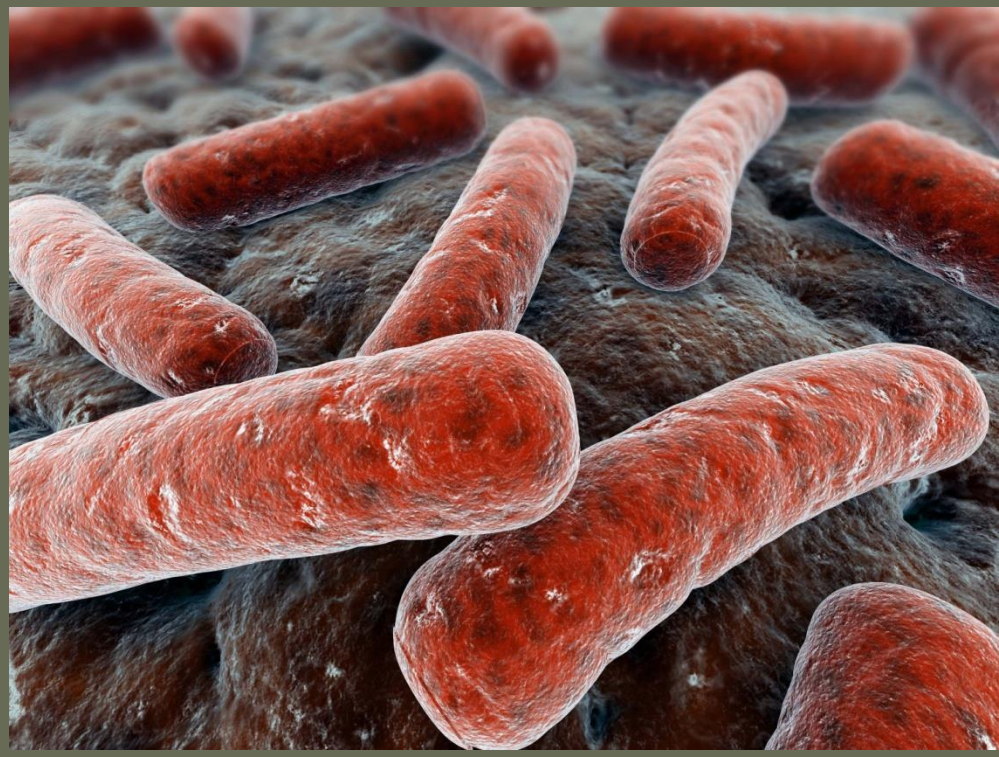
PATHOLOGY OF TUBERCULOSIS



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2016

My objectives

- **Discuss Pathogenesis and different pathologic features seen in TB**

TUBERCULOSIS

- TB is a chronic communicable granulomatous disease in which the lungs are the prime target, although any other organ may be infected.
- Important pulmonary problem as the incidence is rising worldwide.
- This disease is mainly caused by Mycobacterium tuberculosis hominis (Koch bacillus) but also occasionally by Mycobacterium tuberculosis bovis.

Diseases caused by Mycobacterium

The important species are

- **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

Diseases caused by Mycobacterium

Others:

- More than 50 species of the genus Mycobacterium are now recognized as potential human pathogens. Species other than M. tuberculosis and M. leprae have been designated as **"non-tuberculous mycobacteria"**
- **M. kansasii, M. avium intracellulare** cause atypical mycobacterial infections in humans esp in AIDS. They cause respiratory and gastrointestinal symptoms and can involve other organs too.
- They cause atypical TB.

- **M. ulcerans** causes buruli ulcers of skin.

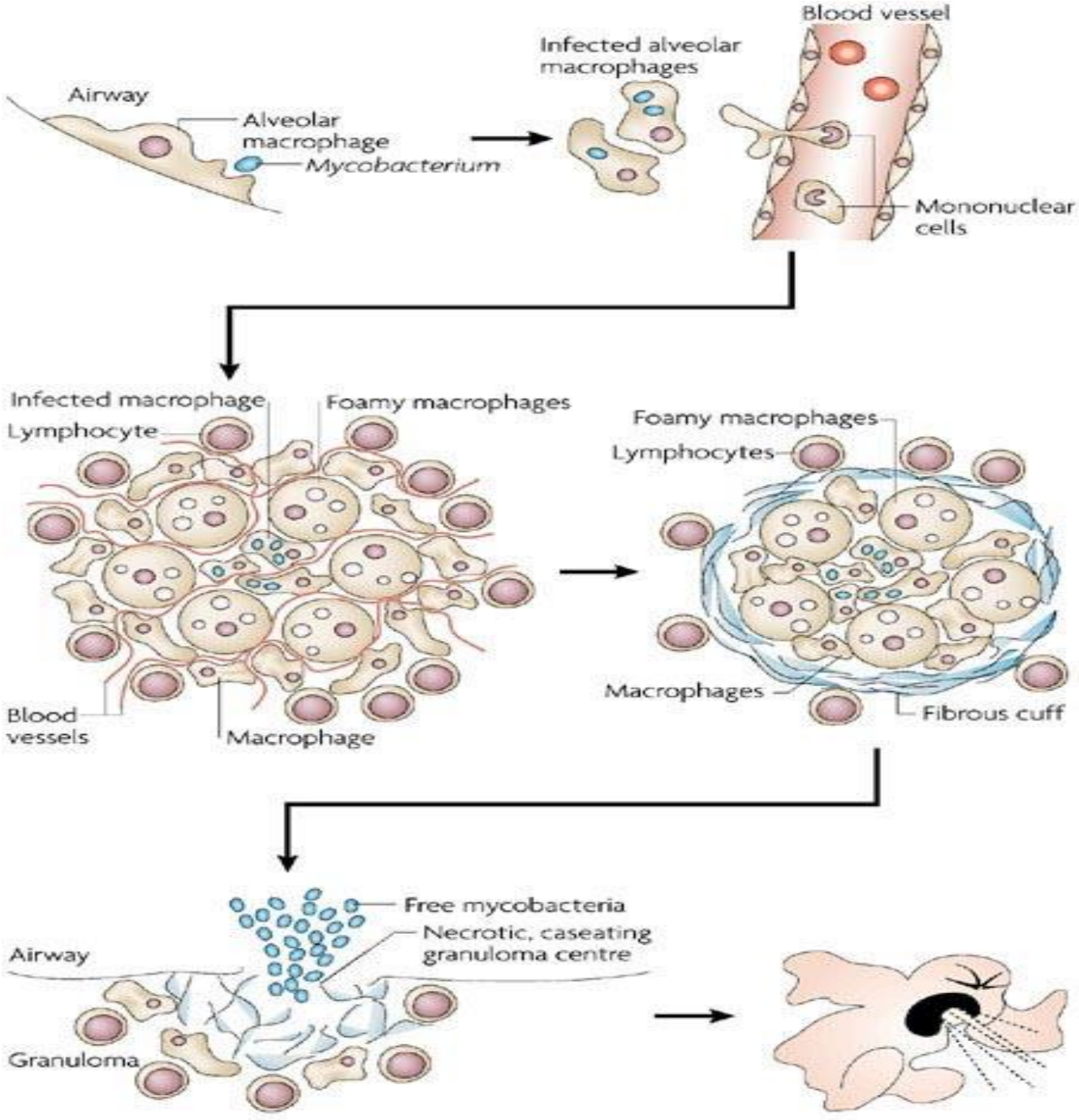
TUBERCULOSIS: Increase risk

Flourishes wherever there is

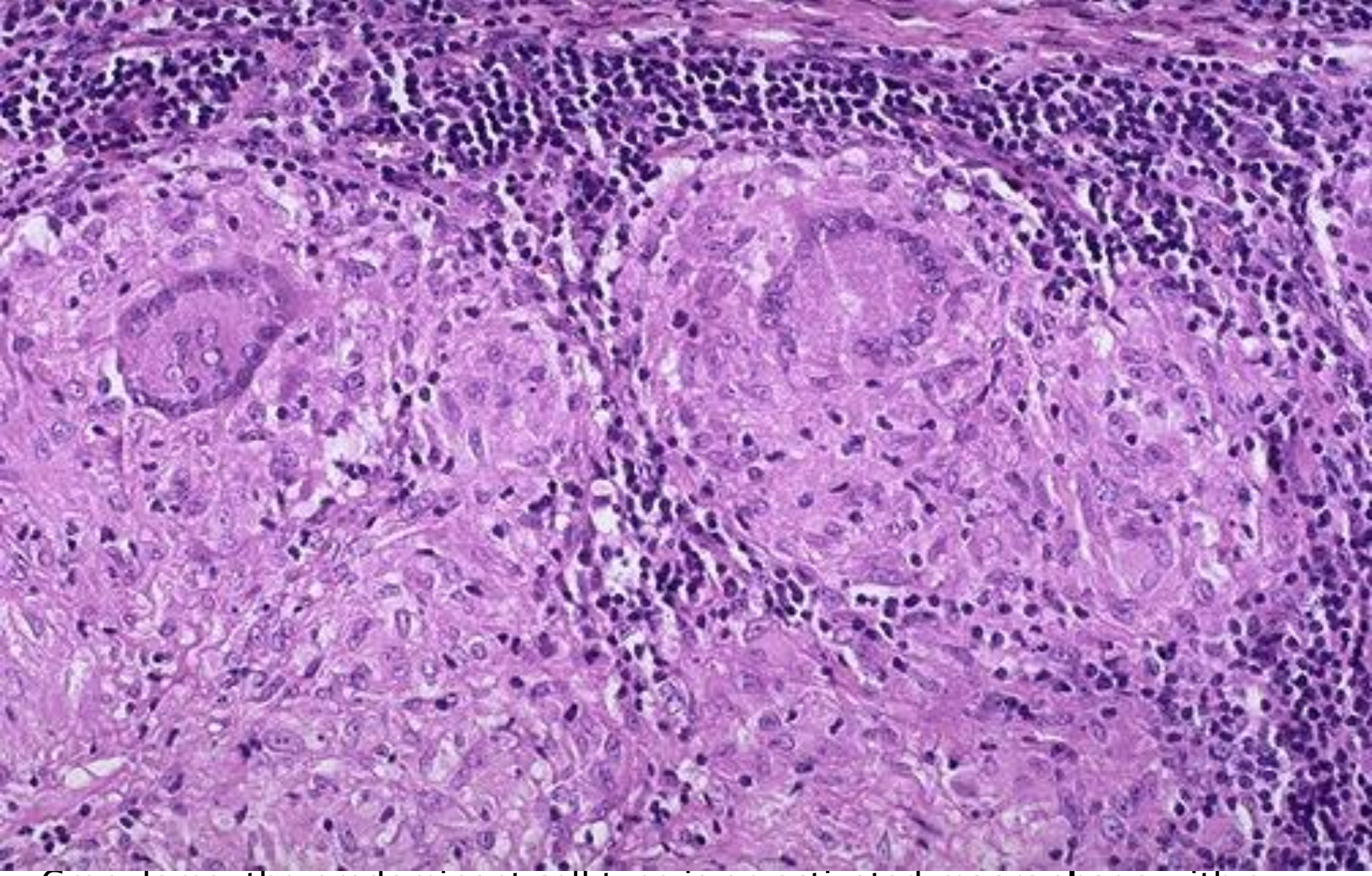
- Poverty
- crowding
- malnutrion
- chronic debilitating illness e.g.chronic lung disease (particularly silicosis), chronic renal failure etc.
- a disease of the elderly,
- people with AIDS,
- Diabetes mellitus,
- Hodgkin's lymphoma,
- Alcoholism,
- Immunosuppression e.g. with glucocorticoids

TB is a Granulomatous disease. What is Granuloma?

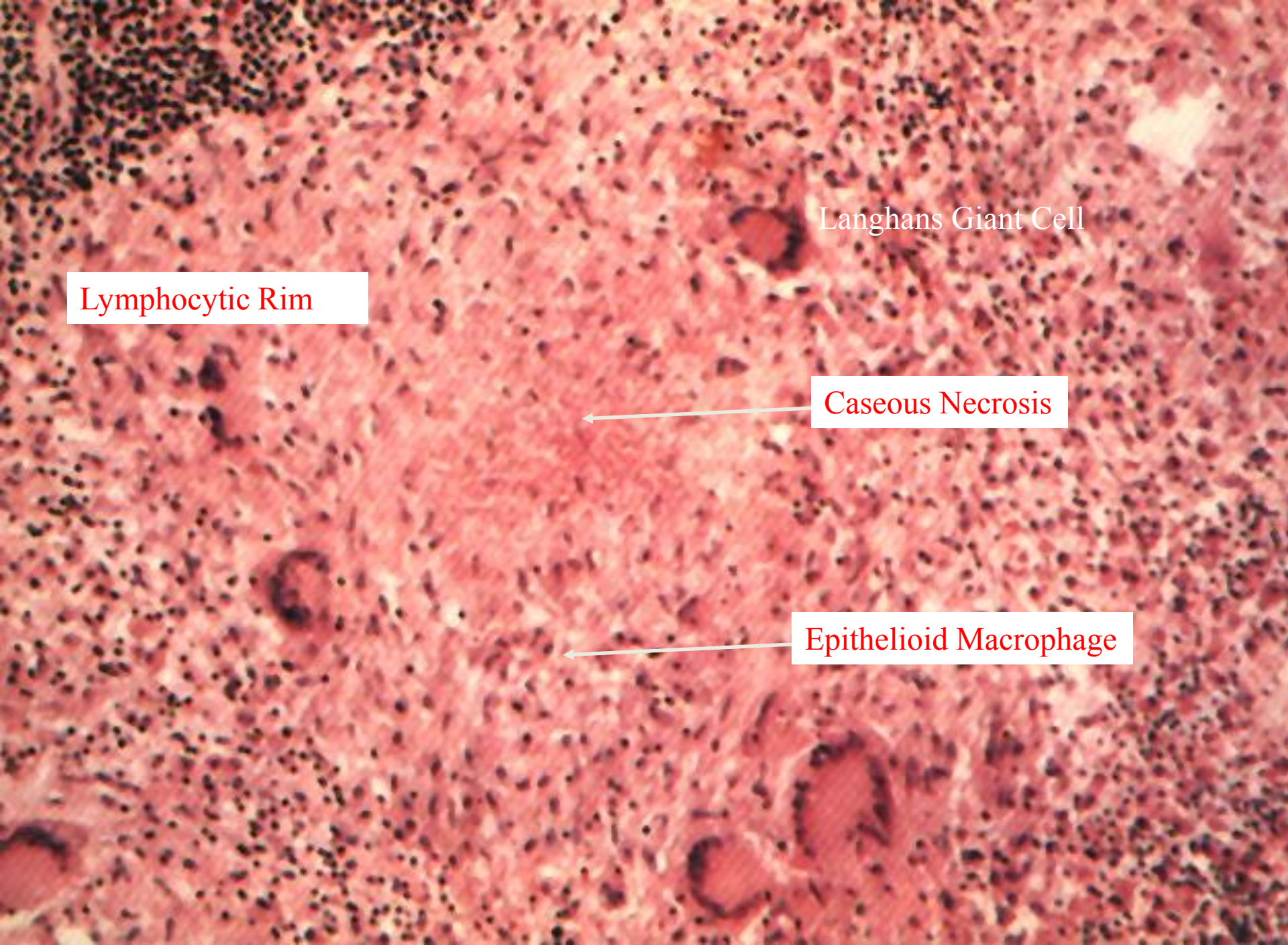
- A granuloma is a microscopic aggregation of macrophages that are transformed into epithelium-like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.
- Epithelioid cells fuse to form giant cells containing 20 or more nuclei.
- The nuclei arranged 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.



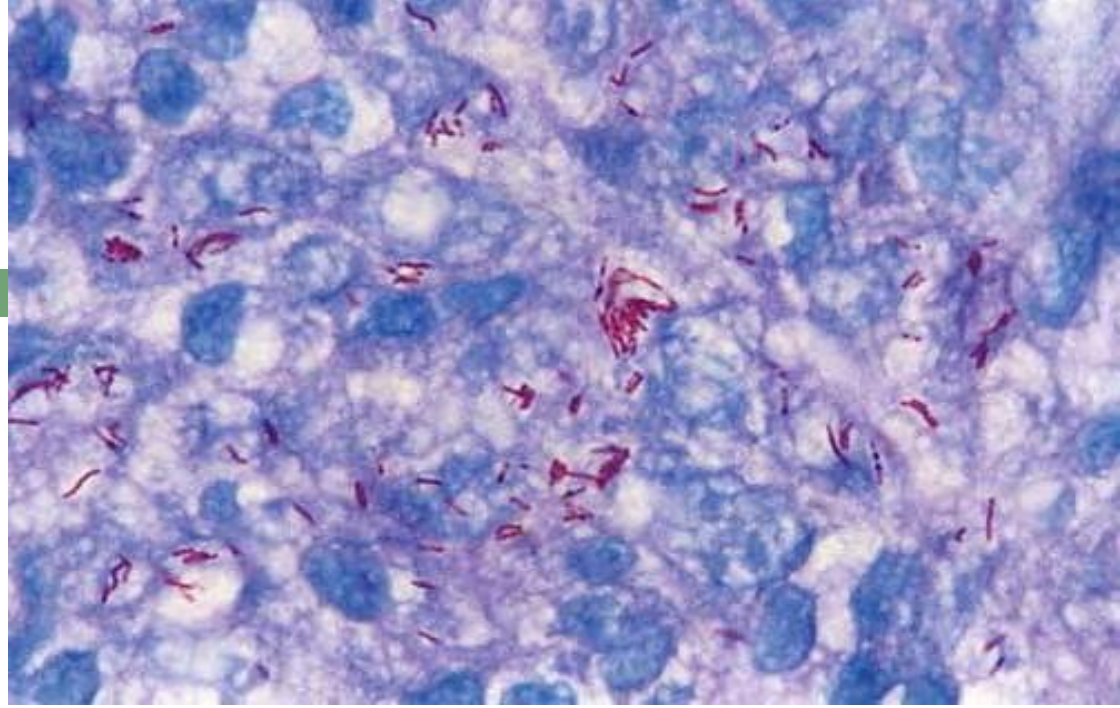
Nature Reviews | Microbiology

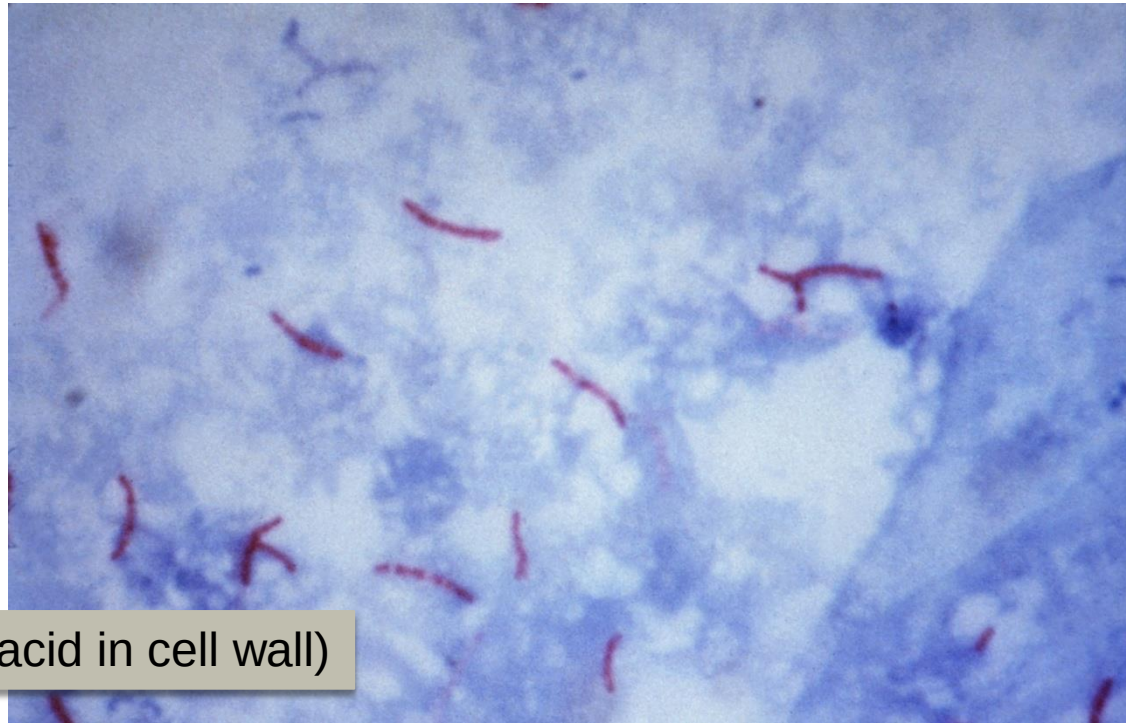


Granuloma: the predominant cell type is an activated **macrophage** with a modified epithelial-like (epithelioid) appearance. Also seen are l**ymphocytes,** multinucealted giant cells and occasional plasma cells.


Langhans Giant Cell
Lymphocytic Rim
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.





Acid-fast (due to mycolic acid in cell wall)

Pathogenesis

The steps in *M. tuberculosis* infection are:

1. Entry into macrophages phagocytosis mediated by several receptors expressed on the phagocyte, including mannose binding lectin and other receptors

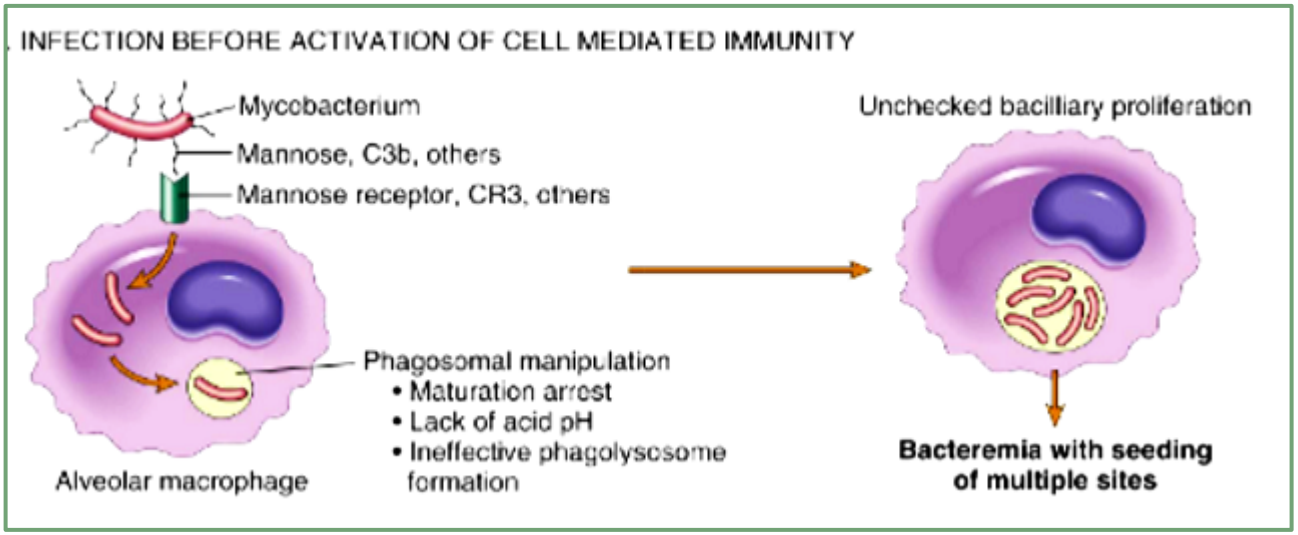
2. Replication in macrophages. *M. tuberculosis* inhibits maturation of the phagosome and blocks formation of the phagolysosome, protected from the microbicidal mechanisms of lysosomes.

The bacterium blocks phagolysosome formation, mechanism:

-Produces a protein (cord factor) that prevents fusion of lysosomes with phagosome

- inhibiting Ca^{2+} signals and the recruitment and assembly of the proteins that mediate phagosome-lysosome fusion.

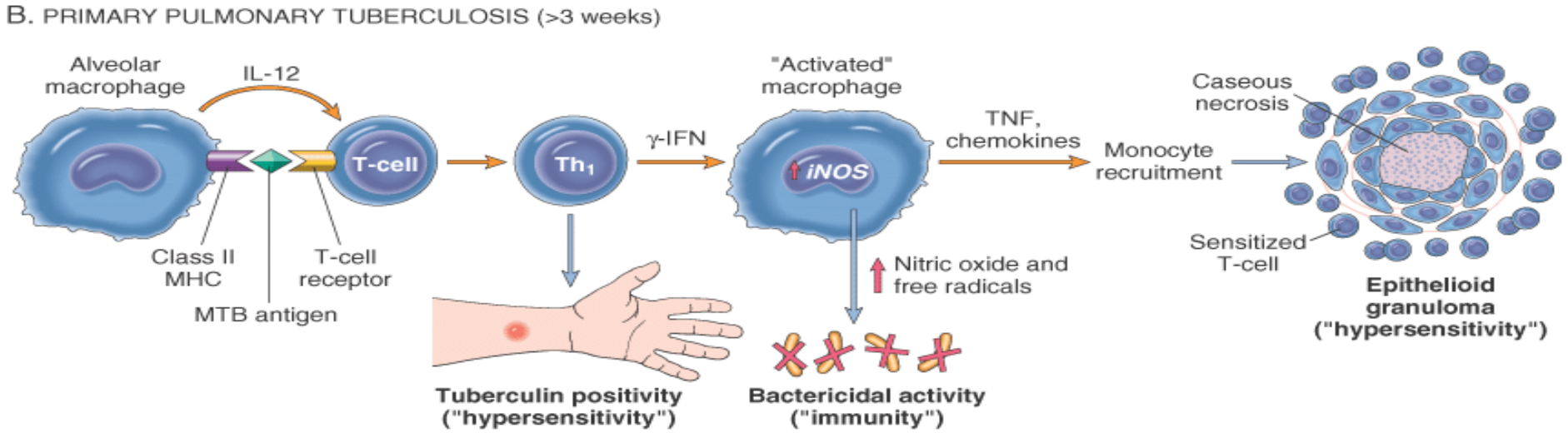
Pathogenesis of granuloma: *Replication in macrophages*



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 granuloma

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.



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

T_H1-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 granuloma
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 gaint cell)

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

Pathogenesis of granuloma

- *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 γδ T-cell receptor, also make IFN-γ.
- However, it is clear that T_H1 cells have a central role in this process, since defects in any of the steps in generating a T_H1 response result in absence of resistance and disease progression.

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, but the contribution of these associations to disease development is still under investigation.

Summary of Pathogensis

- 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

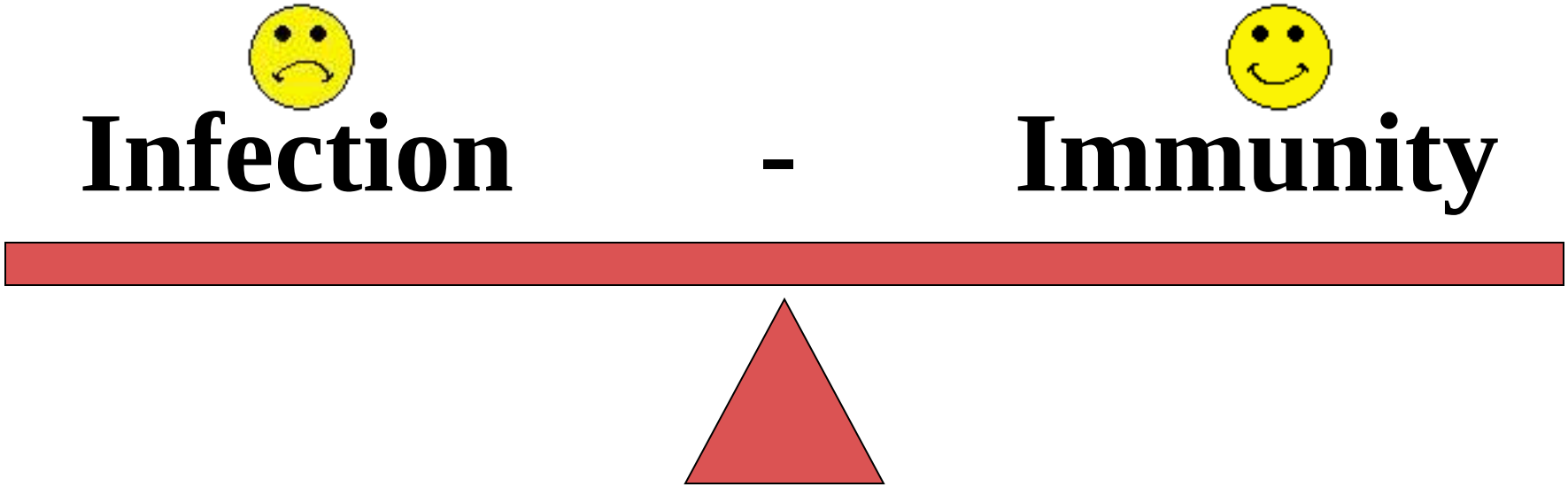
Route of transmission of TB

- 1. person-to-person transmission of airborne organisms from an active case to a susceptible host

Route of transmission of TB

- 2. 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 4 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.

- Not everyone who is infected develops clinical symptoms. Some patients have only an indolent, asymptomatic infection while in others TB is a destructive disseminated disease.

- Clinical tuberculosis is separated into three important pathophysiologic types:
  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

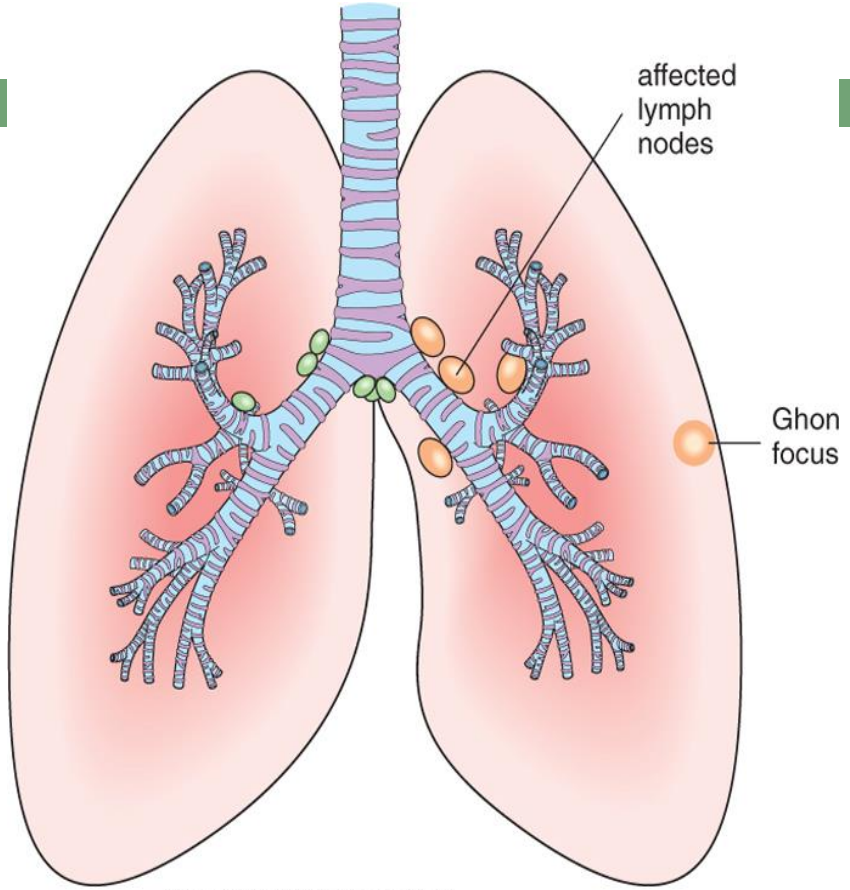
PRIMARY TB

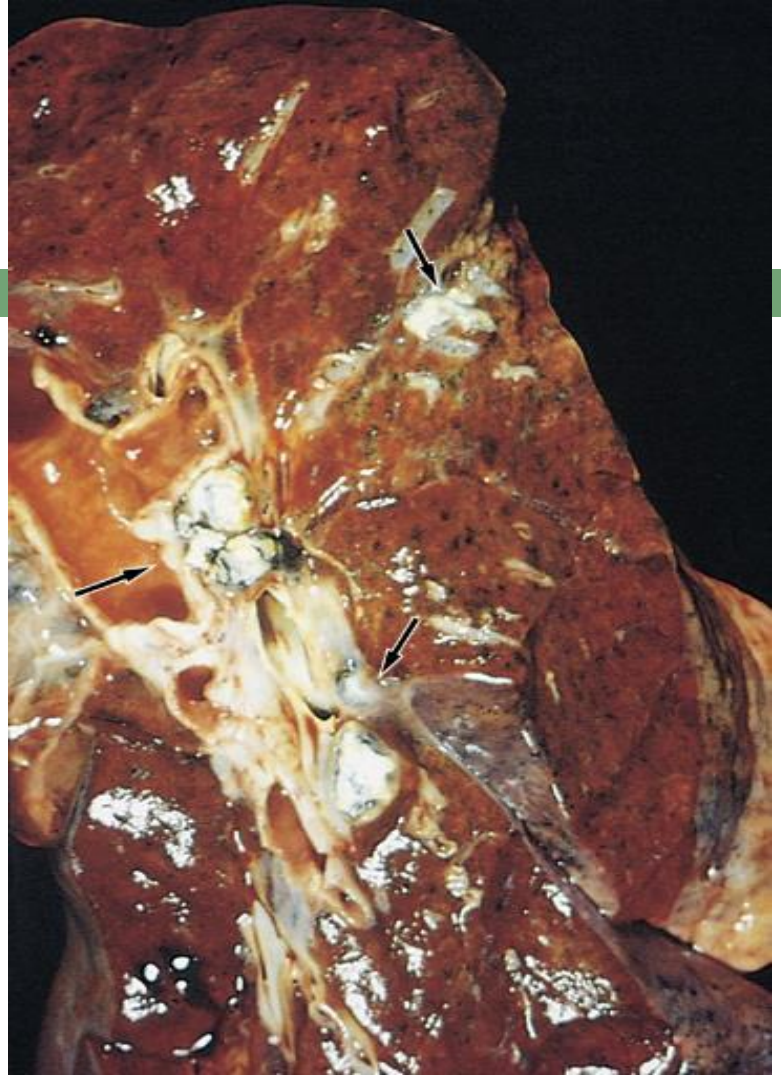
- Primary TB is a first exposure to tubercle bacilli. The inhaled organism is deposited in the alveoli. It is the form of disease that develops in a previously unexposed and unsensitized person.
- They are ingested by macrophages and they ellicit a type IV delayed hypersensitivity response to the tuberculous bacillus which elicit a cell-mediated immune response which will resists the growth and spread of the mycobacterium.
- In a immunologically competent person a granulomatous response in produced. It takes 5-6 days invoke granuloma formation which are usually formed by 3 to 4 weeks. In immunocompromised persons, granulomas are poorly formed or not formed at all.

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 medistinal 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.

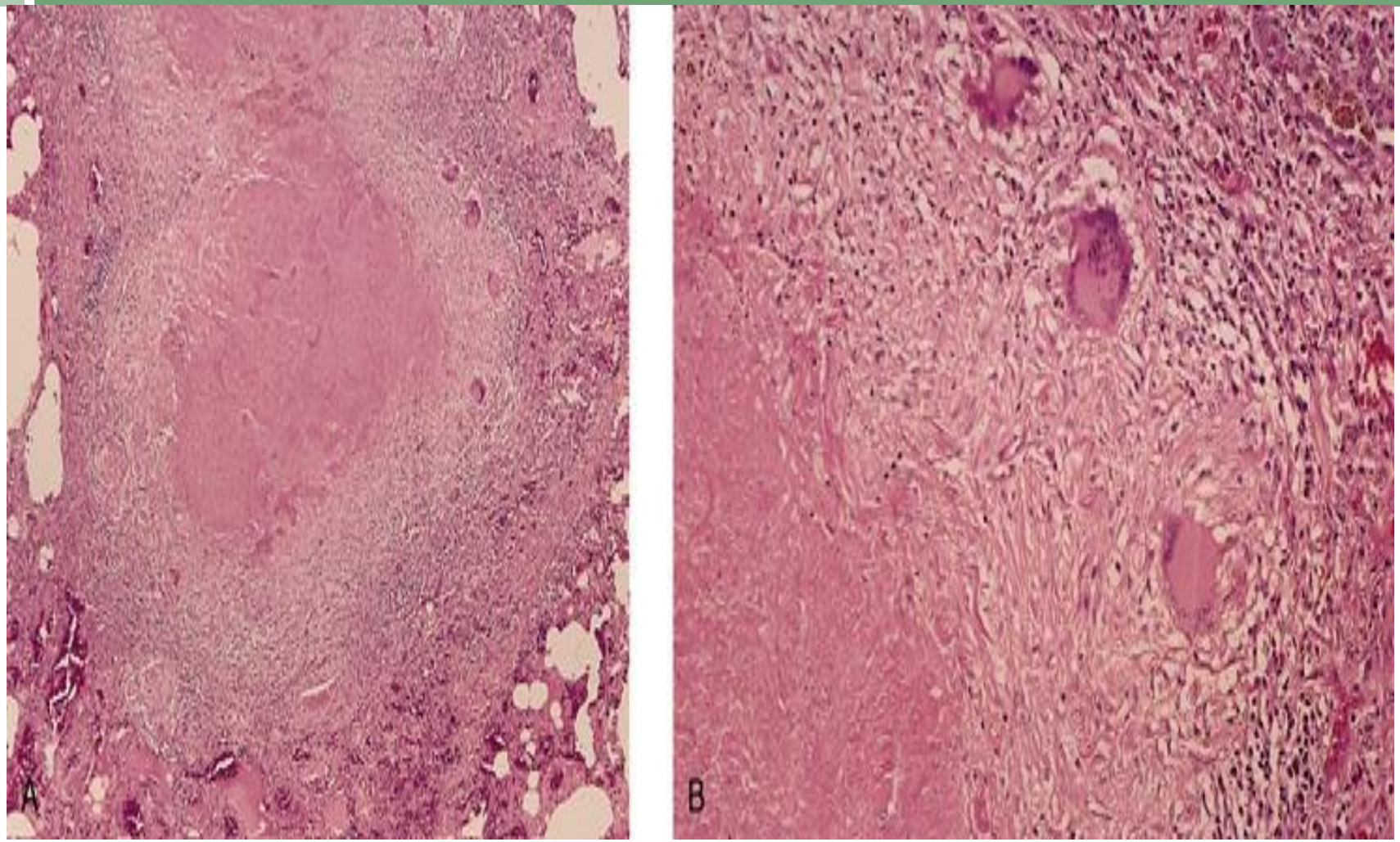
PRIMARY TUBERCULOSIS: Ghon Focus & Ghon complex





- 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

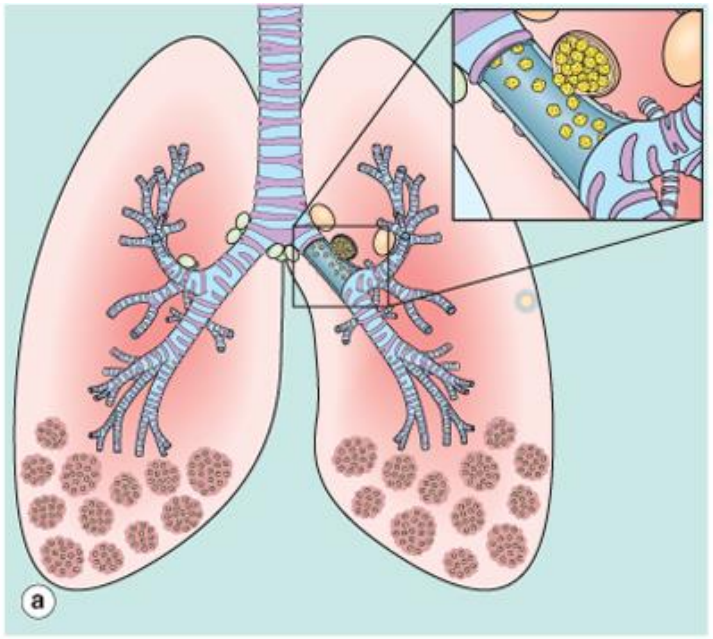
Caseating granulomas

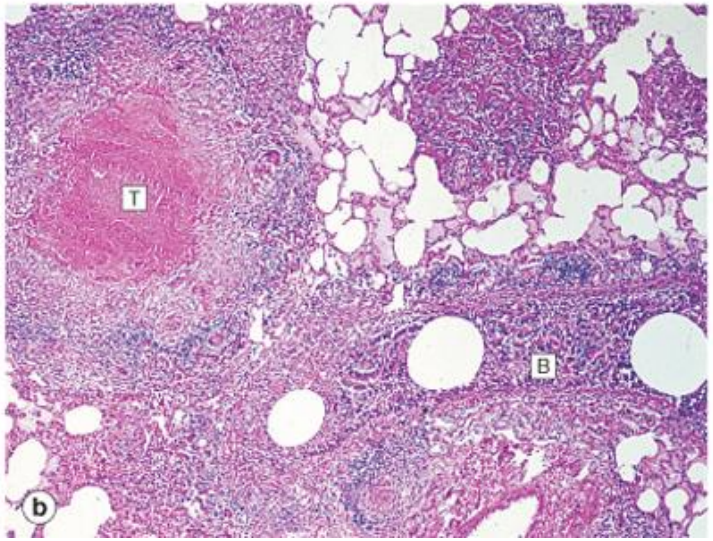


Possible sequalae of primary tuberculosis

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.

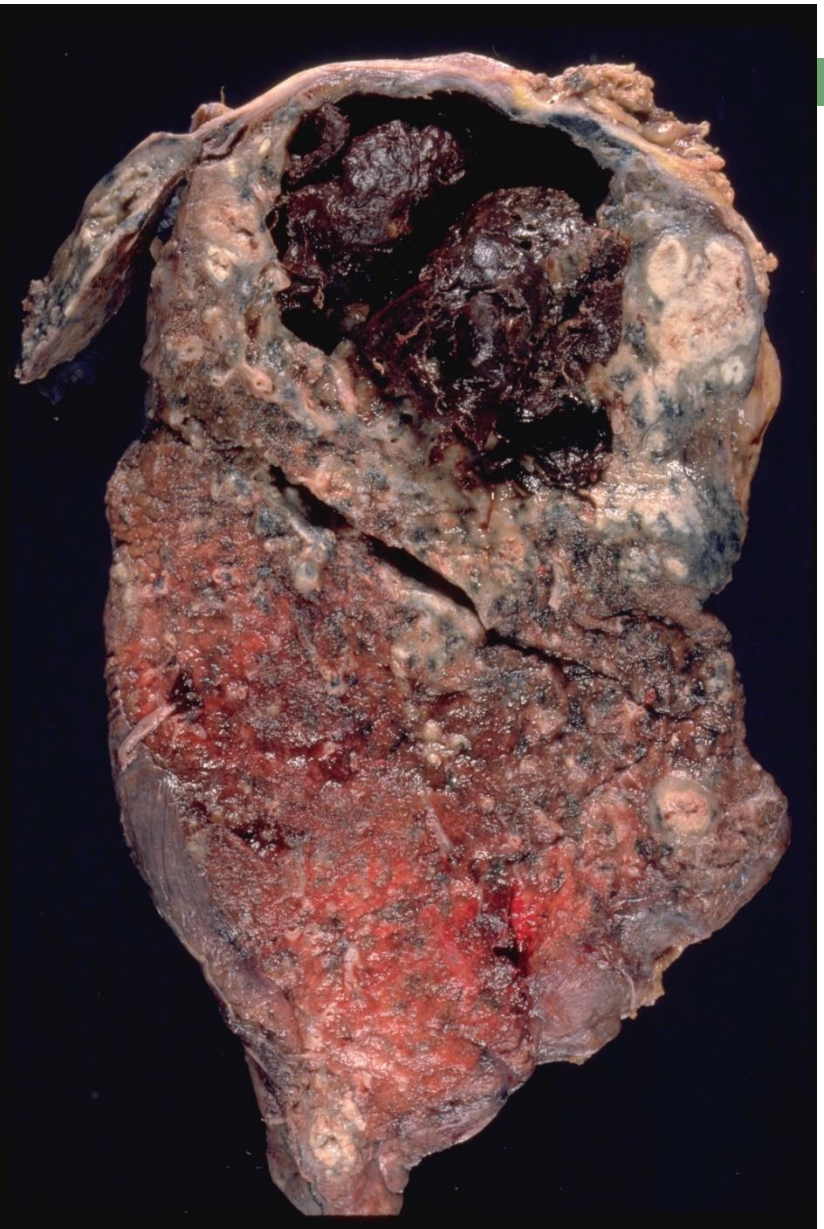
The mycobacteria in secondary TB may be either coming from:

1. A reactivation of dormant organisms from old granulomas (dormant primary lesion) many decades after initial infection when the host resistance is weakened (in a previously sensitized host). This is more common. Various conditions including cancer, chemotherapy, AIDS and old age predispose to the re-emergence of endogenous dormant M. Tuberculosis. It may develop even decades after primary infection.
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 areas with central caseation and cavitation 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 And foreign body type giant cells.

Scondary TB lung



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

Complications of TB

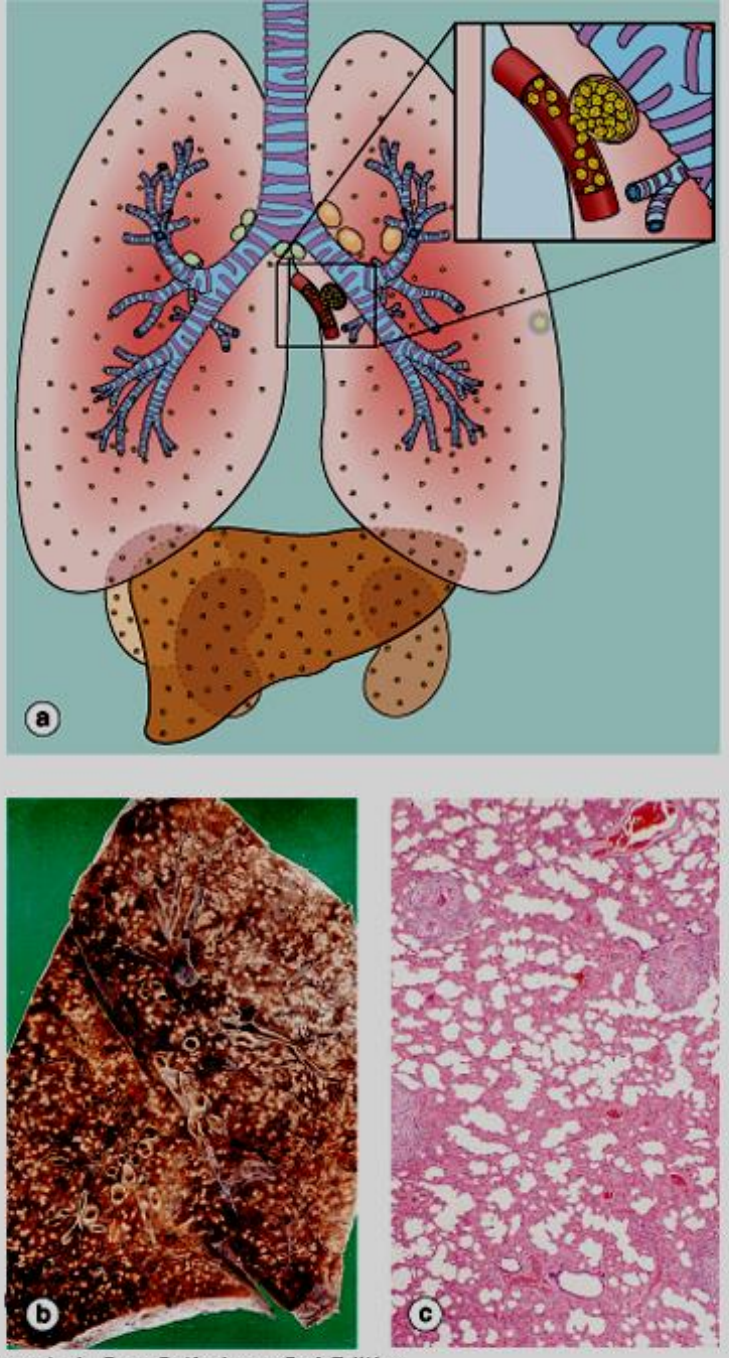
- Scarring: It can heal by fibrosis leaving a residual apical scar.
- Calcification (dystrophic)
- Local spread e.g. implantation of bacteria in the larynx leading to hoarseness or bronchial spread leads to bronchopneumonia
- Systemic spread/milary TB, via:
  - Vein – via left ventricle to whole body
  - Artery – miliary spread within the lung
- Pleural effusion (cause an exudative pleural effusion with a protein content of more than 30g/litre) fibrosis & adhesions
- Rupture of caseous lesion

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

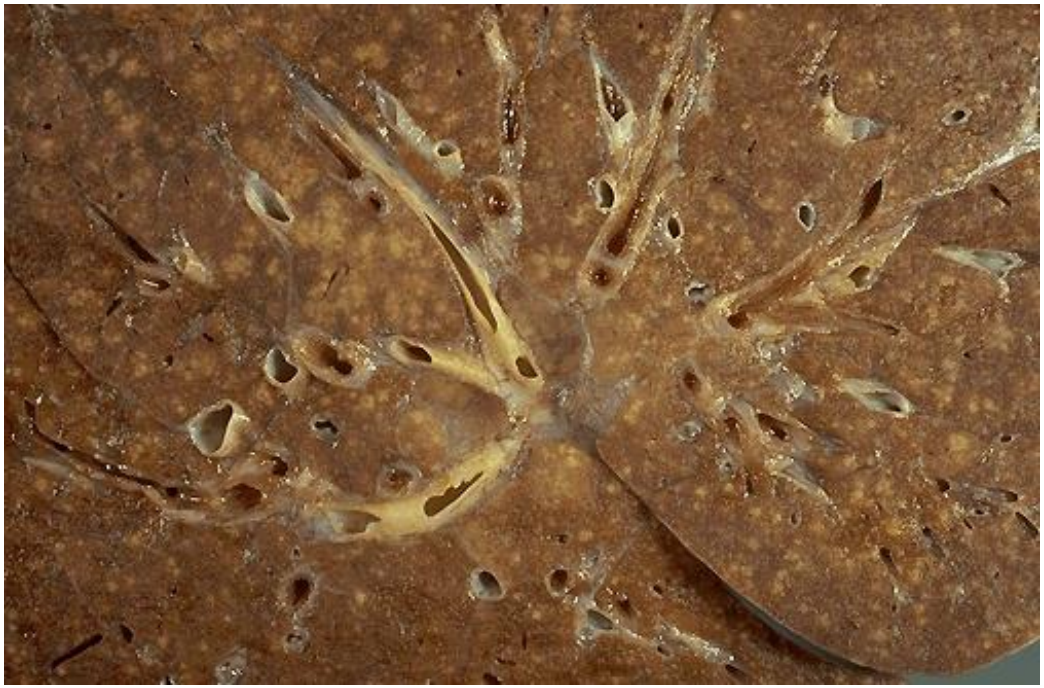
Systemic miliary tuberculosis

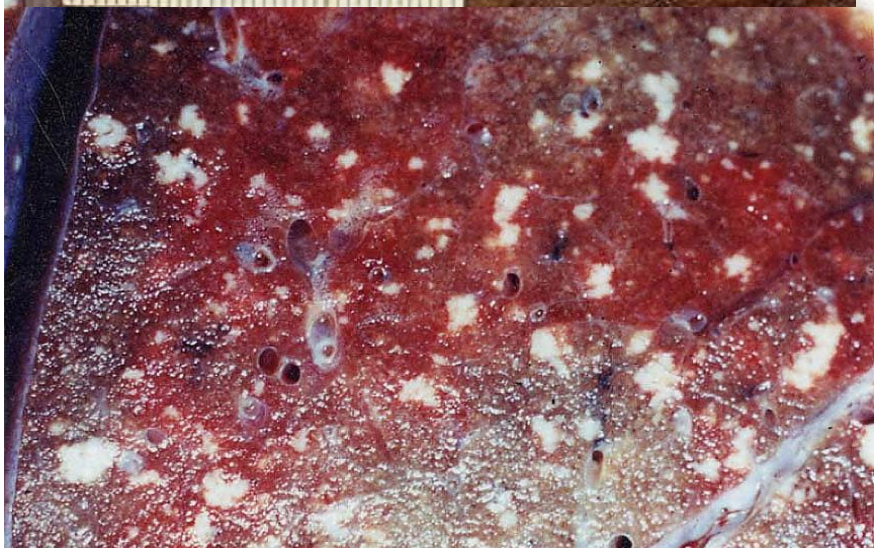
- It produces multiple small yellow nodular lesions in several organs. Almost every organ in the body may be seeded. Lesions resemble those in the lung.
- In the lungs there multiple lesions either microscopic or small, visible (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma.



Miliary TB

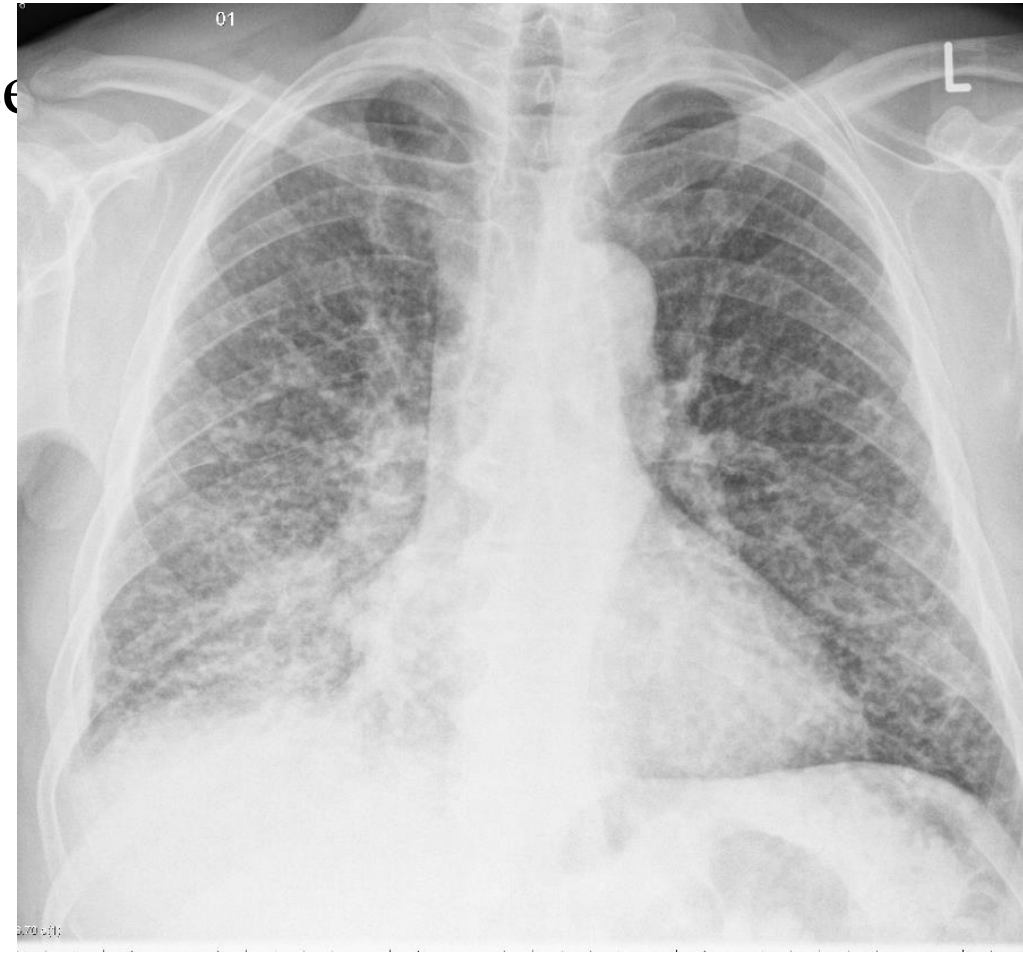
- Millet like – grain.
- blood or bronchial spread





Miliary TB

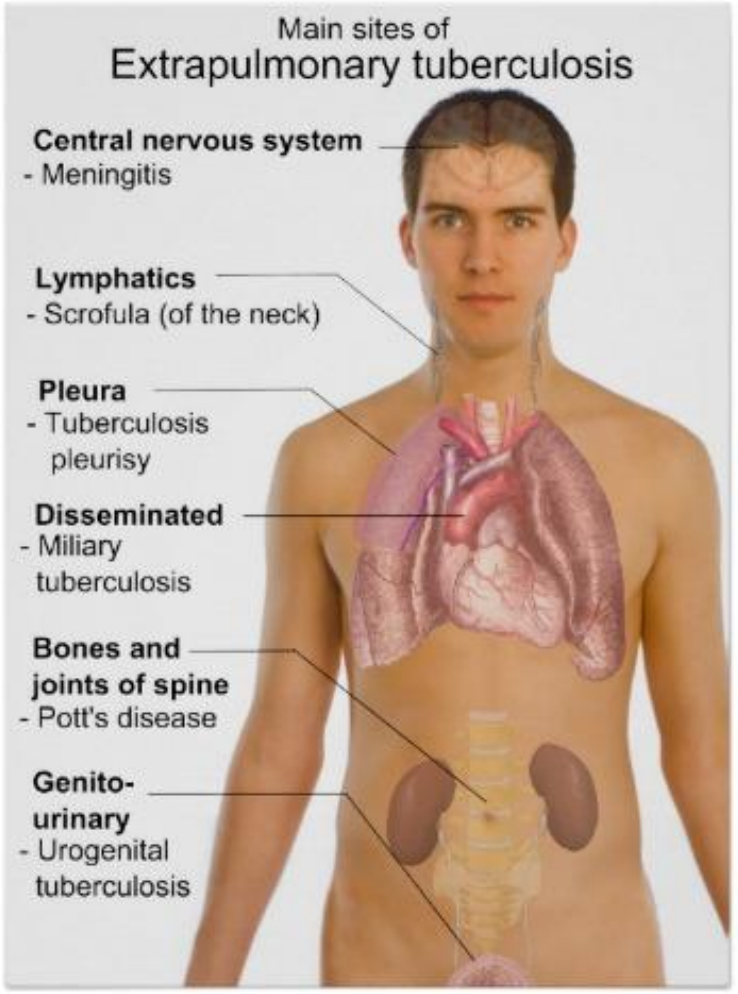
- Chest x-ray shows numerous small dense nodules each measuring 1 to 3 mm in diameter in both lung fields
- Patient present with weight loss, intermittent fever, productive blood-stained cough and night sweats.



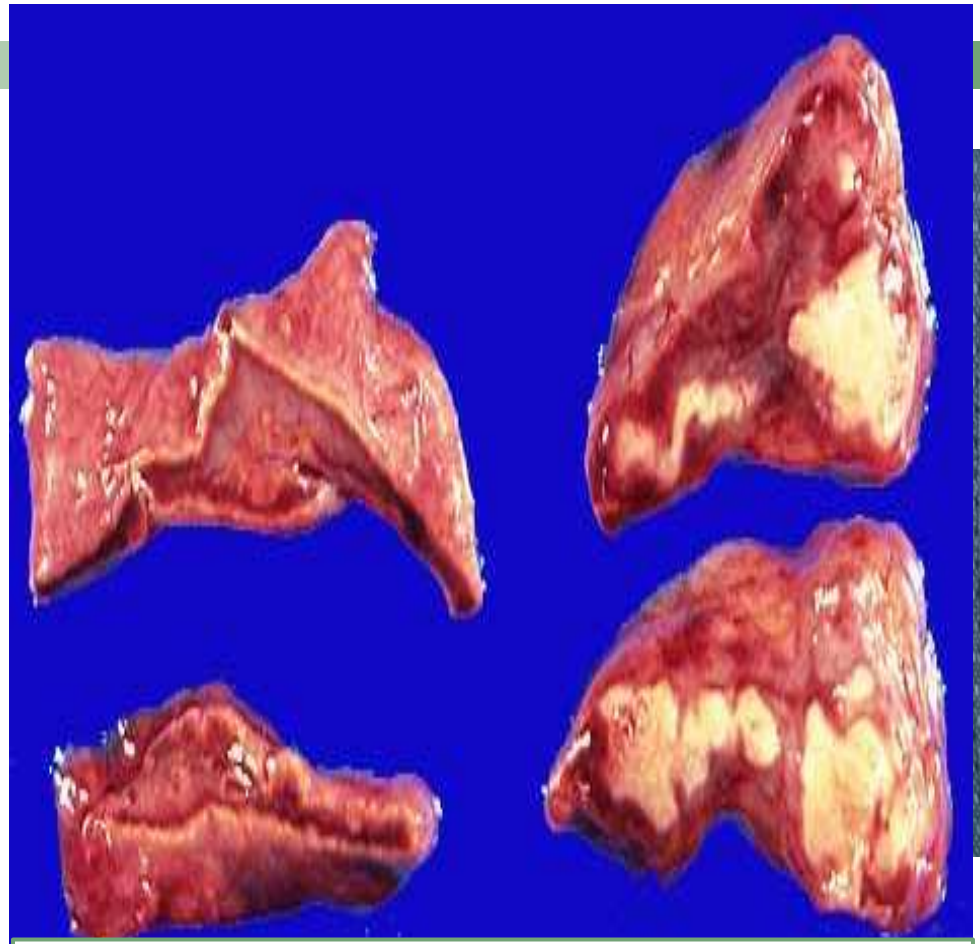
Extrapulmonary tuberculosis

May appear in any of the organs or tissues seeded hematogenously (as in milary TB) and may be the presenting manifestation of tuberculosis.

- Lymph nodes**/ tuberculous lymphadenitis** : are the most frequent form of extrapulmonary tuberculosis esp. in the cervical region ("scrofula").
- 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). 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
- **Intestinal tuberculosis** contracted by the drinking of contaminated milk. In developed countries today, intestinal tuberculosis is more often a complication of protracted advanced secondary tuberculosis, secondary to the swallowing of coughed-up infective material.

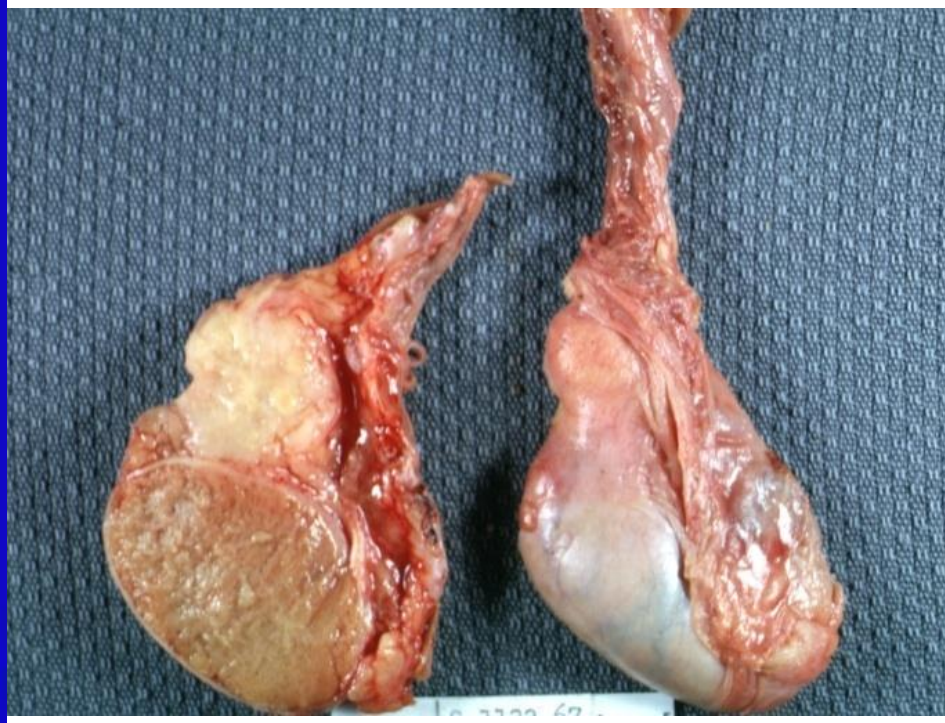


TB adrenal gland

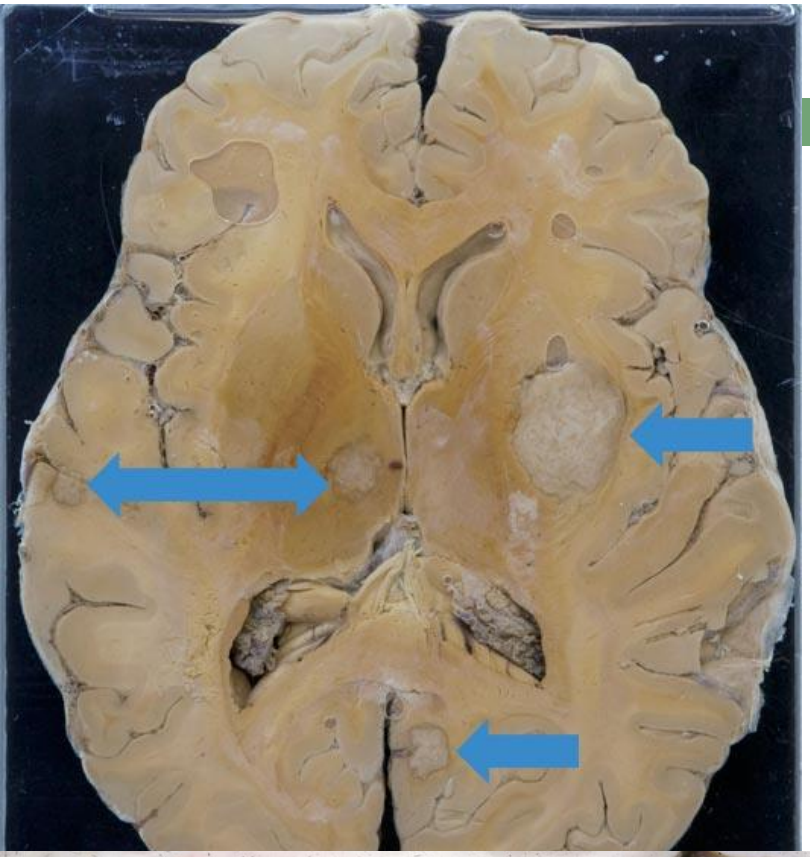


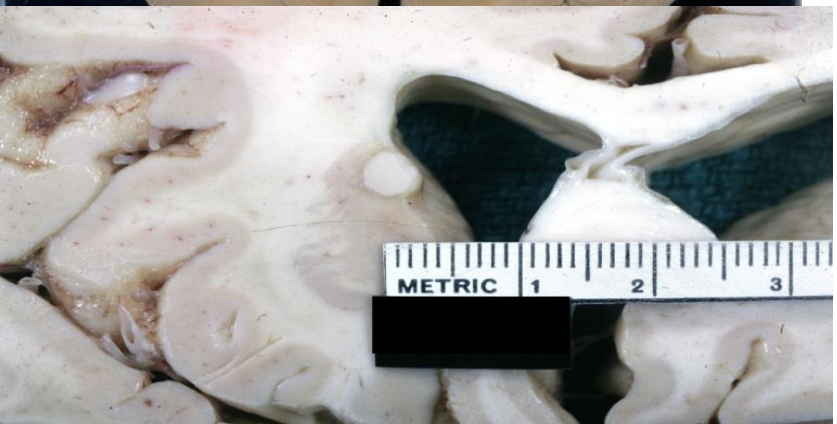
Tuberculous Addison's disease is still an important cause of primary adrenocortical insufficiency particularly in the developing countries.

TB epididymis

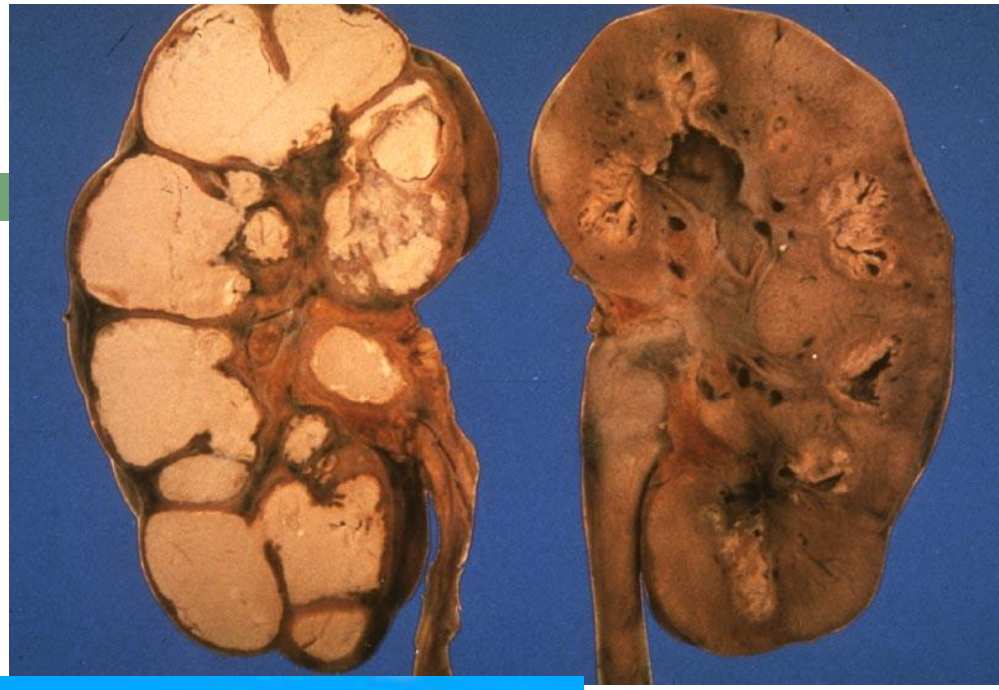


Tuberculoma





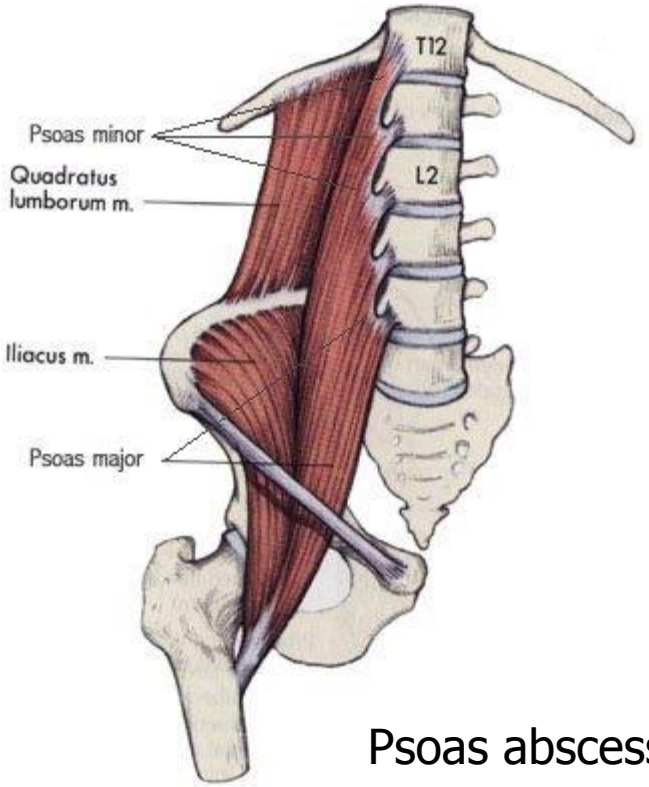
Renal TB



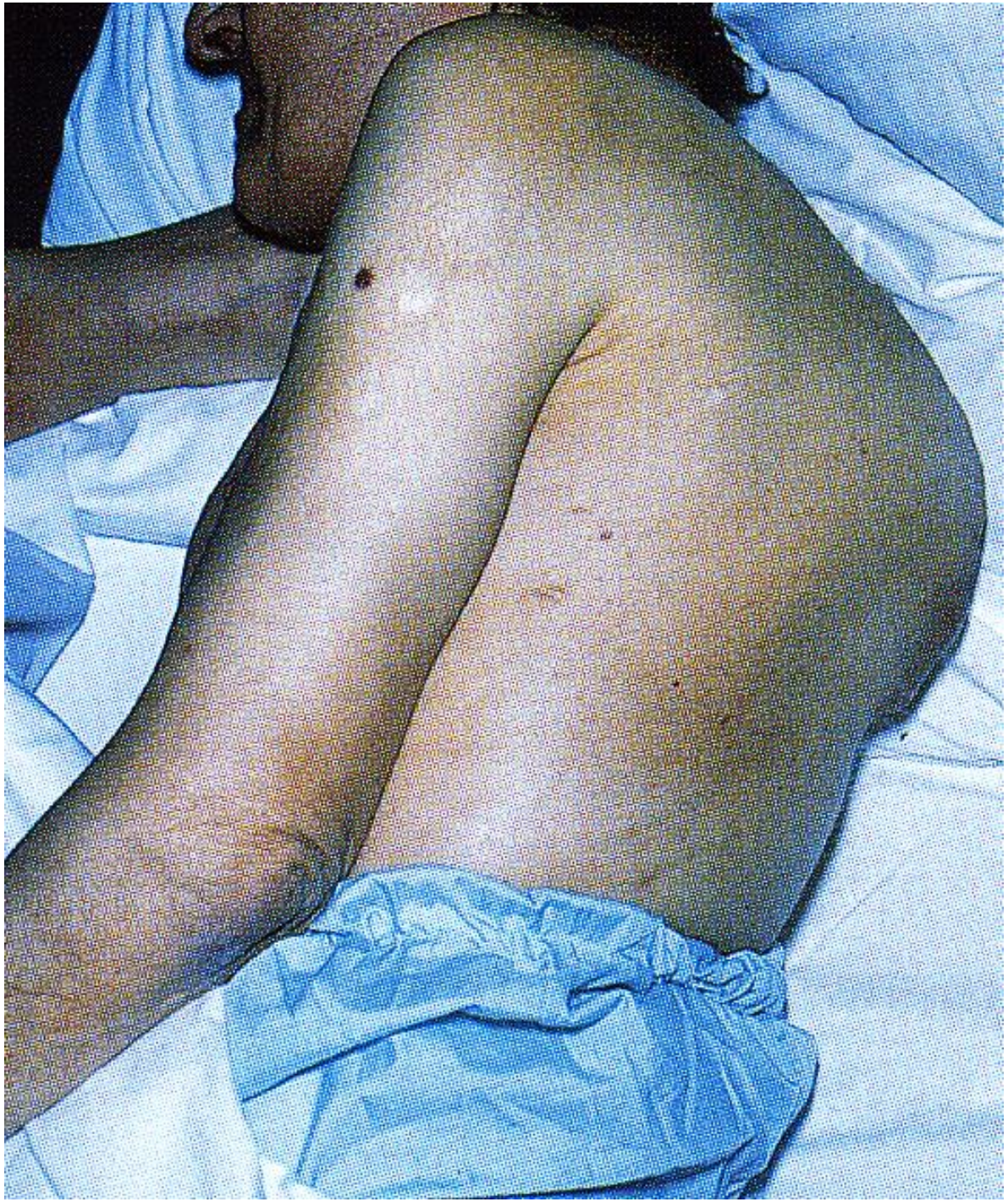
TB Vertebra

(Potts Spine)

Pott's disease



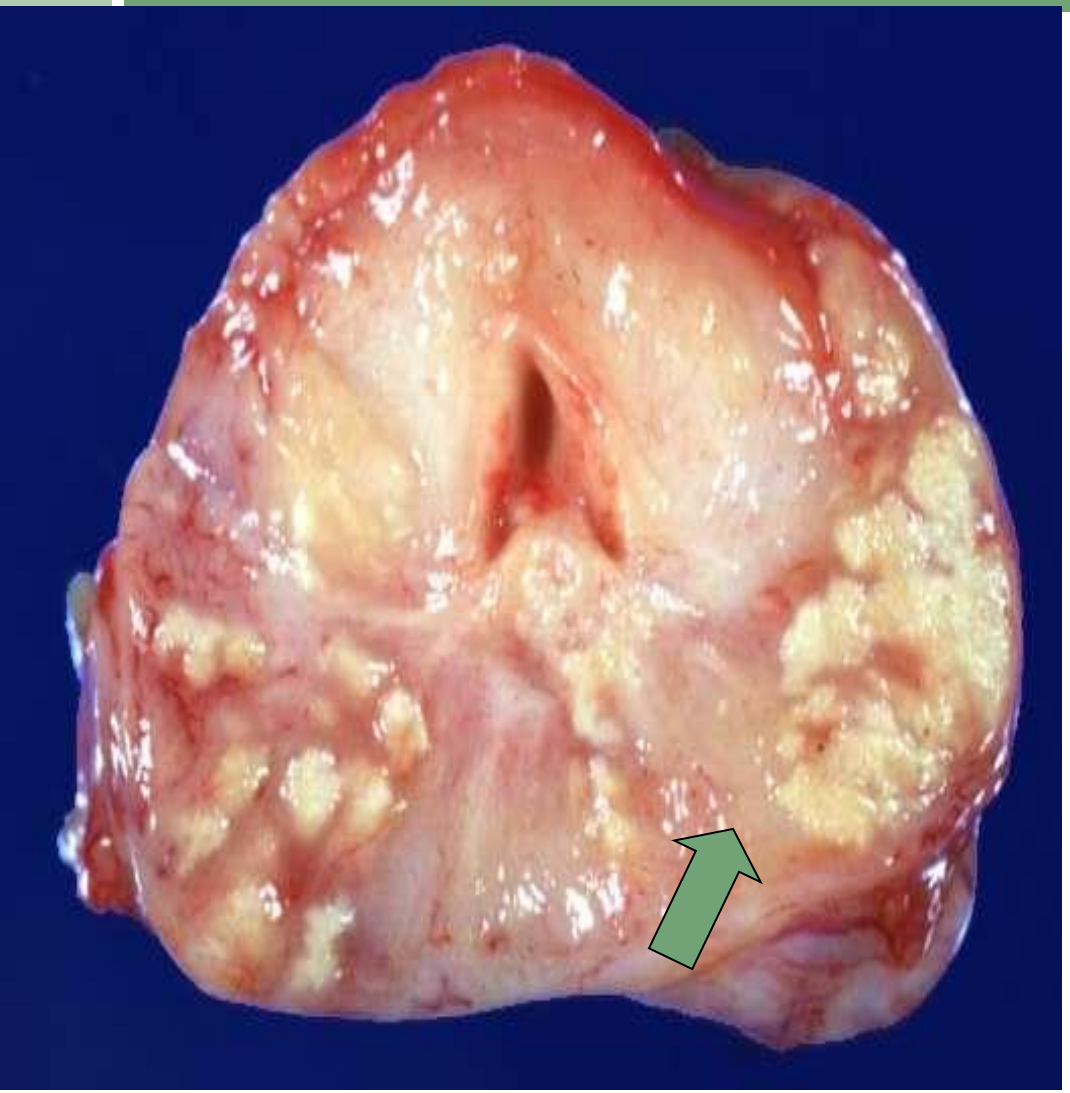
Psoas abscess



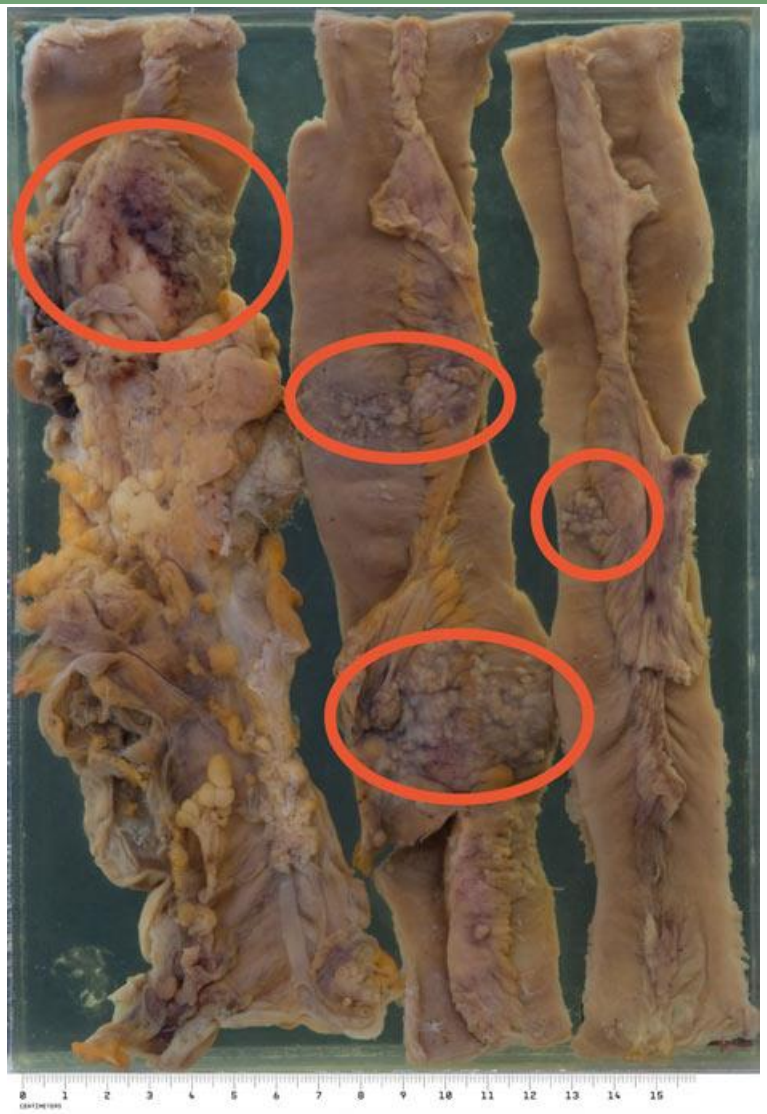
Pott's disease

kyphoscoliosis: Flexion (kyphosis) and lateral deviation (scoliosis)

TB Prostate gland



TB intestine

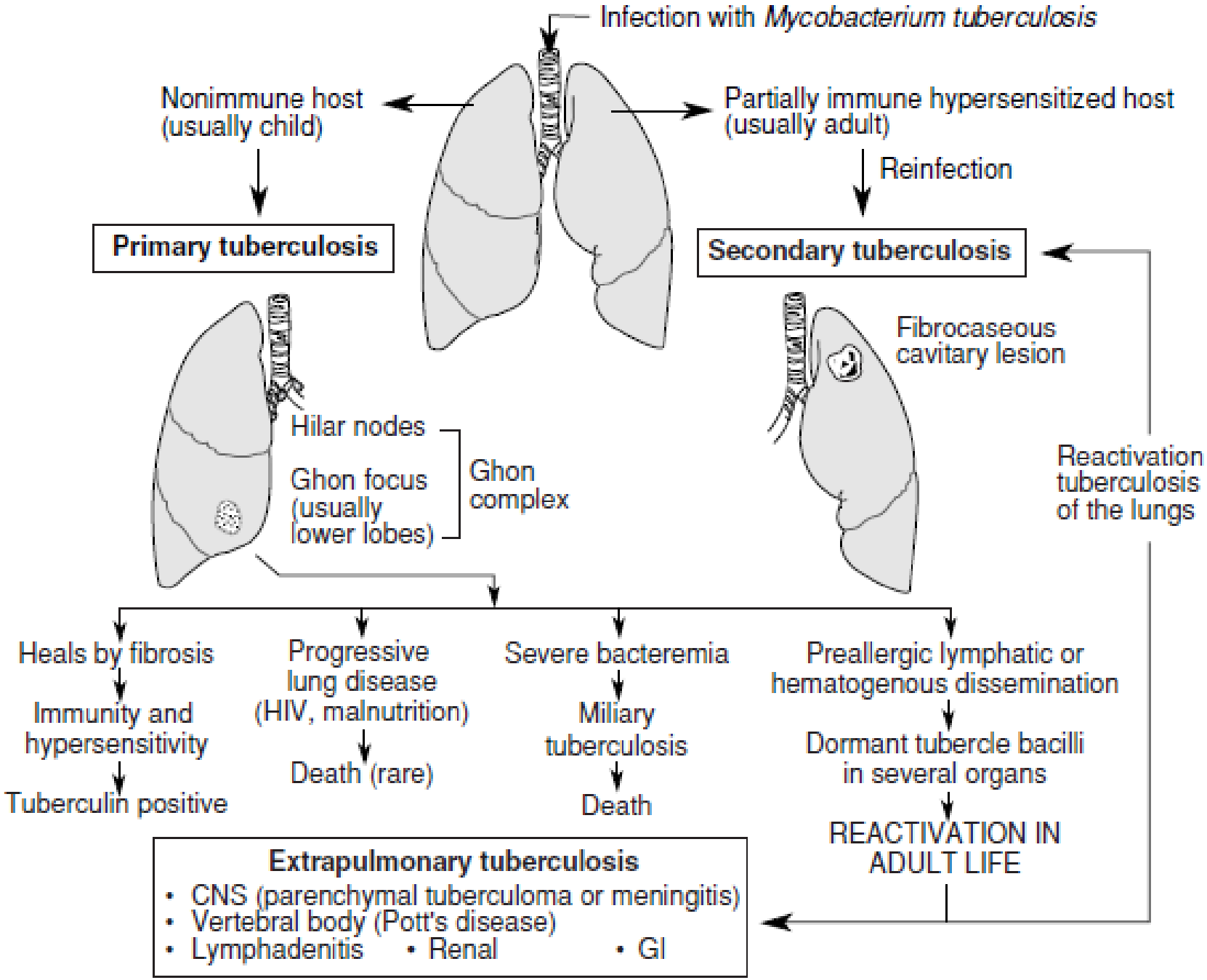


Prognosis

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


Infection with *Mycobacterium tuberculosis*
Nonimmune host (usually child)
Partially immune hypersensitized host (usually adult)
Reinfection
Primary tuberculosis
Secondary tuberculosis
Fibrocaseous cavitary lesion
Hilar nodes
Ghon focus (usually lower lobes)
Ghon complex
Reactivation tuberculosis of the lungs
Heals by fibrosis
Immunity and hypersensitivity
Tuberculin positive
Progressive lung disease (HIV, malnutrition)
Death (rare)
Severe bacteremia
Miliary tuberculosis
Death
Preallergic lymphatic or hematogenous dissemination
Dormant tubercle bacilli in several organs
REACTIVATION IN ADULT LIFE
Extrapulmonary tuberculosis
• CNS (parenchymal tuberculoma or meningitis)
• Vertebral body (Pott's disease)
• Lymphadenitis • Renal • GI