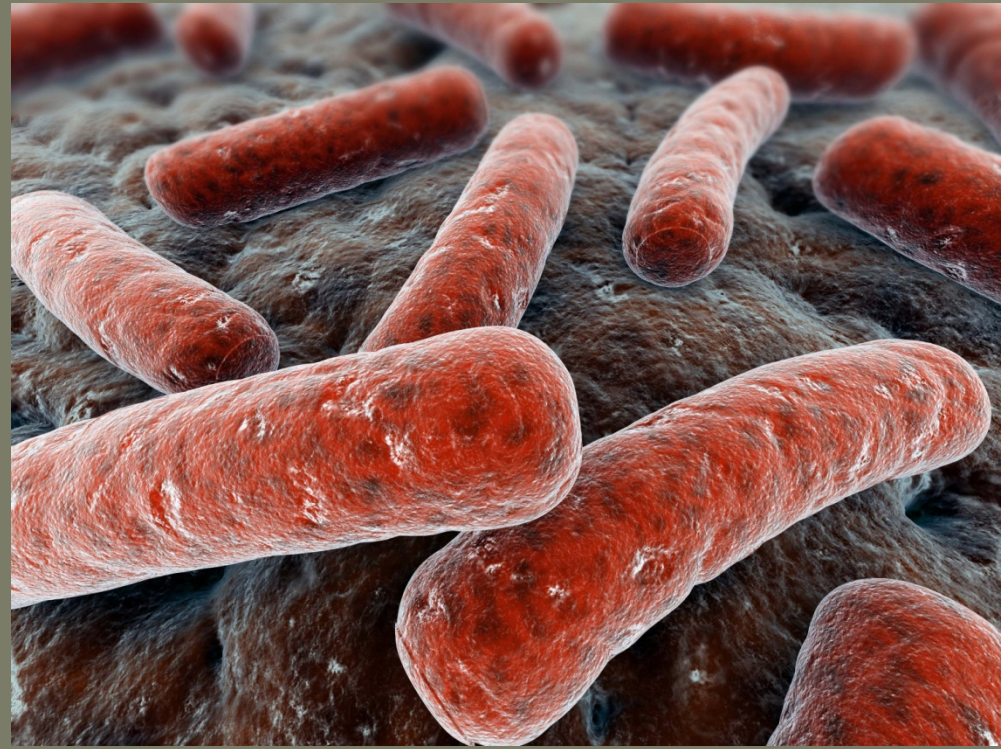


PATHOLOGY OF TUBERCULOSIS



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TUBERCULOSIS

- Define tuberculosis.
- List the diseases caused by Mycobacteria.
- Know the epidemiology of tuberculosis (TB).
- List conditions associated with increased risk of Tuberculosis.
- List factors predisposing to extension of the infection.
- Recognize the morphology of Mycobacteria and its special stain (the Ziehl-Neelsen) as well as the morphology of granulomas in TB (tubercles).
- Know the Pathogenesis of tuberculosis
- In regards to Mycobacterial lung infection: Compare and contrast the following in relation to their gross and histologic lung pathology:
 - Primary tuberculosis (include a definition of the Ghon complex).
 - Secondary or reactivation tuberculosis.
 - Miliary tuberculosis.
- List organs other than lung that are commonly affected by tuberculosis.
- Know the basis and use of tuberculin skin (Mantoux) test.
- List the common clinical presentation of tuberculosis.
- List the complication and prognosis of tuberculosis.

Define tuberculosis.

- **Tuberculosis is a serious chronic pulmonary and systemic disease caused most often by *M. tuberculosis***

List the diseases caused by Mycobacteria

- **Mycobacterium tuberculosis** is the etiologic agent of **Tuberculosis** in humans. Humans are the only reservoir for the bacterium.
-
- **Mycobacterium bovis** is the etiologic agent of TB in cows and rarely in humans. Both cows and humans can serve as reservoirs. Humans can also be infected by the consumption of unpasteurized milk. This route of transmission can lead to the development of **extrapulmonary TB**.
- **M. leprae** : causes **leprosy**

List the diseases caused by Mycobacteria

Others:

- **M. kansasii, M. avium, M. intracellulare** cause **atypical mycobacterial infections** in humans esp in AIDS. They cause respiratory and gastrointestinal symptoms and can involve other organs too.
- **M. ulcerans** causes **buruli ulcers of skin**.

Know the epidemiology of tuberculosis

- According to the World Health Organization (WHO), tuberculosis is estimated to affect more than a billion individuals worldwide, with 8.7 million new cases and 1.4 million deaths each year

List factors predisposing to extension of the infection

Flourishes wherever there is

- Poverty
- crowding
- malnutrition
- chronic debilitating illness e.g. chronic lung disease (particularly silicosis), chronic renal failure etc.

List conditions associated with increased risk of Tuberculosis.

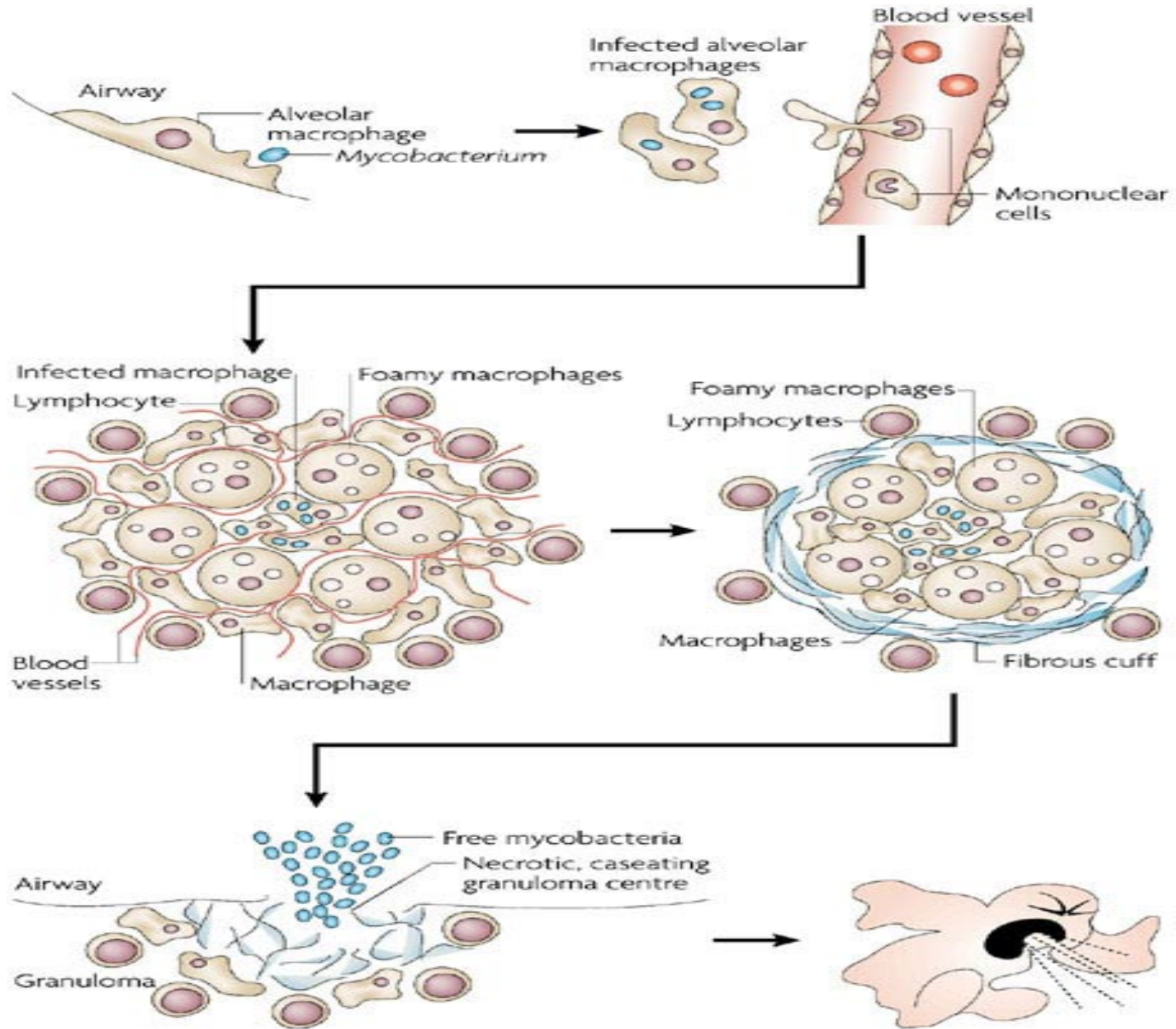
- A disease of the elderly
- People with AIDS
- Diabetes mellitus
- Hodgkin's lymphoma
- Alcoholism
- Chronic lung disease (particularly silicosis)
- Immunosuppression e.g. with glucocorticoids

TB is a Granulomatous disease.

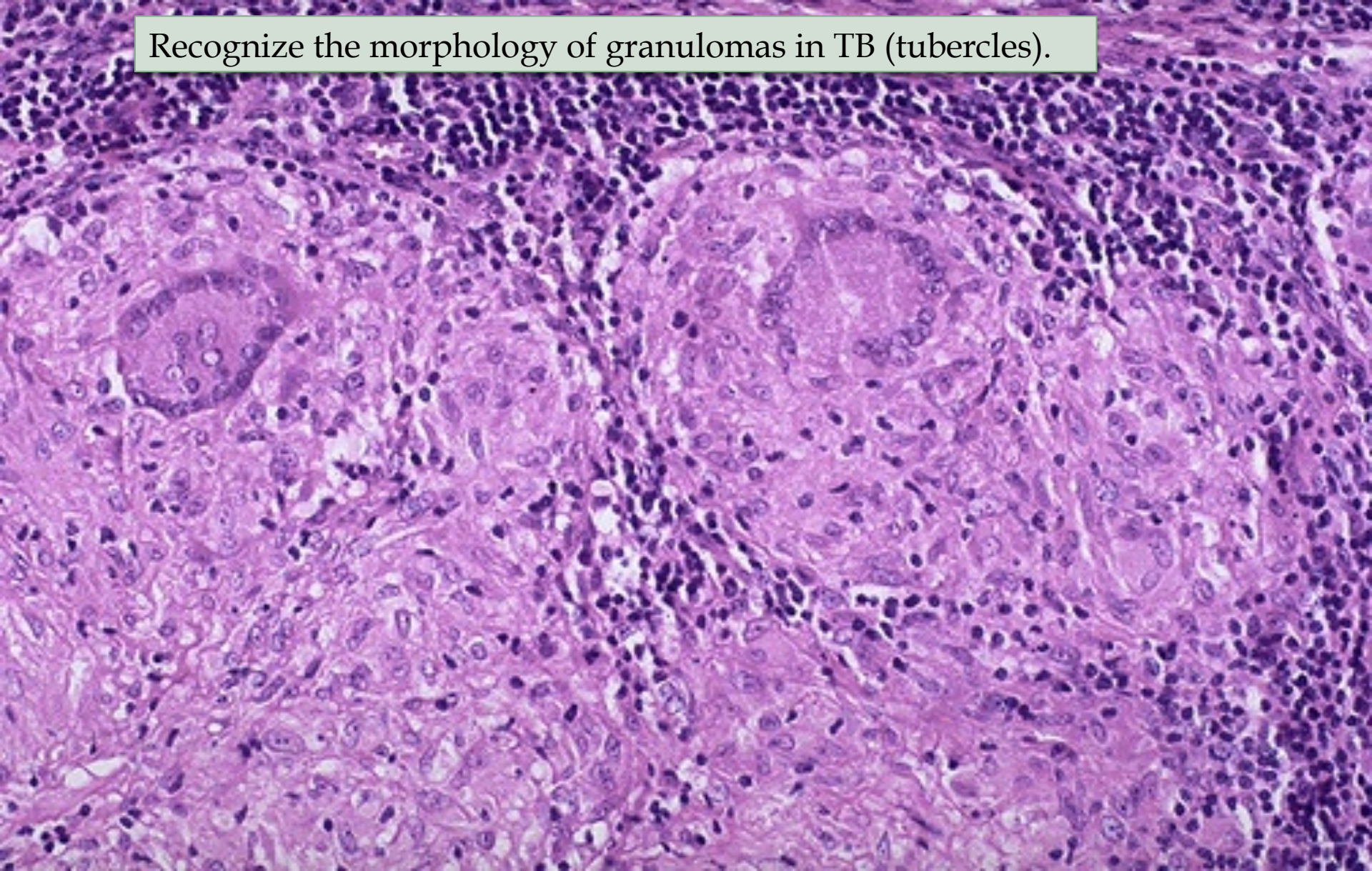
What is Granuloma?

- A granuloma is 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.
- Epithelioid cells fuse to form giant cells containing 20 or more nuclei.
- The nuclei arranged either peripherally (**Langhans-type giant cell**) or haphazardly (**foreign body-type giant cell**). Both Langhans ("classic TB") and foreign-body giant cells are common.
- These giant cells can be found either at the periphery or the center of the granuloma.
- Fibrous connective tissue often surrounds granulomas (remodeling of tissue)
- **In TB Areas within the granuloma can undergo necrosis (caseous necrosis).** Necrosis can lead to **calcification**
- TB granulomas are called tubercles, and if they are caseating in the center, they are called soft tubercles.

Recognize the morphology of granulomas in TB (tubercles).



Recognize the morphology of granulomas in TB (tubercles).



Granuloma: the predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance. Also seen are lymphocytes, multinucleated giant cells and occasional plasma cells.

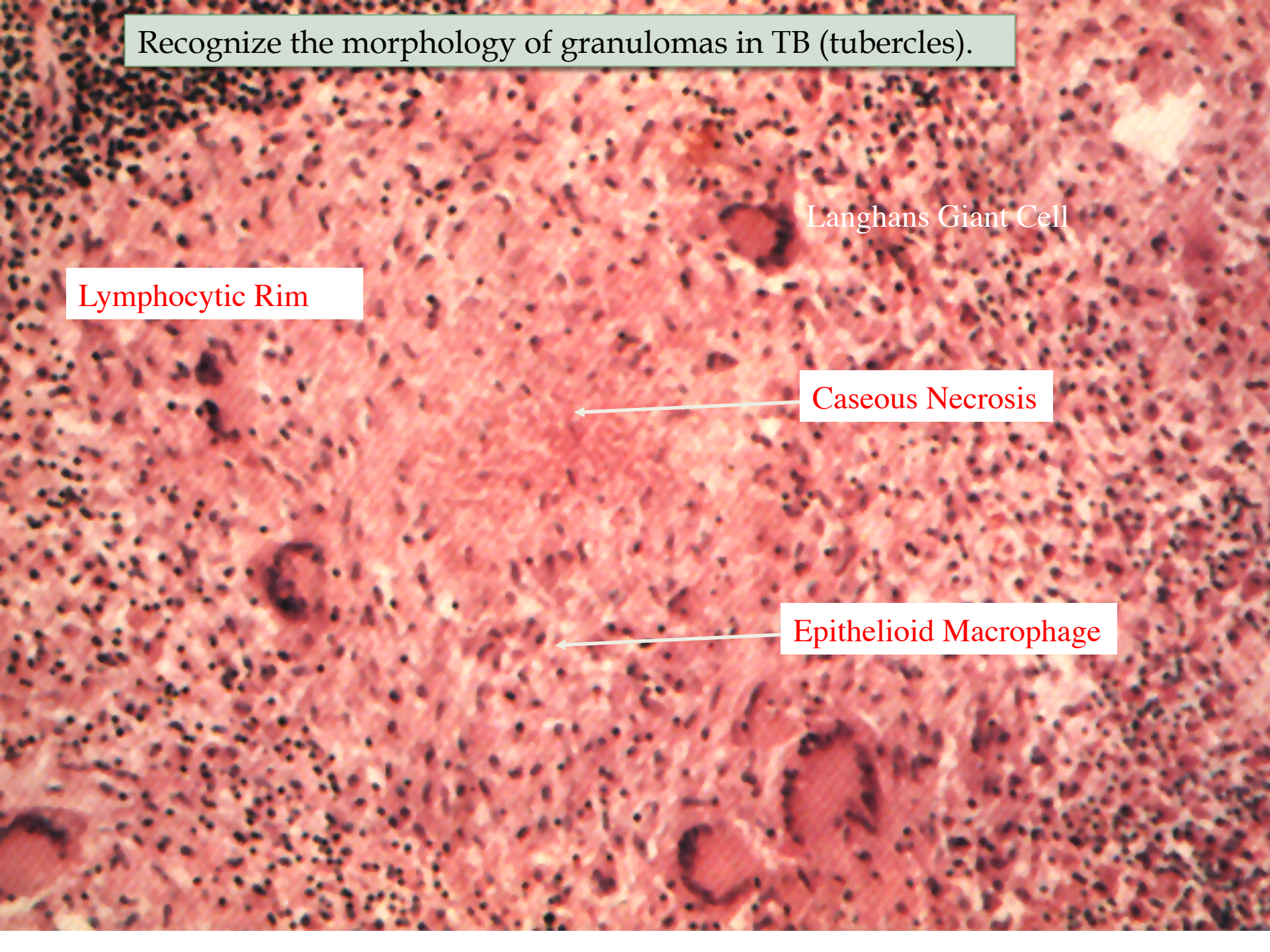
Recognize the morphology of granulomas in TB (tubercles).

Lymphocytic Rim

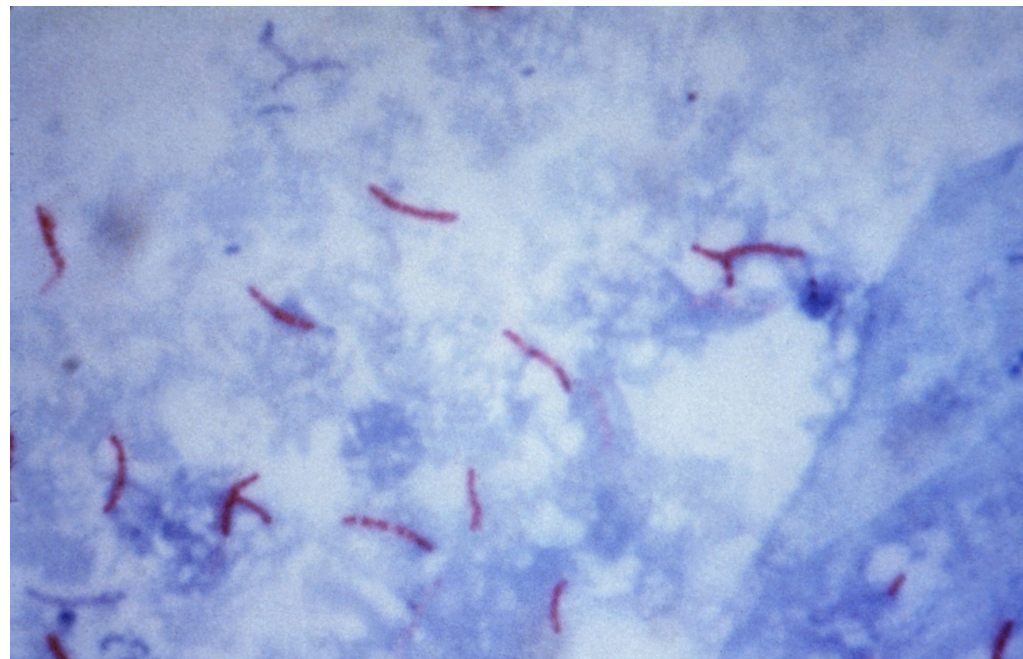
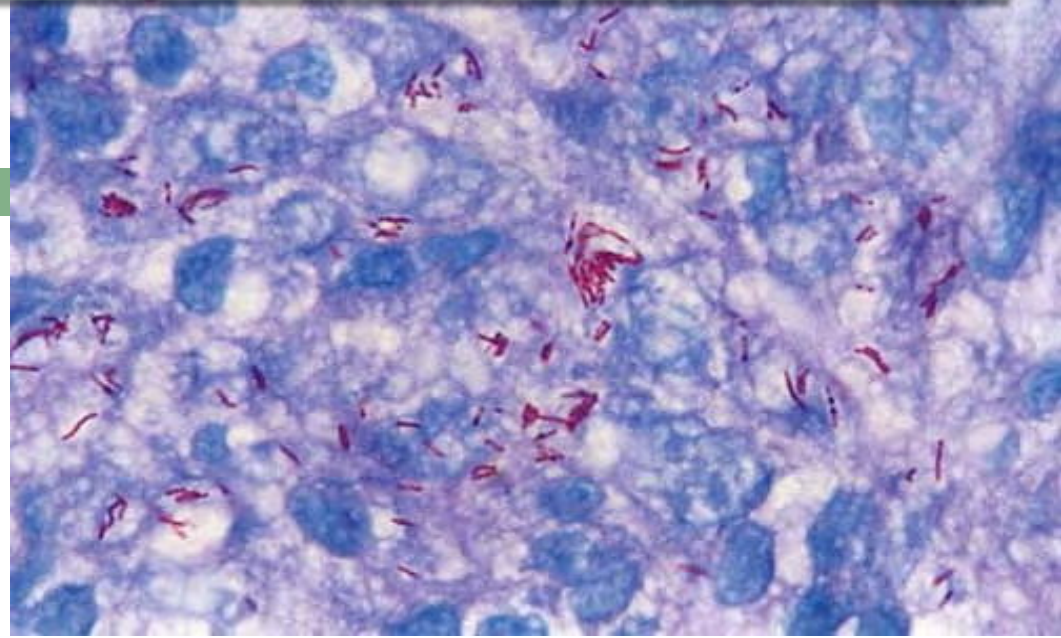
Langhans Giant Cell

Caseous Necrosis

Epithelioid Macrophage



- **Ziehl-Neelsen stain** is an acid-fast staining method to stain *M. tuberculosis*. The Acid-fast bacilli appear pink in a contrasting background.



Pathogenesis of tuberculosis

The steps in *M. tuberculosis* infection are:

1. *Entry into macrophages:*

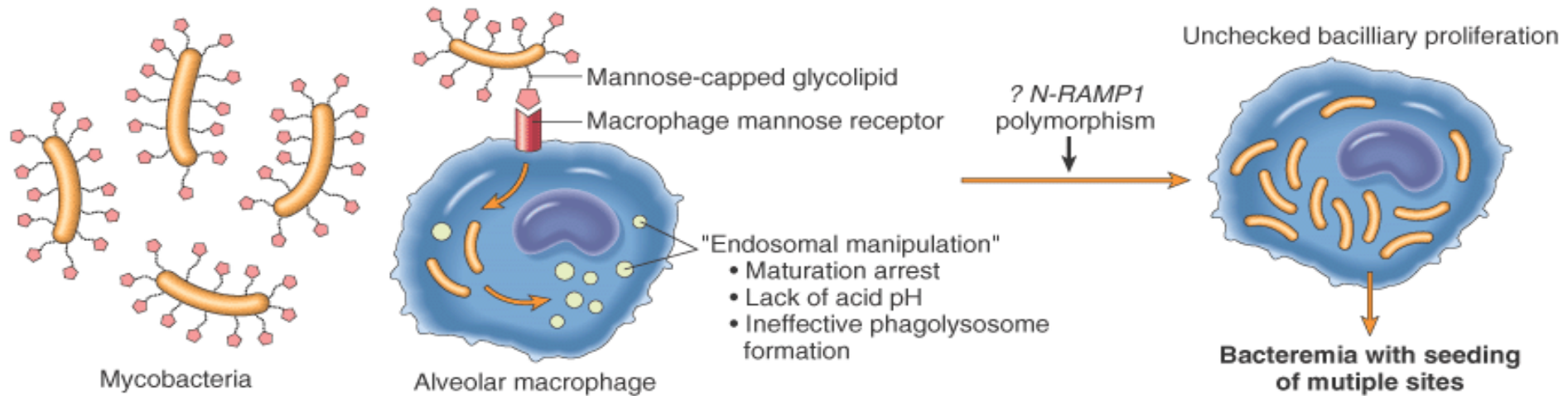
Phagocytosis mediated by several receptors expressed on the phagocyte, including mannose binding lectin

2. *Replication in macrophages.*

M. tuberculosis inhibits maturation of the phagosome and blocks formation of the phagolysosome (by inhibiting Ca^{2+} signals), allowing the bacterium to replicate within the vesicle, protected from the microbicidal mechanisms of lysosomes.

Pathogenesis of primary TB

A. PRIMARY PULMONARY TUBERCULOSIS (0-3 weeks)

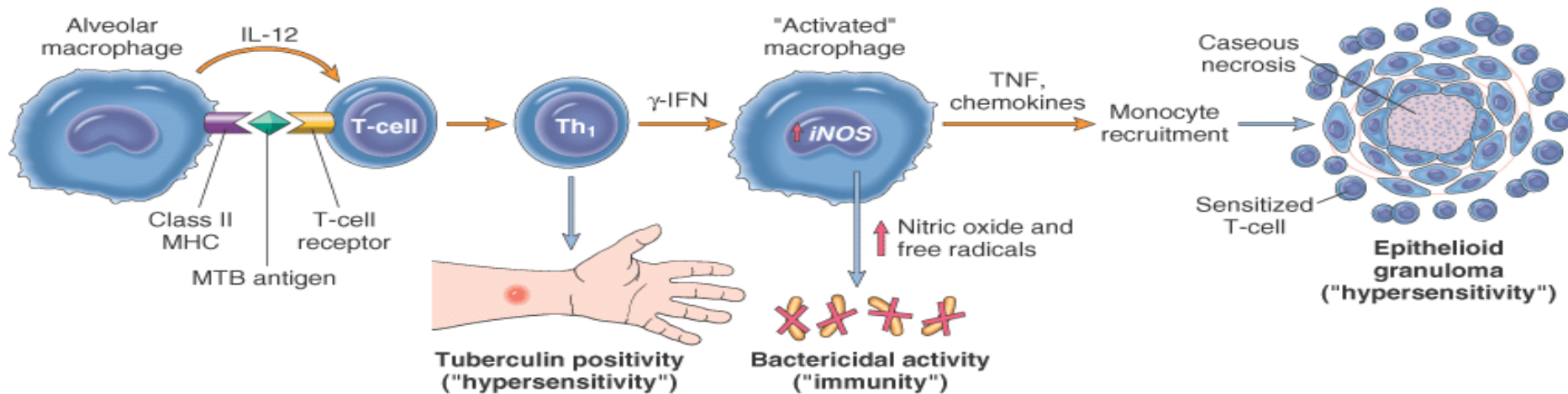


During the earliest stage of primary tuberculosis (<3 weeks) in the nonsensitized individual, bacteria proliferate in the pulmonary alveolar macrophages and air spaces, resulting in bacteremia and seeding of multiple sites. Despite the bacteremia, most people at this stage are asymptomatic or have a mild flu-like illness

Pathogenesis of Primary Tuberculosis

3. *The T_H1 response.* About 3 weeks after infection, a T-helper 1 (T_H1) response is mounted that activates macrophages, enabling them to become bactericidal.

B. PRIMARY PULMONARY TUBERCULOSIS (>3 weeks)



Differentiation of T_H1 cells depends on IL-12, which is produced by antigen-presenting cells that have encountered the bacilli

TH1-mediated macrophage activation and killing of bacteria by produce IFN- γ

Macrophages activated by IFN- γ differentiate into the "epithelioid histiocytes" that aggregate to form granulomas

Pathogenesis of tuberculosis

IFN- γ

4. *T_H1-mediated macrophage activation and killing of bacteria.*
 - **IFN- γ is the critical mediator that enables macrophages to contain the *M. tuberculosis* infection.**

How?

- I. IFN- γ stimulates maturation of the phagolysosome in infected macrophages, exposing the bacteria to a lethal acidic, oxidizing environment.
- II. IFN- γ stimulates expression of inducible nitric oxide synthase, which produces nitric oxide (NO)
- III. IFN- γ mobilizes antimicrobial peptides (defensins) against the bacteria
- IV. IFN- γ stimulates autophagy, a process that sequesters and then destroys damaged organelles and intracellular bacteria such as *M. tuberculosis*.

Pathogenesis of granuloma

5. *Granulomatous inflammation and tissue damage.*

Macrophages activated by IFN- γ differentiate into the “epithelioid histiocytes” that aggregate to form granulomas; some epithelioid cells may fuse to form giant cells (Langhans giant cell)

Activated macrophages also secrete TNF and chemokines, which promote recruitment of more monocytes

Pathogenesis of tuberculosis

- *Role of other immune cells:* In addition to the T_H1 response, NKT cells that recognize mycobacterial lipid antigens bound to CD1 on antigen-presenting cells, or T cells that express a $\gamma\delta$ T-cell receptor, also make IFN- γ .

Pathogenesis of granuloma

- *Host susceptibility to disease.* People with genetic deficiencies in the IL-12 pathway and the IFN- γ pathway, including STAT1 a signal transducer for IFN- γ , are vulnerable to severe mycobacterial infections.
- Polymorphisms in a large number of genes, including HLA, IFN- γ , IFN- γ receptor, and TLR2 have been found to be associated with susceptibility to tuberculosis

Summary of Pathogenesis

- Immunity to *M. tuberculosis* is primarily mediated by T_H1 cells, which stimulate macrophages to kill the bacteria
- This immune response, while largely effective, comes at the cost of accompanying tissue destruction
- Reactivation of the infection or re-exposure to the bacilli in a previously sensitized host results in rapid mobilization of a defensive reaction but also increased tissue necrosis
- loss of T-cell immunity (indicated by tuberculin negativity in a previously tuberculin-positive individual) may be an ominous sign that resistance to the organism has faded

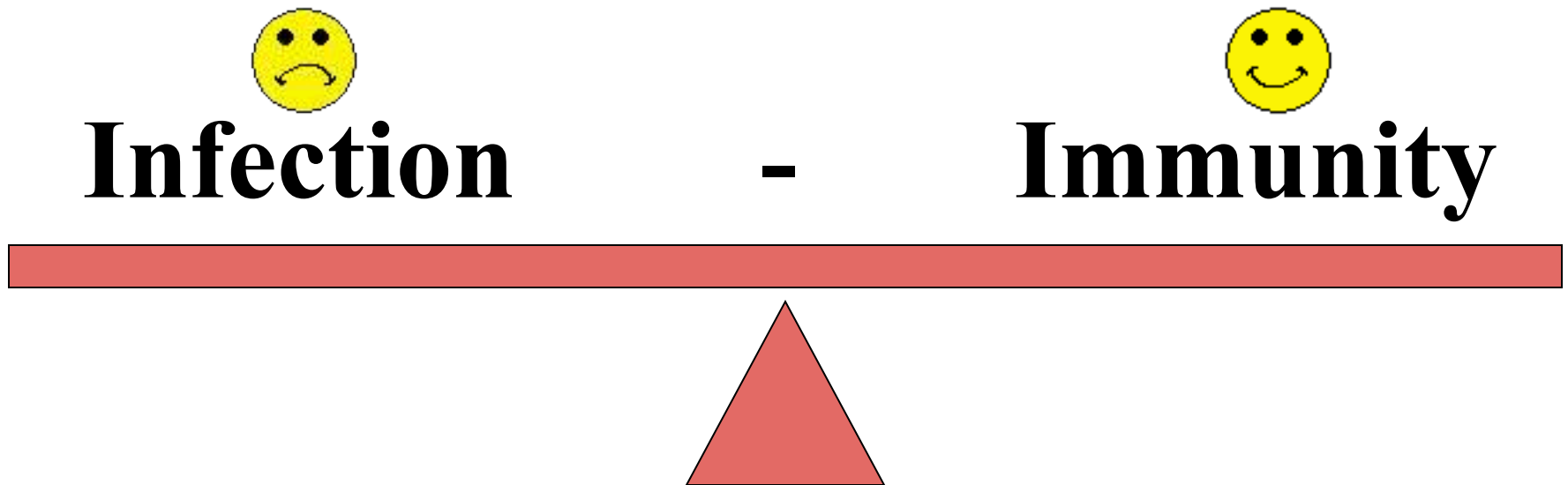
Route of transmission of TB



Route of transmission of TB

- *M. bovis* infections, acquired through drinking infected milk, usually start in the tonsils or Peyer's patches.

Pathogenesis of TB:



Infection with *M. tuberculosis* typically leads to the development of delayed hypersensitivity, which can be detected by the tuberculin (Mantoux) test.

When the bacilli enter the body.....

The bacilli have 5 potential fates upon entering the human body:

1. They may be killed by the immune system,
2. They may multiply and cause primary TB,
3. They may become dormant and remain asymptomatic,
4. They may proliferate after a latency period (reactivation disease).
Reactivation TB may occur following either (2) or (3) above.
5. If immunosuppressed ---- Primary Progressive TB or Miliary TB

The clinical course or presentation of TB

- The course of TB depends on the age and the immunity of the patient and the total burden of organism.
 - Some patients have only an indolent, asymptomatic infection while in others TB is a destructive disseminated disease.
 - There is a difference between infection and active TB. Not everyone who is infected develops clinical symptoms.
1. Primary TB occurs on first exposure to the organism and can pursue either an indolent or aggressive course (primary progressive TB).
 2. Secondary TB develops long after a primary infection, mostly as a result of reactivation of a primary infection. It can also be produced by exposure to exogenous organisms. Secondary TB is always an active disease.
 3. Miliary TB

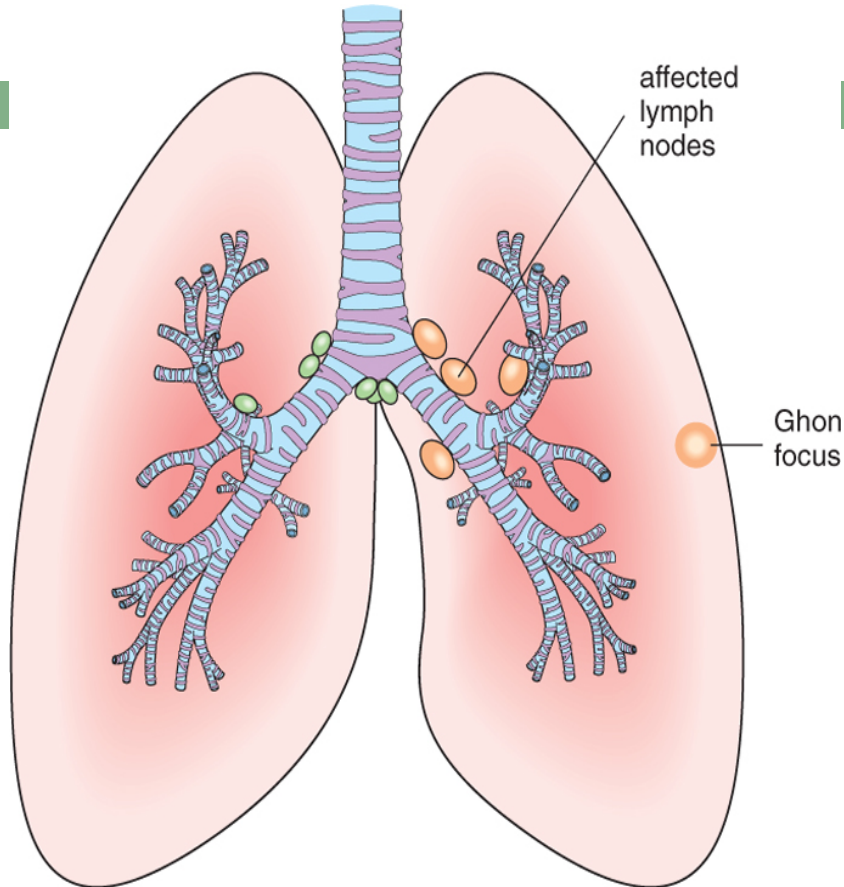
PRIMARY TB

- Primary TB is a first exposure to tubercle bacilli. The inhaled organism is deposited in the alveoli.
- Ingested by macrophages and they elicit a type IV delayed hypersensitivity response
- In an immunologically competent person a granulomatous response is produced. It takes 5-6 days to invoke granuloma formation which are usually formed by 3 to 4 weeks.
- In immunocompromised persons, granulomas are poorly formed.

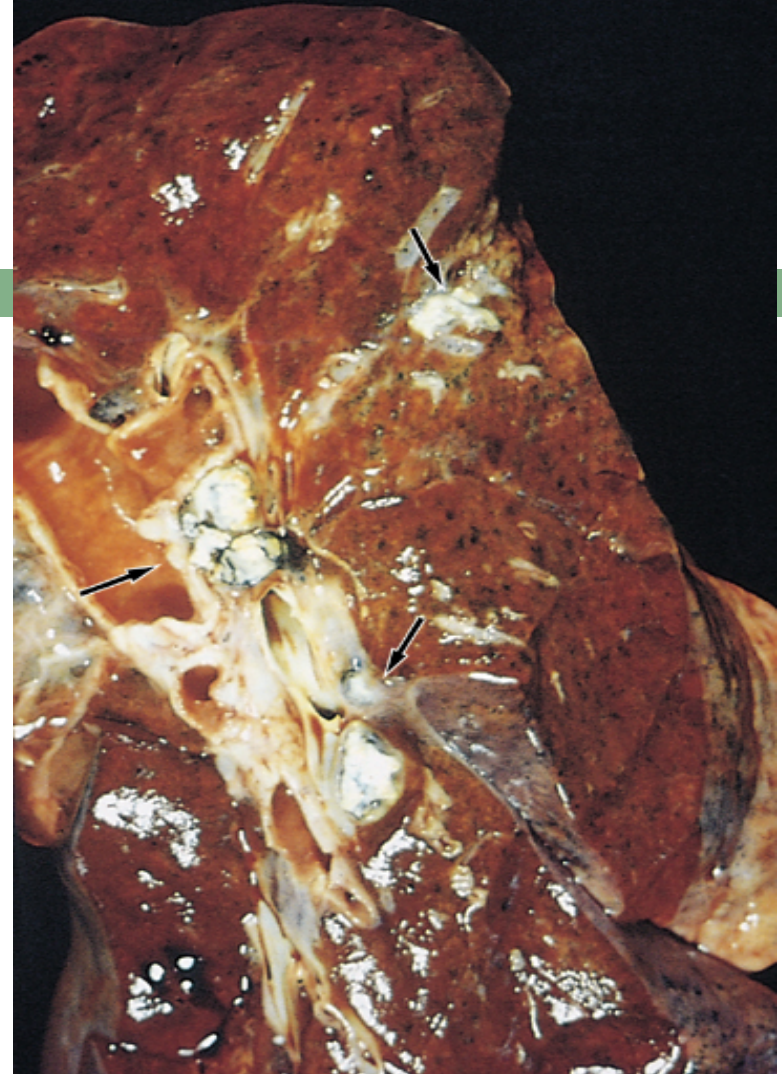
PRIMARY TB

- The lung lesion of primary TB is known as Ghon focus.
- It is commonly found in the sub-pleural area.
- It drains into the hilar lymph nodes.
- The combination of the Ghon focus and the involved mediastinal or hilar lymph nodes is called as Ghon complex.
- Most of the time this Ghon complex heals undergoing shrinkage fibrous scarring and calcification. It takes 2 to 8 weeks for healing.
- Clinically: low grade fever and flu like symptoms
- Chest x-ray shows a subpleural midzonal round lesion with hilar lymph nodes enlargement.
- Tuberculin skin test become positive

PRIMARY TUBERCULOSIS: Ghon Focus & Ghon complex

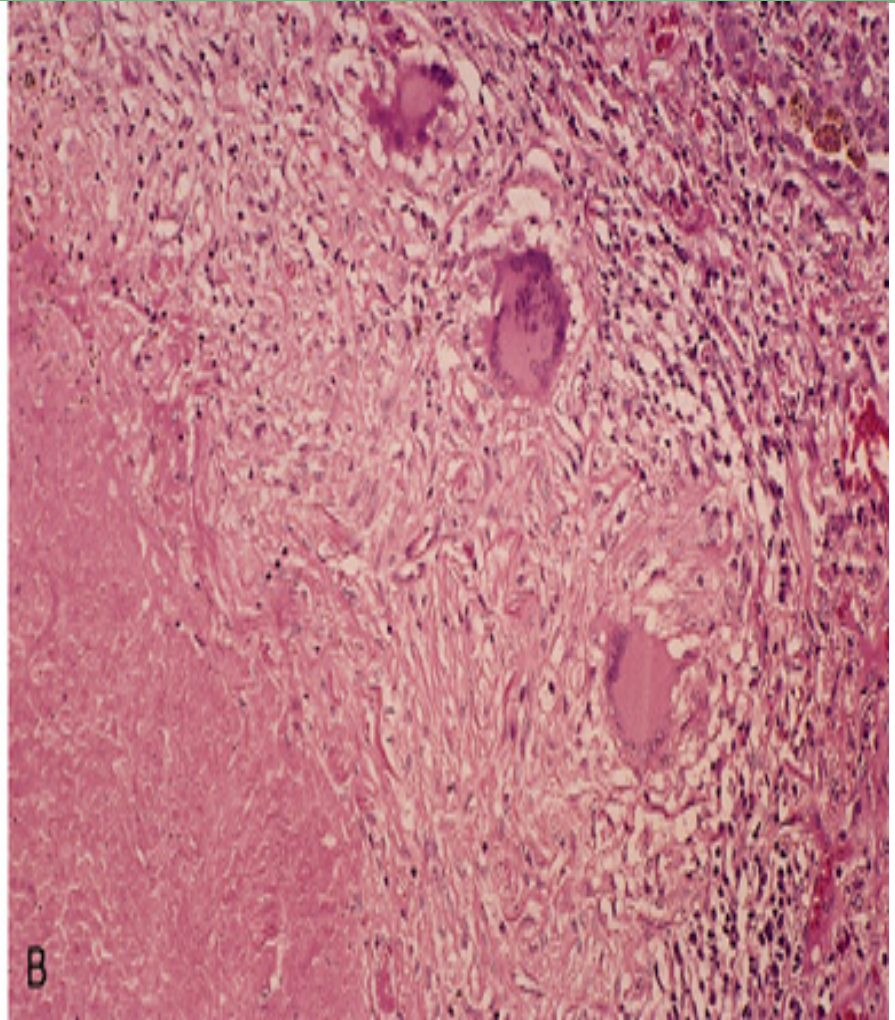
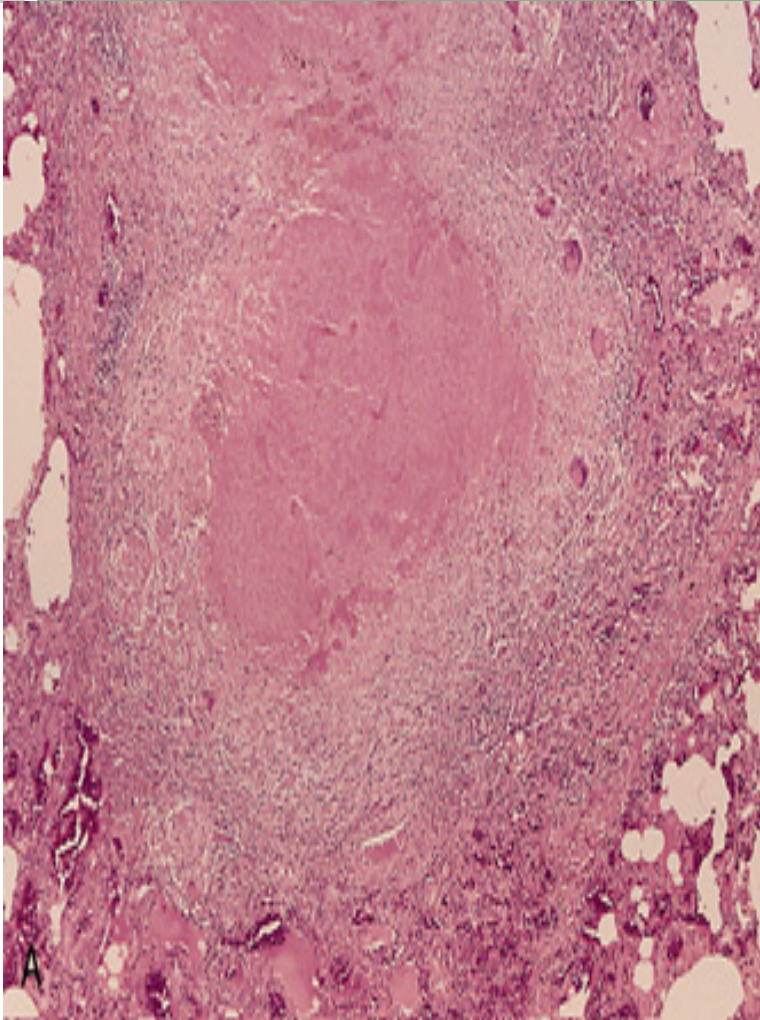


Stevens et al: Core Pathology, 3rd Edition.
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- Ghon Focus: lung lesion of primary TB, involves upper segments of the lower lobes or lower segment of the upper lobe.
- Ghon complex: combination of a peripheral ghon focus and involved mediastinal or hilar lymphnode.
- Microscopically the classic lesion of TB is a caseous granuloma

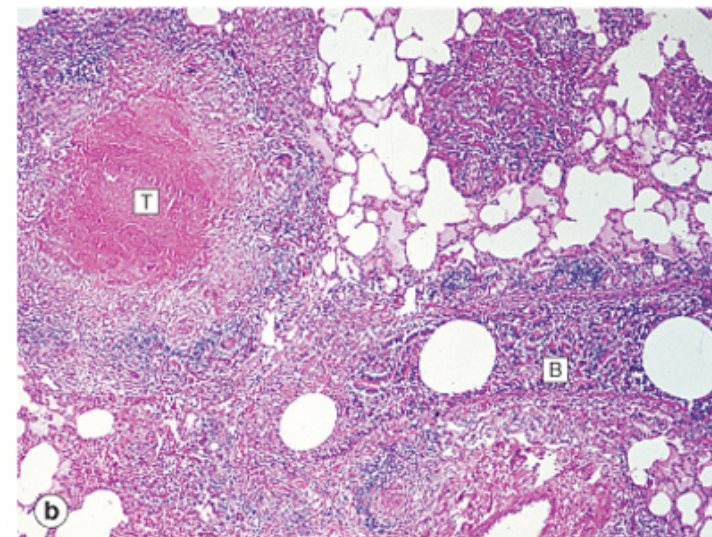
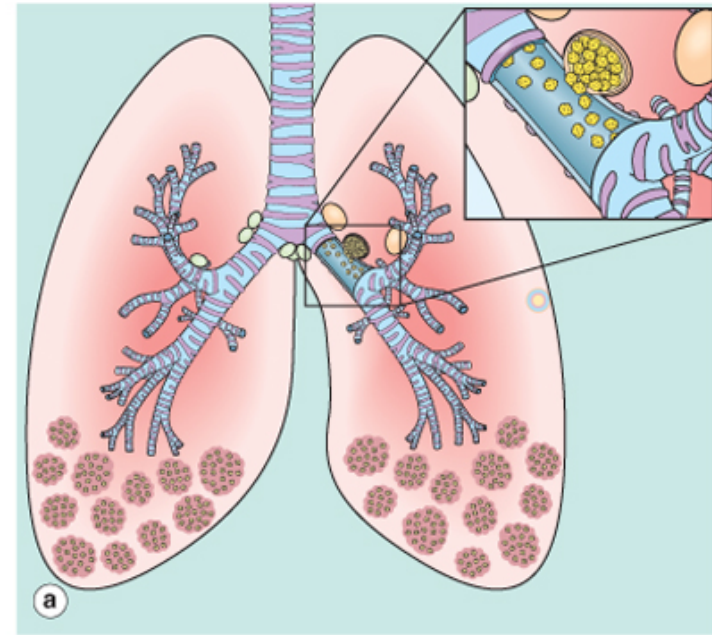
Caseating granulomas



Possible sequelae of primary tuberculosis

1. **No problems.**
2. The disease may advance into **progressive primary tuberculosis** in immunocompromised patients such as AIDS patients, elderly, and malnourished children. The infection progresses and spreads to other areas of lung, lymph nodes or other multiple sites.
3. The foci of scarring may harbor a small number of organisms that remain viable for years and later if immune mechanisms wane or fail, these bacilli may multiply and cause reactivation of TB (**secondary TB**).

progressive primary tuberculosis



SECONDARY TUBERCULOSIS

It is post primary infection in an immunized individual.

The mycobacteria in secondary TB may be either coming from:

1. A reactivation of dormant organisms from old granulomas (dormant primary lesion).

- ▣ This is more common.
- ▣ It may develop even decades after primary infection.
- ▣ Causes: various conditions including:
 - Cancer
 - Chemotherapy
 - AIDS
 - Old age

2. Or

Exogenous re-infection (newly acquired bacilli) by a high dose of virulent bacilli.

- Seen more in endemic areas.

Pathologic features of secondary tuberculosis:

- Secondary pulmonary tuberculosis can involve any organ but the lungs are the most common site.
 - In the lungs it is classically localized to the apex of the upper lobes of one or both lungs.
 - (M.tuberculosis bacilli love oxygen and prefer to grow where it is most abundant so it starts at the apical and subapical regions of the lungs).
 - Appear grossly as sharply circumscribed firm mass with central cavity surrounded by fibrous wall.
 - The cavitation is loaded with the mycobacteria. It becomes an important source of infection because the patient now coughs sputum that contains bacilli.
 - Histologically: epithelioid granulomas with central caseation and Langhan's type

Scndary TB lung



Cavitary tuberculosis with intracavitary hemorrhage. Extensive necrosis with cavitation, usually occurring in the upper lung lobe .

Complications of TB

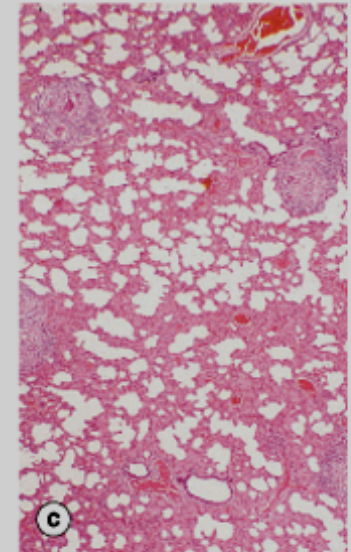
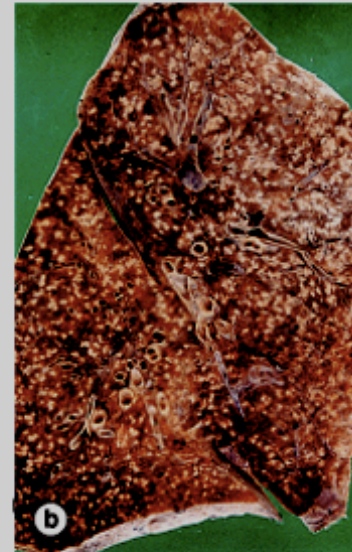
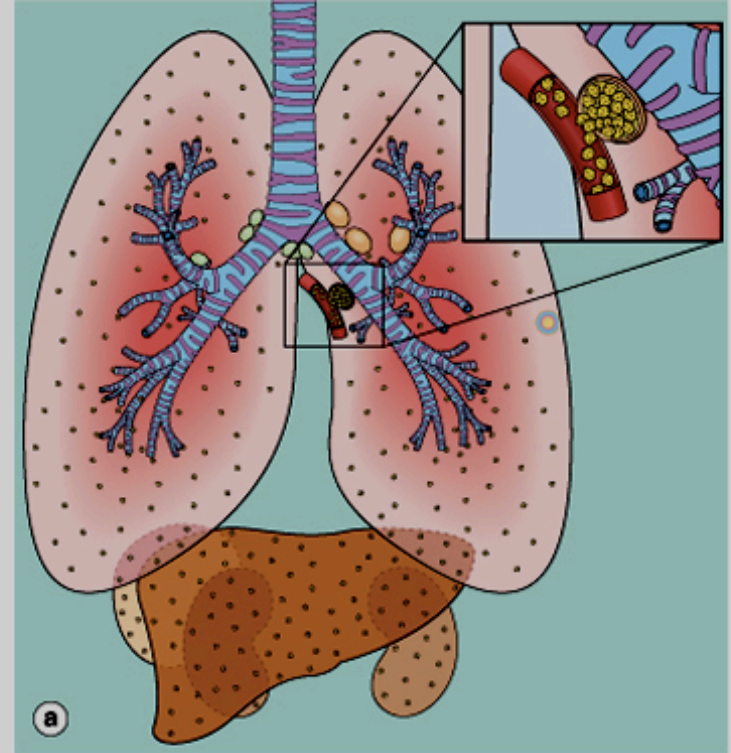
- Scarring: It can heal by fibrosis leaving a residual apical scar.
- Calcification (dystrophic)
- Pleural fibrosis & adhesions
- Local spread e.g. implantation of bacteria in the larynx leading to hoarseness or bronchial spread leads to bronchopneumonia
- Systemic spread/miliary TB, via:
 - Vein – via left ventricle to whole body
 - Artery – miliary spread within the lung

Miliary Tuberculosis:

- when bacteria in the lungs enters the pulmonary venous return to the heart; the organisms subsequently disseminate through the systemic arterial system and the lymphatic channels

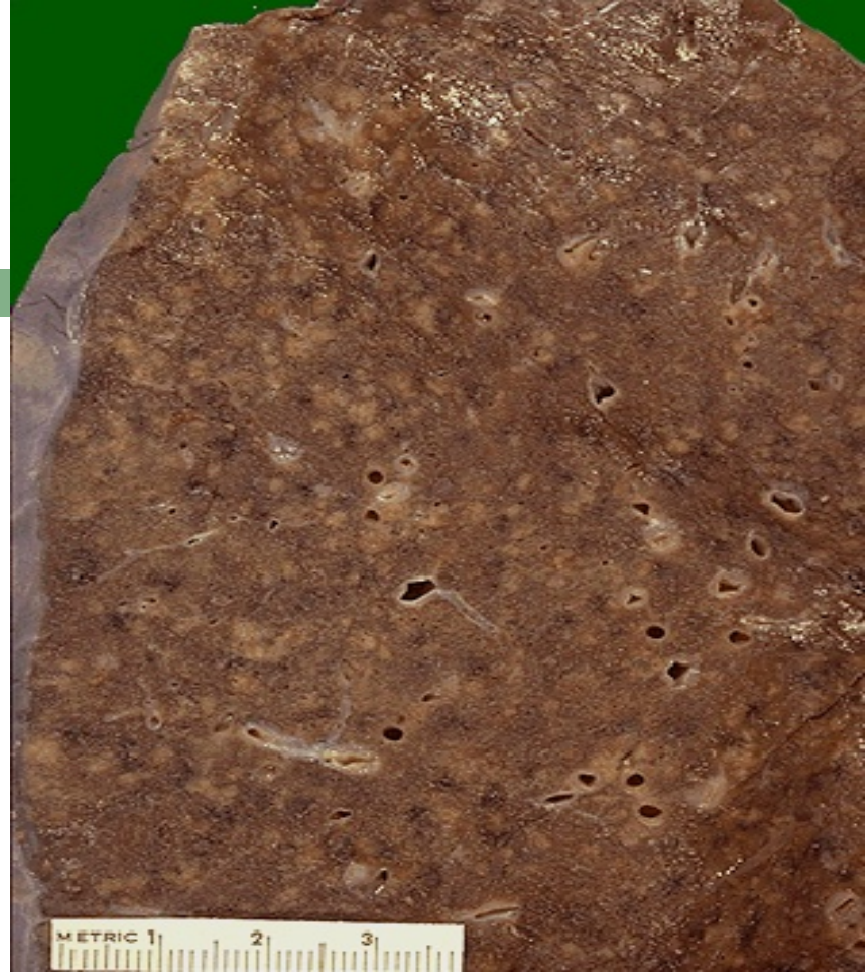
Systemic miliary tuberculosis

- It produces multiple small yellow nodular lesions in several organs. Almost every organ in the body may be seeded. Lesions resemble those in the lung.
- In the lungs there multiple lesions either microscopic or small, visible (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma.



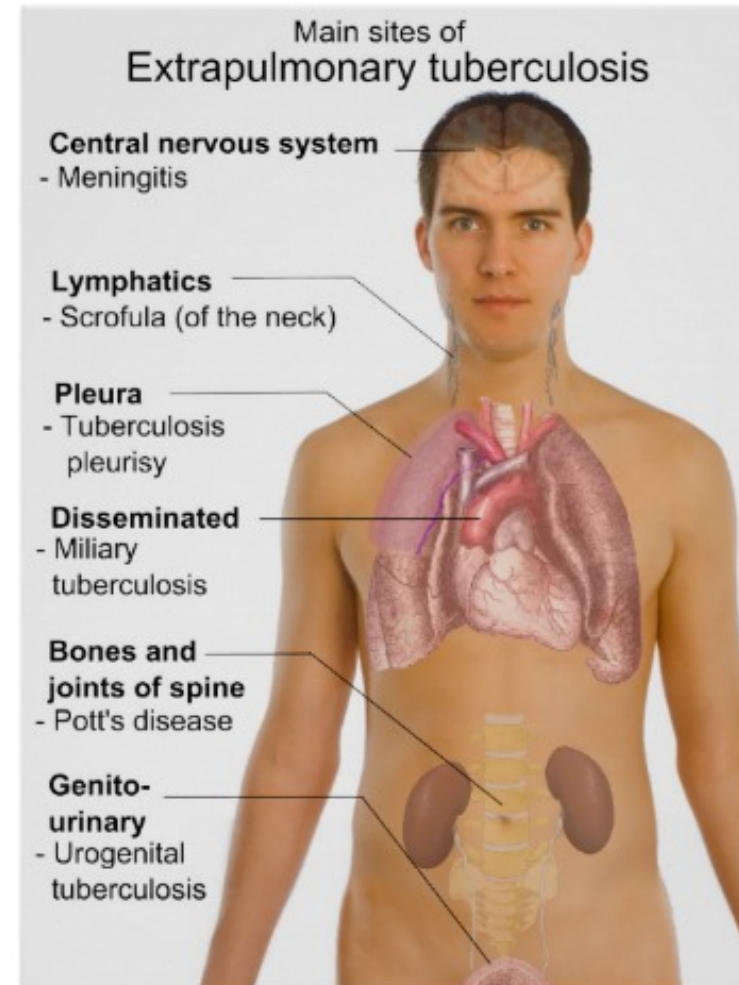
Miliary TB

- Millet like – grain.
- blood or bronchial spread

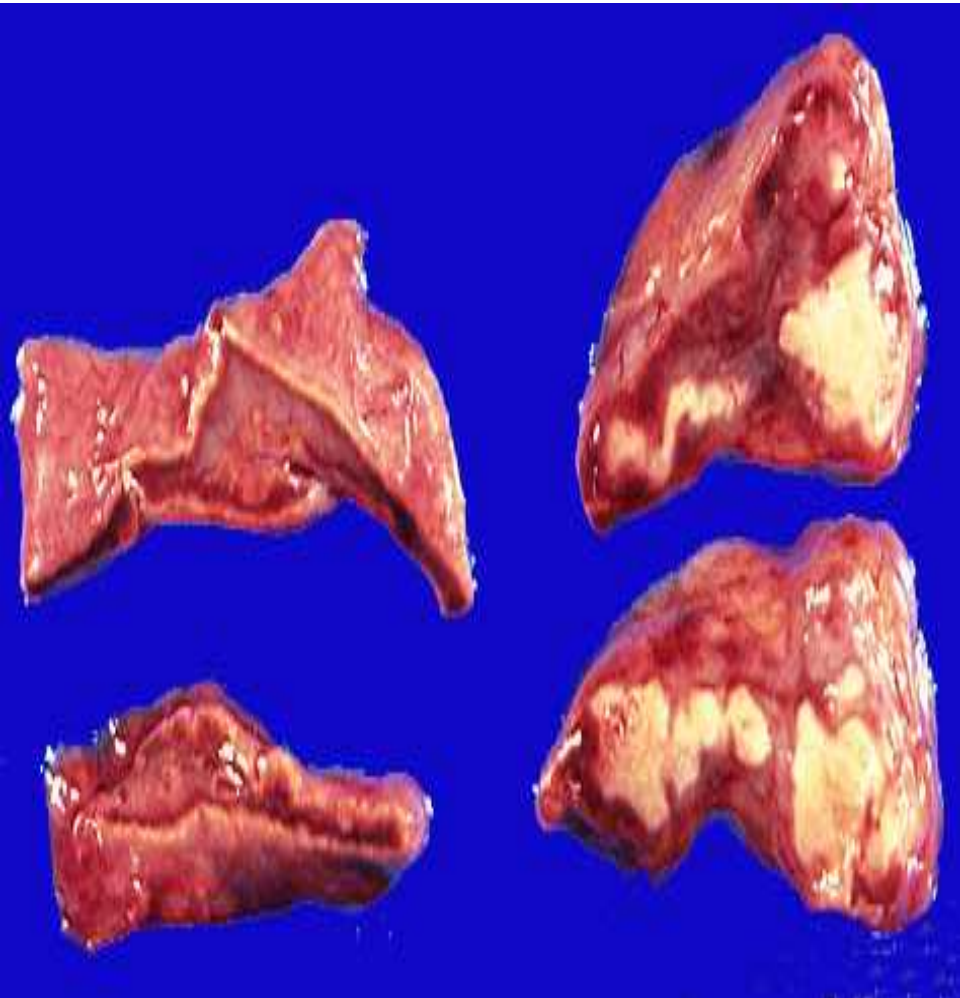


Extrapulmonary tuberculosis

- Lymph nodes/ **tuberculous lymphadenitis** : are the most frequent form of extrapulmonary tuberculosis esp. in the cervical region
- **Liver and spleen**
- **adrenals**
- **fallopian tube and endometrium**
- **Epididymis and prostate**
- **kidneys**
- **meninges around the base of the brain (tuberculous meningitis),**
- **Bone marrow**
- **Vertebrae (Pott's disease).**
- **Intestinal tuberculosis** contracted by



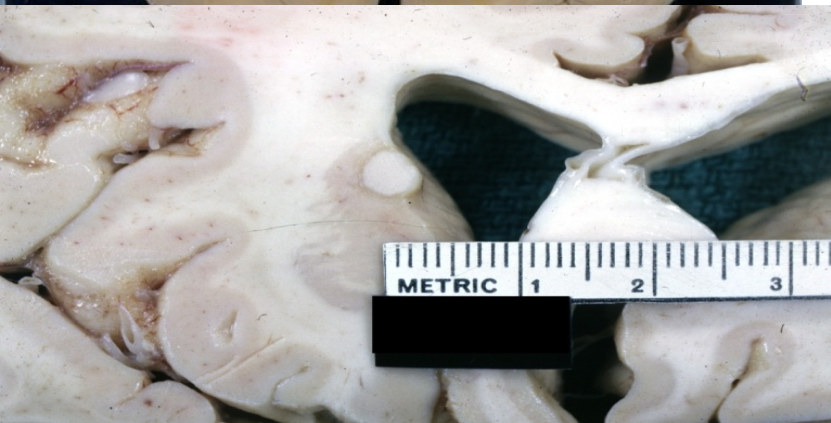
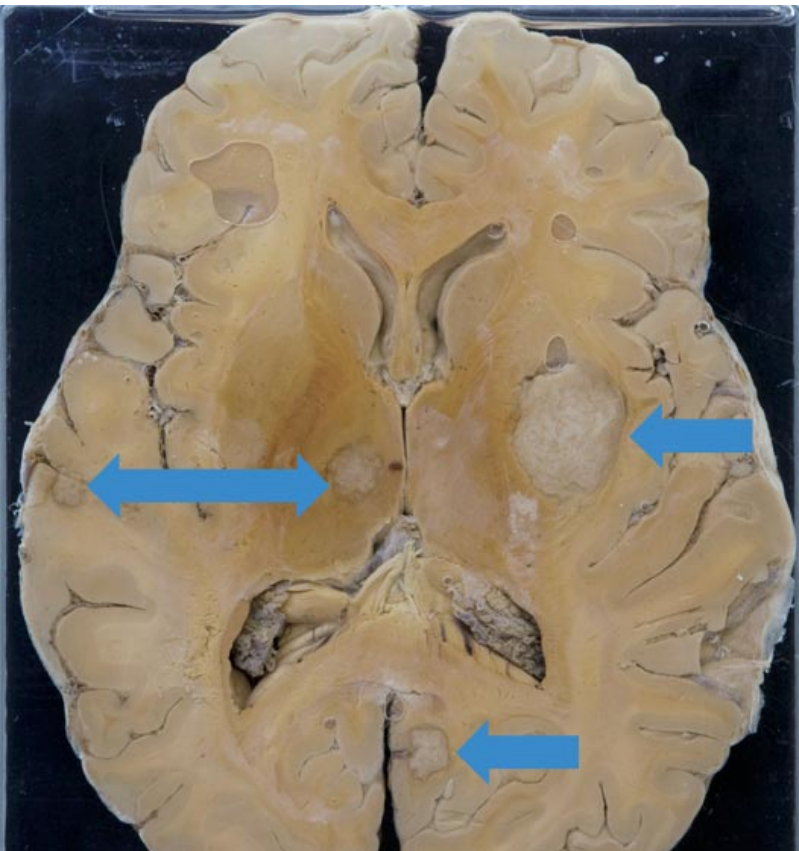
TB adrenal gland



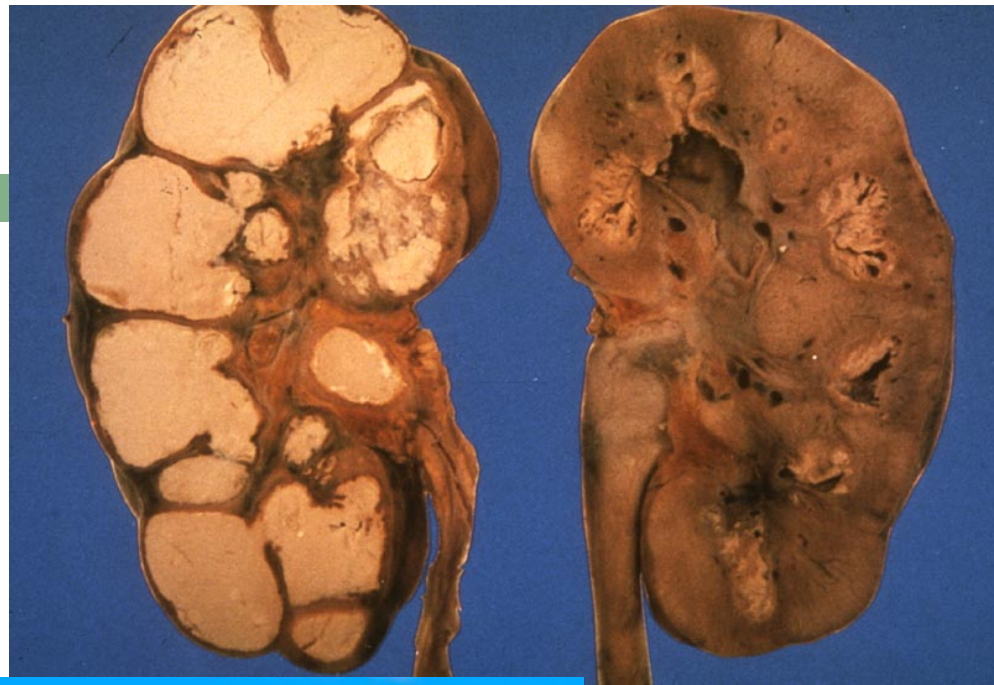
TB epididymis



Tuberculoma

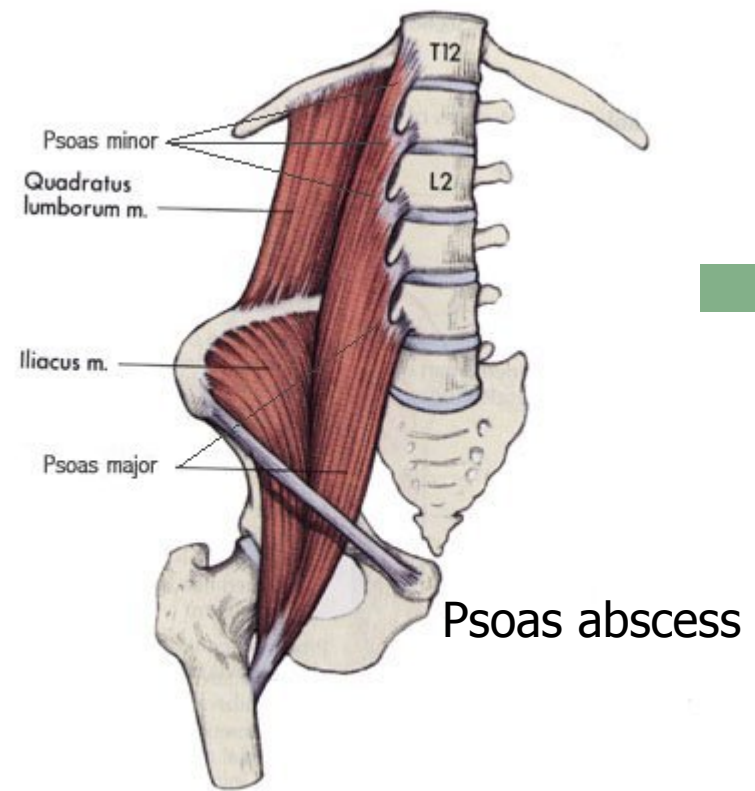


Renal TB



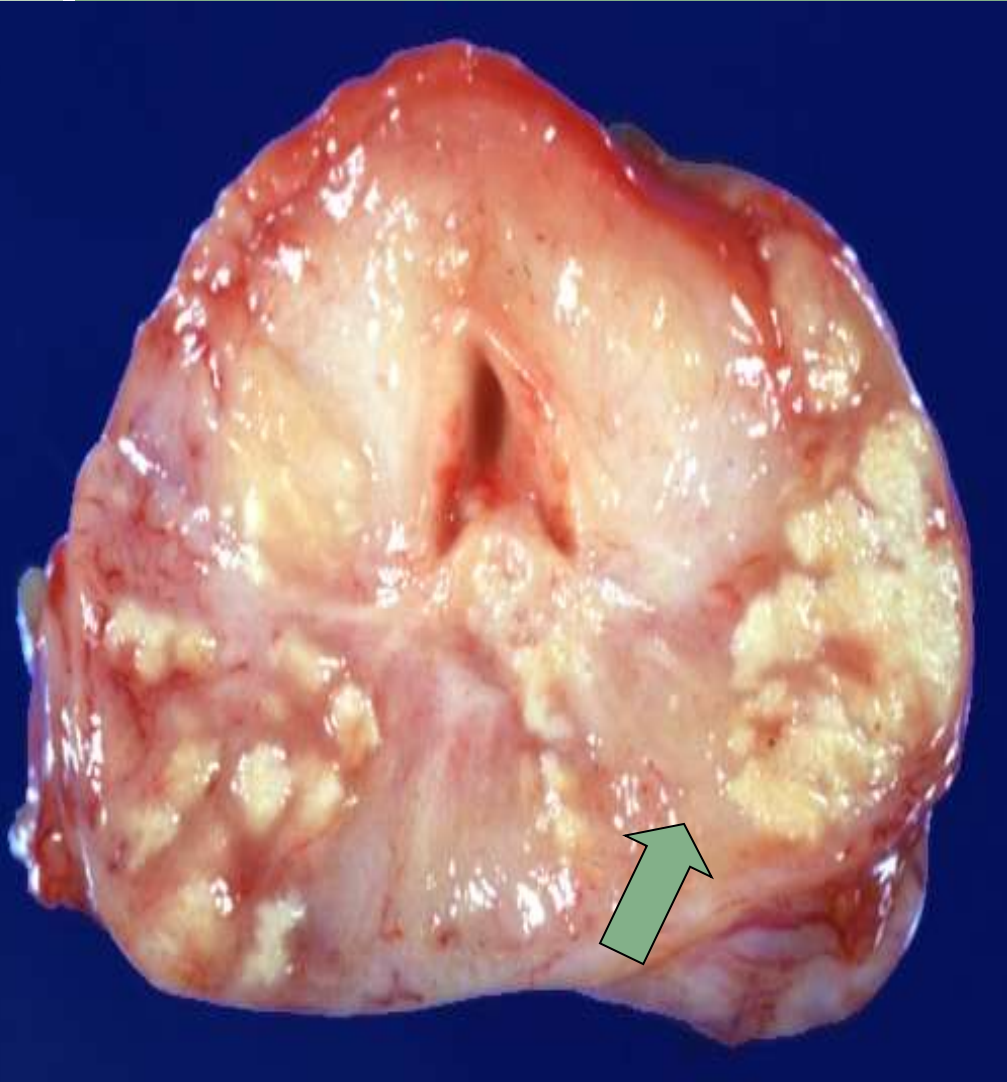
TB Vertebra
(Potts
Spine)

Pott's disease



- **Vertebrae** (Pott's disease). It collapses the spine and leads to paraspinal "cold" abscesses
- in these patients may track along the tissue planes to present as an abdominal or pelvic mass

TB Prostate gland



TB intestine



Mantoux) test



The size of induration is measured 48-72 hours later



Prognosis

- The prognosis with proper treatment is generally good if infections are localized to the lungs, except when they are caused by drug-resistant strains or occur in aged debilitated, or immunosuppressed persons, who are at high risk for developing miliary TB.

TAKE HOME MESSAGES:

1. ***Mycobacterium tuberculosis* is the causative organism of tuberculosis (TB) in the lungs and elsewhere.**
2. **It gains access to the lung by inhalation and causes pulmonary TB.**
3. **A granuloma in TB is composed of activated macrophages, Langhans' giant cells with surrounding lymphoid cells and fibroblasts with central caseation necrosis.**
 - ▣ **Primary tuberculosis is the form of disease that develops in a previously unexposed, and therefore unsensitized, person.**
 - ▣ **Secondary (reactivation) tuberculosis arises in previously exposed individuals when host immune defenses are compromised, and usually manifests as cavitory lesions in the lung apices.**
 - ▣ **Both progressive primary tuberculosis and secondary tuberculosis can result in systemic seeding, causing life-threatening forms such as miliary tuberculosis and tuberculous meningitis.**
4. **The outcome depends on the adequacy of the host immune response and treatment**

