Tuberculosis

@pathology434

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.

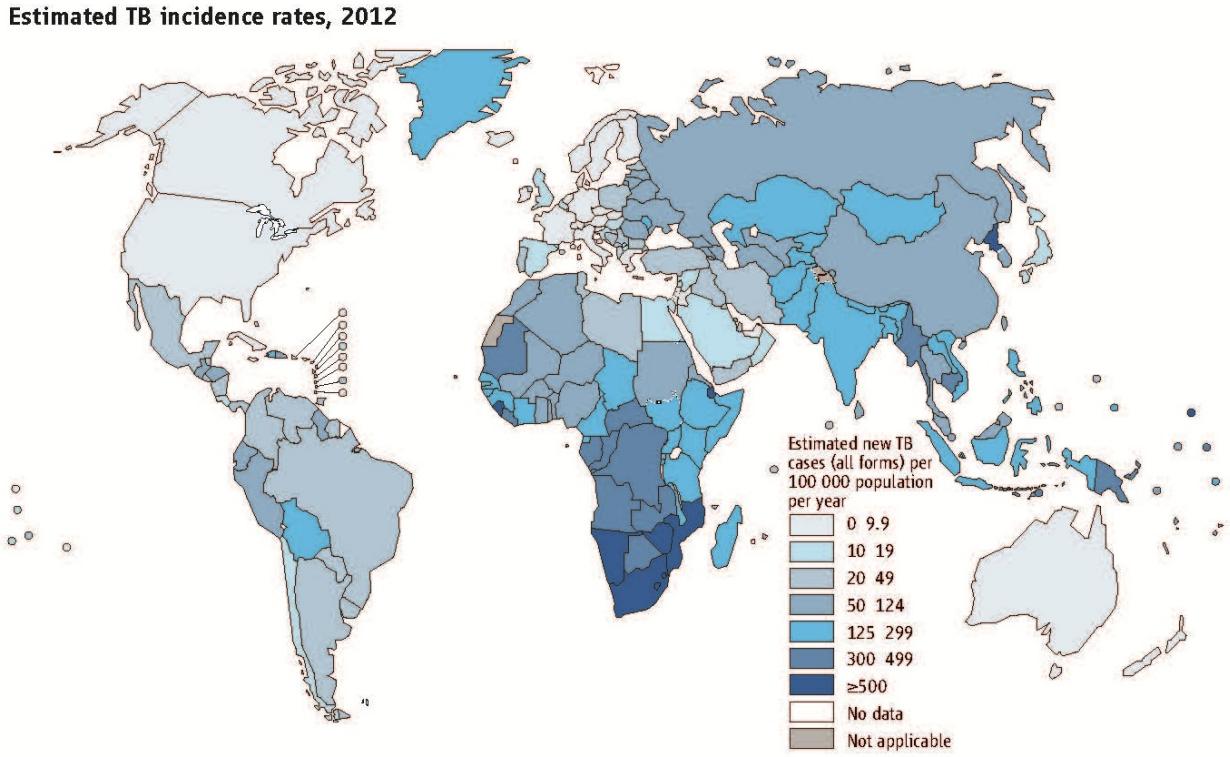
Important note: During the previous blocks, we noticed some mistakes just before the exam and we didn't have the time to edit the files. To make sure that all students are aware of any changes, please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: **Pathology Edit**

Introduction.

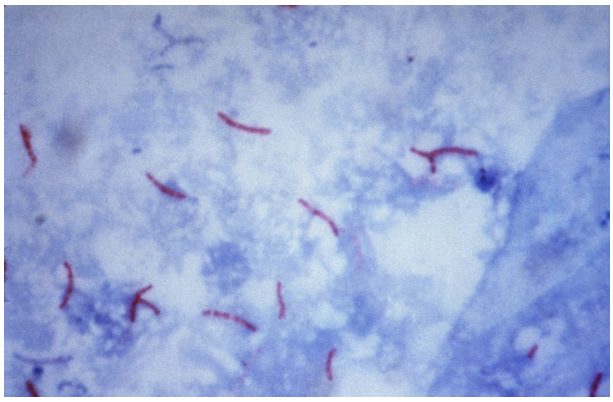
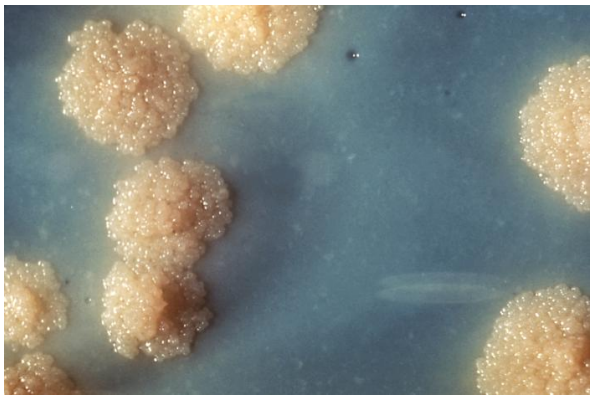
Tuberculosis is a communicable chronic granulomatous disease caused by ***Mycobacterium tuberculosis***. It usually involves the lungs but may affect any organ or tissue in the body. Typically, the centers of tubercular granulomas undergo ***caseous necrosis***.

Tuberculosis is an incredibly invasive disease, it is considered to be one of the major endemic diseases in the kingdom, particularly involving the elderly, AIDS patients, and the urban poor.

- Despite getting the BCG vaccine, some may develop tuberculosis now the reason behind this is yet unknown, it could be due to a decrease in immunity over a long period of time.



Let's take a close look to the bacteria!

The mycobacterium tuberculosis is an *acid-fast bacilli*, which resists decolourization with acid alcohol, due to the presence of lipids within their cell walls. This high lipid content makes them acid-fast on staining; it also allows them to live in harsh environments such as:
1) Within the inflammatory cells: as it multiplies inside macrophages
2) Sun/heat - harsh conditions.

The bacteria are rich in ***glycolipids***, it also has a carbohydrate coat made up of mannose - which is a sugar -. Mycobacterium tuberculosis is ***aerobic*** in nature, it mainly invades areas where the oxygen content is high and/or areas of high vascularization like the lungs, heart, kidney..etc. In the lungs, it mainly stays in the upper and middle lobes where the oxygen content is at its highest.

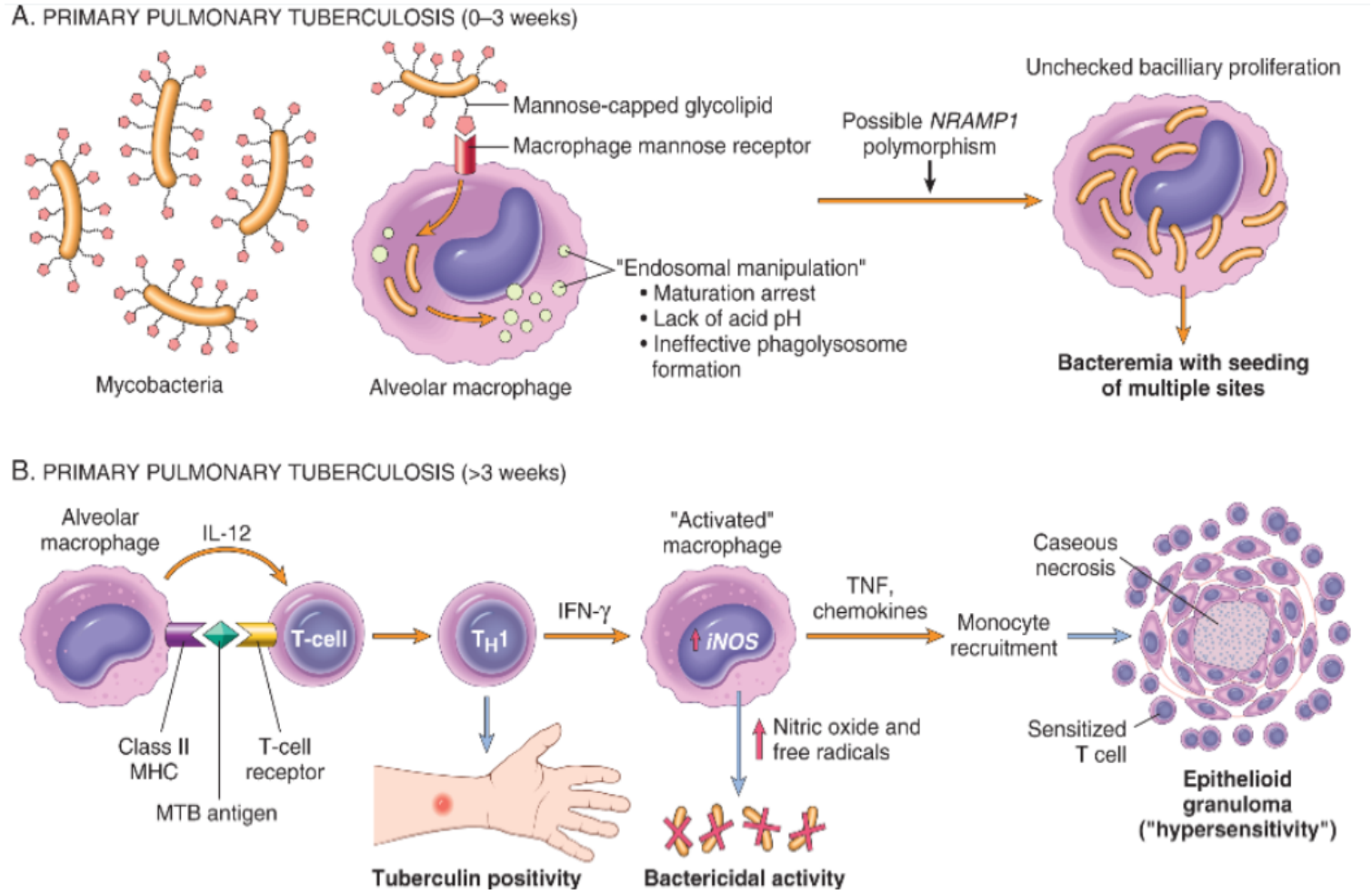
How does the bacterium enter?

M.*tuberculosis hominis* is responsible for most cases of tuberculosis the reservoir of infection are humans, transmission usually is direct by inhalation of airborne.
Mycobacterium bovis also causes tuberculosis in human. M. *bovis* is found in cow's milk, which unless pasteurized, can cause *gastrointestinal tuberculosis* in human.

Pathogenesis:
1: alveolar macrophages recognize it (a process mediated by several macrophage receptors, including mannose receptor, that recognize a substance on the wall of M.*tuberculosis* is called, Mannose)
2: macrophages engulf it but it can not kill it, usually M.*tuberculosis* proliferate and multiply inside the macrophage, because of the abnormality in (NRAMP1) gene.
3: then it go out and cause bacteremia .

Differences between bacteremia and septicemia?
Septicemia: proliferation of the organism within the blood causing an infection & activating a systemic immune response. (this is never the case in T.B)
Bacteremia: presence of the bacteria within the blood, however it ***does not*** cause an infection in contrast to septicemia. Brushing teeth could cause transient & harmless bacteremia.

CMI (Cell Mediated Immunity) in T.B.

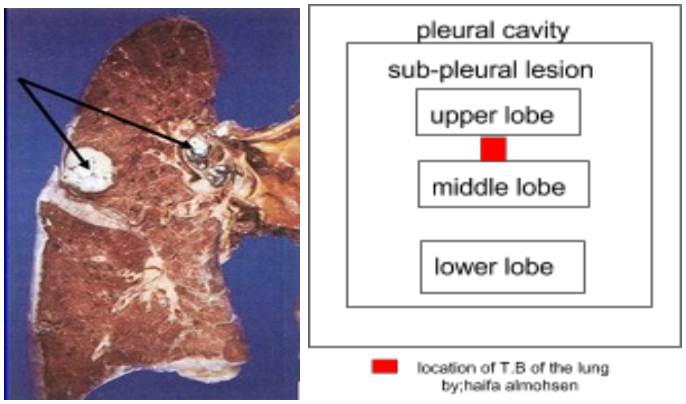


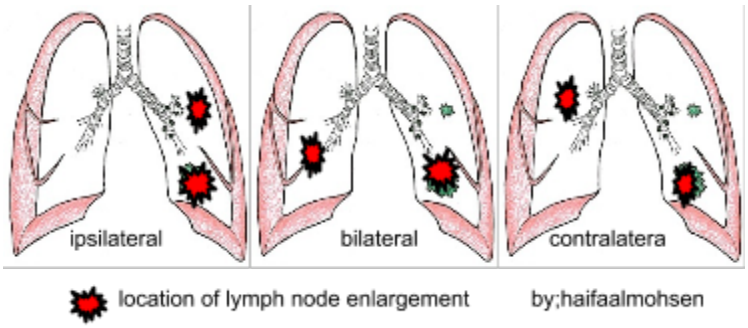
When the Mycobacterium tuberculosis enters your alveoli → some alveolar **macrophages** succeed in phagocytosing and breaking up the invading bacteria → These macrophages then run toward a local **lymph node** and present parts of the bacteria to **T-helper cells (CD4)** → The sensitized T-cells then **multiply** and enter the circulation to search for Mycobacterium tuberculosis. When the T-cells encounter their antigenic target → they release some **lymphokines** that serve attracting the macrophages and activate them when they arrive → other lymphokines include **IL-12** which will be released for transforms **CD4** cells into **Th1** which is the hypersensitive form responsible for cell mediated immunity → Other lymphokines include **TNF**, **IFN-γ** that helps in the transformation of macrophages and monocytes into **epithelioid histiocytes** → aggregates of histiocytes form a **granuloma** → these activated macrophage forming the granuloma (by the help of Th cells) now start fighting the antigen (mycobacterium tuberculosis)

During this stage, the macrophages attacking results in local **destruction** and **necrosis** of the lung tissue. The necrosed tissue looks like a granular creamy cheese and is called **caseous necrosis** (sometimes this is not present). This soft caseous center is surrounded by **macrophages**, **multinucleated giant cells**, **fibroblasts**, and **collagen deposits**. It may also be calcified.It is possible for TB to grow again after many years due to depression in the host's resistance.

What are the types of TB?

TB is always present as a sub-pleural lesion in the lower part of the upper lobe or the upper parts of the lower and middle lobes.

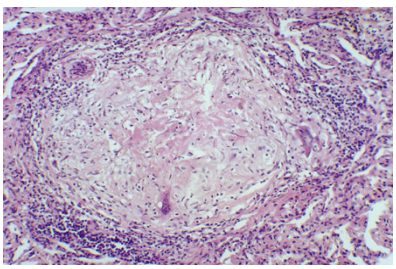




Ghons focus- primary tuberculosis -Ghon's complex-.
The acid-fast bacilli will drain from the lymphatic system into the lymph nodes where they form an ipsilateral hilar lymph node enlargement contra-lateral enlargement *differing sizes*
There are two possibilities:

- Immune system is fully functioning → probably develop fibrosis, scarring
- Impaired immunity (AIDS for example)→ most probably will develop symptomatic T.B

Most of the time in 80-90% f the cases Primary T.B shows no clinical signs and hence the person can go on living his entire life **without** ever exhibiting the usual clinical signs of T.B like
-Night sweats –mild/severe fever –weight loss. Primary TB is characterized by ghon complex which is consist ghon focus and enlargement of lymph node with granuloma. In some cases the dormant bacteria can be reactivated due to the exposure to certain **drugs** or the development of diseases like cancer, AIDS, or any disease that leads to lower immunity. This is called secondary T.B.

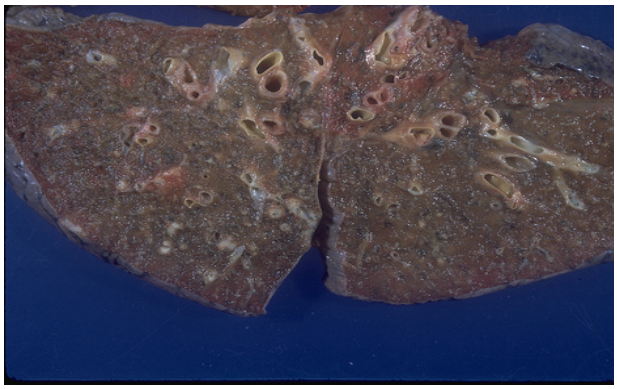


How does Secondary T.B rise?
1- Reactivation of the old bacteria: most probably because of dysfunctional immunity (AIDS)
2- New infection: re-exposure to TB after the first infection

Secondary TB is usually localized in the apex of one or both of the lungs. Clinical signs manifest, and less lymph node involvement than primary TB.

It progresses to one of two things:

- Causes open TB (cavitation), with a productive cough, sputum positive, and caseous necrosis with granulomas. The patient should be isolated for 10-14 from starting treatment.
- Causes miliary TB: into lymphatic vessels→ lymph nodes→ thoracic duct → venous system spreading of T.B. It can go anywhere & symptoms depend on the location. For example: epididymis = infertility.



How do we test for tuberculosis?

First Method: PPD, Tuberculin Test, "The bubble test"

Following induction of cell-mediated immunity against Mycobacterium tuberculosis, exposure to this organism will result in a localized delayed type hypersensitivity reaction (type IV hypersensitivity) remember type 4 means Th & macrophages are involved and thats what causes the bubble to be formed "cellular reaction". **Intradermal injection** of antigenic protein particles from killed Mycobacterium tuberculosis, called PPD (Purified Protein Derivative), results in localized skin induration and erythema.

Therefore, intradermal injection of PPD will reveal whether or not a person has been EXPOSED with Mycobacterium tuberculosis.

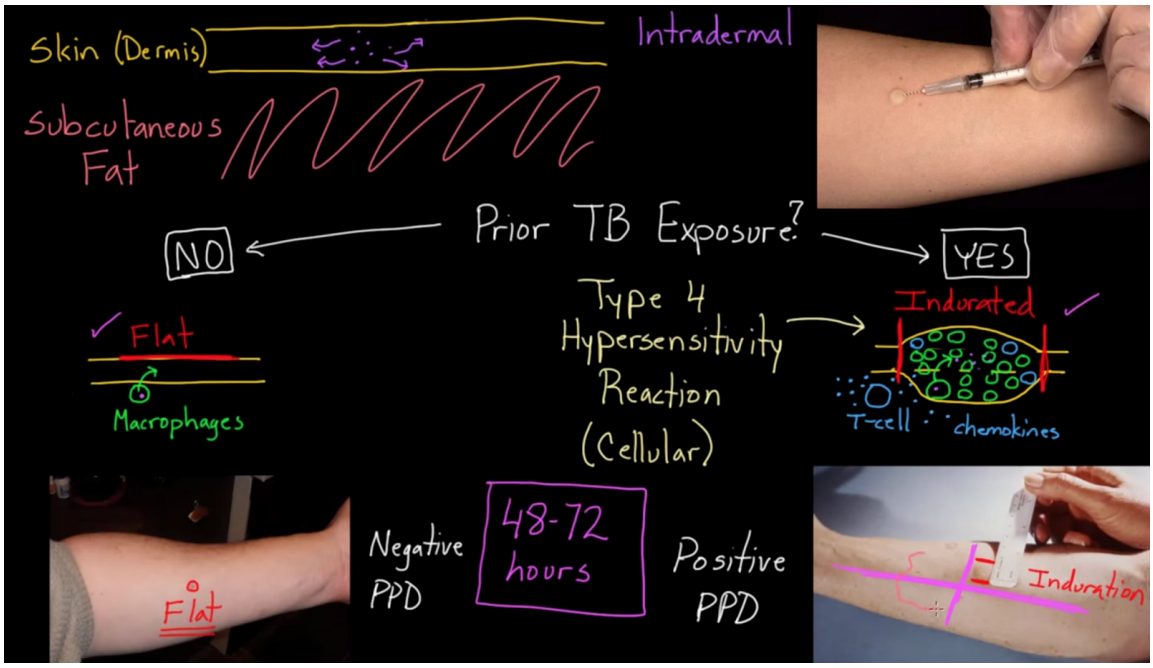
Note: vaccinated individuals against TB are positive in tuberculin test.

The test will be ***negative*** if:

- Patient was NOT previously exposed to TB.
- It is safe to say that the patient does NOT have TB
- Be careful with AIDS patient, they will show NEGATIVE because they have very few Th cells to react to this antigen.

T-cell did not recognize it, then it didn't make a "big deal about it" → You will see the site you inserted in it PPD after 48-72 hours you will find it **FLAT, This is the key word.**

When it's ***positive***, same process will happen again but now the macrophage when it present it to T-cell, it will get EXCITED, it will release chemokines and let more macrophage to that site (hypersensitivity reaction type 4) and that will simply cause the **BUBBLE (induration).**



This is important because many infected individuals will not manifest a clinical infection for years. When a positive PPD test occurs, you can treat and eradicate the disease before it significantly damages the lungs or other organs.

Their 2 ways of tuberculin skin test:

- Mantoux test (by a needle).
- Heaf Test (screening) (Used in schools generally).

Does it means the individual is affected if it is positive? it indicates exposure and infection to Mycobacterium tuberculosis at some time in the past.

Summary: what does positive tuberculin test mean? It means that the subject was exposed to this antigen. So, the subject might have one or more of the following: active infection, latent infection, cured from the infection, or have been vaccinated (BCG vaccine).

Note: one of the reasons some countries such as the USA don't use the BCG vaccine is to keep this test working properly.

Second Method: AFB/Ziehl neelsen & Auramine stain

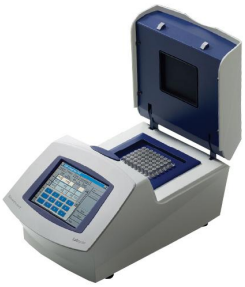
Why not gram stain?

Because mycobacterium tuberculosis contain high lipid concentration (Mycolic acid) in their cell wall, which resists staining. It has an atypical cell wall.

After taking a smear we'll use either Ziehl Neelsen method or the auramine stain. The auramine stain involves staining the antibody with an immunofluorescence dye and then reacting it with the antigen of the bacteria. If there is a reaction then it is positive. (If you are curious to know how Processing of samples)

Third Method: Take a sample in LJ (Lowenstein - Jensen) medium, culture will takes about 2-12 weeks.

Fourth method: By recognizing the DNA of the bacteria via molecular means, by performing a polymerase chain reaction (PCR) this is very accurate as there are no limiting factors such as time, the amount of specimen or even deterioration of the tissue. It takes around two days or so to obtain the results.



Ways in which you can obtain a specimen.

1-Bronchoalveolar lavage (BAL): is a medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid squirted into a small part of the lung and then collect for examination.

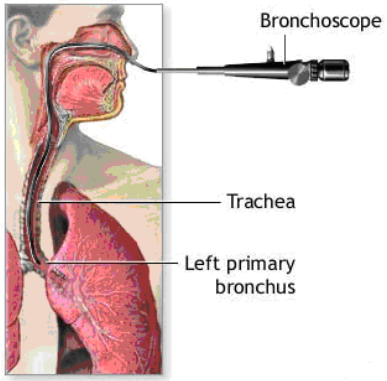
2- 3 Early morning sputum (means 3 days not 3 sputum at one day) * mostly taken

3- 3 Early morning urine

4- CSF

5- lymph nodes, Pus or tissue not swab

6- Joint, bone aspiration



If you are curious to know the difference between Ziehl-Neelsen and Auramine stain you can check this **LINK**.

Clinical Cases.

Case one:
A five-year-old patient spends a lot of time with his grandma. He eats with her, and he does various other activities with her. They even share the same nebulizer! This patient acquired T.B from his grandma.

- *Infection usually is required from old people.*

Case two:
If a patient has mild-high fever, enlargement of the lymph nodes, granuloma and necrosis the patient has probably got tuberculosis.

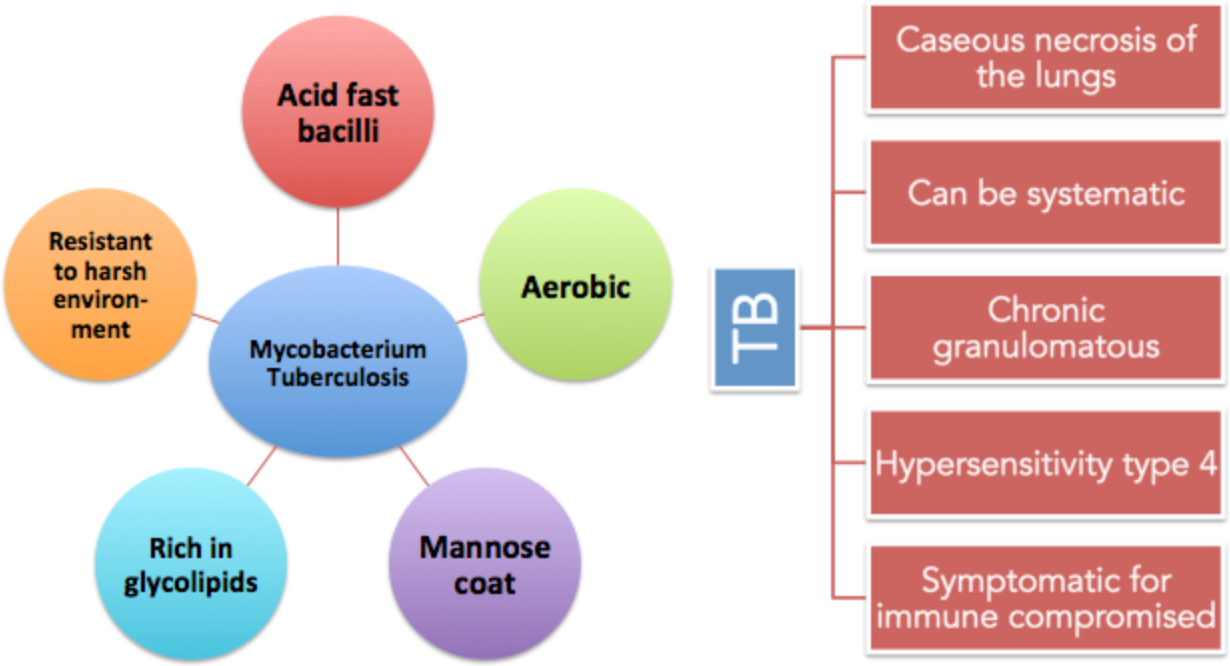
Case three:
Chest pain, he may or may not have fever -very mild one-, you perform a chest x-ray and he shows some pleural effusion.
The causes of pleural effusion could be any of the following: cancer, T.B, infection and autoimmune disease.
To confirm your diagnosis you can use the ***Z.H stain*** and ***auramine stain*** if these tests show negative results you can then ask for a culture, by taking a tissue from the site of infection and grow it.

SUMMARY

Tuberculosis

- Tuberculosis is a chronic granulomatous disease caused by *M. tuberculosis*, usually affecting the lungs, but virtually any extrapulmonary organ can be involved in isolated infection.
- Initial exposure to mycobacteria results in development of an immune response that confers resistance but also leads to hypersensitivity (as determined by a positive result on the *tuberculin skin test*).
- CD4+ T cells of the T_H1 subset have a crucial role in cell-mediated immunity against mycobacteria; mediators of inflammation and bacterial containment include IFN-γ, TNF, and nitric oxide.
- The histopathologic hallmark of host reaction to tuberculosis in immunocompetent persons is the presence of *granulomas,* usually with central caseating necrosis.
- Secondary (reactivation) tuberculosis arises in previously exposed persons when host immune defenses are compromised, and usually manifests as cavitary lesions in the lung apices.
- Both progressive primary tuberculosis and secondary tuberculosis can result in systemic seeding, causing life-threatening forms of disease such as miliary tuberculosis and tuberculous meningitis.
- HIV-seropositive status is a well-known risk factor for development or recrudescence of active tuberculosis.

Summary.



T.B bovis	M. tuberculosis hominis
Their host mammals like cows.. can affect humans by drinking untreated milk that causes gastrointestinal T.b.	infect humans, transmitted by inhalation of airborne.

Affects:

- Elderly
- AIDS patients
- Urban poor

How does the bacterium (which causes T.B) enter? (Pathogenesis).

1- If the macrophages succeed in phagocytosing and breaking up the invading bacteria > These macrophages then run toward a local lymph node > macrophages then present parts of the bacteria to T-helper cells (CD4)> T-cells sensitized(multiply)> then T-cells enter the circulation > T-cells search of Mycobacterium tuberculosis> T-cells encounter their antigenic target> then T-cells release lymphokines> transformation of macrophages/monocytes into epithelioid histiocytes necrosis tissue.

2- if the macrophage unable to phagocytosing and breaking up the invading bacteria > bacteria replicate within the macrophage > then the macrophage burst (die!) However the bacteria do not die > then bacteria continues to span the body causing bacteremia [the proliferation of the bacteria within the blood, however it does not cause an infection in contrast to septicemia] not cause septicemia[: the proliferation of the organism within the blood causing an infection * this is never the case in T.B*.

Direct Questions.

1. **Can mycobacterium tuberculosis bovis transmit by inhalation ?**

NO , it transmit by drinking unpasteurized milk

2. **When the tuberculin test is positive what does that mean ??**

than mean the TH1 get activated and that does not mean the patient have the disease , its mean he met the bacteria before (ex: vaccine)

3. **When does the pathogenesis of TB stop in immunocompromised patient ??**

it stops at the level of macrophage
ex: HIV patient can't develop granuloma (why) because there is no activated T lymphocyte (no cellular immunity)i

4. **What is Gohn's complex ??**

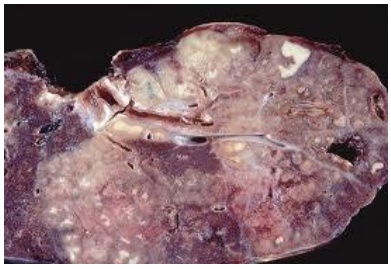
enlarge lymph node + gohn focus

5. **Where dose secondary TB like to effect ??**

apical part of the lung (upper part of both lobe (bilateral)

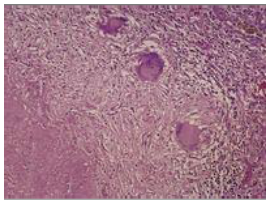
MCQ's

1. A previously healthy, 20-year-old woman has had a low-grade fever for the past 2 weeks. On physical examination, her temperature is 37.7°C; there are no other remarkable findings. The gross appearance of the lung shown in the figure is representative of her disease. Which of the following studies is most likely to report a positive result?
   a) Antinuclear antibody
   b) Tuberculin skin test
   c) Mantoux test
   d) Both b,c



Ans:D, Tuberculin skin and mantoux tests are the same test but different names. It used to know the diagnosis of TB.

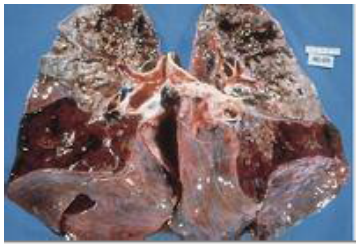
2. A 46-year-old woman goes to the physician for a routine health maintenance examination. On physical examination, there are no remarkable findings. Her body mass index is 22. She does not smoke. A tuberculin skin test is positive. A chest radiograph shows a solitary, 3-cm left upper lobe mass. The mass is removed at thoracotomy by wedge resection. The microscopic appearance of this lesion is shown in the figure. Which of the following is the most likely diagnosis?



a) Pulmonary infarction
b) Mycobacterium tuberculosis infection
c) Lung abscess
d) Primary adenocarcinoma

Ans:B, The figure shows pink, amorphous tissue at the lower left, representing caseous necrosis. The rim of the granuloma has epithelioid cells and Langhans giant cells. Caseating granulomatous inflammation is most typical of *Mycobacterium tuberculosis* infection.

3. A 56-year-old man has had fever, night sweats, and a 3-kg weight loss over the past 4 months. In the past month, he has had episodes of hemoptysis. He dies of respiratory failure and hypoxemia. The appearance of the lungs at autopsy is shown in the figure. Infection with which of the following organisms is most likely to have produced these findings?



a) Candida albicans
b) s.aureus
c) Mycobacterium tuberculosis
d) Mycoplasma pneumoniae

Ans:C, The figure shows a prominent upper lobe cavitation in the tan-to-white caseating granulomas.

4. The lesion areas of Ghon's focus:
a) Upper part of the lower lobe.
b) Lower part of the upper lobe.
c) Around the main bronchus.
d) Both A+B

Ans:D

5. IL12 is secreted by which cell of the following:
   a) Neutrophils
   b) TH2
   c) Activated macrophages
   d) TH1

Ans:C

6. Secretion of INF-γ by TH1 cells results in:
   a) Ceases necrosis
   b) Granuloma formation
   c) Edema
   d) Activation of macrophages

Ans:D, Most accurate

7. what is the substances give M.tubeculosis pink colour in Ziehl-Neelsen stain :
A. a)PPD.
B. b)Lipoprotein
C. c)Glycoprotein
D. d)Both B+C

Ans:A, Presence of purified protein derivative (PPD)

8.The macrophages can recognize M.tuberculosis by:

a) FAS recptor
b) Mannose receptor.
c) Intracellular receptor.
d) None of them

Ans:B

9.The macrophages can recognize M.tuberculosis because :

a) Has Glycoprotein + lipoprotein on its surface
b) Is parasitic.
c) Lack of Has Glycoprotein + lipoprotein on its surface
d) None of them

Ans:A

T & F

1. Tuberculosis can affect only the lungs.
2. Liquefactive is the type of necrosis in pulmonary TB
3. Primary TB usually don`t have symptoms
4. Miliary TB occurs in primary TB and secondary TB by carrying of the bacilli in the bloodstream to many parts of the body.
5. Systemic spread of TB (military) is by arteries

Ans:

1. **F (lungs and other organs)**
2. **F (Caseous necrosis)**
3. **T**
4. **T**
5. **F (by veins, arteries transmit it to the lungs)**

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Good Luck!

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ريما الرشيد