Team 435

PATHOLOGY

As a doctor you should know what can threaten your patient's life
should know what makes your patient suffers from pain

That's why you study pathology

Lecture 5

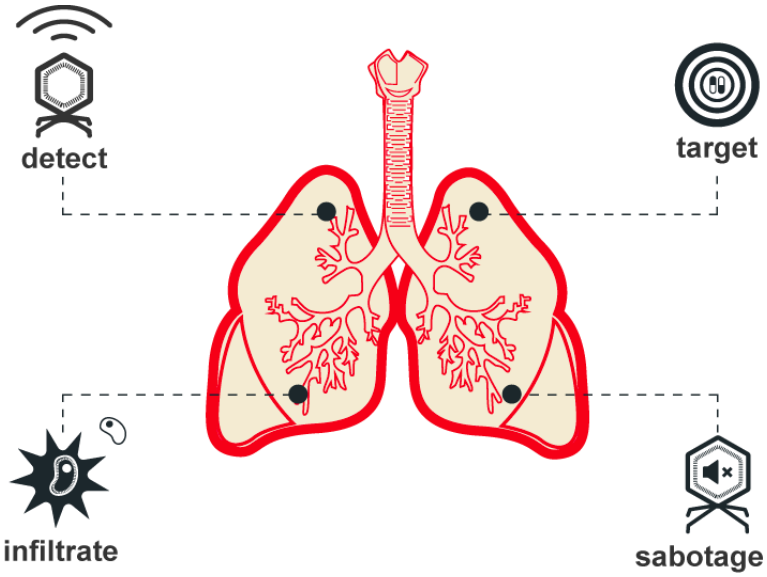
Lecture Five: (TB)

Objectives:

A- Define tuberculosis.
B- List the diseases caused by Mycobacteria.
C- Know the epidemiology of tuberculosis (TB).
D- List conditions associated with increased risk of Tuberculosis
E- List factors predisposing to extension of the infection.
F- Recognize the morphology of Mycobacteria and its special stain (the Ziehl-Neelsen) as well as the morphology of granulomas in TB (tubercles).
G- In regards to Mycobacterial lung infection: Compare and contrast the following in relation to their gross and histologic lung pathology:

1. Primary tuberculosis (include a definition of the Ghon complex).
2. . Secondary or reactivation tuberculosis.
3. Miliary tuberculosis

H- List organs other than lung that are commonly affected by tuberculosis.
I- Know the basis and use of tuberculin skin (Mantoux) test.
J- List the common clinical presentation of tuberculosis.
K- List the complication and prognosis of tuberculosis.



Introduction:

Chronic Pneumonias

Most often it's a localized lesion in an immunocompetent person, with or without regional lymph node involvement. There is typically granulomatous inflammation, which may be due to bacteria (e.g., M. tuberculosis) or fungi. In immunocompromised patients, such as those with debilitating illness, on immunosuppressive regimens, or with human immunodeficiency virus (HIV) infection. Tuberculosis is by far the most important entity within the spectrum of chronic pneumonias most common cause of death resulting from a single infectious agent.

Tuberculosis

As we all know by now, **tuberculosis** is a very important communicable[1] chronic granulomatous disease caused by *Mycobacterium tuberculosis.* It loves oxygen; so it usually involves the lungs but may affect any organ or tissue in the body. Typically, the centers of tubercular granulomas undergo ***caseous necrosis.***

[1] transmittable

Epidemiology:

It remains a leading cause of death. Tuberculosis flourishes[2] in poverty, crowding, chronic debilitating illness, the elderly, those with weakened defenses (eg. AIDS), minorities. Certain diseases also increase the risk of TB those include diabetes mellitus, Hodgkin lymphoma, chronic lung disease (silicosis), chronic renal failure, malnutrition, alcoholism, and immunosuppression. *However the single most important risk factor for the development of TB is HIV infection.*

Mycobacteria: (you should be able to recall most of this information)

Mycobacteria are **acid-fast bacilli** with a high content of complex lipids within cell wall that allow it to do the following:

- Readily bind the Ziehl-Neelsen stain and **resist decolorization**
- Live in harsh environments (within inflammatory cells/hot areas)

In addition to the high content of **glycolipids**, they also have a carbohydrate coat made up of mannose (sugar). Mycobacterium TB are aerobic in nature, they mainly invade areas of high oxygen content or high vascularization like the lungs, heart, kidney. In the lungs, they mainly stay in the upper and middle lobes in which the oxygen content is at its highest.

What could cause TB?

- M. tuberculosis hominis:

  Responsible for most cases of tuberculosis; the reservoir of infection typically is found in persons with active pulmonary disease, transmission is usually by direct inhalation.

- Mycobacterium bovis:

  Rare and most commonly seen in developing countries that sell unpasteurized milk (raw milk). causes Oropharyngeal and intestinal tuberculosis

- Mycobacterium avium complex:

  Less virulent than M. TB however can cause disease in 10%-30% of patients with AIDS.

[2] thrives/lives

Pathogenesis:

(We recommend understanding this from immunology as this may be a little confusing)

➔ Alveolar macrophage **receptors** will recognize and detect the mycobacterium.
[**How?** Well, like we've said mycobacterium TB have a coat made up of mannose, this receptor is called a mannose receptor and like it's name implies, detects mannose.]

➔ Macrophages engulf the mycobacterium but will not be able to kill it.
[**Why?** Because the organisms are able to inhibit normal microbicidal responses by preventing the fusion of the lysosomes with the phagocytic vacuole., leading to mycobacterial proliferation.]

➔ Engulfed mycobacterium will proliferate and multiply inside the macrophage.
[NRAMP1[3] gene abnormality might lead to progression of this disease without an effective immune response. Why? because it contributes to microbial killing]

➔ Escapes the macrophage and causes **bacteremia** (enters the circulation) (Takes 2-3 weeks)
[This is the earliest phase of primary tuberculosis (in the first 3 weeks) and it's characterized by bacillary proliferation with resulting bacteremia and seeding of multiple sites. Despite the bacteremia, most persons at this stage are asymptomatic or have a mild flu-like illness.]

➔ After 3 weeks, Body achieves **type 4** immunity (T cell mediated), **CD4** cells will recognize the TB and become activated $\mathbf{TH_1}$ cells. (IL-12 from macrophages may also help in this activation)
[**How does it achieve this?** The processed mycobacterial antigens will reach the draining lymph nodes and then will be presented to CD4 T cells by dendritic cells and macrophages.]

➔ **IFN-γ** which i secreted by CD4+ T cells of the TH1 subset activates macrophages.

➔ Macrophages then will release a couple of mediators such as:

- Other lymphokines such as **TNF which** helps in the transformation of macrophages and monocytes into **epithelioid**[4] **histiocytes** which aggregate and form a granuloma (characterize the granulomatous response)
- Inducible nitric oxide synthase (iNOS) gene, which results in **elevated nitric oxide levels** at the site of infection, with excellent antibacterial activity.
- Generation of **reactive oxygen species**, which can have antibacterial activity.

➔ Ending with local destruction and necrosis of the lung tissue.

In summary, immunity to a tubercular infection is primarily mediated by TH1 cells, which stimulate macrophages to kill bacteria.

[3] Natural resistance associated protein 1
[4] look like epithelial cells

Note that:

- The pathogenesis in an **unexposed immunocompetent** person is centered on the development of a targeted cell-mediated immunity that confers **resistance** to the organism and results in development of **tissue hypersensitivity** to tubercular antigens.
- Defects in any of the steps of a TH1 response (including IL-12, IFN-γ, TNF, or nitric oxide production) result in poorly formed granulomas, absence of resistance, and disease progression. Persons with inherited mutations in any component of the TH1 pathway are extremely susceptible to infections with mycobacteria.
- The pathologic features of tuberculosis, such as caseating granulomas and cavitation, are the result of the destructive tissue hypersensitivity that is part and parcel of the host immune response.

The necrotized tissue looks like a granular creamy cheese and is referred to as caseous necrosis, the caseous center is surrounded by **macrophages**, **multinucleated giant cells**, **fibroblasts**, and **collagen deposits**.

Bacteremia	Presence of bacteria in the blood without causing an infection
Septicemia	Proliferation of the bacteria within the blood causing an infection & activating a systemic immune response

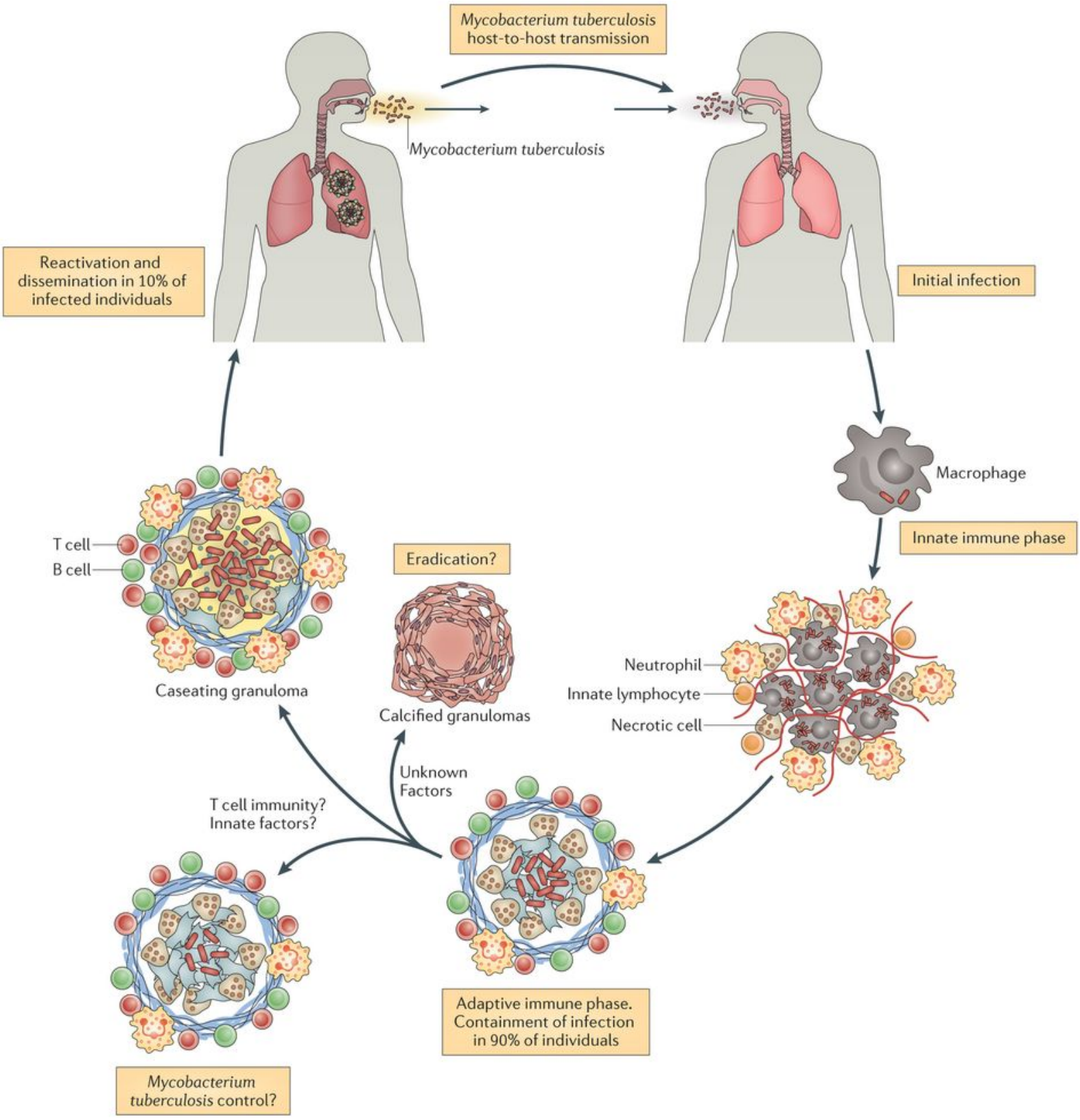
How can we differentiate between infection and disease?

It's very important for us to know the difference between them.
It is important that *infection* be differentiated from *disease.* Infection implies seeding of a focus with organisms, which may or may not cause clinically significant tissue damage (i.e., disease).

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

In most persons, an asymptomatic focus of pulmonary infection appears that is self-limited, although uncommonly, primary tuberculosis may result in the development of fever and pleural effusions.

Generally, the only evidence of infection, if any remains, is a tiny, telltale fibrocalcific nodule at the site of the infection.

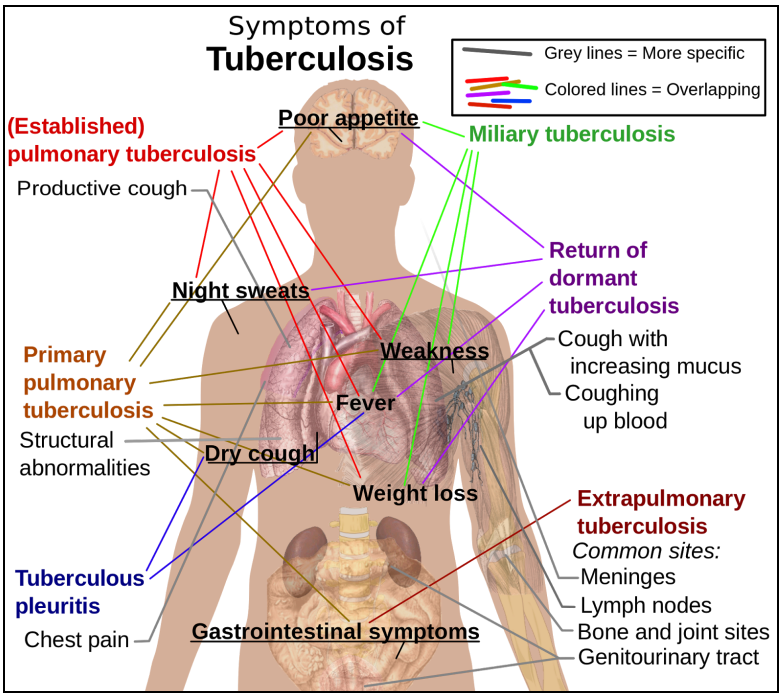

Mycobacterium tuberculosis
host-to-host transmission
Mycobacterium tuberculosis
Reactivation and dissemination in 10% of infected individuals
Initial infection
Macrophage
Innate immune phase
T cell
B cell
Caseating granuloma
Eradication?
Calcified granulomas
Neutrophil
Innate lymphocyte
Necrotic cell
Unknown Factors
T cell immunity?
Innate factors?
Adaptive immune phase. Containment of infection in 90% of individuals
Mycobacterium tuberculosis control?

Clinical Features:

Localized secondary tuberculosis may be **asymptomatic.** When manifestations appear, they are usually *insidious* in onset.

Symptoms:

In primary TB, mostly only immunocompromised patients will present with these symptoms (we will talk about this in the next page)



- **Systemic manifestations:**
  probably related to the release of cytokines by activated macrophages (e.g., TNF and IL-1), often appear early in the disease course and include:
  - **Chronic cough**: cough that lasts to three or more weeks
  - **Malaise**
  - **Night sweats:** fever
  - **Loss of weight**
  - **Anemia**
  - **Chills**
  - **Fatigue**
  - **Fever** (Commonly, the *fever is low grade*)

- **With progressive pulmonary involvement:**
  Increasing amounts of sputum, at first mucoid and later purulent, appear. When cavitation is present, the sputum will contain tubercle bacilli.

- Some degree of *hemoptysis* is present in about half of all cases of pulmonary tuberculosis.

- *Pleuritic pain* may result from extension of the infection to the pleural surfaces.

- Extrapulmonary manifestations of tuberculosis depend on the organ system involved (for example, tuberculous meningitis with headache and neurologic deficits, Pott disease with back pain and paraplegia).

The diagnosis of pulmonary disease is based in part on the history and on physical and radiographic findings of *consolidation or cavitation in the apices of the lungs.* Ultimately, however, *tubercle bacilli must be identified.*

Prognosis:

Generally is favorable if infection is localized to the lungs, but it worsens significantly when the disease occurs in aged, debilitated, or immunosuppressed persons, who are at high risk for the development of miliary tuberculosis, and in those with multidrug-resistant tuberculosis. Amyloidosis may develop in persistent cases.

Primary TB:

Primary tuberculosis is the form of disease that develops in a previously unexposed and therefore unsensitized patient. It almost always begins in the lungs.

In primary tuberculosis, the lesion likes to deposit peripherally/sub-pleurally in either:

- Lower part of the upper lobe
- Upper part of the lower or middle lobe

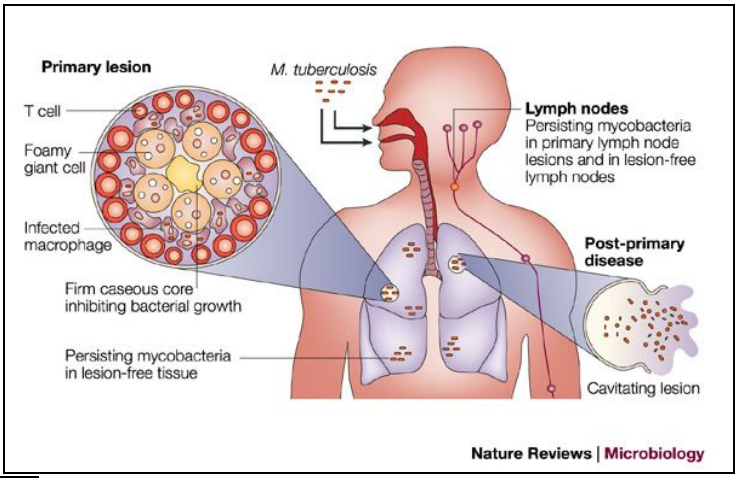
Patients are usually **asymptomatic** (or presented wild mild fever and malaise) in primary TB unless they are immunocompromised (patients with AIDs).

Morphology:

Primary TB is characterized by **Ghon's complex** which consists of: **Ghon's focus**[5], and **enlarged lymph nodes** with granuloma.

Development of cell-mediated immunity controls the infection. Hence, the Ghon complex undergoes progressive fibrosis, often followed by radiologically detectable calcification (Ranke complex), and despite seeding of other organs, **no lesions develop.**

On histologic examination, sites of active involvement are marked by a characteristic granulomatous inflammatory reaction that forms both caseating and noncaseating granulomas, which consist of epithelioid histiocytes and multinucleate giant cells.



[5] 1- to 1.5-cm area of gray-white inflammatory consolidation

Secondary TB:

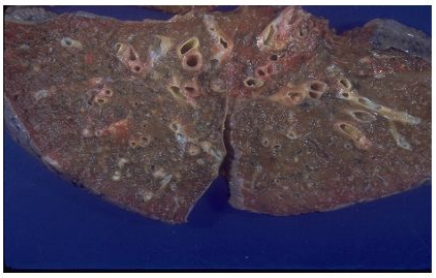
Secondary tuberculosis is the pattern of disease that arises in a previously sensitized host.

Overtime, patients could develop a 2nd infection because of either:

1. **Reactivation of the primary focus and flare up of the disease**:
   the bacteria would be dormant[6] and become reactivated by exposure to drug, or the development of a disease such as cancer.
2. **New infection:** re-exposure to a new TB after their first infection.

Here, the regional lymph nodes are **less prominently involved** early in the disease than they are in primary tuberculosis (because of preexistence hypersensitivity). On the other hand, cavitation occurs readily in the secondary form, leading to erosion into and dissemination along airways. Such changes become an important source of infectivity, because the patient now produces sputum-containing bacilli.

Secondary TB is usually localized in the **apex** of one or both lungs and occurs with less lymph node involvement. (Picture)



Morphology:

The initial lesion usually is a small focus of consolidation, within the **apical pleura.** It's sharply circumscribed, firm, and gray-white to yellow areas that have a variable amount of central caseation and peripheral fibrosis.

In favorable cases, the initial parenchymal focus undergoes progressive fibrous encapsulation, leaving only fibrocalcific scars.

Histologically, the active lesions show characteristic coalescent tubercles with central caseation.
(Although tubercle bacilli can be demonstrated by appropriate methods in early exudative and caseous phases of granuloma formation, it is usually impossible to find them in the late, fibrocalcific stages).

Localized, apical, secondary pulmonary tuberculosis may heal with fibrosis either spontaneously or after therapy, or the disease may progress and extend along several different pathways.

[6] inactive

Progressive pulmonary tuberculosis[7] may ensue. Thus, the fate of the eroding lesion in secondary TB could be one of the following:

1. **The patient becomes infectious (open TB):**
   Lesion will keep eroding until the bronchi and bronchioles, a secondary lesion will also develop in the trachea, pharynx, and (sometimes) larynx.

2. **Develop miliary TB:**
   Lesion erodes blood vessels through lymphatics → lymph nodes → oxygen poor veins → heart, the blood will return through the pulmonary artery to the lung and cause **miliary TB** in both lungs.

3. **Develop organ miliary TB (Systemic miliary TB):**
   Erodes through branches of artery, and can go to every organ in the body, such as the meninges, fallopian tube[8], or to the epidermis[9] .

   Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis

4. **Isolated-organ tuberculosis :**
   It may appear in any one of the organs or tissues seeded hematogenously and may be the presenting manifestation of tuberculosis.

   Organs typically involved include the meninges (tuberculous meningitis), kidneys (renal tuberculosis), adrenals, bones (osteomyelitis), and fallopian tubes (salpingitis).

   Pott's disease: spread arterially and could cause pott's disease which is TB in the vertebral column where we will get psoas abscess (cold abscess).

5. **Lymphadenitis:**
   It's the most frequent form of extrapulmonary tuberculosis, usually occurring in the cervical region ("scrofula").

6. **Intestinal tuberculosis:**
   In years past, contracted by the drinking of contaminated milk was fairly common as a primary focus of tuberculosis. Nowadays, it's more often a complication of protracted advanced secondary tuberculosis, secondary to the swallowing of coughed-up infective material.

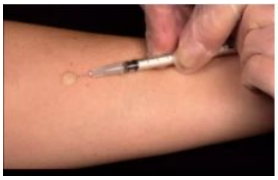
[7] the apical lesion enlarges with expansion of the area of caseation
[8] What happens when it goes to the fallopian tube?
TB causes chronic inflammation → we get fibrosis → obstruction → infertility
[9] What happens when it goes to the epidermis?
It will cause pus, granuloma, and caseation in that area.

Vaccines and tests:

➔ **BCG vaccine:**

We inject weakened mycobacterium TB to produce cellular immunity against test

➔ **Mantoux test** (also known as: tuberculin skin test/bubble test):



It's a test that replaced the old *Heaf* skin test, we intradermally inject 1-2ml of tuberculin protein derivative and read the test after 72h.

It's used to know if the patient has been exposed to the bacteria before or not; it only indicates previous exposure to the bacteria.

❑ **Positive:**

If the T cells recognizes it, it will become *excited* and will release chemokines and call in more macrophages leaving the injected area with a "**bubble**".

❑ **Negative:** If the T cells do not recognize it, the site of injection will remain **flat**.

Flaws: [10]

- **If our patient has taken the BCG vaccine** (most developed communities), **the test will be positive thus making it useless in developed countries.**
- **If our patient has AIDS the test will almost always be negative even if he has TB.** This is because they have very few TH cells to react with the antigen.

➔ **AFB/Ziehl neelsen and Auramine stain:**

After taking the specimen, we either use Ziehl Neelsen method or the auramine stain. Auramine stain involves staining the antibody with an **immunofluorescence** dye and then reacting it with the antigen of the bacteria, if a reaction occurs then it's **positive**.

➔ **Lowenstein-Jensen (LJ) medium:** culture for 2-12 weeks.

➔ **Polymerase chain reaction (PCR):**

A molecular genetics test that recognizes the DNA of the bacteria via molecular means, it's a highly sensitive.

[10] مشاكل

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قال صلى الله عليه وسلم: من سلك طريقاً يلتمس به علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.