Pathology team

Respiratory block

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Lecture 4 - Tumors

Tumors of the lung

Facts about lung tumors:

· The lungs are frequent sites of both primary and secondary tumors. However, those that arise from metastases from other primary tumors (secondary) are more common than those originating from the lung itself (primary).

· Lung tumors are the 2nd most common cancer of the body and the 1st cause of death in both sexes

· 95% of primary lung tumors arise from the bronchial epithelium.

· 5% are miscellaneous group (C.T., cartilage, blood vessels, fibrous tissue)

· most lung tumors are malignant.

· The most common benign lesions are hamartomas [A benign malformation seen as a non-neoplasmic mass of disorganized lung tissue. Usually coincidentally found by x-ray as a coin-like structure]

Most of lung tumors are malignant (benign tumors are rare).

Malignant tumors are subdivided into:

1-Primary: this is less than the other type (metastatic).

2-Metastatic: the most common type of lung tumors.

Why metastatic tumors most common?

Because of high vascular tissue of the lung.

Note: it appears as cannon ball so that we call it cannon ball metastasis.

Benign tumors of the lung: (not found in the hand out)

Adenochondroma

Present as well circumscribed nodules (coins) in the middle of the lung. It is not associated with any symptoms. It is sometimes removed because of differential diagnosis or we can just leave it.

Histopathology: consist of:

1. **cartilage**
2. **adipocytes**
3. **connective tissue**
4. **glandular tissue**
5. **blood vessels**

These tissues are endogenous (found in the normal lung) so it is a type of hamartoma.

Primary tumor of the lung risk factors:

1-Smoking history

2-Air pollution

3-Radiation

4-exposure to nickel and chromates

General symptoms of cancer:

1-Weight Loss

2-Fatigue

3-Anemia

4- Fever = Pyrexia

5-Anorexia nervosa

specific symptoms:

1-Chronic cough with hemoptysis

2-Chest pain

3-Dyspnea

Bronchogenic carcinoma is subclassified into:

1-Squamous cell carcinoma: it is related to smoking. (30-35%) of primary tumors.

Features:

Arise from squamous cell epithelium. Present from hilur (Not peripheral) of lung. It Extents to the other lung. Inappropriate secretion of parathyroid like protein which lead to hypercalcaemia. May present with pleural effusion. May produce keratin so it is moderate to well differentiated.

Diagnosis:

We do fine needle aspiration and cytology of lymph nodes.

Clinical presentation:

1-Hemoptysis

2-Obstruction

3-Obstructive pneumonia

4-Pleural effusion

5-Clubbing

6-weight loss

7-anxiety

8- Cachexia = وهن بسبب ورم

Complication:

It can cause metastasis to the brain and the bone to present with a pathological fracture usually in the femur. Finally metastasis to the adjacent lymph nodes.

2-Adenocarcinoma:

a-Bronchial derived

b-Bronchioalveolar carcinoma

3-Small cell carcinoma (oat cell)

4-Large cell carcinoma

First:

Bronchial derived: arise in peripheral region and closely associated with prior pulmonary inflammation or scar carcinoma. Less linked to smoking.

Second:

Bronchioalveolar carcinoma: arise from clara (peripheral) cell and show better diagnosis than bronchial derived.

Third:

Small cell carcinoma (oat cell): arising from neuroendocrine cells. In the center (hilur mass). It is very aggressive. Note : it is not treated by surgery, only by chemotherapy.

Fourth:

Large cell carcinoma: it is poorly differentiated and appear as peripheral mass.

3-Other type of carcinoma:

1-Carcinoid: arise inside the bronchus from neuroendocrine cells. When transfer to the liver it cause carcinoid syndrome like motility of intestine and diarrhea

Note: it is well differentiated.

2-Pancost tumor: located in the upper part of the lung with Horner's syndrome because it invades the sympathetic nerves.

Horner's syndrome: Symptoms 1) Ptosis. 2) Miosis. 3) Anhidrosis

Treatment of these tumors:

We treat all these kinds by surgery except small cell carcinoma by chemotherapy.

Pulmonary effusion: it is two types:

1) Transudate: low protein. (Increase hydrostatic pressure) This indicates :

1-Cardiac failure

2-Renal failure

3-Hepatic failure

2) Exudate: high protein. This indicates:

1-Infection

2-Neoplasia

3-Pulmonary inflammation

Bronchogenic carcinoma:

Is the number one cause of cancer-related deaths in industrialized countries (ex:USA), accounting for 13% of all cancer deaths in men and women, which is about one third of cancer deaths in men.

Why? It is the most aggressive type of cancer and the least responsive to treatment.

It's incidence increases in parallel with cigarette smoking however has decreased in men between 1984 and 1998 (from 8.6 to 69.8 per 100,00) mainly due to increased awareness and laws against public smoking.

It usually affects old age groups, ranging between 40 to 70 years of age.

Etiology:

Tobacco Smoking:

This type of carcinoma is directly proportional in incidence to the number of cigarettes smoked daily, the number of years of smoking as well as the tendency to inhale. Experimental evidence proves that cigarettes contain more than 1200 carcinogenic and promoter substances that progressively alter the lining epithelium.

Increased risk becomes 20 times greater among habitual heavy smokers. Passive smoking (second-hand smoking) increases the risk to twice than non-smokers.

Its incidence is inversely proportional with the cessation of smoking. The risk of developing this type of carcinoma decreases after cessation for at least 15 years.

Industrial Hazards:

Certain industrial exposures increase the risk of developing lung cancer, for example:

· All types of radiation

· Uranium miners (4x) – Uranium miners who are smokers (10x)

· Asbestos workers (5x) – Astebestos workers who are smokers (50-90x)

· Other exposures include: nickel, chromates, coal, mustard gas, arsenic, iron and newspaper workers.

Air Pollution:

Increases the incidence.

May include indoor pollutants like radon.

Scarring:

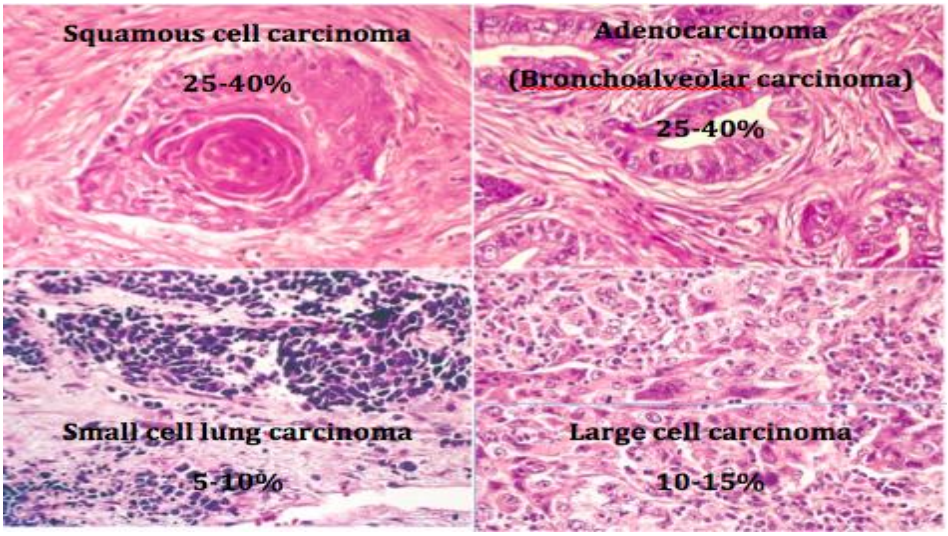
Increase the risk mainly of adenocarcinoma at the site of scarring, regardless of the cause of the scar. (old infarcts, wounds, granulomatous infection)

Precursor Epithelial Lesions:

1. Squamous dyslasia and carcinoma in situ
2. Atypical adenomatous hyperplasia
3. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

It should be noted that the term "precursor" does not imply that progression to invasion will occur in all cases.

Histological Classification of Bronchogenic Carcinoma and their Incidence:



Also may occur as combine patterns (5%-10%): Most frequent patterns:

- Mixed squamous cell carcinoma and adenocarcinoma.
- Mixed squamous cell carcinoma and SCLC.

Other mode of classification [Therapeutic]:

For therapeutic purposes, bronchigenic carcinomas and subclassified into:

	Small Cell Lung Carcinoma (SCLC)	Non-Small Cell Carcinoma (squamous cell carcinoma-adenocarcinoma-large cell carcinoma)
Histology	Scant cytoplasm, small, hyperchromatic nuclei with fine chromatin pattern; nucleoli indistinct; diffuse sheets of cells	Abundant cytoplasm, pleomorphic nuclei with coarse chromatin pattern; nucleoli often prominent; glandular or squamous architecture
Markers	**Neuroendocrine Markers** Usually present (dense core granules on electron microscopy; expression of chromogranin, neuron-specific enolase and synaptophysin) **Epithelial Markers:** Usually absent **Mucin:** Absent	Usually absent Usually present Present in adenoarcinoma
Peptide Hormone Production	Adrenocorticotropic hormone, antidiuretic hormone, gastrin-releasing peptide, calcitonin	Parathyroid hormone-related peptide (PTH-rp) in squamous cell carcinoma
Genetic Differences	• high frequency of TP53 and RB gene mutation • deletion of the short arm of chromosome 3 • MYC family overexpression occur in <u>both</u>	• *p16/CDKN2A* is commonly inactivated • *K-RAS* oncogene mutation occur in adenocarcinoma • EGFR mutation is important for Rx of adenocacinoma
Response to Chemotherapy	Often complete response to but recur invariably	Uncommonly complete response
Surgical Intervention	Not considered effective	Is curable when spread is limited to the lungs

Among the major histologic subtypes of lung cancer, squamous and small-cell carcinomas show the strongest association with tobacco exposure. While adenocarcinoma is mostly associated with scars.

Morphology:

Arise in the lining epithelium of major bronchi. All are aggressive.

All varieties have the capacity to synthesize bioactive products.

> Small mucosal lesions, firm and gray-white, form intraluminal masses, invade into adjacent lung parenchyma, central necrosis, areas of hemorrhage, extend to the pleura, invade the pleural activity.

Type	Location	Characteristics
Squamous cell carcinoma	Central in major bronchi	Preceded for years by atypical metaplasia or dysplasia Histologically range from well-differentiated to poorly differentiated neoplasm; appears as a hilar mass and frequently results in cavitation Clearly linked to smoking; incidence greatly increased in smokers May be marked by inappropriate parathyroid hormone (PTH) like activity with resultant hypercalcemia
Adenocarcinoma: Bronchial-derived	Peripheral	Develops on site of prior pulmonary inflammation or injury (scar carcinoma) Histologically, they assume a variety of forms, including typical adenocarcinoma with mucus secretion and papillary or bronchioloalveolar patterns Less clearly linked to smoking; mostly affecting women under age of 40 Tend to metastasize widely at early stages
Bronchioloalveolar	Peripheral (as single nodule or multiple diffuse nodules)	Less clearly related to smoking; columnar to cuboidal tumor cells line alveolar walls and multiple densities on x-ray. The disease often mimicks interstitial pneumonia.
Small cell (oat cell) carcinoma	Central	Undifferentiated tumor; most aggressive broncho-genic carcinoma and cannot be treated by surgery Usually causes metastases at time of diagnosis with extension into the lung parenchyma and early involvement of the hilar and mediastinal nodes Composed of small, dark, round to oval, lymphocyte-like cells derived from neuroendocrine cells of the lung. It is often associated with ectopic production of corticotrophin (ACTH), antidiuretic hormone (ADH), calcitonin, gastrin-releasing peptide and chromogranin.
Large cell carcinoma	Peripheral	Undifferentiated tumor which may show features of squamous cell or adenocarcinoma on electron microscopy.
Other carcinomas of the lung: Carcinoid	Major bronchi	Low malignancy, spreading by direct extension into adjacent tissues, may result in carcinoid syndrome [intermittent attacks of diarrhea, flushing, and cyanosis] Arises from neuroendocrine cells, Kulchitsky cells in the bronchial mucosa.
Carcinoma, metastatic TO the lung		Higher incidence than primary lung cancer; origin could be GIT, breast or genitourinary systems or other sites Characterized by the presence of multiple nodular densities on X-ray.

* when the cancer is primary it will appear solitary, however with it is secondary is usually develops as multiple lesions

Spread:

1. Lymphatic spread.

Spread to trachial and mediastinal lymph nodes.

Successive chains of nodes (scalene nodes).

Involvement of the supraclavicular node (Virchow's node).

2. Extend into the pericardial or pleural spaces. Infiltrate the superior vena cava. May invade the brachial or cervical sympathetic plexus (Homer's Syndrome). May extend locally to ribs.

3. Distant metastasis (via hematological spread) to [BLAB]: bone (20%), liver (30-50%), adrenals (>50%) or brain (20%)

Clinical Course:

Outlook is poor for most patients (5-year survival rate is less than 10%) however, NSCLC have a better prognosis than SCLC.

· Silent, insidious lesions. Symptoms due to metastatic spread.

· Chronic cough with expectoration and hemoptysis.

· Hoarseness [from recurrent laryngeal nerve paralysis]

· Latent chest pain when the pleura is affected because the lung itself has no pain receptors

· Superior vena cava syndrome [compression or invasion of the superior vena cava, resulting in facial swelling and cyanosis along with dilattion of the veins of the head, neck and upper extremities]

· Pericardial or pleural effusion [often bloody (bloody pleural effusion suggests malignancy, tuberculosis or trauma)]

Other Clinical Manifestations Include:

· Partial obstruction – emphysema. Or complete obstruction – atelectasis and chronic bronchitis.

· Pulmonary abscess.

· Pneumonitis or pleuritis.

· Pancoast tumor (superior sulcus tumor): involvement of the apex of the lung, often with Horner syndrome (ptosis, miosis and anhidrosis): due to involvement of the cervical sympathetic plexus.

· Paraneoplastic endocrine syndrome (3-10%): symptoms include neuromuscular syndromes, clubbing of the fingers and hematological and endocrine manifestations.

The most frequent of which is adrenocorticotropic hormone (ACTH) or ACTH-like activity with small cell carcinoma.

· Homer's Syndrome: ipsilateral enophthalmos, ptosis, miosis, and anhidrosis

Diagnosis:

By smear + stain of sputum or biopsy sample

Diseases of the Pleura:

Can be divided for practical purposes into:

Inflammatory conditions (pleuritis) which can be acute or chronic and is often caused by pyogenic organisms or tuberculosis causing empyema, pleural effusions and adhesions.

Neoplastic lesions of the pleura which can be caused by direct spread of a bronchogenic carcinoma, metastases from other parts of the body (secondaries) or a primary neoplasm called **mesothelioma.**

Mesothelioma:

are rare except after exposure to asbestos. After exposure, there may be a latent period of up to 50 years before development of the tumour. Patients usually present with chest pain and breathlessness and there is commonly a pleural effusion.

Histologically:

Mesotheliomas may have spindle cells (sarcoma like) and glandular patterns. Mesotheliomas are highly malignant tumours that spread to adjacent structures like the pericardium, lung or diaphragm, but metastases are rare. Death usually occur 10 months after diagnosis. Exposure to asbestos also causes development of benign collagenous thickening of the pleura termed pleural plaques.

Diagnosis:

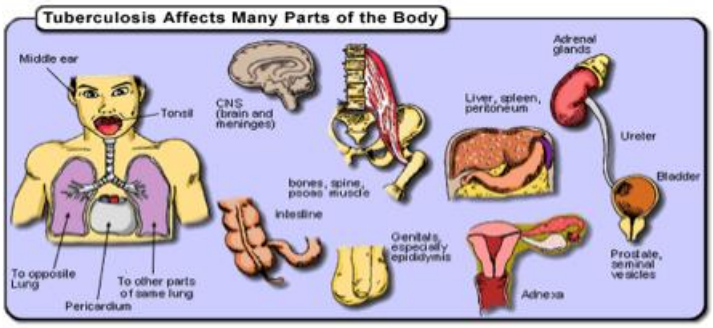
In general is made by radiological investigations, cytological and histological assessments (cytological examination of pleural fluid and also pleural biopsies) in addition to bacteriological assessment and culture.

Lecture 5 - T.B.

Tuberculosis

Tuberculosis is a communicable chronic granulomatous (CONTAGIOUS) disease caused by Mycobacterium tuberculosis.

- It usually involves the lungs but may affect any organ or tissue in the body.
- Typically, Epitheloid granuloma in which the centers of tubercular granulomas undergo caseous necrosis.



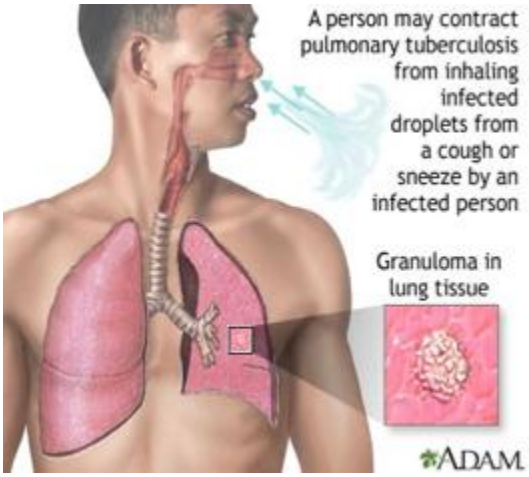
The picture shows other organs that can be affected.

· Pulmonary tuberculosis is an example of a granulomatous disease.
· The histopathological characteristics is granulomatous inflammation.
· A characteristic feature of the granulomata that develop in tuberculosis is the presence of necrosis, termed caseation.

Remember : there are other diseases that make a granuloma . for example, sarcoidosis, but it does not make a caseous necrosis as TB.
Epidemic: Diseases that come and go . وبائي
Endemic: Diseases that are here in the country does not go .مستوطن

Epidemiology of T.B.

- Worldwide; a third of the world's population is infected with this organism
- A total of 8.8 million new cases each year and 2 million deaths
- Disease most common in Southeast Asia, Sub-Saharan Africa, and Eastern Europe.
- Humans are the only natural reservoir
- Person-to-person spread by infectious aerosols(sneezing , coughing).



- Populations at greatest risk for disease are:
  1. individuals exposed to diseased patients.
  2. People with poverty, crowding, and chronic debilitating illness
  3. drug or alcohol abusers and homeless persons

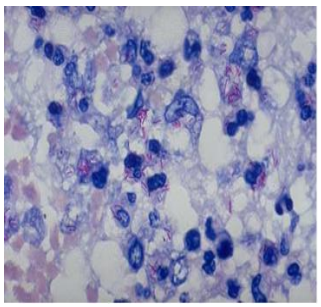
- Infected cases at greatest risk for progressive disease are:
    1. immunocompromised patients (particularly those with HIV infection)
    2. Certain disease states :

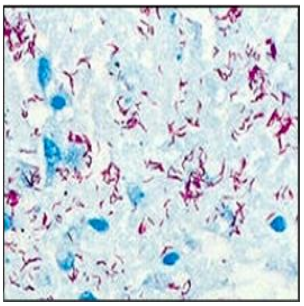
  - Diabetes mellitus, Hodgkin disease, chronic lung disease (particularly silicosis),
  - Chronic renal failure, malnutrition, alcoholism, and immunosuppression.

- Humans are the most affected species .
- aerosols : A gaseous suspension of fine solid or liquid particles , it can be transmitted by coughing or sneezing .
- chronic debilitating illness : Patient with chronic disease and having weak immunity
- Hodgkin disease : a type of cancer characterized by progressive chronic inflammation and enlargement of the lymph nodes
- silicosis: a disease of the lungs caused by continued inhalation of the dust of minerals that contain silica and characterized by progressive fibrosis and a chronic shortness of breath ..

- There are different tissue patterns **according to the level of host immunity.**
- If there has been no previous exposure to the organism, a pattern of disease termed **primary tuberculosis** develops.
- If a person has previously been exposed and is sensitized to the organism, a pattern called **secondary tuberculosis** develops.
- If exposure has occurred, but immune responses become abnormal (e.g. by immunosuppression), the pattern of **primary TB** develops.

Etiology of T.B





***Mycobacterum tuberculosis*:**

Mycobacteria – 'fungus like..
(from its name "myco" it is look like a fungal)

slender rods.

acid fast bacilli [AFB]
(i.e., they have a high content of complex lipids that readily bind the Ziehl-Neelsen [carbol fuchsin] stain and subsequently resist decolorization).

Virulence:

Capable of intracellular growth in unactivated alveolar macrophages.
(Because it is rich with lipoprotein . it's very tough, it does not die easily).

Disease primarily from host response to infection.

Infection VS Disease

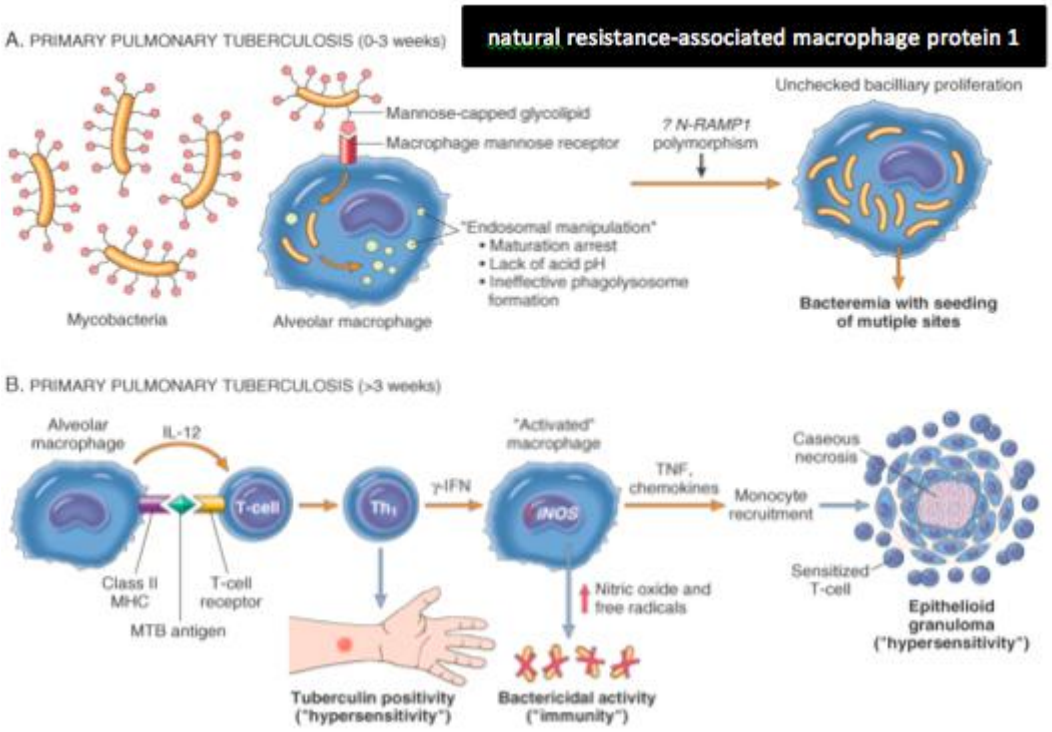
- **Other types of Mycobacteruim :**

- Mycobacterium bovis …..intestinal TB
- M. leprae (Hansen bacillus) ..Leprosy
- M. kansasii, M. avium, M. intracellulare … Atypical mycobacterial infections
- M. ulcerans ……..Buruli ulcer

- M. bovis is usually transmitted to humans via infected milk

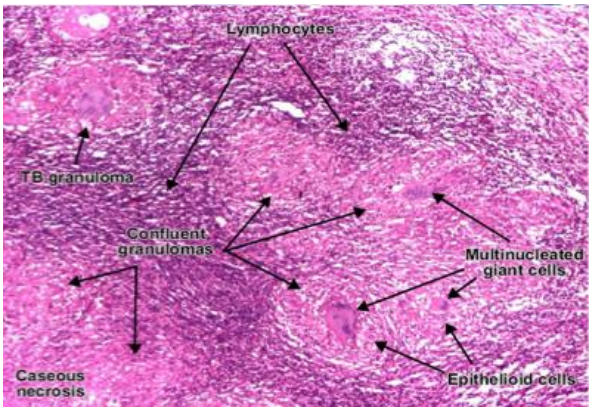
Pathogenesis of granuloma

this picture is so important



• Pathogenesis of T.B :

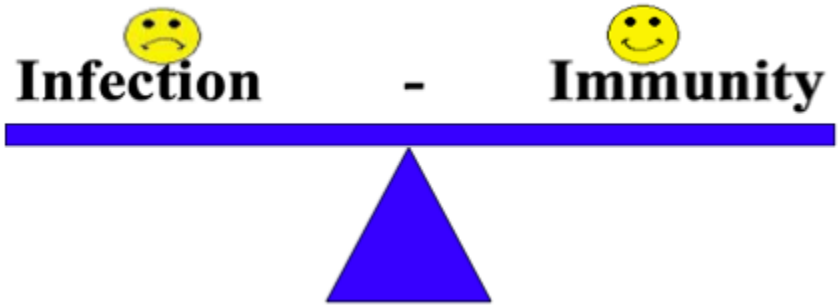
- Bacterial entry > Macrophages > T Lymphocytes > Epitheloid cells > Proliferation > Giant cell formation > Central Necrosis > Fibrosis.



(see slid 12,13 of Dr. Maha's Arafah slides)

Infection with M. tuberculosis typically leads to the development of delayed hypersensitivity, which can be detected by the tuberculin (Mantoux) test.
(it takes usually from 3 to 4 weeks) .

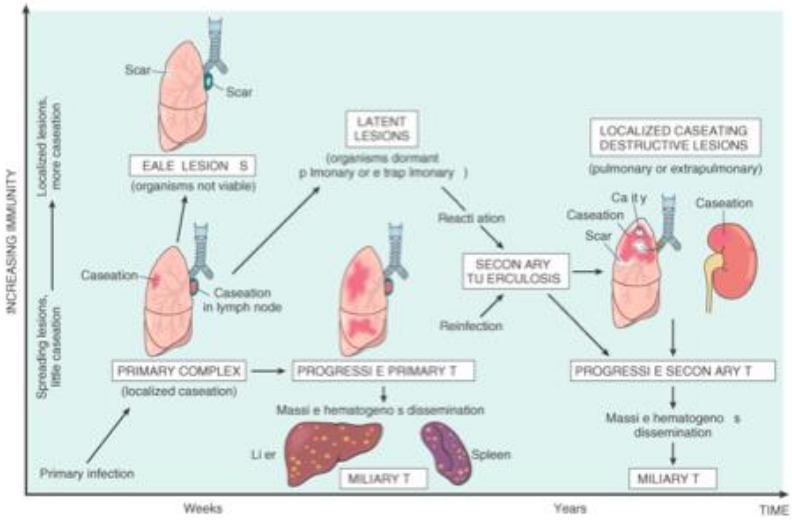
If the patient has a good immunity , he will not get the disease (only infected).
If the patient immunocompromised , he will develop the disease .



- **WHEN the bacilli enter the body, it have 4 potential fates:**

- They may be killed by the immune system
- they may multiply and cause (primary TB)
- they may become dormant (inactive) and remain asymptomatic. (Mantoux test will be +)
- they may proliferate after a latency period (reactivation disease).

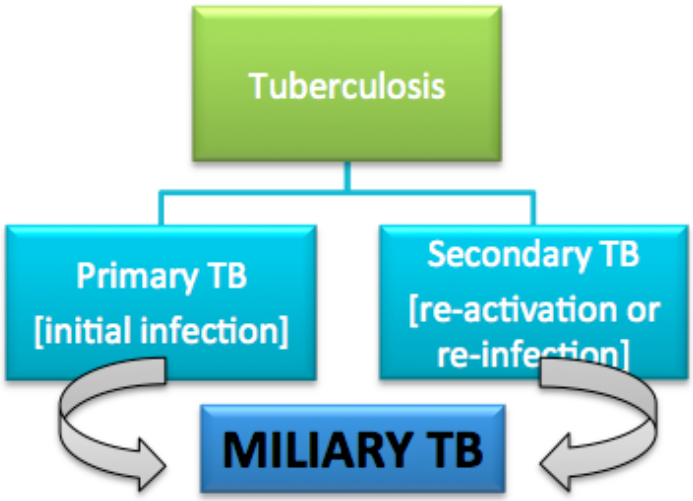
- **If immunosuppressed > Primary Progressive Miliary TB**



1- organism killed

2- the macrophages will engulf the organism > remain asymptomatic (it will be taken to the lymph node to calcified) * later it appears as a small granule in the x-ray

3- low immunity > organism multiply (if it's the first time so it is primary , If a person has previously been exposed so the disease will be reactivate (secondary)



Primary T.B. or Ghon's Complex :

Initial infection.

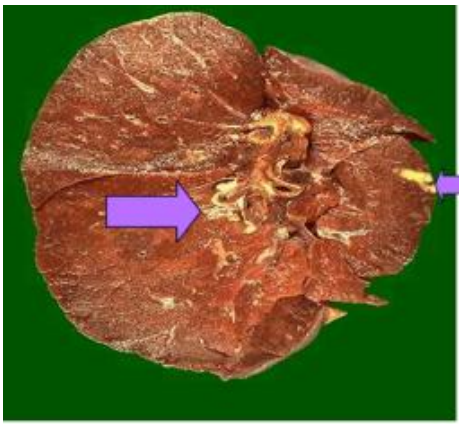
Non immunized individual .

After 3 weeks of being infected, there will be granuloma.

5th to 8th week ... healing. (fibrosis).

Subpleural zone … Ghon focus.

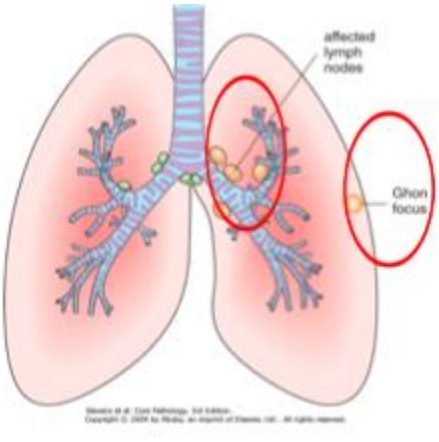
In addition to Ghon focus,lymph nodes enlargement > we called them " Ghon complex".



Early changes may produce no significant symptoms.

The outcome of the infection will depend on:

the balance between the host response to disease.
the virulence and number of organisms.



If immunity is low as in pateint with HIV infection > the disease advances to " Progressive or clinical Primary Tuberculosis" .

In primary TB the initial lung lesion remains small, but infection spreads to peribronchial lymph nodes:

When infection with TB first occurs (e.g. in childhood), the organisms are inhaled and cause an area of infection and

necrosis at the periphery of the lung, often just beneath the pleura (a **Ghon focus**). Bacteria are then conveyed to local nodes at the lung hilum which enlarge through granulomatous inflammation and caseation.

These early changes may produce no significant symptoms, and the outcome of the infection will depend on the balance between the host response to disease and the virulence and number of organisms.

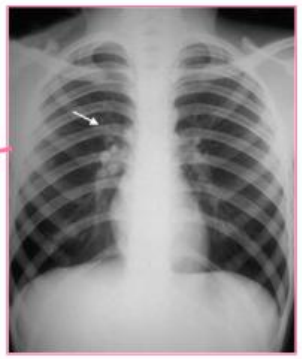
In the vast majority of cases the Ghon focus and caseating granulomas in the lymph nodes heal leaving a zone of caseation surrounded by a wall of collagen. Once the immune system has been exposed to M. tuberculosis the patient is sensitized to the organism. The disease does not progress, and organisms are confined within the shell of collagen. Importantly, viable bacteria may remain walled off within the healed primary complex (latent tuberculosis).

Rarely, the primary complex will progress in patients with poor natural immunity:

In patients who are unable to mount a vigorous immune and reparative response, further spread of mycobacteria occurs, with continuing enlargement of the caseating granulomas in the lymph nodes. Known as **progressive primary tuberculosis**, spread occurs by the enlarging nodes eroding either through the wall of a bronchus or into a thin-walled blood vessel. The Ghon focus usually remains small, although rarely it may rupture through the visceral pleura, *discharging organisms into the pleural cavity to produce tuberculous pleurisy.*

- ## Tuberculin skin testing (Mantoux test, HEAF TEST, PPD):

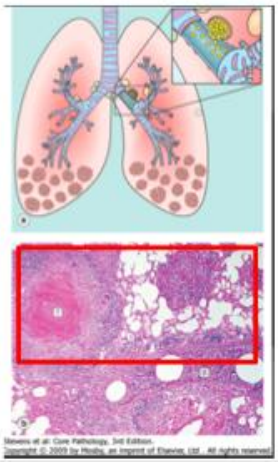
A child with peripheral subpleural parenchymal lesion with enlarged hilar lymph nodes



- Intradermal injection of purified protein derivative (PPD).
- The response is measured as the amount of induration at 48-72 hours.
- The size of induration, rather than erythema, is diagnostic.
- If the patient has taken BCG gives (+) result

Mantoux : a method of testing exposure to tuberculosis by injection of diluted tuberculin

Injection > wait for response > measure the size of exudation not the redness



Bronchial spread of organisms produces tuberculous bronchopneumonia:

If an infected lymph node erodes into a bronchus, tuberculous caseous material containing living tubercle bacilli passes down bronchi and bronchioles under the influence of gravity, spreading the infection to the furthest reaches of the lungs, where extensive, confluent caseating granulomatous lesions develop.

Bloodstream spread of organisms produces miliary TB:

If the enlarging caseating infected lymph node erodes a vessel wall, tubercle bacilli are carried in the bloodstream to many parts of the body, including the remainder of the lung, causing **miliary tuberculosis**. Patients are generally extremely ill, and this pattern carries a high mortality.
In adults with vigorous immune responses, healing of the apical lesion occurs, leaving a central area of caseous necrotic material containing bacteria surrounded by a thick, dense collagenous wall, which may also be calcified. If the patient's immune response becomes weakened later in life this latent tuberculosis can lead to spreading infection (reactivated fibrocaseous tuberculosis).

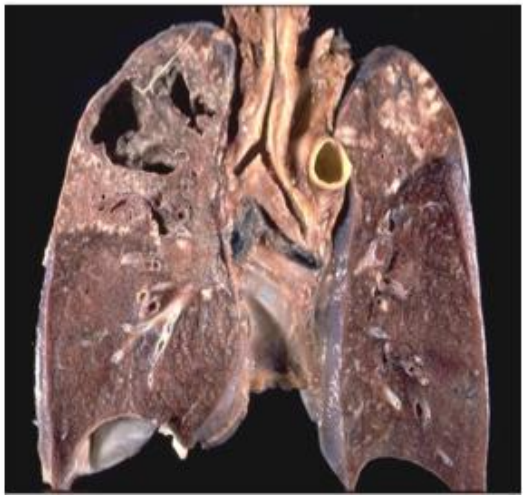
In adults with poor immune responses, secondary TB progresses locally:

In adults with poor immune responses, progressive enlargement of the apical lesion occurs, with caseous necrosis destroying lung tissue. A large caseous mass is formed as a result, which is surrounded by a thin cellular reaction, inducing little collagen to wall off the lesion (progressive pulmonary tuberculosis). As the lesion grows, so too does the risk of erosion into blood vessels or airways.
The release of tubercle bacilli into the main bronchi allows them to be coughed into the atmosphere in droplets, transmitting the infection to other people (so-called open tuberculosis), as well as producing TB bronchopneumonia by passage down bronchi to the lower lobes.

Secondary Tuberculosis:

Post Primary in immunized individuals.
Reactivation or Reinfection
Cavitary granulomatous response.
Apical lobes or upper part of lower lobes .
Caseation, cavity - soft granuloma
Pulmonary or extra-pulmonary
Local or systemic spread (Miliary) :
Vein – via left ventricle to whole body
Artery – miliary spread within the lung

cavitary lesions in the lung apices



when infective foci in the lungs seed the pulmonary venous return to the heart; the organisms subsequently disseminate through the systemic arterial system " Systemic miliary tuberculosis " .
Almost every organ in the body may be seeded. Lesions resemble those in the lung.

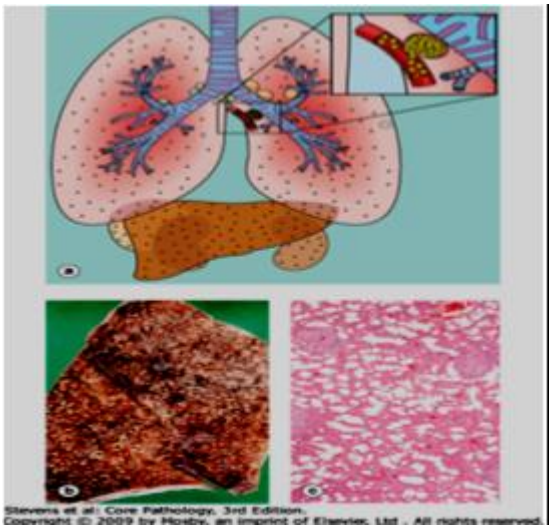
Miliary tuberculosis is most prominent in the liver, bone marrow, spleen, adrenals, meninges, kidneys, fallopian tubes, and epididymis .

Symptoms of secondary T.B.

Cough, sputum, pleural Effusion, Low grade fever, night sweats, fatigue and weight loss.
Hemoptysis or pleuritic pain = severe disease.

Hemoptysis The spitting of blood derived from the lungs or from the bronchial tubes.

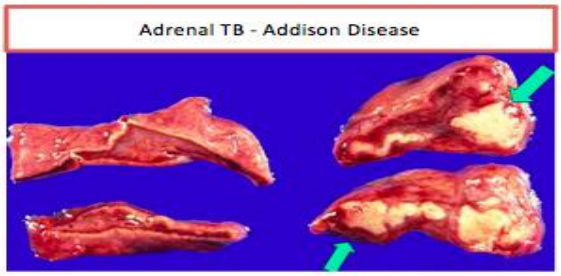
Upper part of lower lobes? Because the organism like to live in high conc. of oxygen.

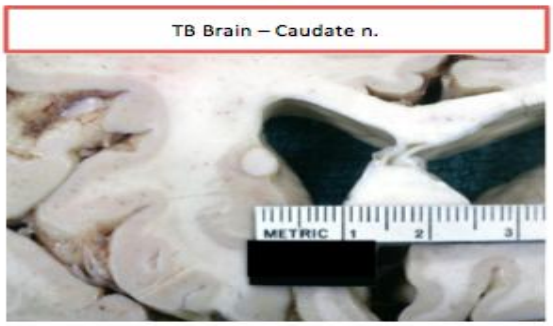


Miliary T.B.:

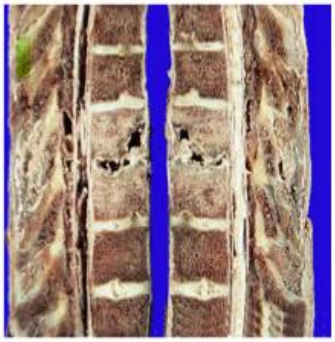
Millet like – grain.
Low immunity.
blood or bronchial spread:
it may erode the arteries or veins or bronchi
It has two types:

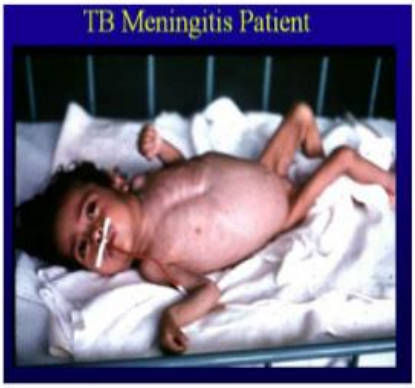
- Pulmonary type.
- Systemic type (go in the whole body) .





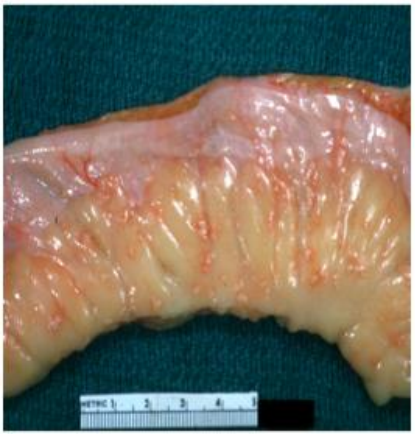
> Pott's disease: Tuberculosis of the spine with distraction of bone resulting in curvature of the spine, and occasionally paralysis of the lower extremities.

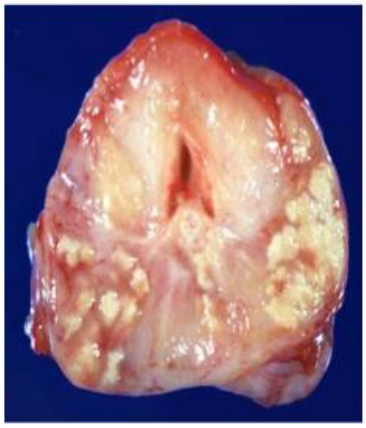




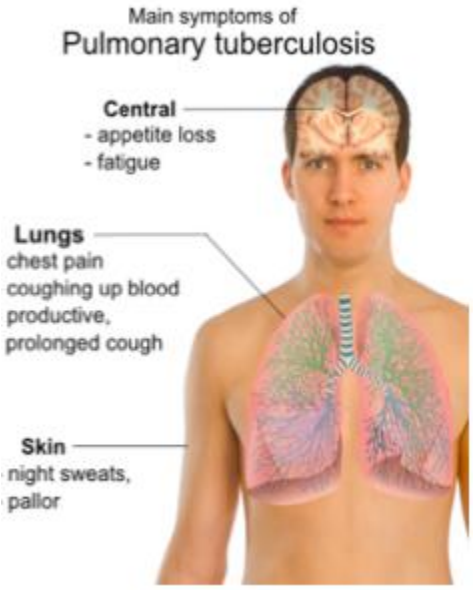
TB Intestine any part can be affected IN ileum

Prostate TB





Diagnosis of T.B.



Clinical features Depend on organ involved.
Pulmonary tuberculosis :

productive cough, fever, and weight loss, night sweats.

Investigations OF T.B.

IF we have Patients suspected of having tuberculosis (TB) we do :

Tuberculin skin testing (Mantoux test, PPD)
Sputum, bronchial wash or biopsy :

Acid fast smear (ZN stain)

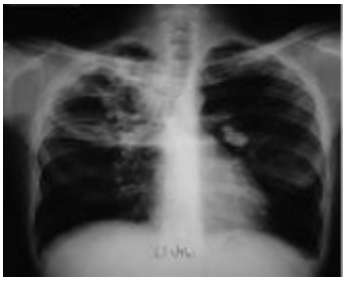
cultures require weeks for growth and identification

- Newer technologies, including ribosomal RNA probes or DNA polymerase chain reaction, allow identification within 24 hours.

Chest radiographs :

- patchy or nodular infiltrate.

may be found in any part of the lung, but upper-lobe involvement is most common.



What should be done after diagnosis … ?

Patients with TB should remain in isolation until sputum becomes smear-negative.

Rx:

RIPE—Rifampin, Isoniazid (INH), Pyrazinamide, and Ethambutol daily for eight weeks followed by INH and rifampin for an additional 16 weeks.

○ Give vitamin B6? to prevent INH-associated neuropathy.

Prognosis of tuberculosis :

usually good ,It is generally favorable if infections are localized to the lungs.

but it worsens significantly when:

The disease occurs aged, debilitated, or immunosuppressed persons
(who are at high risk for developing miliary tuberculosis, and in those with Multi-drug-resistant tuberculosis (MDR-TB).
Amyloidosis may appear in persistent cases.

Atypical features of TB in HIV+ :

These make the diagnosis of tuberculosis particularly challenging: Why?

An increased frequency of sputum-smear negativity for acid-fast bacilli compared with HIV-negative controls.?!

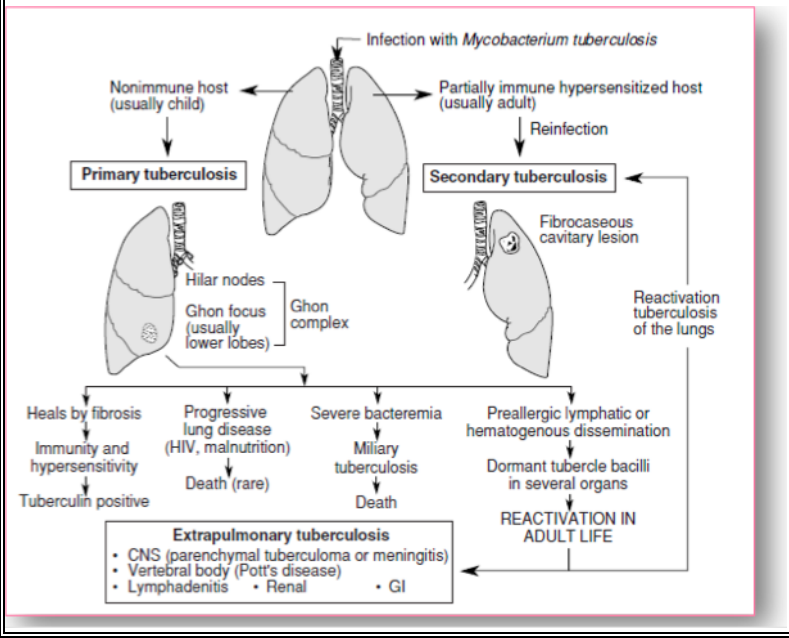
(This is because the incidence of cavitation and endobronchial damage is more in immunocompetent individuals and therefore induced sputum elicits more AFB)

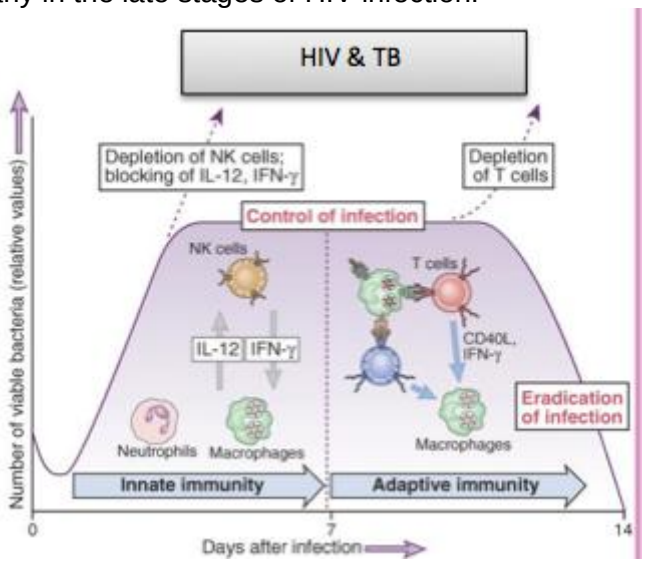
There is no immunity to make type IV hyper sensitivity reaction.

The absence of tissue (bronchial wall) destruction due to suppressed type IV hypersensitivity results in fewer bacilli in the sputum (despite the higher tissue bacillary load).

False-negative PPD (because of tuberculin anergy)

-The lack of characteristic granulomas in tissues, particularly in the late stages of HIV infection.





Bloodstream spread of organisms can lead to single-organ infections:
Sometimes only small numbers of tubercle bacilli escape into the blood and, if host defenses are effective, most of the organisms die. However, for reasons that are not yet certain, some bacilli settle in specific organs and may remain dormant for many years, only proliferating and producing overt disease at a later date, often after the initial lung and lymph node lesions have healed. Known as metastatic tuberculosis or isolated organ tuberculosis, the organs particularly involved in this pattern of disease include the adrenal glands, kidney, fallopian tube, epididymis, brain and meninges, and bones and joints.

SAMMARRY OF T.B :

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.

Lecture 6 - Pulmonary Infection

Pneumonia (lung infections)

1. **General considerations and clinical characteristics:**

(a) Pneumonia is an inflammatory process of infectious origin affecting the pulmonary parenchyma.

(b) It is characterized by **chills and fever**, productive cough, blood tinged or **rusty sputum**, pleuritic pain, hypoxia with shortness of breath and sometimes cyanosis. In very young children vomiting is a symptom not coughing.

(c) Classification according to criteria of pneumonia:

-Clinical (community acquired and hospital acquired)
-Pathological (based on the anatomic part of lung affected)
-Etiology (organism causing the pneumonia like: staph.pneumonia and strept.pneumonia … etc)

(d) If bacterial, it is most characteristically associated with neutrophilic leukocytosis with an increase in band neutrophils ("shift-to-the-left").

· Pulmonary Infection (Pneumonia) be very broadly defined as any infection in the lung.
· Respiratory tract infections are more frequent than infections of any other organ and account for the largest number of workdays lost in the general population, why?
– The epithelium of the lung is exposed to liters of contaminated air
– Nasopharyngeal flora are aspirated during sleep
– Underlying lung diseases render the lung parenchyma vulnerable to virulent organism.

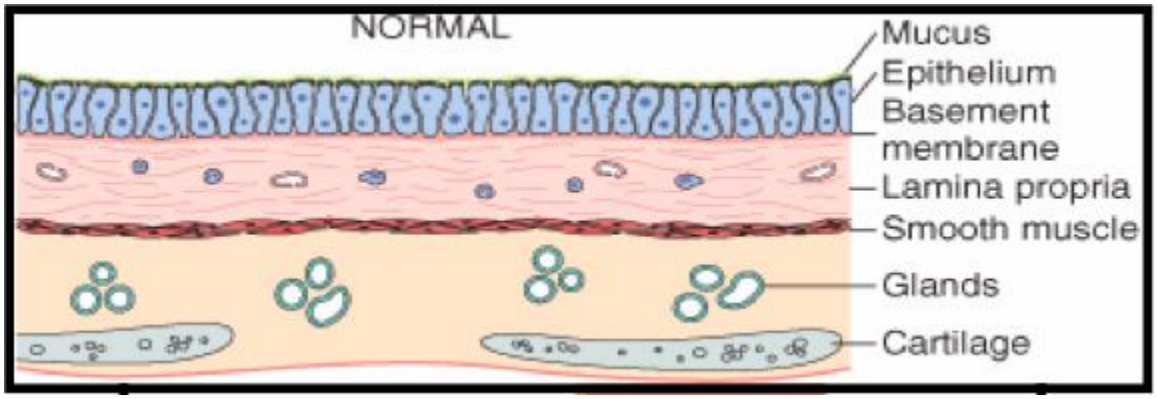
Pathogenesis of Pneumonia:
Each day, the respiratory tract is exposed to more
than 10,000 liters of air containing hazardous dust,
Chemicals and microorganisms.

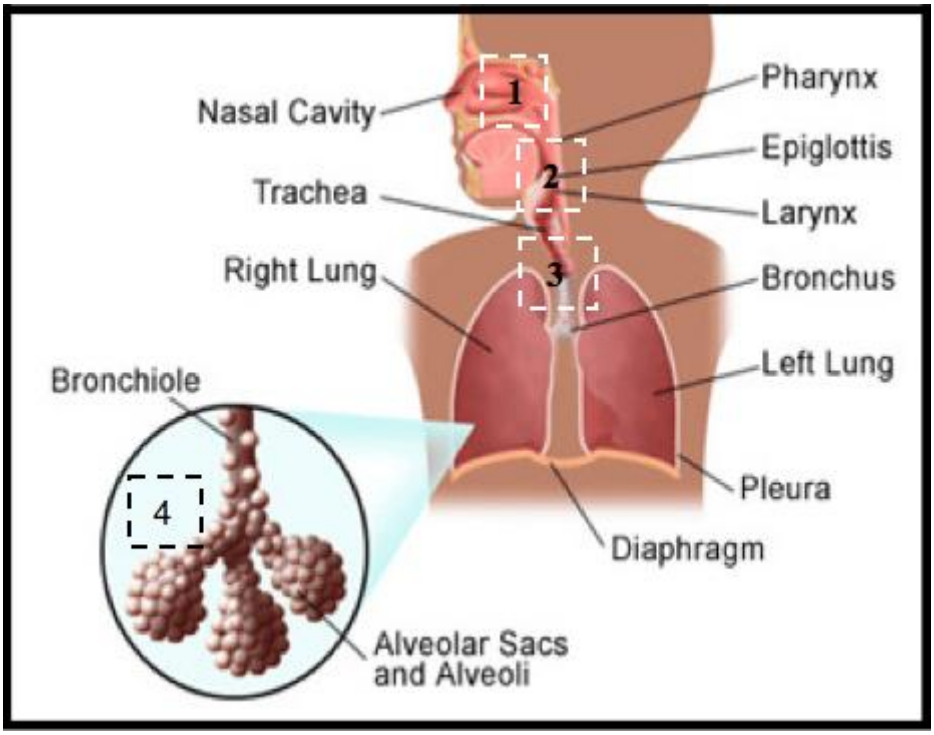
Particle > 10 µ	Particle 3-10 µ	the most important) Particle 1-3 µ (bacteria)	Smaller particles < 1 µ
Deposited in nose	Impacted in trachea and bronchi	Deposited in terminal airways and alveoli which may lead to pneumonia	may remain suspended in air

– Normal lung is free from bacteria.
• Pneumonia can result whenever:
– Defense mechanisms are impaired
– The resistance of the host in general is lowered

· Pulmonary Host Defenses: All of these host defenses are working together to make the lung sterile

Upper Airways:	Conducting airways:	Lower Respiratory Tract:
- Nasopharynx (1): Nasal hair, turbinates, mucociliary apparatus, IgA secretion - Oropharynx (2): Saliva, sloughing of epithelium, local complement production, interference from resident flora	- Trachea and Bronchi (3): Cough, epiglottic reflexes, sharp angled branches of the airways, mucociliary apparatus, Immunoglobulin (IgM, IgG, and IgA) secretion	- (4) Alveolar lining fluid (surfactant, immunoglobulin, complement and fibronectin), Cytokines (IL-1, TNF), alveolar macrophages, polymorphonuclear leukocyte, cell mediated immunity





· Impaired defense mechanisms:
- Loss or suppression of the cough reflex, as a result of coma, anesthesia, neuromuscular disorders, drugs, or chest pain.
- Injury to the mucociliary apparatus, by either impairment of ciliary function or destruction of ciliated epithelium e.g. cigarette smoke, inhalation of hot or corrosive gases, viral diseases, or genetic disturbances
- Interference with the phagocytic or bactericidal action of alveolar macrophages,by alcohol, tobacco smoke, anoxia, or oxygen intoxication
- Pulmonary congestion and edema
- Accumulation of secretions, e.g. cystic fibrosis and bronchial obstruction
- Defect in innate immunity, Include neutrophil, complement, humoral and cell mediated immune defects
Any of these conditions can lead to overgrowth of bacteria in the lung, which will further cause Pneumonia

- General factors that affect resistance:

– Chronic diseases (e.g. chronic bronchitis, bronchiolitis, cancer, DM,,, etc)
– Immunologic deficiency (e.g. AIDS)
– Treatment with immunosuppressive agents (e.g. patients with tissue transplantation- renal failure- sometimes cancer patients)
– Leucopenia: is a decreased in the number of white blood cells found in blood, which places individuals at increased risk of infection. The reduction may be drug related or due to problem in the bone marrow.
– Unusually virulent infections (e.g. legionella pneumophila)

- One type of pneumonia sometimes predisposes to another, especially in debilitated patients. Especially cancer patients and diabetic patients.
- Portal of entry for most pneumonia is the respiratory tract (most common pathway), hematogenous spread from one organ to other organs can occur (not the common pathway).
- Many patients with chronic diseases acquire terminal pneumonias while hospitalized (nosocomial infection).

Pathology of Pneumonia

- Pneumonia can be acute or chronic
- The histologic spectrum may vary:

1. Fibrinopurulent alveolar exudates: Pneumonia
2. Mononuclear interstitial infiltrate: Atypical Pneumonia
3. Granulomatous inflammation: e.g. Tuberculosis

The pneumonia syndromes

- Community-Acquired Acute Pneumonia (bacterial pneumonia)
- Community-Acquired Atypical Pneumonia
- Nosocomial Pneumonia (hospital acquired pneumonia)
- Aspiration Pneumonia
- Chronic Pneumonia
- Pneumonia in the Immunocompromised Host.

2. **Morphologic types of pneumonia** (pathological classification)**.** There are three morphologic and clinical patterns**: lobar pneumonia, bronchopneumonia** and **interstitial pneumonia.**

3. **Bacterial pneumonias.**

(a) **Lobar pneumonia** is most often caused by Streptococcus pneumonia (the pneumococcus). It is characterized by a predominantly **intra-alveolar exudate** and **may involve an entire lobe (one or more)** of the lung. It is not patchy or focal causing consolidation. It affects old and debilitated people. It has 4 stages:
-congestion (vascular congestion with little fibrin and neutrophils in alveoli)
-red hepatisation (looks like liver: firm because of a lot of exudate)
-grey or brown hepatisation (lots of macrophages)
-resolution (healing and little exudates)

(Patients with lobar pneumonia have pleural effusion so you have to measure protein in it and culture the fluid. If there is a patient with non resolving pneumonia specially an old man or smoker, think of an obstructed lesion.)

(b) **Bronchopneumonia** is caused by a wide variety of organisms. It is characterized by a **patchy distribution** involving **one or more lobes** and normal parenchyma interfering the affected parts, with **an inflammatory infiltrate extending from the bronchioles into the adjacent alveoli.** There are foci around the affected area (bronchi, bronchioles and adjacent alveoli). It likes lower lobes most of the time.

– Bacterial Pneumonia:

- Bacterial invasion of lung parenchyma evoke exudation of fibrinpurulent fluid in the alveoli and solidification.
- Classification may be made according to causative agent or gross anatomic distribution of the disease.

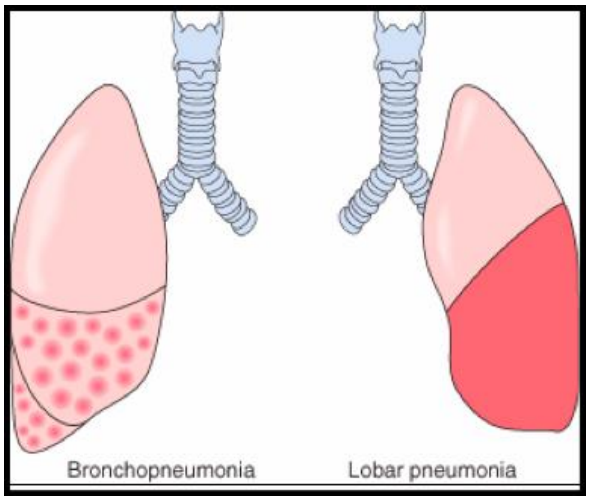
Anatomic distribution of pneumonia:

Bronchopneumonia:

- Represent an extension from preexisting bronchitis or bronchiolitis.
- Extremely common tends to occur in two extremes of life.

Lobar pneumonia:

- Acute bacterial infection of a large portion of a lobe or entire lobe.
- Classic lobar pneumonia is now infrequent



- Overlap of the two patterns often occur.
- Identification of clinical pattern is more important. Nowadays this classification is not widely used

Bronchopneumonia	Lobar pneumonia
most common agents are: - *Streptococcus pneumonea,* - *Haemophilus Influenza,* - *Pseudomonas Aeroginosa* - Coliform bacteria.	• 90-95% are caused by pneumococci (type 1,3,7 & 2) • Rare agents: *K. pneumoniae* staphylococci - streptococci *H. influenzae* - Pseudomonas and Proteus

Etiology of pneumonia

- ***Community-Acquired Acute Pneumonia:***

– Bacterial

– Can follows viral URT infection

– Sudden onset of high fever, chills, pleuritic chest pain and productive cough, may be with hemoptysis

– Streptococcus pneumoniae is the most common cause of Community-Acquired Acute Pneumonia

– Frequently affected pt. are those with:

1. Underlying chronic disease e.g. DM, COPD, and CHF
2. Congenital or acquired immune deficiency
3. Decreased or absent splenic function

– Other causative organisms are:

1. Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Legionella pneumophila, Enterobacteriaceae (Klebsiella pneumoniae) and Pseudomonas spp.

S. aureus lung: abscess and empyema

Empyema: pus in pleural cavity

▪*P. aeruginosa* is most commonly seen in nosocomial pneumonia, is associated with infections in cystic fibrosis

Morphology of pneumonia

Community-Acquired Acute Pneumonia

- Lobar or bronchopneumonia may occur.
- The lower lobes or the right middle lobe are most frequently involved.
- Widespread fibrinosuppurative consolidation.

.

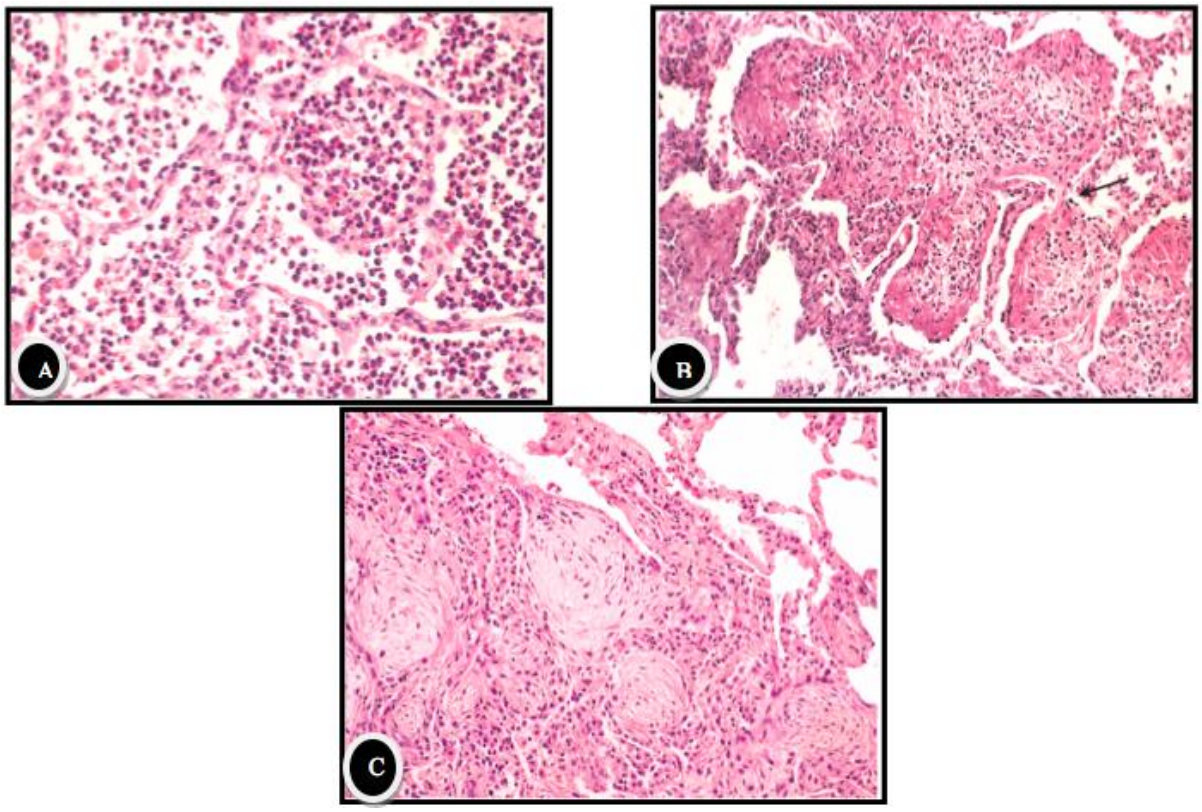
Stages of pneumonia:

1. **Congestion –** vascular congestion can be seen with proteinaceous fluid, scattered neutrophils and many bacteria in the alveoli.

2. **Red hepatization –** alveolar spaces are packed with neutrophils, red cells, and fibrin, pleura fibrinous or fibrinopurulent exudate

3. **Gray hepatization –**fibrinous exudate persists within the alveoli.

4. **Resolution –** exudates within the alveoli are enzymatically digested.



Clinical features:

- Abrupt onset of high fever, shaking chills, and cough productive of mucopurulent sputum; occasional patients may have hemoptysis.

- When fibrinosuppurative pleuritis is present, it is accompanied by pleuritic pain and pleural friction rub

Complications of pneumonia:

- Tissue destruction (abscess).

- Empyema.

- Organization of alveolar exudate – solid fibrinous tissue.

- Bacteremic dissemination may lead to meningitis, arthritis or infective endocarditis.

· ***Dx & Rx of Community-Acquired Acute Pneumonia***

- Examination of Gram-stained sputum smear is helpful in diagnosis
- Blood culture is more specific (only +ve in 20% to 30% of pt.)
- Pneumococcal pneumonia respond to penicillin Rx

- ***Community-Acquired Atypical Pneumonia:***

Primary atypical pneumonia

– Pt. Usually present with flulike symptoms with pharyngitis evolved into laryngitis, trachiobronchitis and pneumonia with little sputum and no lung consolidation

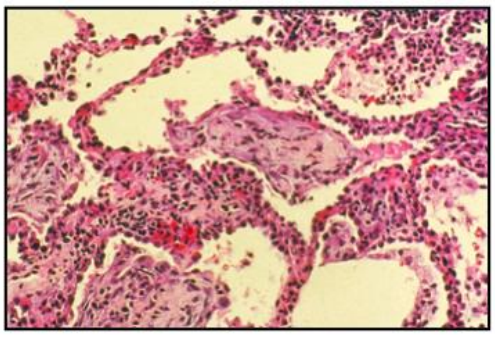
– *Mycoplasma pneumoniae, Chlamydia* spp. (*C. pneumoniae, C. psittaci, C. trachomatis*)

– Inhalation of dried excreta of birds lead to Ornithosis **(Psittacosis)** due to chlamydia infection

– *Coxiella burnetti* (Q fever)

– Viruses: respiratory syncytial virus, parainfluenza virus (children); influenza A and B (adults); adenovirus and SARS virus *(Severe Acute Respiratory Syndrome).*

-- Acute febrile respiratory disease characterized by patchy inflammatory infiltration by lymphocyte and plasma cells largely confined to the alveolar septa and pulmonary interstitium- (Interstitial pneumonitis).



4. **Interstitial (primary atypical) pneumonia** is caused by various infectious agents, most commonly **Mycoplasma pneumoniae** or **viruses or clamydia.** It is characterized by **diffuse, patchy inflammation** localized to interstitial areas **of alveolar walls.** On x-ray it looks like restrictive lung diseases.

(a) **Mycoplasma pneumonia**. (Gram negative with no cell wall)

(1) This is the **most common form of interstitial pneumonia**; it usually occurs in children and young adults and it **may occur in epidemics.**
(2) Onset is more insidious compared to bacterial pneumonia and usually follows a mild, self-limited course.
(3) Characteristics include an inflammatory reaction confined to the interstitiium, with no exudate in alveolar spaces and intra-alveolar hyaline membranes.

(4) **Diagnosis** by cold agglutinin test and sputum cultures, requiring several weeks of incubation and by complement fixing antibodies.

(5) Mycoplasma pneumonia may be associated with non specific cold agglutinins reactive to red cells. This phenomenon is the basis for a quick and easy laboratory test that can provide early diagnostic information.

Morphologic Variants of Pneumonia: Causative Organisms and Characteristics

Variant	Causative Organism	Characteristics
Lobar pneumonia	Most frequently strep-tococcus pneumoniae (pneumococcus)	Predominantly intra-alveolar exudate resulting in consolidation. May involve **the entire lobe**. If untreated, may morphologi-cally evolve through **four stages:** congestion, red hepati-zation, gray hepatization and resolution.
Bronchopneumonia	Many organisms including staphylococcus aureus, haemophilus influenza, Klebsiella pneumoniae, and streptococcus pyogenes	Acute inflammatory infiltrates extending from the bron-chioles into the adjacent alveoli. **Patchy or focal distribution** involving one or more lobes.
Interstitial Pneumonia	Most frequently viruses or mycoplasma pneumoniae	Diffuse, patchy inflammation localized to interstitial areas of the alveolar walls. Distribution involving one or more lobes.

- ***Aspiration pneumonia***

– Occur in debilitated patients or those who aspirated gastric contents
– Chemical injury due gastric acid and bacterial infection including:
• Anaerobic oral flora (*Bacteroides, Prevotella, Fusobacterium, Peptostreptococcus*), admixed with aerobic bacteria *(Streptococcus pneumoniae, Staphylococcus aureus, Haemophilas influenzae,* and *Pseudomonas aeruginosa*
• A necrotizing pneumonia with fulminant clinical course, common complication (abscess) and frequent cause of death.

- ***Chronic Pneumonia***

Tuberculosis is by far the most important entity within the spectrum of chronic pneumonias

(b) **Viral pneumonias** are **the most common types of pneumonia in childhood.** They are cause most commonly by influenza viruses, adenoviruses, rhinovirus and respiratory syncytial virus, may also arise after childhood exanthems (viral eruptions) such as rubeola (measles) or varicella (chicken pox); the measles virus produces giant cell pneumonia, marked by numerous giant cells and often complicated by tracheobronchitis.

(c) **Ornithosis (psittacosis)** is caused by an organism of the genus **Chlamydia,** (also causes trachoma conjunctivitis and urethritis) which is transmitted by inhalation of dried excreta of infected birds.

- ***Pneumonia in the Immunocompromised Host***

- Cytomegalovirus
- Pneumocystis jiroveci
- Mycobacterium avium-intracellulare
- Invasive aspergillosis
- Invasive candidiasis
- "Usual" bacterial, viral, and fungal organisms

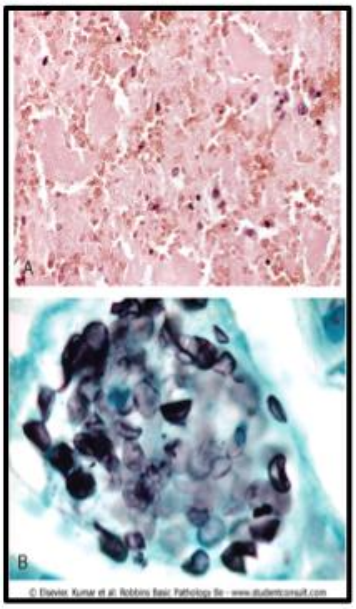
5. **Pneumocytis carinii pneumonia** is the most common **opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS);** it also occurs in other forms of immunodeficiency.

(a) It is caused by pneumocystis carinii (recently renamed Pneumocystis jiroveci) which **is now classified as a fungus**.

(b) Diagnosis is by morphologic demonstration of the organism in biopsy or bronchial washing specimens. (In bronchial washing there is a "soup bubble exudate" shape with no inflammatory cells because of immunodeficiency. Silver stain is used for showing cysts having a comma shaped organisms inside) Treatment by tetracycline.

Pneumocystis Pneumonia

Microscopically, involved areas of the lung demonstrate a characteristic **intra-alveolar foamy, pink-staining exudate** with H&E stains



Silver stain demonstrates cup-shaped cyst walls within the exudate

- ***Nosocomial pneumonia***

hospital acquired pneumonia

– Common in pt. with sever underlying conditions e.g. immunosuppression, prolonged antibiotic therapy, intravascular catheter and pt. with mechanical ventlator

6. **Hospital-acquired gram-negative pneumonias.**

(a) These pneumonias are often fatal and occur in hospitalized patients, usually those with serious and debilitating diseases.

(b) Causes include many **gram-negative organisms** **belonging to Enterobacteriaceae**, including Klebsiella, Serratia marcescens,Pseudomonas aeruginosa and Escherichia coli. Endotoxins products by these organisms play an important role in the infection.

7. Aspergillus Pneumonia in immune-compromised patients. It causes bronchopneumonia or interstitial pneumonia. Under microscopy using PS stain, there are septated fungal organisms branching in acute angle.

LUNG ABSCESS

1. It is a collection of neutrophils, fibrin and cellular debris with bacteria lined by vascular granulation tissue. This is a **localized area of suppuration** within the parenchyma, **usually resulting from bronchial obstruction (often by cancer)** or from **aspiration of gastric contents;** may also be **a complication of bacterial pneumonia**.

- Features: tissue necrosis and marked acute inflammation
- Posssile causes: aerobic and anaerobic e.g. streptococci, *Staphylococcus aureus,* and many gram negative organisms

- Can follow aspiration (one abscess of Rt. lung)

- Occur as complication of pneumonia (multiple)

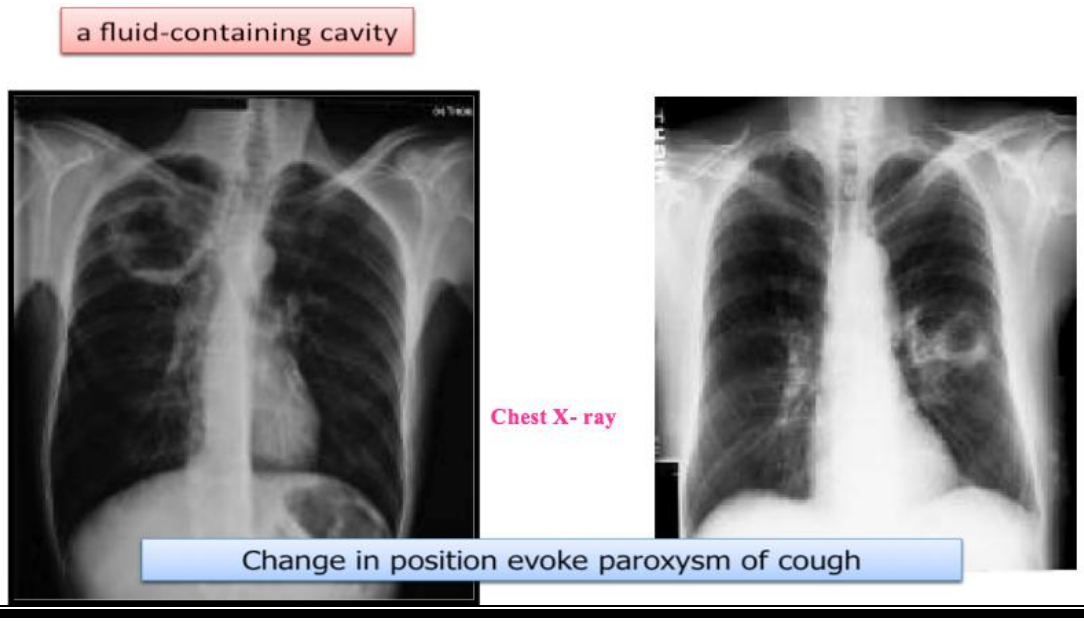
- Abscess is filled with necrotic suppurative debri

2. Patients predisposed to the formation of lung abscesses are those who have aspiration by **loss of consciousness** from alcohol or drug overdose, neurologic disorders, or geneal anaesthesia.

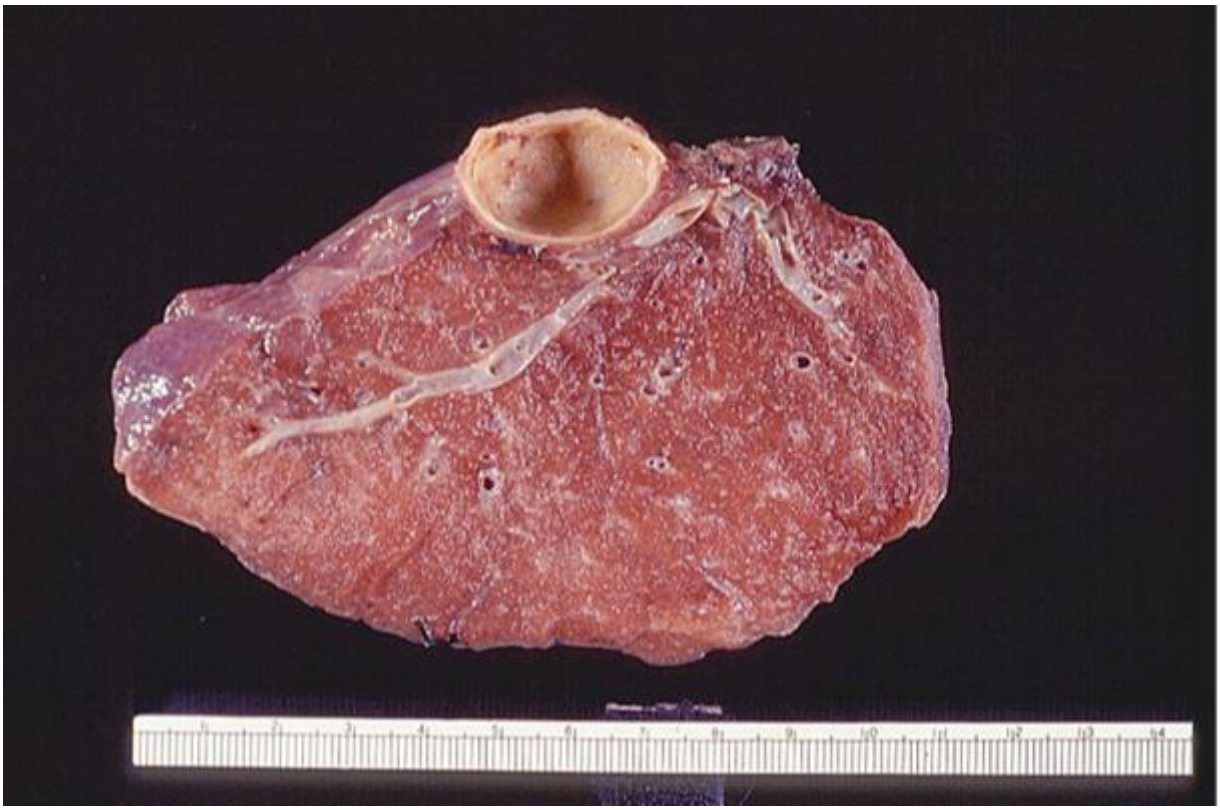
3. Frequent **causes** include Staphylococcus, pseudomonas, Klebsiella or Proteus, often in combination with anaerobic organisms.

4. **Clinical manifestations** include fever, foul-smelling purulent sputum and radiographic (chest xray) show evidence of a fluid-filled cavity.

• Chest radiograph of a patient who had fever, cough, foul-smelling and bad-tasting sputum, an almost diagnostic feature of anaerobic lung abscess.



Lung abscess



- **Complications of lung abscess:**

- Pleural involvement (empyema) formation resulting from a bronchopleural fistula
- massive hemoptysis, spontaneous rupture into uninvolved lung segments
- non-resolution of abscess cavity
- Bacteremia could result in brain abscess and meningitis
- with antibiotic therapy 75% of abscess resolve