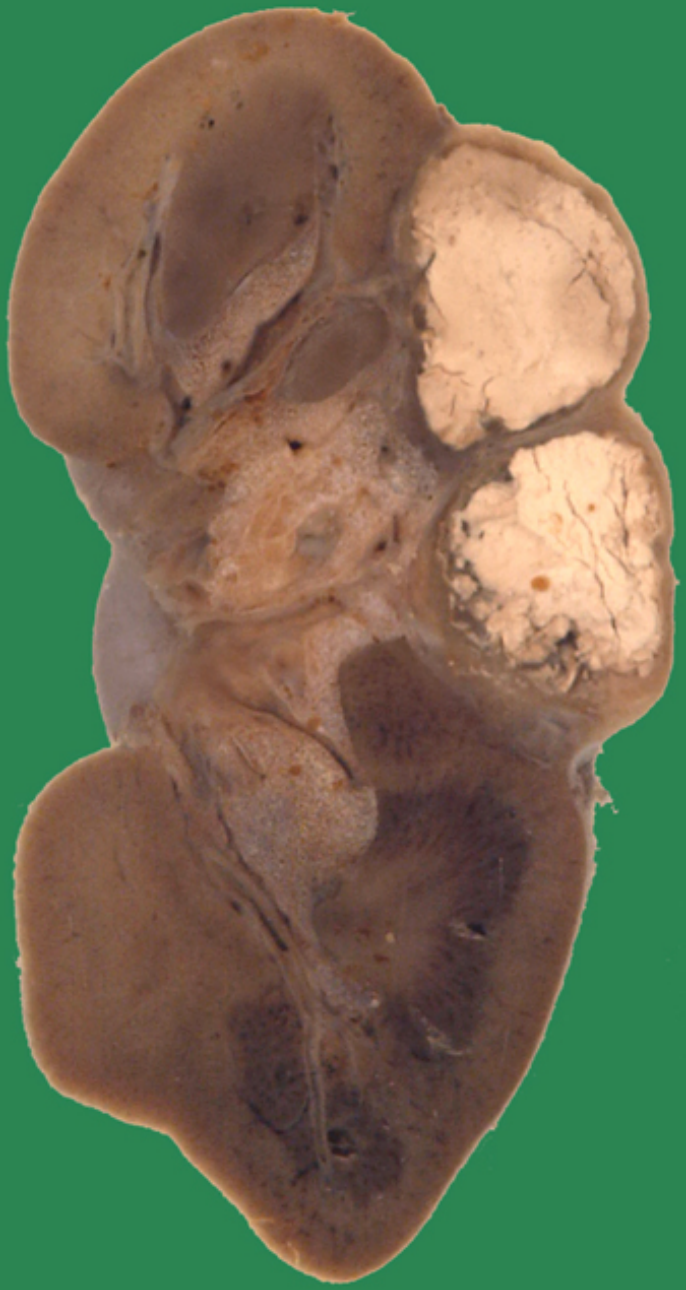




Tuberculosis

- Pathogenesis
  - Phagocytosis by Macrophages – Ag presentation to CD4 T helper lymphocytes
  - CD4 T lymphocytes – proliferate, secrete cytokines – more lymphs and Mphages recruitment
  - Macrophages assume specific morphology (epithelioid, Langhans giant cells)
  - Liquefaction of necrotic cells (infected cells killed in the inflammatory process)

- **GRANULOMATOUS INFLAMMATION is a distinctive pattern of inflammatory reaction in which the predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance encountered in a relatively few but widespread chronic immune and infectious diseases.**
- **Its genesis is firmly linked to immune reactions.**
- **Recognition of the granulomatous pattern in a biopsy specimen is important because of the limited number of possible conditions that cause it.**

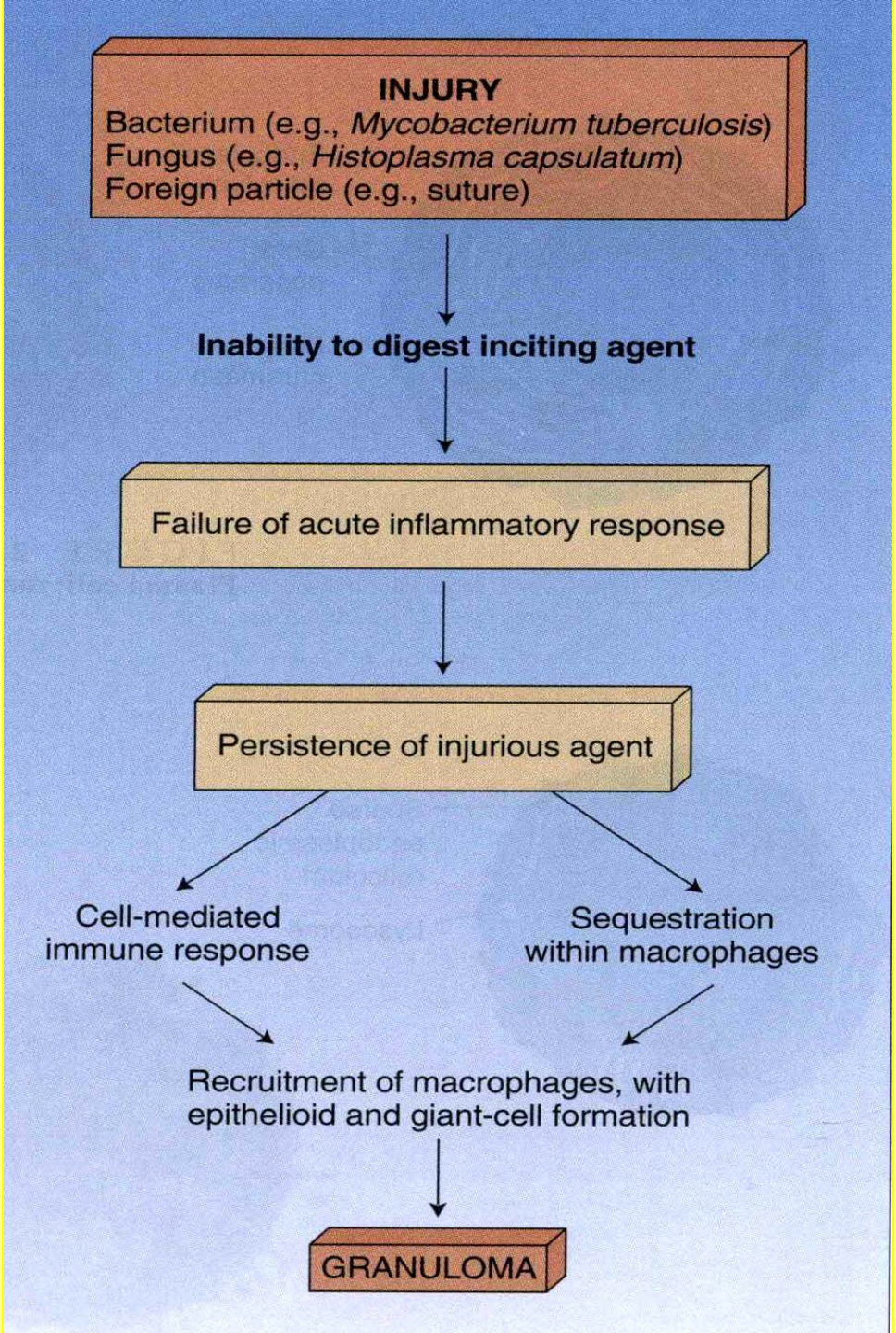
- Granulomatous inflammation is a specific type of chronic reaction characterized by accumulations of modified macrophages (epitheloid cells) and initiated by a variety of infectious and noninfectious agents.

- It is usually seen in TB!

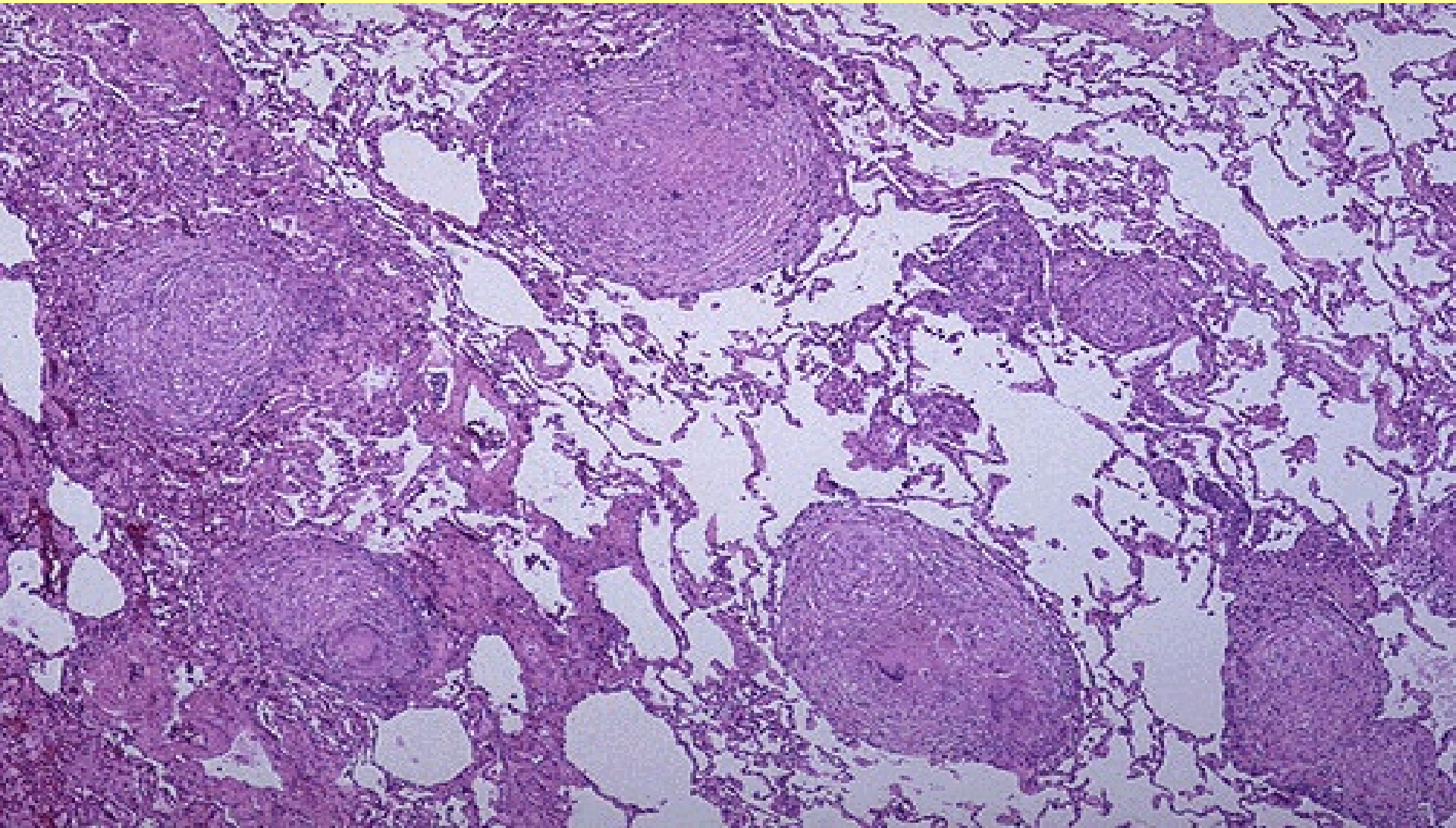
- **A granuloma is a focal area of granulomatous inflammation. It consists of a microscopic aggregation of macrophages that are transformed into epithelium-like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells**
- In the usual hematoxylin and eosin preparations the epithelioid cells have a pale pink granular cytoplasm with indistinct cell boundaries, often appearing to merge into one another. The nucleus is less dense than that of a lymphocyte (vesicular), is oval or elongate, and may show folding of the nuclear membrane.

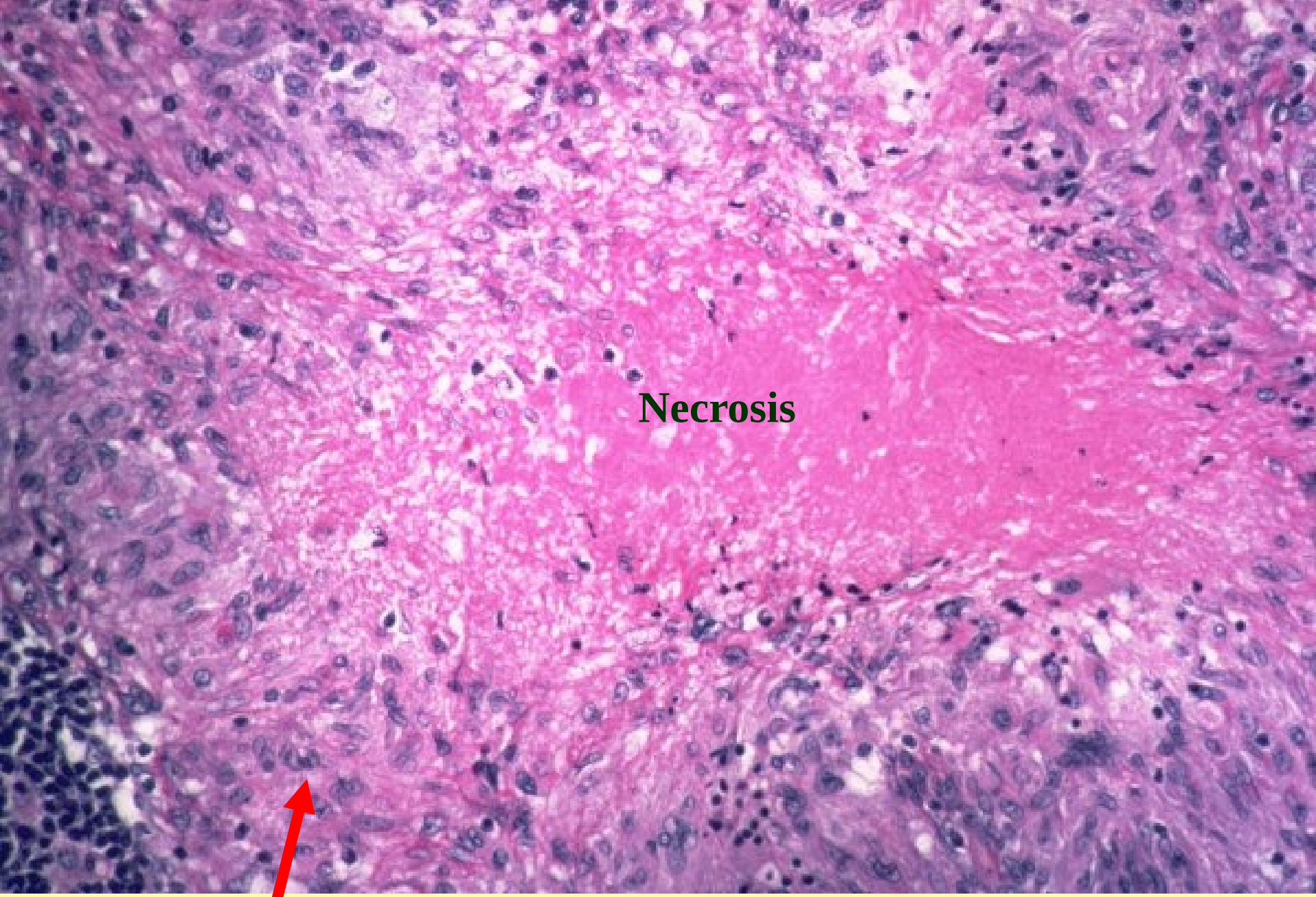
Table 3–9. EXAMPLES OF GRANULOMATOUS INFLAMMATIONS

Disease	Cause	Tissue Reaction
Tuberculosis	• *Mycobacterium tuberculosis*	Noncaseating tubercle (granuloma prototype): a focus of epithelioid cells, rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cell; caseating tubercle: central amorphous granular debris, loss of all cellular detail; acid-fast bacilli
Leprosy	• *Mycobacterium leprae*	Acid-fast bacilli in macrophages; granulomas and epithelioid types
Syphilis	• *Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; center cells are necrotic without loss of cellular outline
Cat-scratch disease	• Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon


INJURY
Bacterium (e.g., *Mycobacterium tuberculosis*)
Fungus (e.g., *Histoplasma capsulatum*)
Foreign particle (e.g., suture)
Inability to digest inciting agent
Failure of acute inflammatory response
Persistence of injurious agent
Cell-mediated immune response
Sequestration within macrophages
Recruitment of macrophages, with epithelioid and giant-cell formation
GRANULOMA

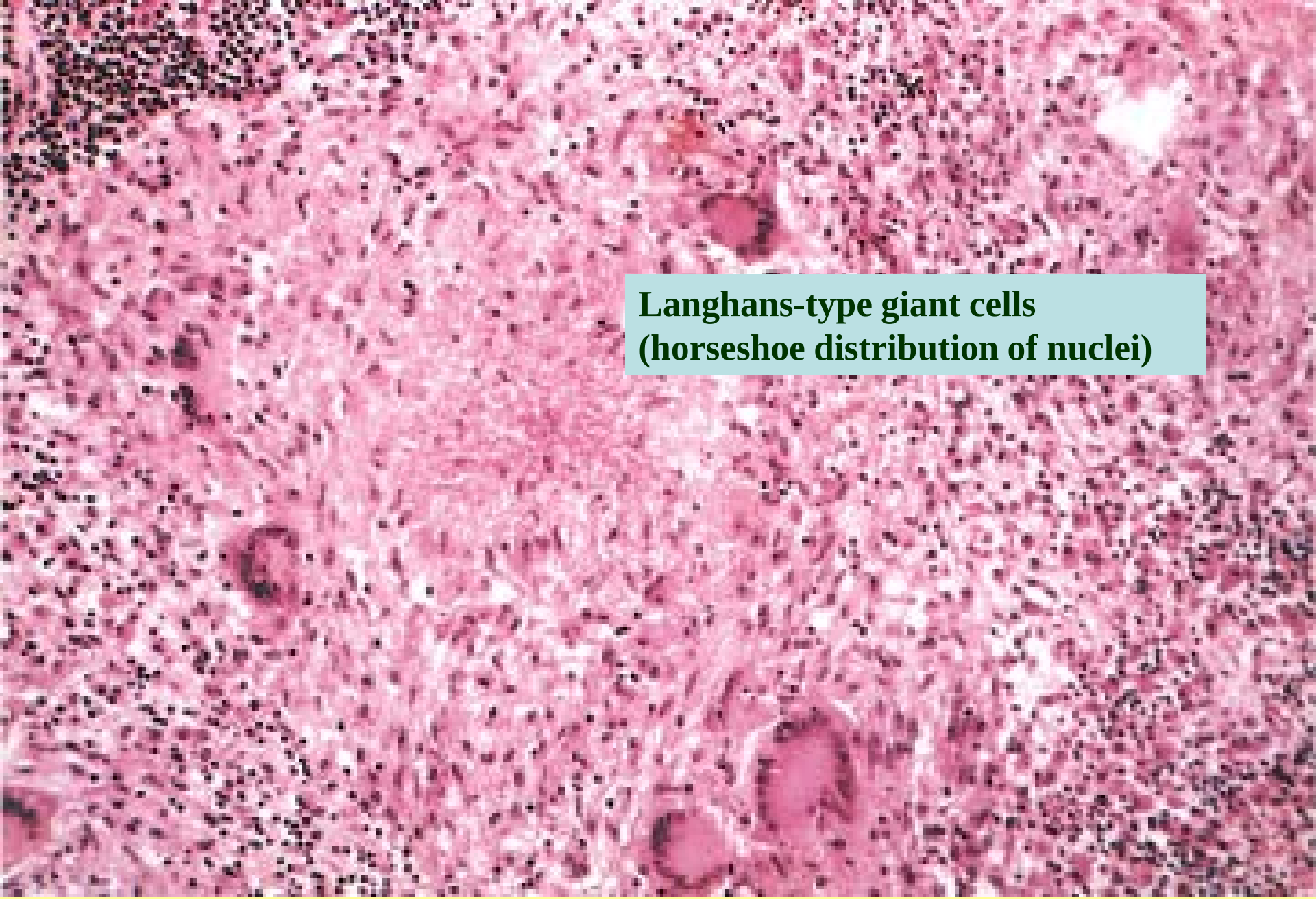
The focal nature of granulomatous inflammation is demonstrated in this microscopic section of lung in which there are scattered granulomas in the parenchyma. This is why the chest radiograph with tuberculosis or other granulomatous diseases is often described as "reticulonodular". A biopsy could miss such lesions from sampling error, too.





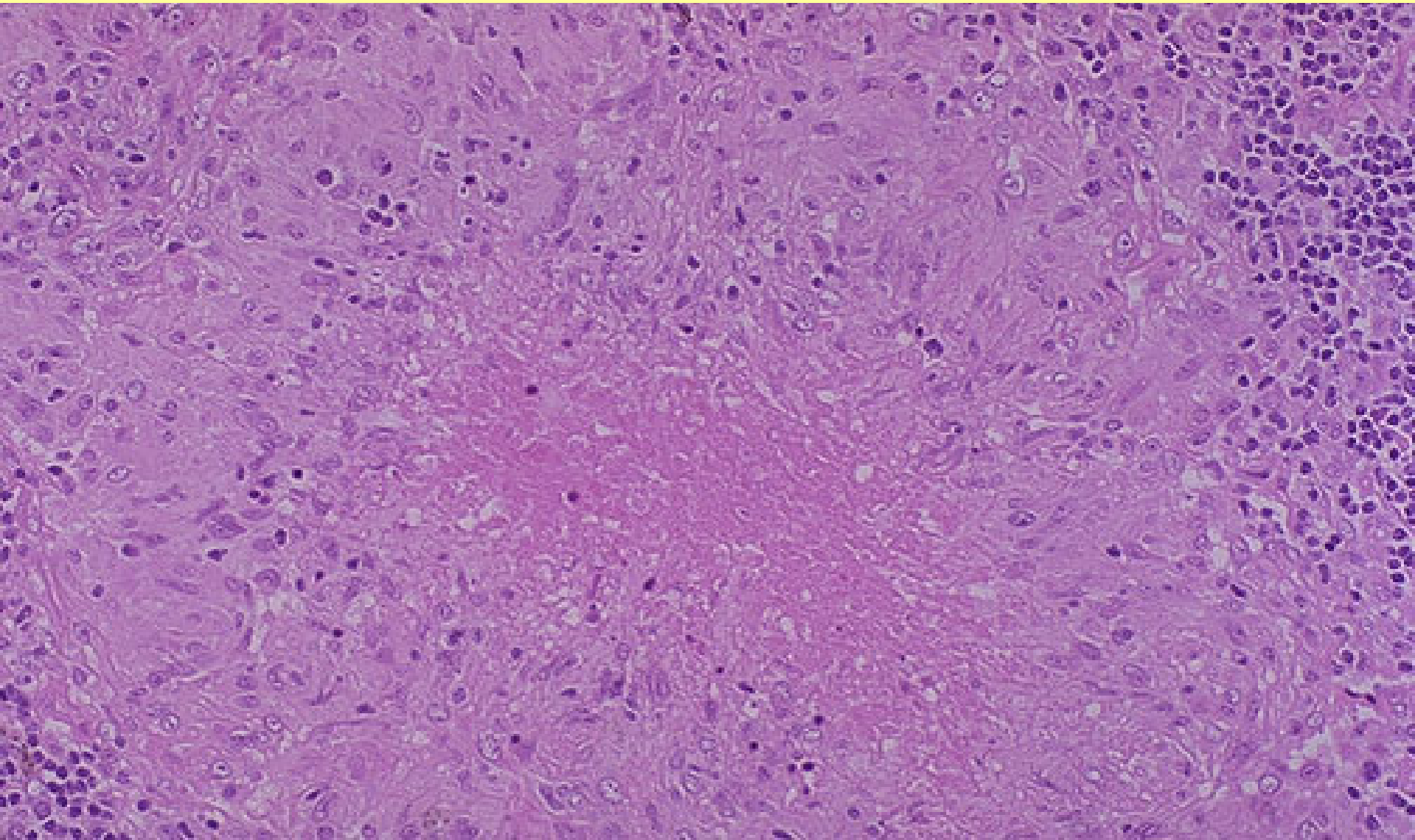
Rim of epithelioid histiocytes

Granuloma with central necrosis (necrotizing/caseating granuloma - TB)

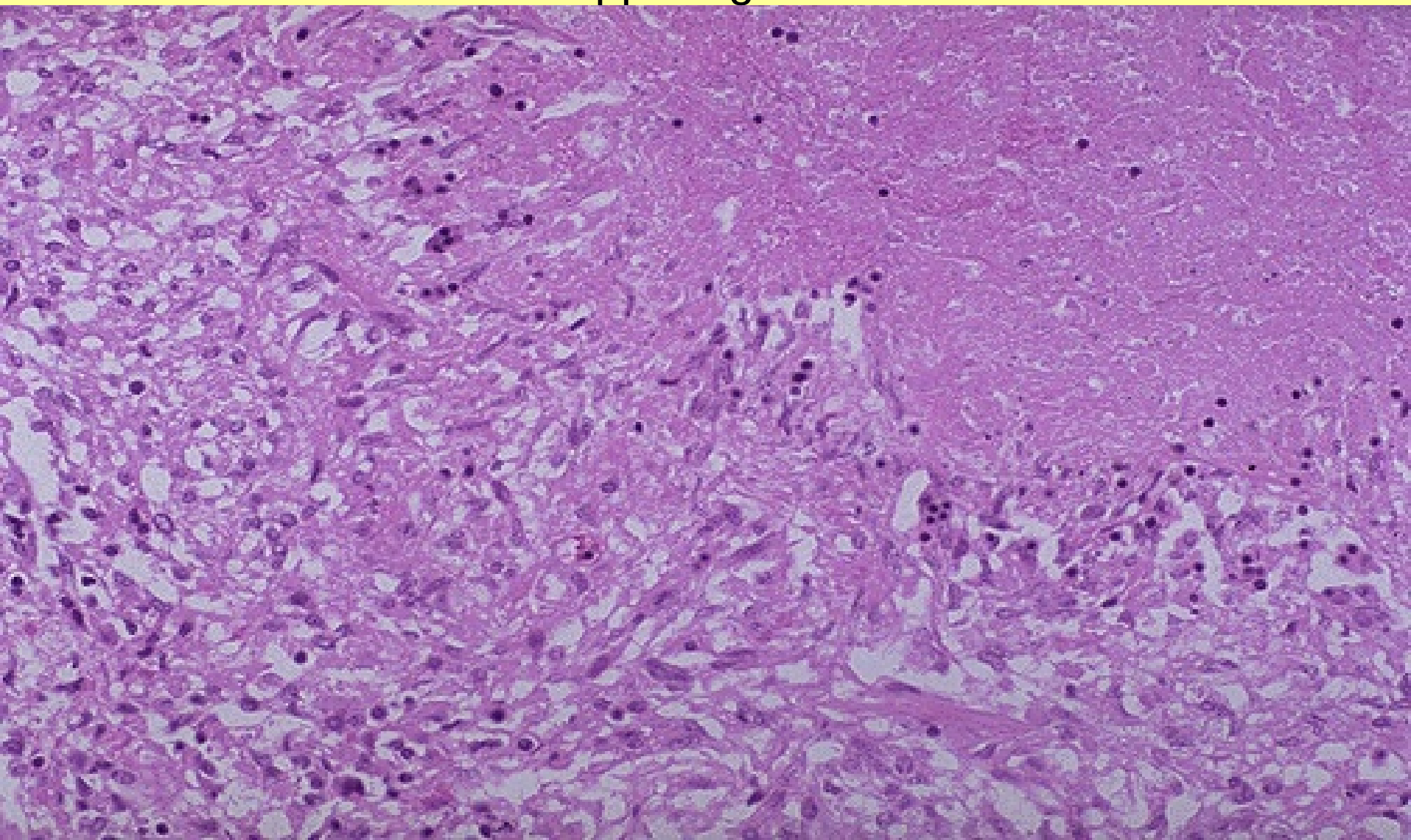


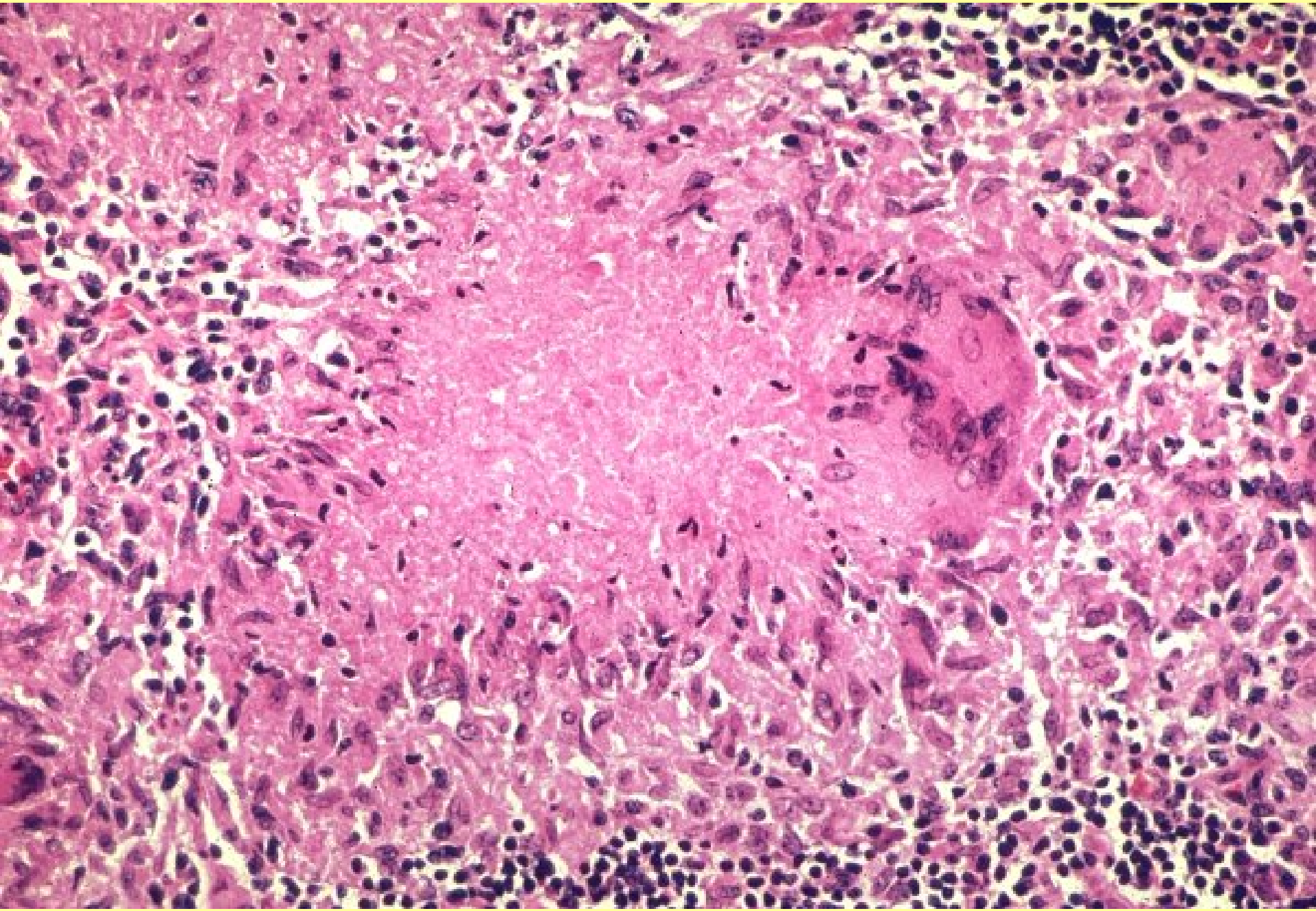
Necrotizing granuloma with numerous multinucleated giant cells - TB

This is a **caseating granuloma.** **Epithelioid cells** surround a central area of necrosis that appears irregular, amorphous, and pink. Grossly, areas of caseation appear cheese-like.



Granulomas caused by tuberculosis and by pathogenic fungi such as *Histoplasma capsulatum* or *Cryptococcus neoformans* are often caseating. Here, the area of caseation is seen at the upper right.





Tuberculous necrotizing granuloma

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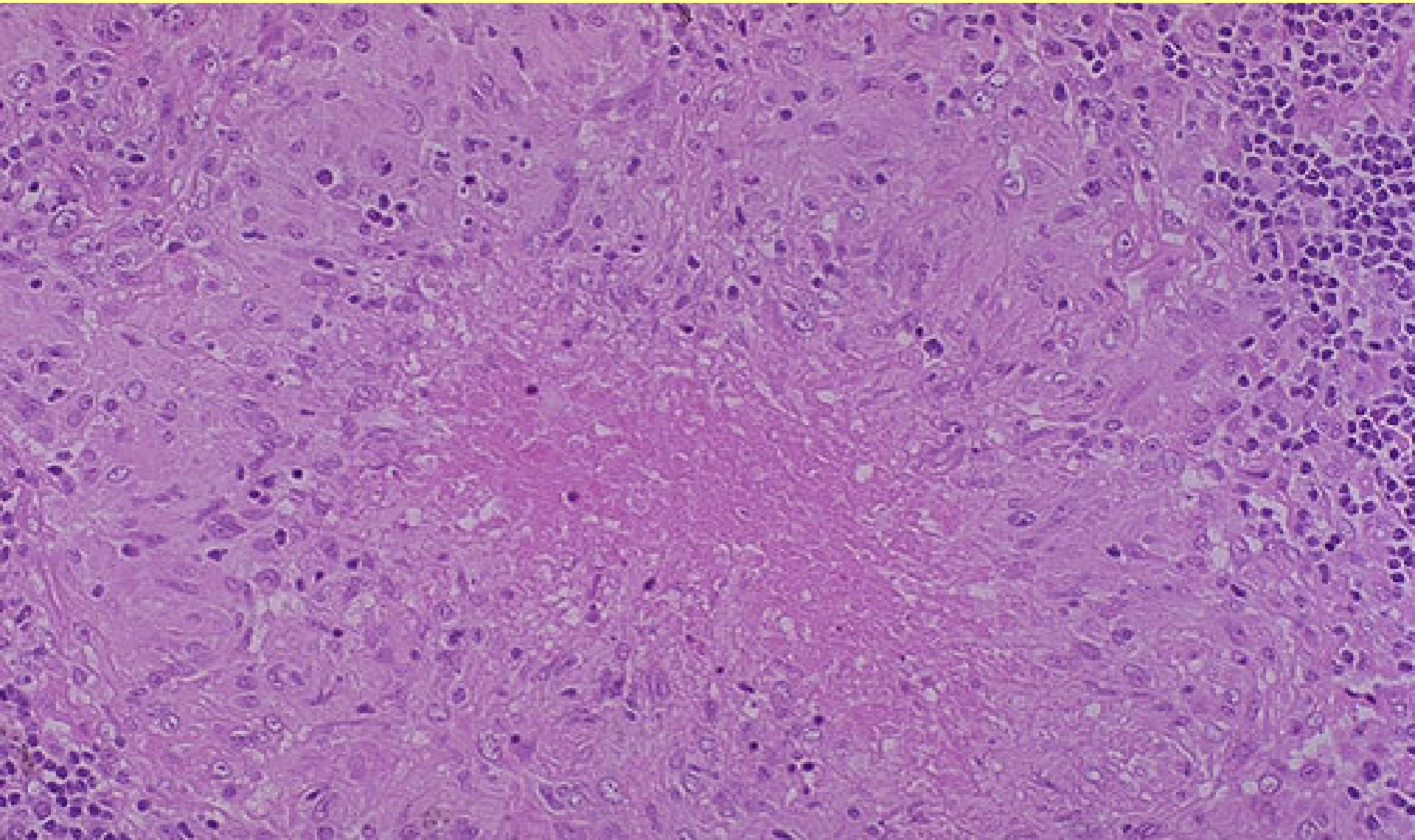

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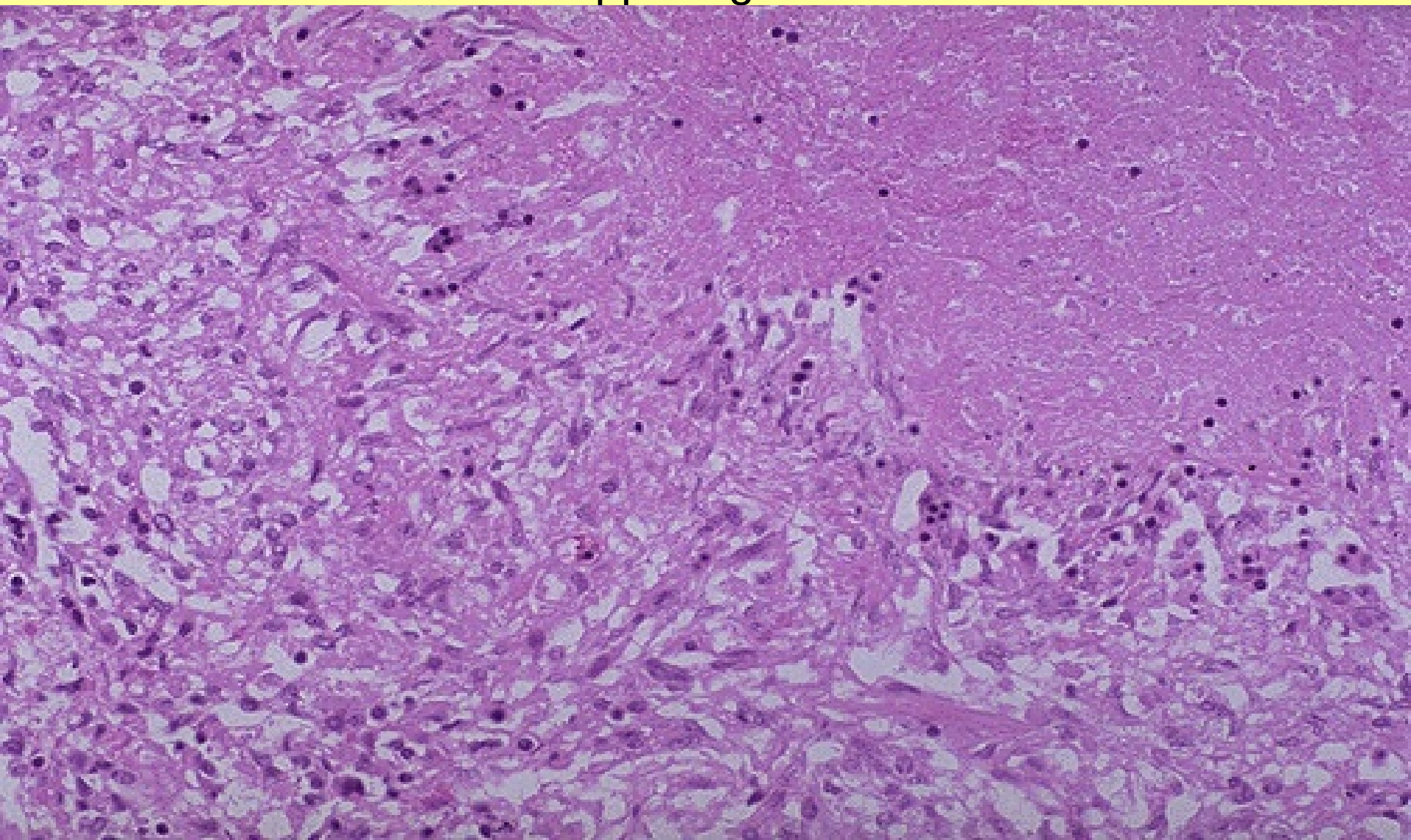

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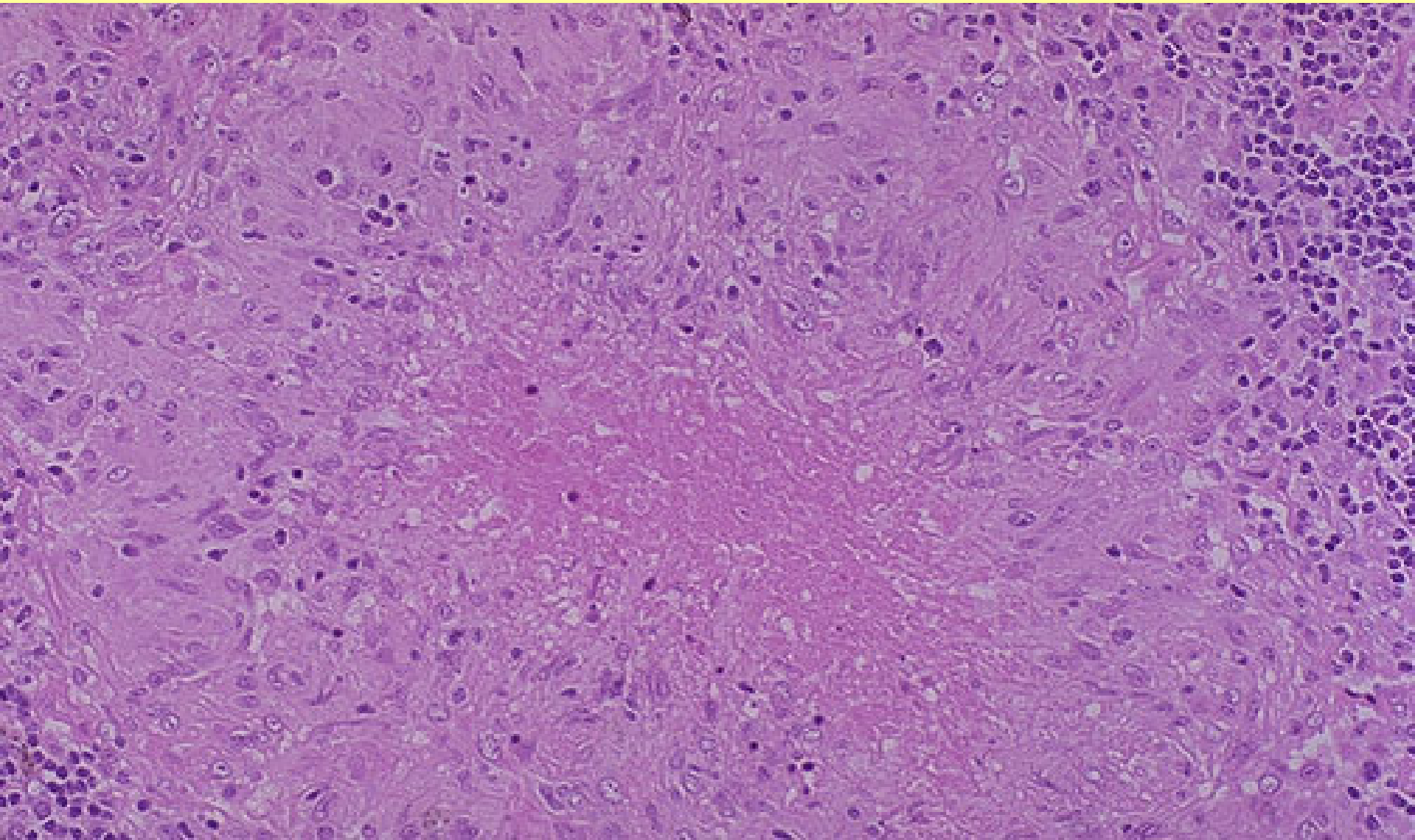

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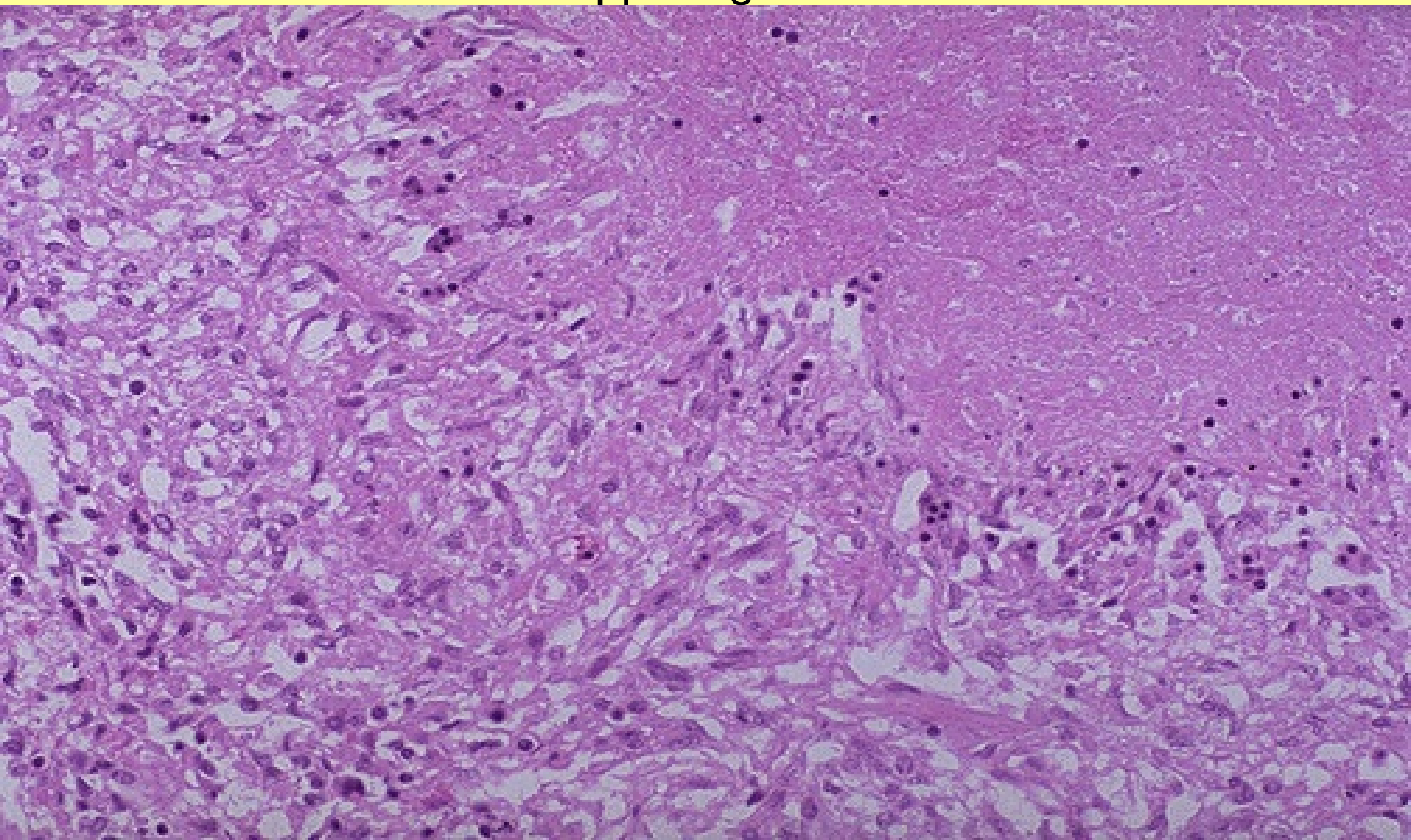

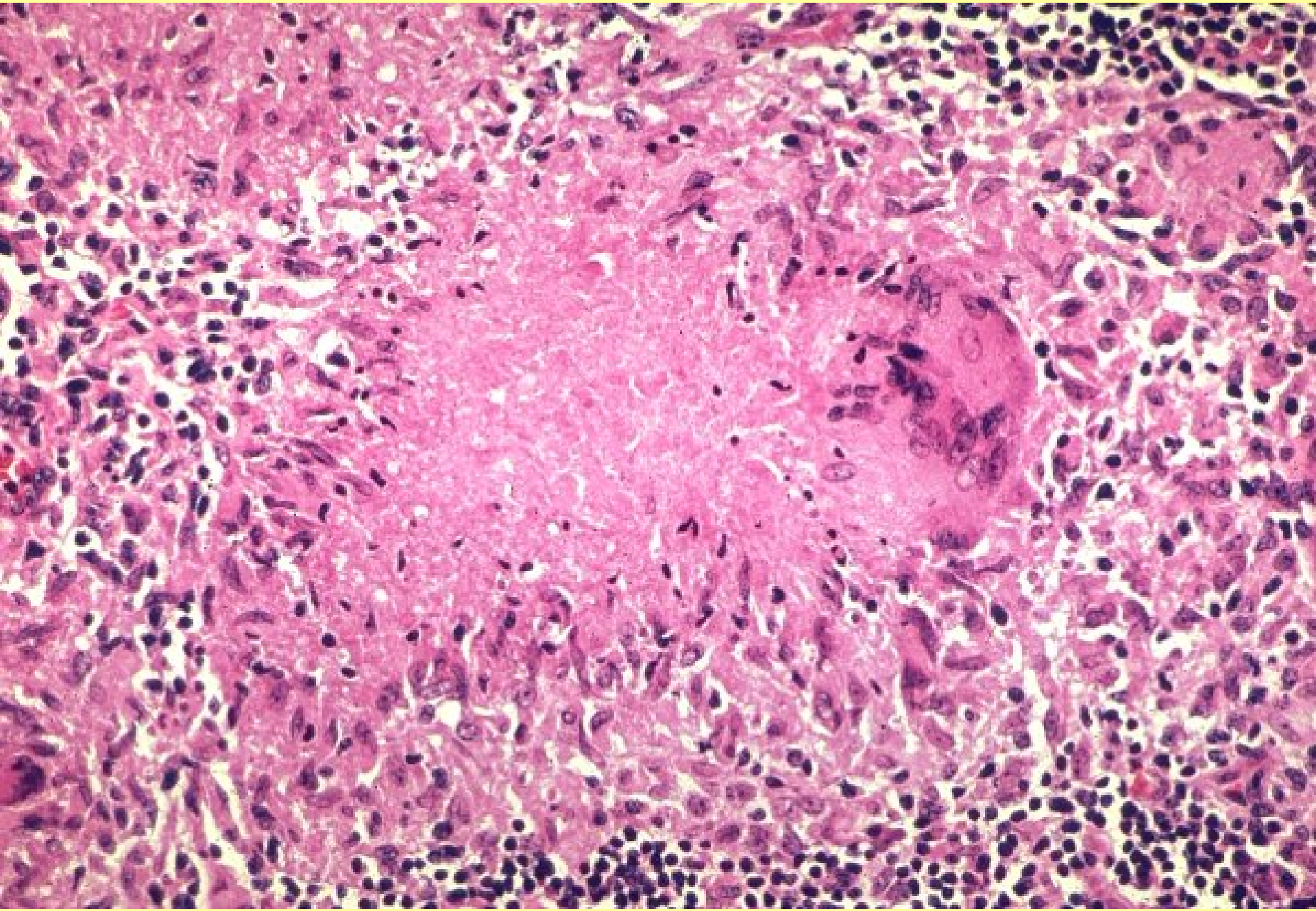

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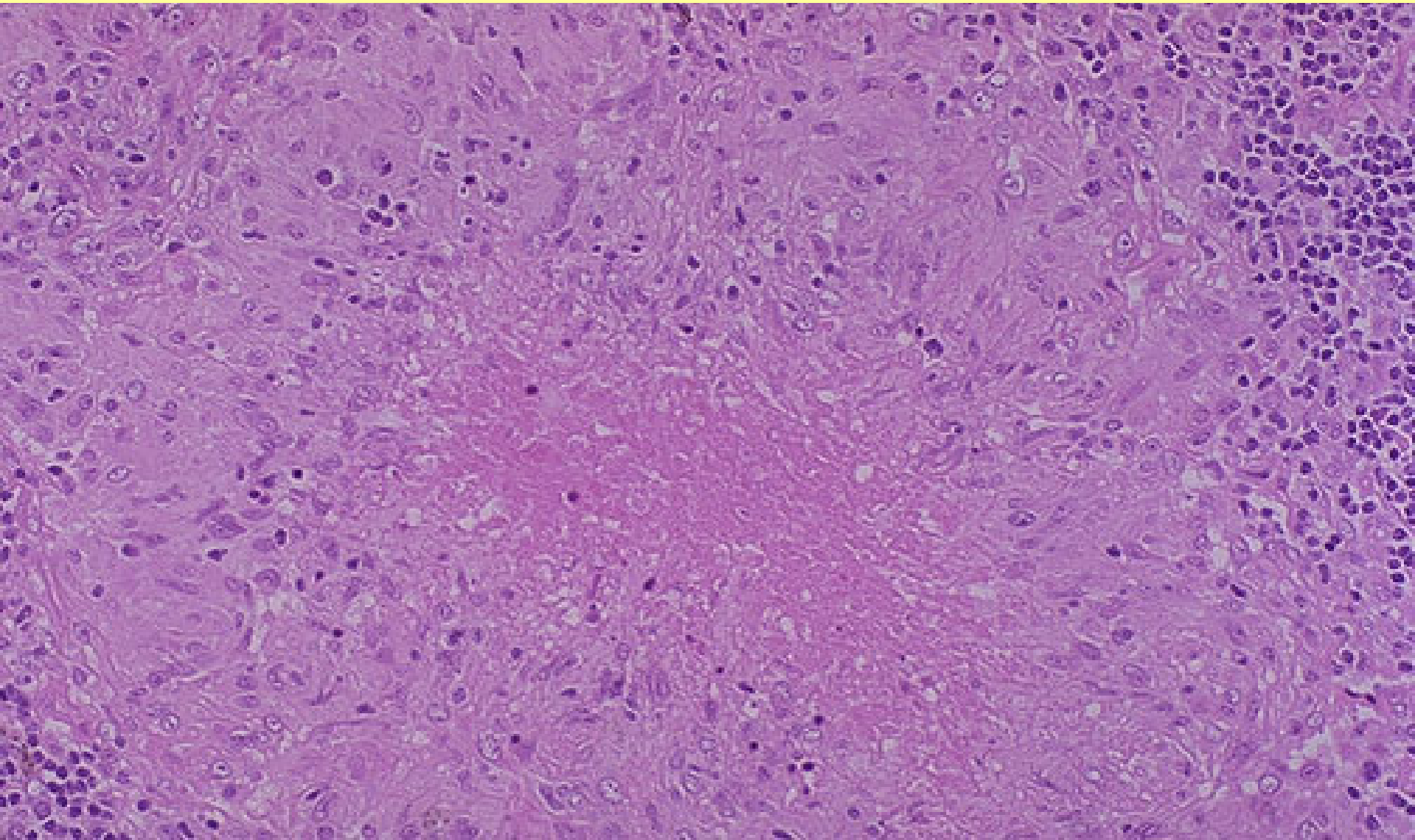

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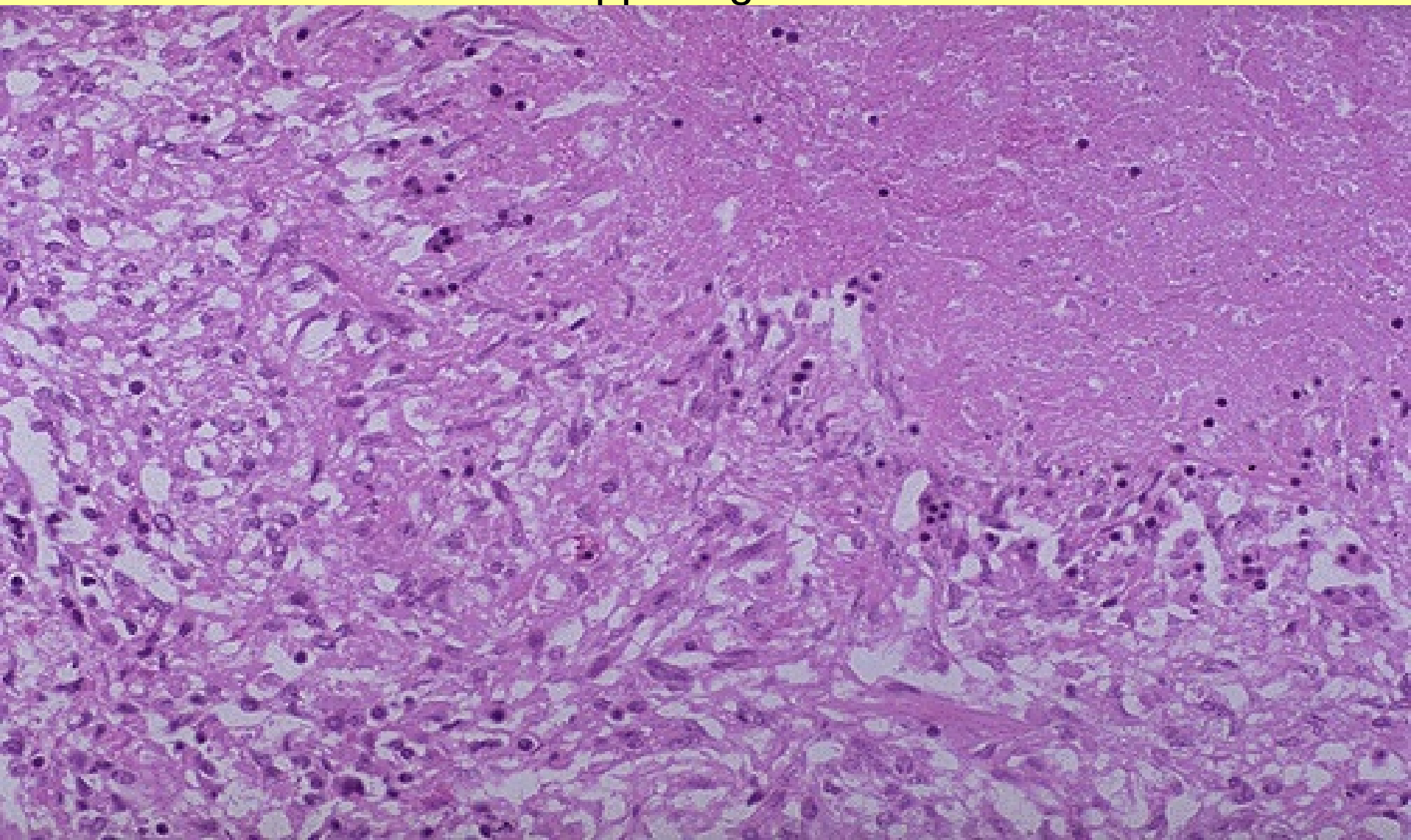
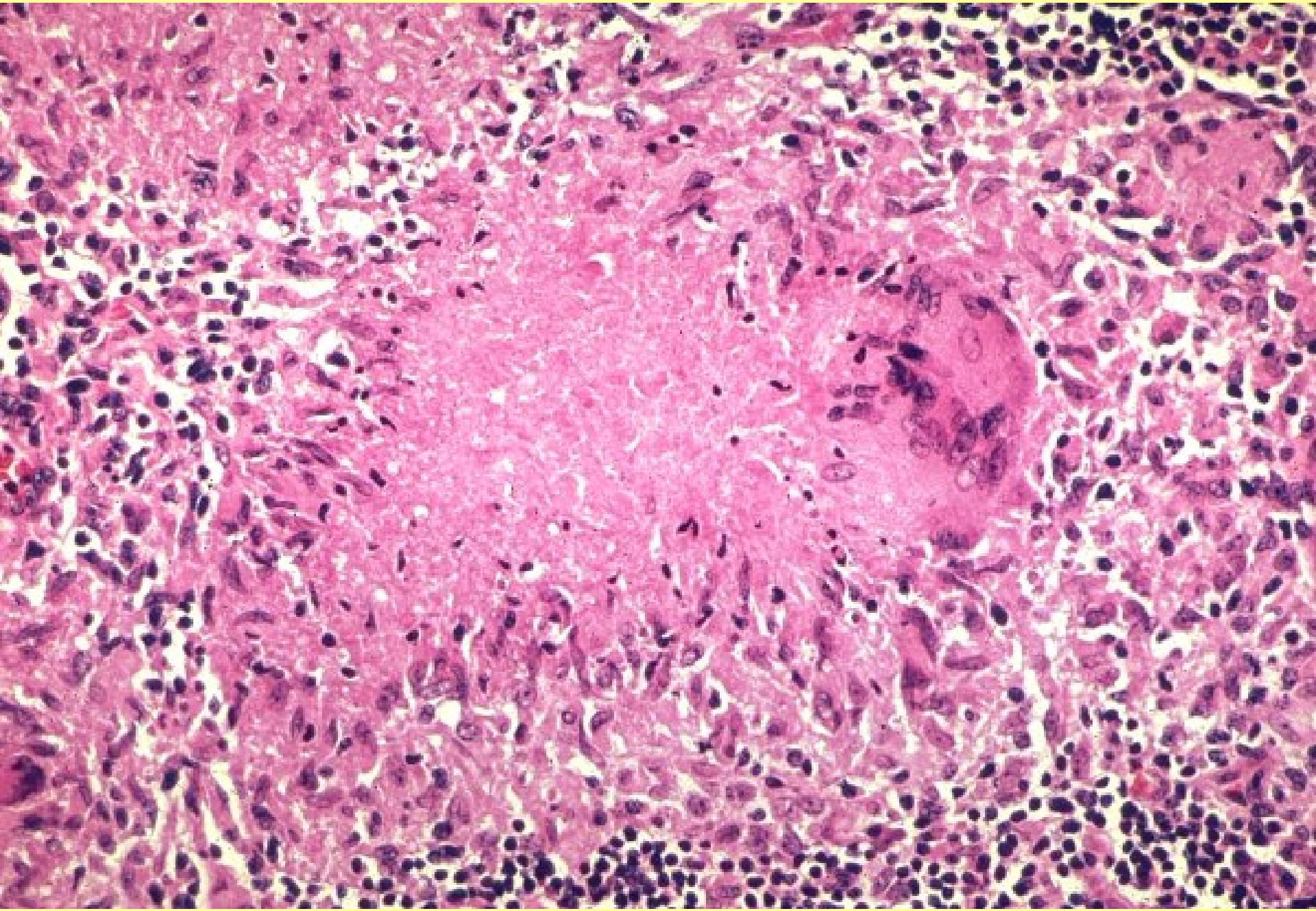
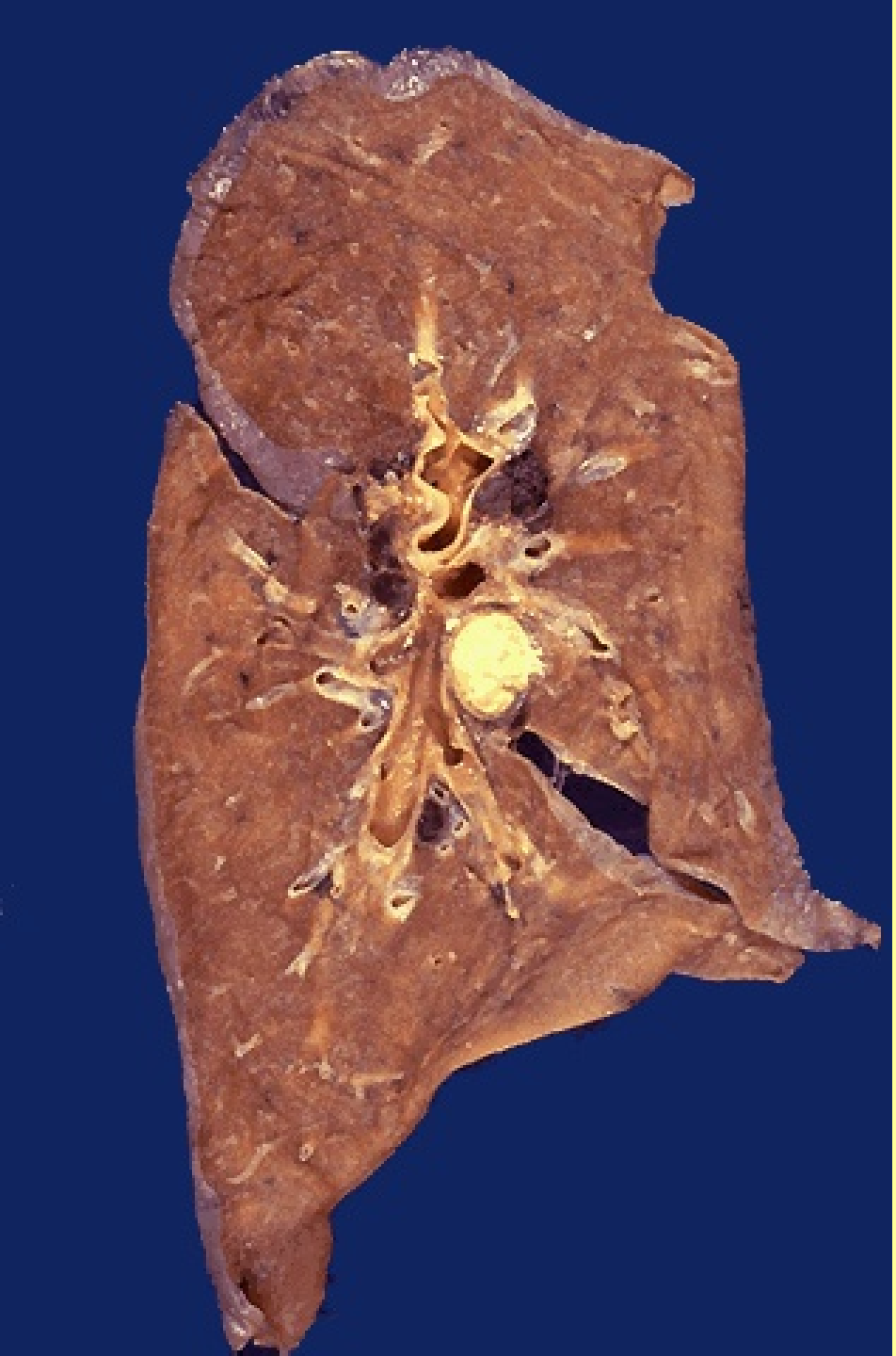
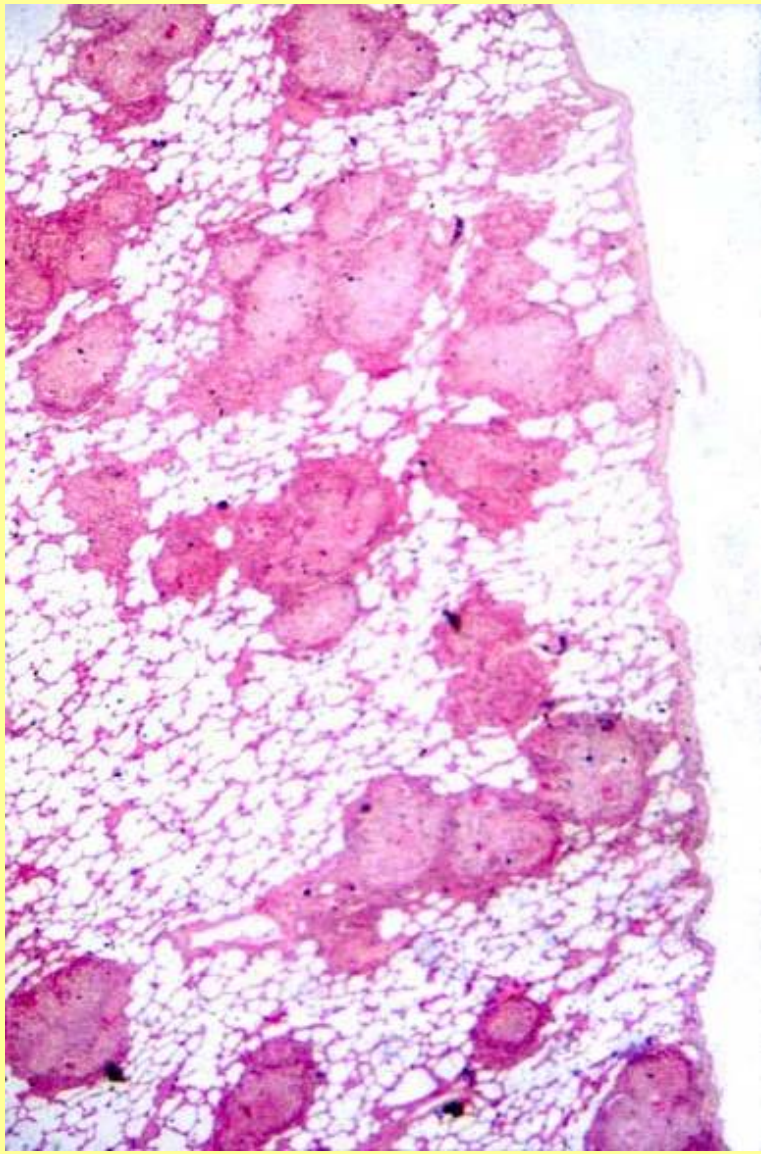
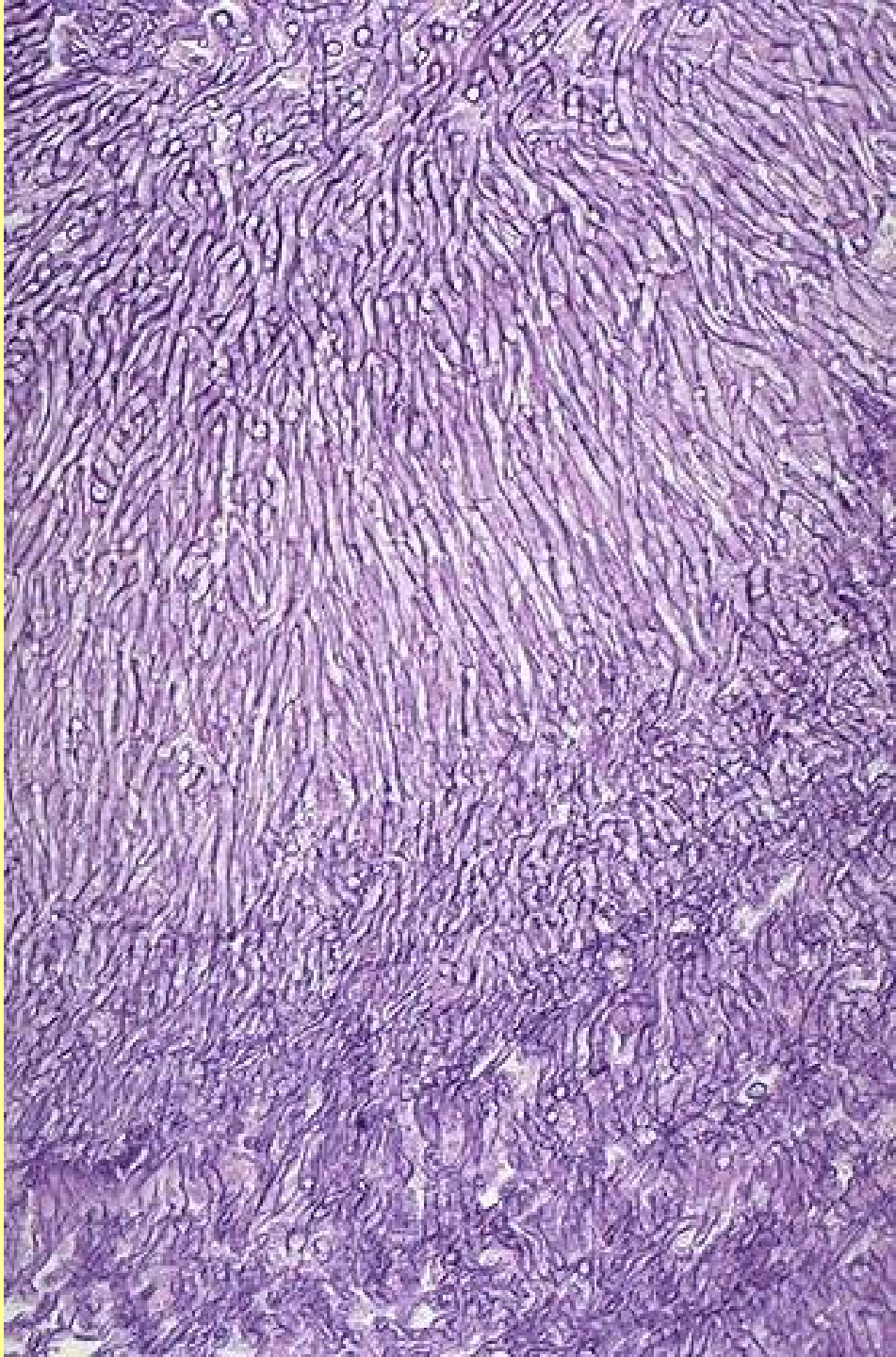


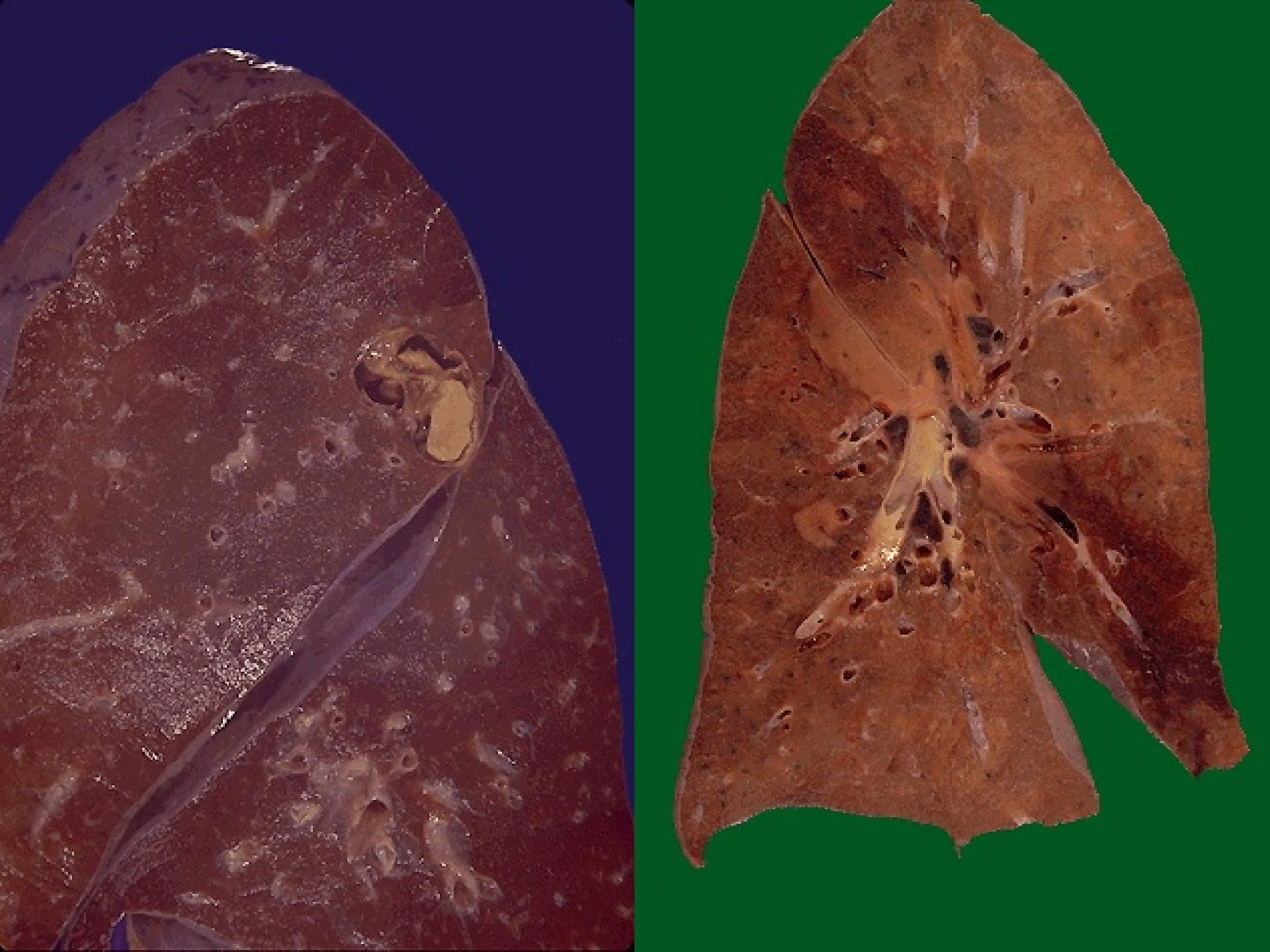


Tuberculous necrotizing granuloma









TUBERCULOSIS part 3

Resource for Lab 1

TREATMENT OF TUBERCULOSIS

- Physicians once recommended fresh air for the treatment of tuberculosis, but now **they treat it with such drugs as isoniazid (INH), pyrazinamide, and rifampin.**
- ***First line: SIPER***
- ***Second line: PECFK***

Antimicrobics Commonly Used in Treatment of Tuberculosis

First-Line Drug	Second-Line Drug[a]
Isoniazid	*para*-Aminosalicylic acid
Ethambutol	Ethionamide
Rifampin	Cycloserine
Pyrazinamide	Fluoroquinolones
Streptomycin	Kanamycin, etc

- The recent appearance of **multidrug-resistant *Myco*bacterium *tuberculosis* (MDR-TB)** has necessitated the use of ethambutol and streptomycin to help delay the emergence of resistant strains.

DRUGS FOR TUBERCULOSIS

Five first-line antimicrobial agents are currently recommended for antituberculosis therapy (Figure 34.1).

The major drugs used in tuberculosis are

isoniazid (INH),

rifampin,

ethambutol,

pyrazinamide, and

streptomycin.

Actions of these agents on M tuberculosis are bactericidal or bacteriostatic depending on drug concentration and strain susceptibility.

Initiation of treatment of pulmonary tuberculosis usually involves a 3- or 4-drug combination regimen depending on the known or anticipated rate of resistance to isomazid (INH).

Directly observed therapy (DOT) regimens are recommended in noncompliant patients and in drug-resistant tuberculosis.

Second-line medications are either less effective, more toxic, or have not been studied as extensively. They are useful in patients who cannot tolerate the first-line drugs or who are infected with myobacteria that are resistant to the first-line agents.

Figure 34.1 Summary of drugs used to treat mycobacterial infections.

Challenges in treating tuberculosis

- **The chemotherapy of infections caused by Mycobacterium tuberculosis, M leprae, and M avium-intracellulare is a therapeutic challenge, since it is complicated by numerous unique therapeutic problems factors.**
- **These include**
  (1) limited information about the mechanisms of antimycobacterial drug actions;
  (2) the cell wall is not susceptible to classic cell wall inhibitors
  (3) the intra-cellular location of mycobacteria. Many mycobacterial organisms are intracellular (residing in macrophages, for example),and infection may be walled off in tubercles which reduce antibiotic penetration
  (4) the chronic nature of mycobacterial disease as the organism grows slowly. Slow growth rate reduces efficacy of antibiotics that prevent rapid synthesis of proteins and DNA. The slow growth characteristic also results in relative resistance to antibiotic therapy, since antibiotic activity is usually directly dependent on the rate of cell division

- (5) the development of resistance; resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol. Single drug treatment of mycobacterial infections readily promotes development of resistance.
- (6) the chronic nature of mycobacterial disease, and its slow growth characteristics requires protracted drug treatment of the disease for up to six months to two years. This is associated with
- (7) combination therapy over an extended period of time is required for effective treatment. Chemotherapy of mycobacterial infections almost always involves the use of drug combinations to delay the emergence of resistance and to enhance antimycobacterial efficacy. This leads to problems with
- (8)drug toxicities; and
  (9) patient compliance.
- (10) infections occur frequently in immunocompromised hosts which reduces the utility of bacteriostatic antibiotics (which rely on intact host immunity).

- In addition, antimicrobial drug therapy is intensive and must be extended over a period of six to nine months or more, partly because the organism multiplies at a very slow rate (its generation time is about 18 hours).
- Early relief, boredom, and forgetfulness often cause the patient to stop taking the medication, and the disease flares anew.
- **In 1998, the FDA approved the drug rifapentine, which is taken only once a week.**

- **Principles of treating tuberculosis**
- **In the years since the advent of antituberculosis chemotherapy, controlled clinical trials have yielded three basic principles upon which recommendations for treatment are based:**
- **(1) regimens for treatment of disease must contain multiple drugs to which the organisms are susceptible,**
- **(2) the drugs must be taken regularly, and**
- **(3) drug therapy must continue for a sufficient period of time.**

- **The aim of treatment should be to provide the safest and most effective therapy in the shortest period of time**
- **Treatment guidelines continue to be revised as multi-drug resistance increases.**
- **Prophylactic treatment is recommended for asymptomatic patients that develop skin test positivity and for young (<4 years) or immunocompromised patients that are exposed to an infectious case of tuberculosis.**

- **There are a large number of possible combinations of drugs and rhythms of administration. But the initial phase of treatment is crucial for preventing emerging drug resistance and determining the ultimate outcome of the regimen.**
- **Despite considerable price variation from time to time and place to place, short-course regimens rely heavily on generally expensive drugs; however, these regimens are probably more cost effective than cheaper regimens, and drug cost should not preclude access to effective and appropriate treatment.**
- **Utilization of resources and the potential for adverse reactions are also considerations in selecting a treatment regimen.**

- **Any regimen is irrelevant if drugs do not enter the patient's body. Promoting and monitoring adherence to the drug regimen are essential for treatment to be successful.**
- **A variety of techniques have been developed to assist in identifying the nonadherent patient.**
- **All patients should be asked routinely about their adherence with medication taking, and sporadic urine tests and pill counts may be used to monitor drug ingestion.**
- **Record systems for clinic appointments and drug pickups are very important to identify persons who fail to return for follow-up visits.**
- **An effective communication system is also needed to ensure that failure to keep appointments comes to the attention of the responsible public health officials.**
- **To improve adherence a number of modifications in the organization of treatment have been tried with varying degrees of success.**

- **These include setting clinic hours and locations to suit the patients' needs and giving directly observed treatment in the clinic,home, workplace, or other location.**
- **The offering of incentives and enablers, such as food, carfare money, babysitting services, or small gifts, may improve adherence by facilitating the patients' medication-taking and appointment-keeping.**
- **Tuberculosis control depends on more than just the science of chemotherapy; chemotherapy can be successful only within the framework of the overall clinical and social management of patients and their contacts.**
- **The ultimate elimination of tuberculosis requires an organized and smoothly functioning network of primary and referral services based on cooperation between clinicians and public health officials, between health care facilities and community outreach programs, and between the private and public sectors of medical care.**

- **Strategies for addressing drug resistance**
- Strains of M- tuberculosis that are resistant to a particular agent emerge during treatment with a single drug.
- For example, Figure 34.2 shows that resistance rapidly develops in patients given only *streptomycin*.
- Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of resistant strains.
- Isoniazid, rifampin, ethambutol, streptomycin, and pyrazinamide are the principal or so-called "first-line" drugs because of their efficacy and acceptable degree of toxicity.
- However today, because of poor patient compliance and other factors, the number of multidrug-resistant organisms has risen.

- Some bacteria have been identified that are resistant to as many as seven antitubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs preferably with both being bactericidal.
- The combination of drugs should prevent the emergence of resistant strains.
- The multi-drug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms.
- For example, the short-course chemotherapy for tuberculosis includes isoniazid, rifampin, and pyrazinamide for two months and then isoniazid and rifampin for the next four months (the "continuation phase," Figure 34.3). Ethambutol or streptomycin may also be added to this regimen. Patient compliance is often low when multidrug schedules last for six months or longer. One successful strategy for achieving better treatment completion rates is "directly observed therapy," in which patients take their medication while being supervised and observed.

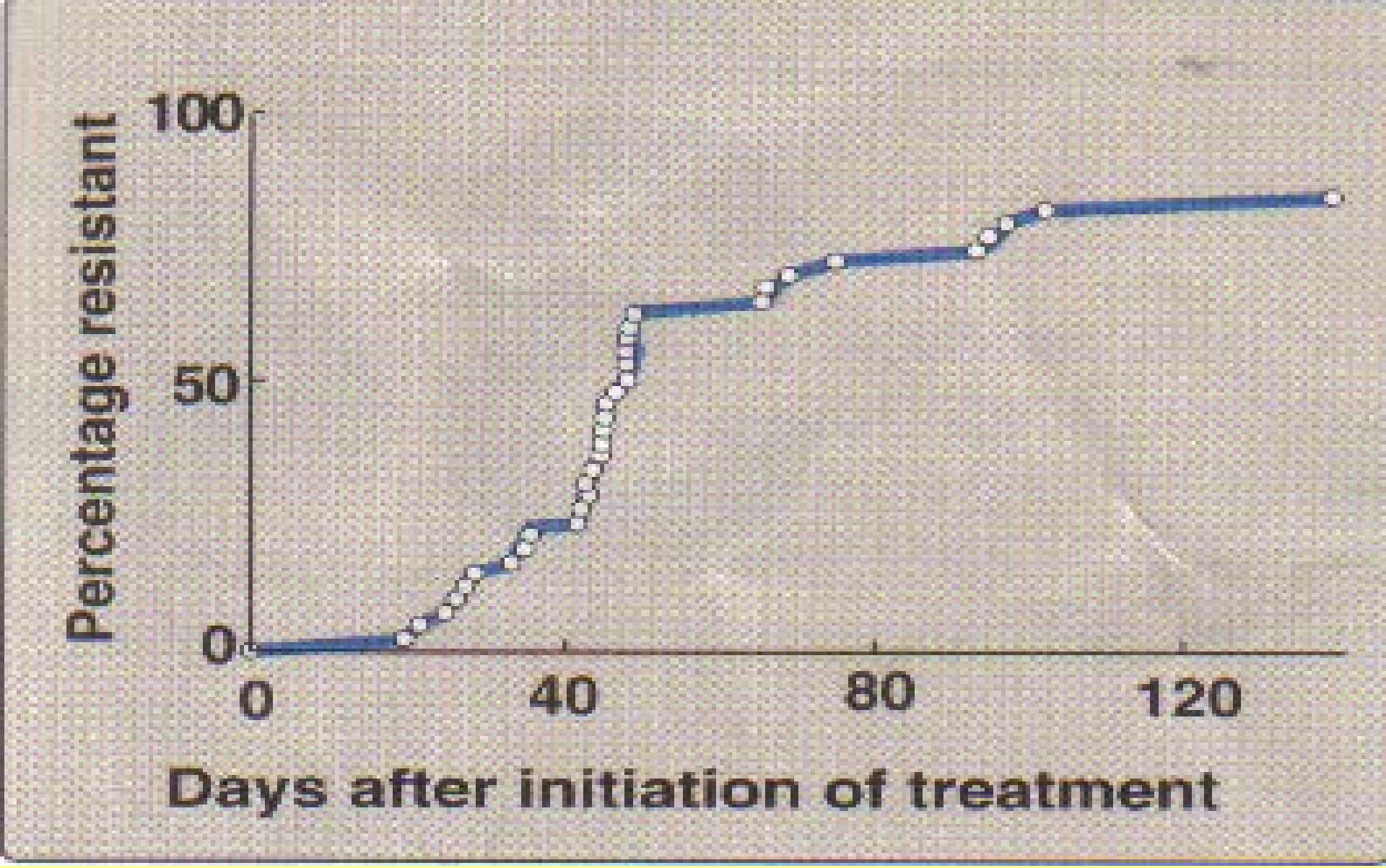


Figure 34.2
Cumulative percentage of strains **of** Mycobacterium tuberculosis showing resistance to *streptomycin.*

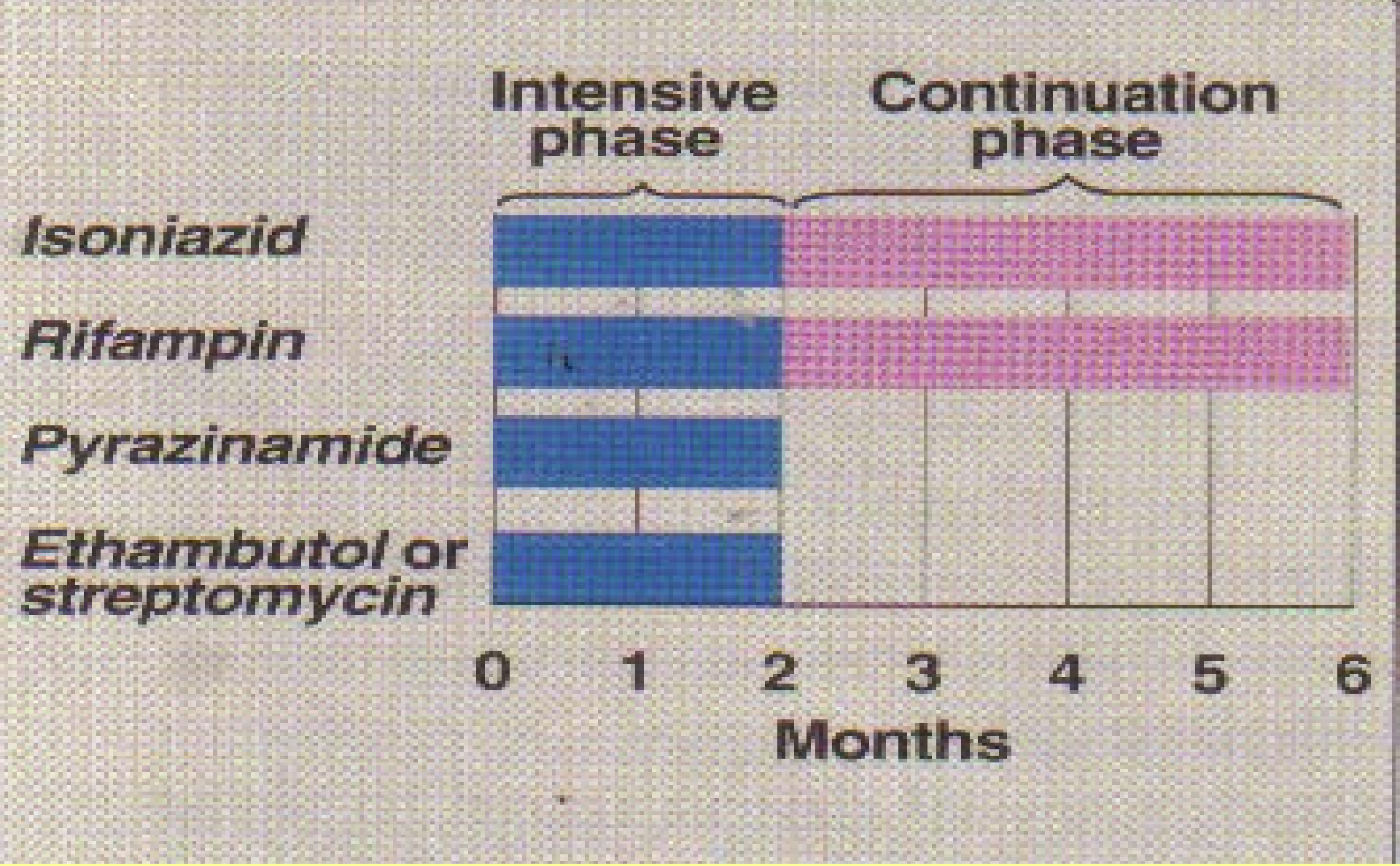


Figure 34.3
One of several recommended multi-drug schedules for the treatment of tuberculosis.