TUBERCULOSIS

Respiratory Block

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Objectives

- Recognize that tuberculosis as a chronic disease mainly affecting the respiratory system.
- Know the epidemiology of tuberculosis world wide and in the kingdom of Saudi Arabia
- Understand the methods of transmission of tuberculosis and the people at risk.

- Know the causative agents and their characteristic and classification and methods of detection.
- Understand the pathogenesis of tuberculosis.
- Differentiate between primary and secondary tuberculosis and the clinical features of each.

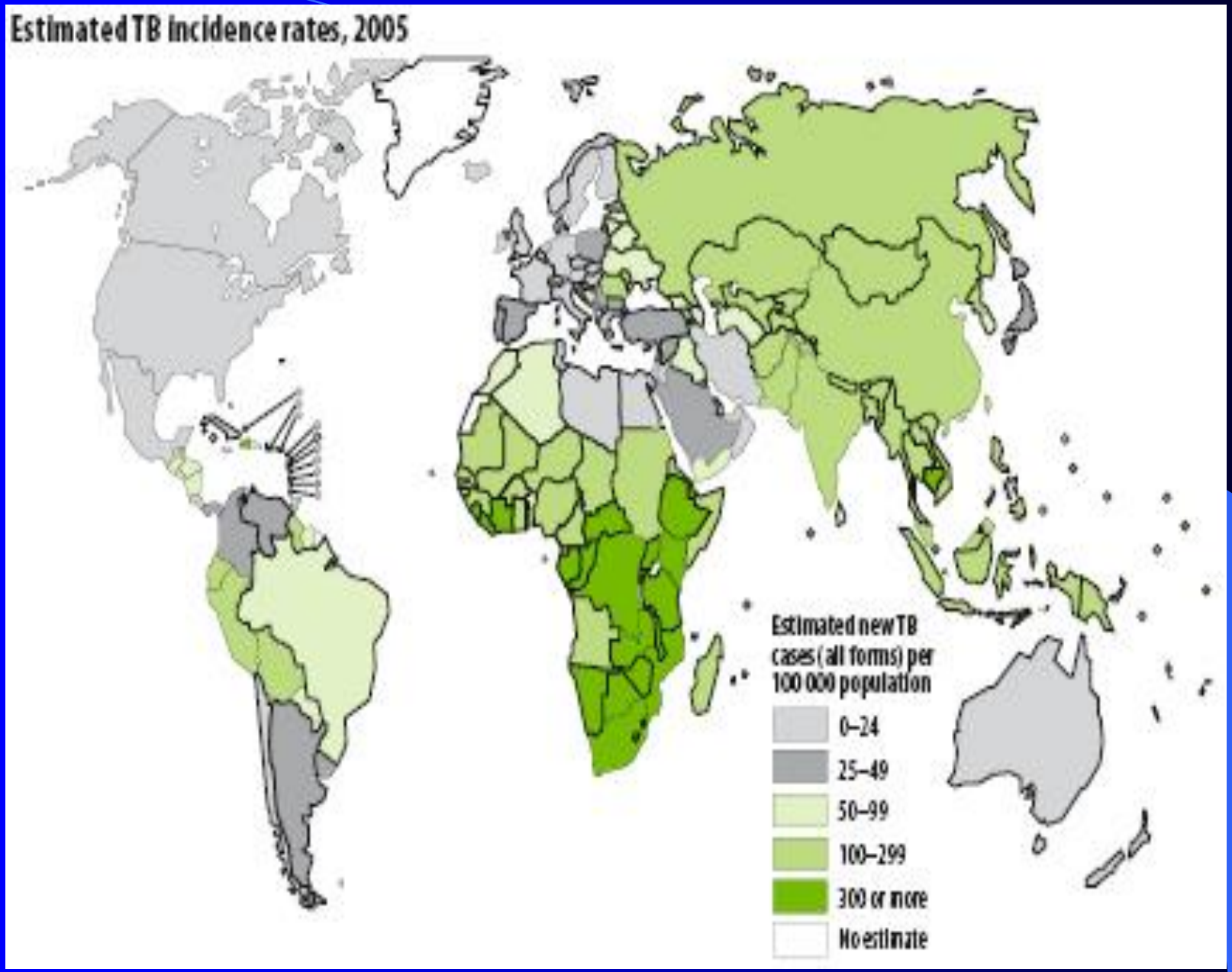
- Understand the method of tuberculin skin test and result interpretation ..
- Know the laboratory and radiological diagnostic methods.
- Know the chemotherapeutic and other methods of management of tuberculosis cases.
- Describe the methods of prevention and control of tuberculosis.

Introduction

- Tuberculosis (TB) is an ancient ,chronic disease affects humans, caused by *Mycobacterium tuberculosis* complex.
- A major cause of death worldwide.
- Usually affects the lungs, other organs can be affected in one third of cases.
- If properly treated is curable, but fatal if untreated in most cases.

Epidemiology

- TB affects 1/3 of human race (2 billions) as a latent dormant tuberculosis.
- **Incidence**: a world wide disease , more common in developing countries.
- Affects all age groups who are subject to get the infection.


Estimated TB incidence rates, 2005
Estimated new TB cases (all forms) per 100 000 population
0–24
25–49
50–99
100–299
300 or more
No estimate

Epidemiology

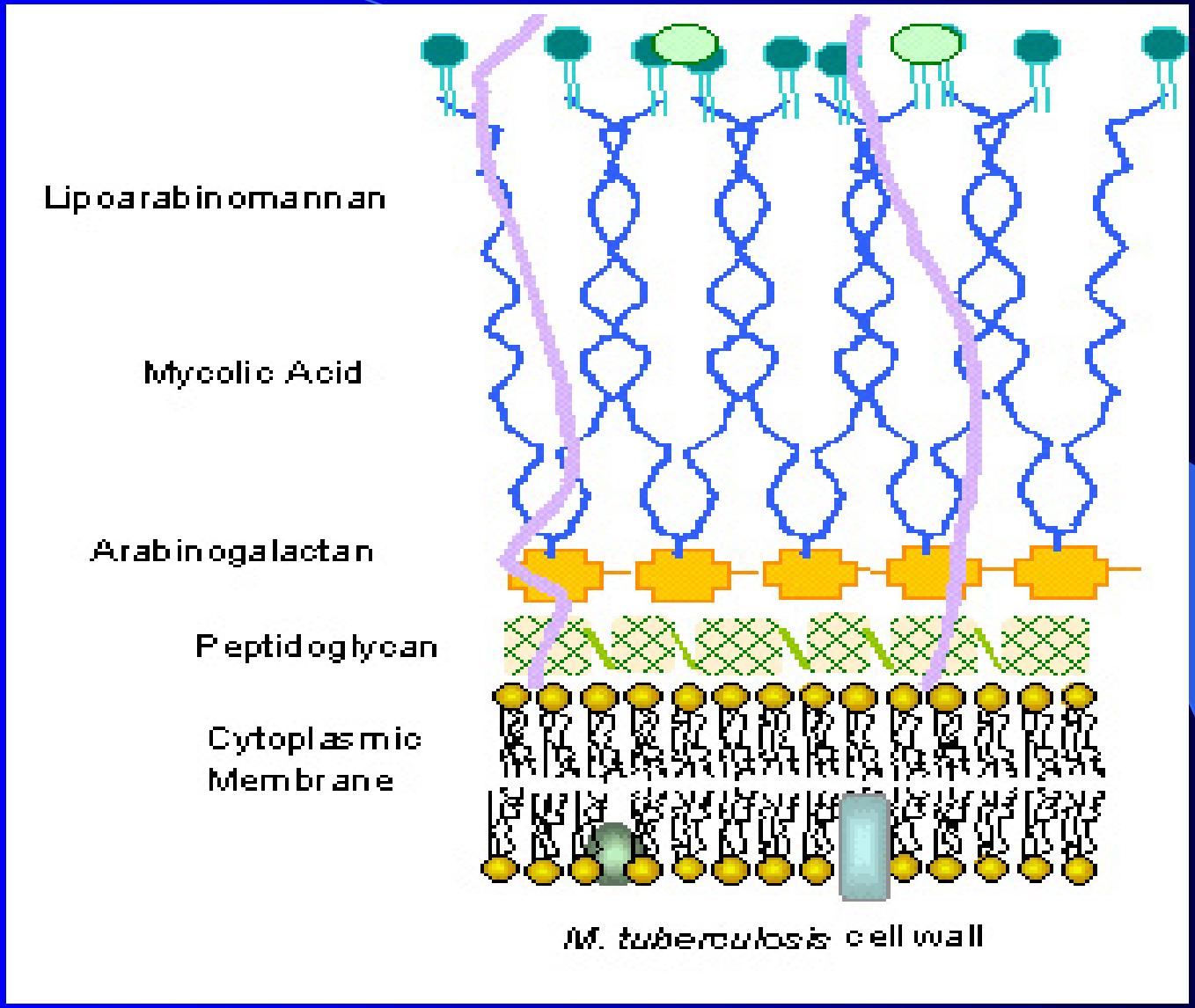
- The WHO estimated 8.9 million new cases in 2004 & 2 - 4 million death.
- **Incidence :**
- **in KSA** : 32-64 cases /100,000
- **in USA** : 5.2 cases/100,000
- **in South Ease Africa** : 290 cases /10,000 due to coupling with HIV infection.

Epidemiology

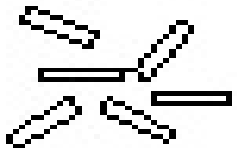
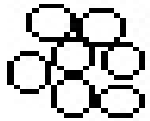
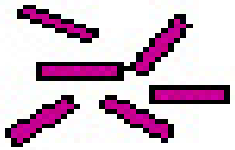
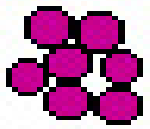
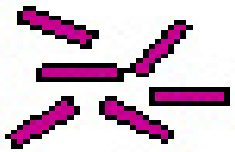
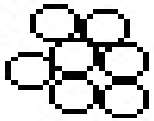
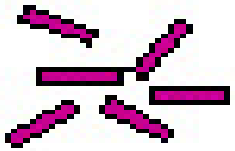
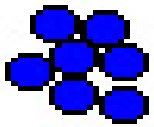
- Transmission mainly through inhalation of airborne droplet nuclei (< 5 μm) in pulmonary diseases case , rarely through GIT & skin
- **Reservoir:** patients with open TB.
- **Age***:* young children & adults
- **People at risk :** lab. technicians, workers in mines, doctors ,nurses. HIV pts., diabetics end stage renal failure, contacts with index case.

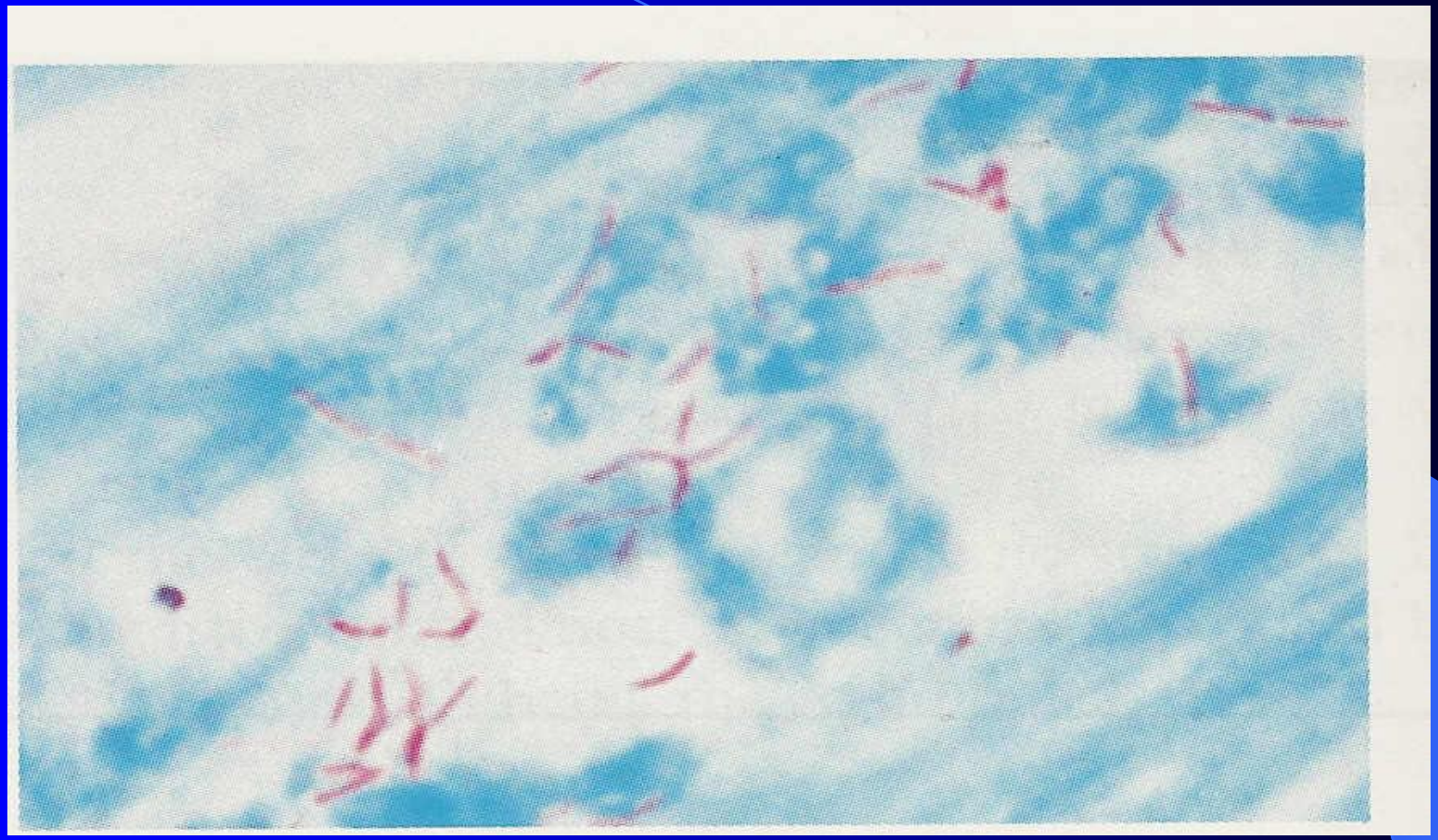
Characteristics of the Genus Mycobacteria

- Slim, rod shaped, non-motile, do not form spores.
- Do not stain by Gram stain . Why ?
- Contain high lipid conc. (Mycolic acid) in the cell wall which resist staining . It is called **Acid- alcohol fast bacili (AFB)**, Why ? It resists decolorization with up to 3% HCL, 5%ethanol or both.


Lipoarabinomannan
Mycolic Acid
Arabinogalactan
Peptidoglycan
Cytoplasmic Membrane
M. tuberculosis cell wall

Ziehl-Neelson Stain
Kinyoun Modification

Acid Fast Organisms		Not Acid Fast Organisms
	A small amount of organism suspended in saline solution is fixed on a slide.	
	Slide is flooded with Carbol Fuchsin and phenol for 3 minutes, and gently rinsed with water.	
	Slide is decolorized with 3% HCl in 70% alcohol until color appears to be removed (approx. 2 mins), and rinsed with water.	
	Slide is flooded with methylene blue counterstain for 30 secs, rinsed with water and air-dried.	



Mycobacterium tuberculosis **(approx. x 1000)**

Acid-Fast Bacilli (AFB)

- Stain used : **Ziehl-Neelsen** stain (ZN stain)
- Strict aerobe
- Multiply intracellularily
- Delayed hypersensitivity reaction type of immune response
- Slowly growing (2 - 8 wks.)

Mycobacterium tuberculosis complex

- 1- ***M.tuberculosis*** (Human type)
- *2-* ***M. bovis*** (Bovine type)
- 3- *M. Africanum*
- 4- *BCG strains*

All are called *Mycobacterium tuberculosis* Complex and cause tuberculosis (TB) .

Pathogenesis of Tuberculosis

- Mycobacteria acquired by airborne droplet reaches the alveolar macrophages , able to survive their (main virulence factor).
- This starts cell mediated immune response which controls the multiplication of the organism but does not kill it.
- Granuloma formed , organism lives in dormant state (latent tuberculosis infection)

Pathogenesis of Tuberculosis

- Patient show evidence of delayed cell mediated immunity (CMI).
- Disease results due to destructive effect of CMI .
- Clinically the disease is divided into primary or secondary .

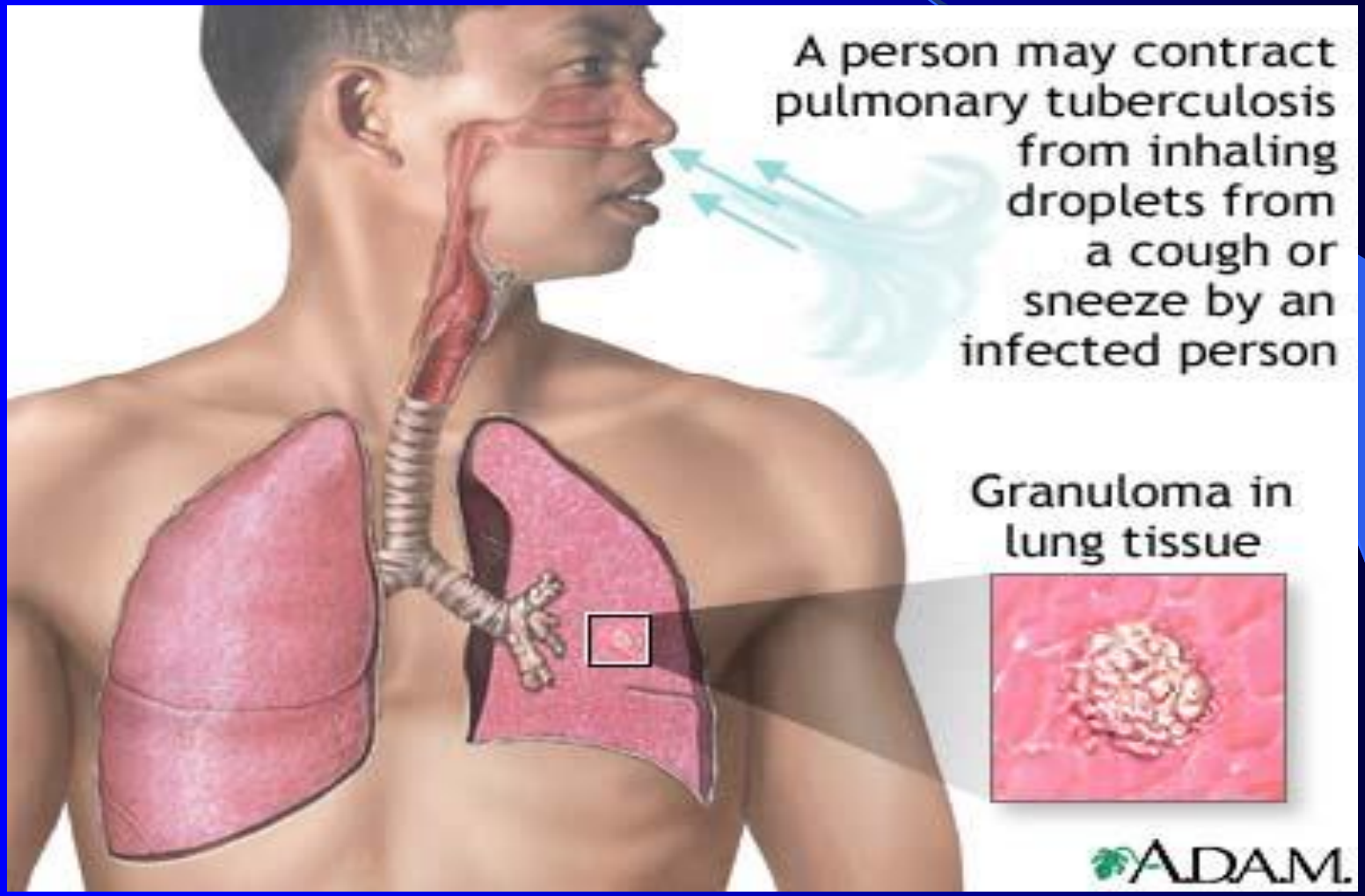
Pathogenesis of Tuberculosis

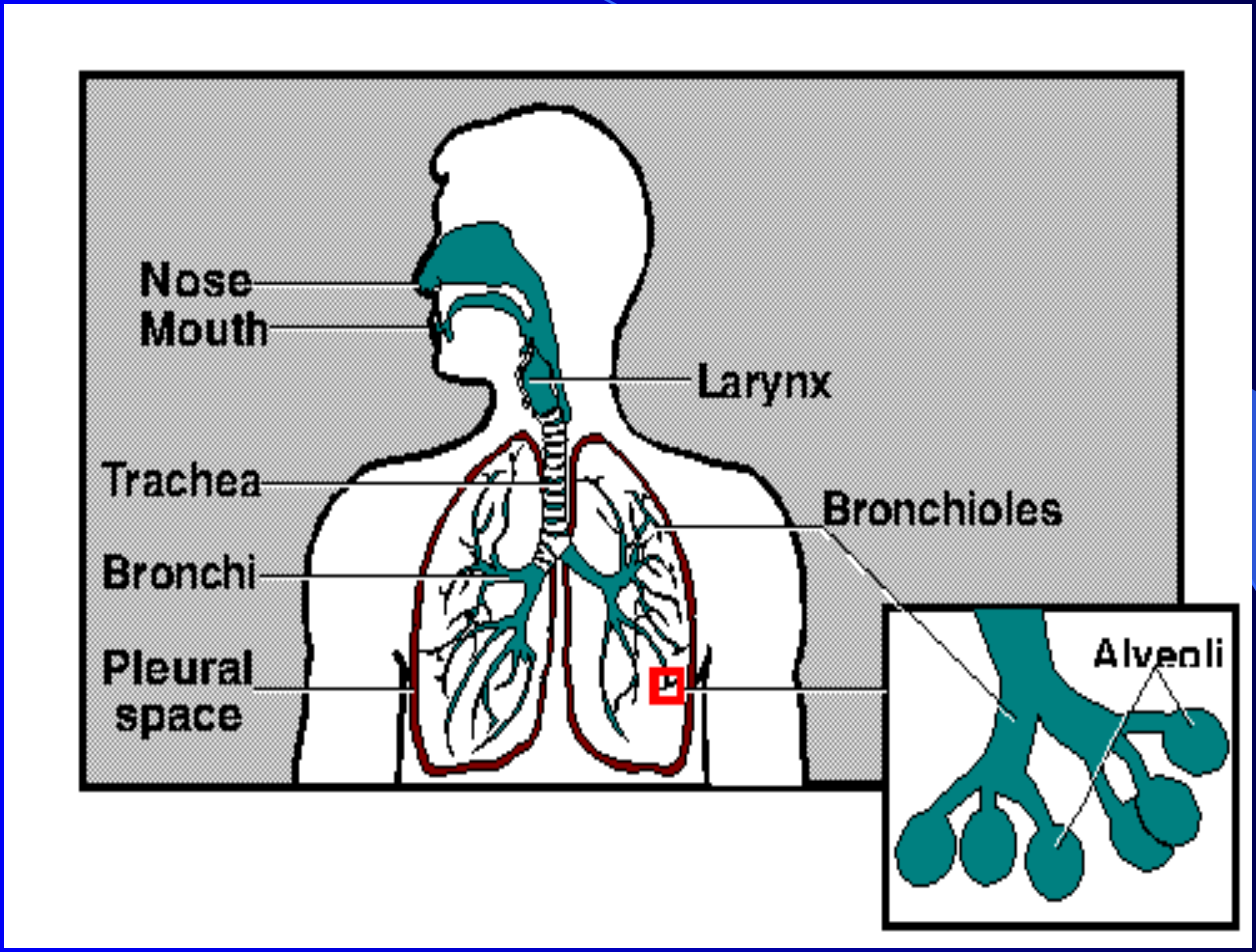
- **Primary Tuberculosis**

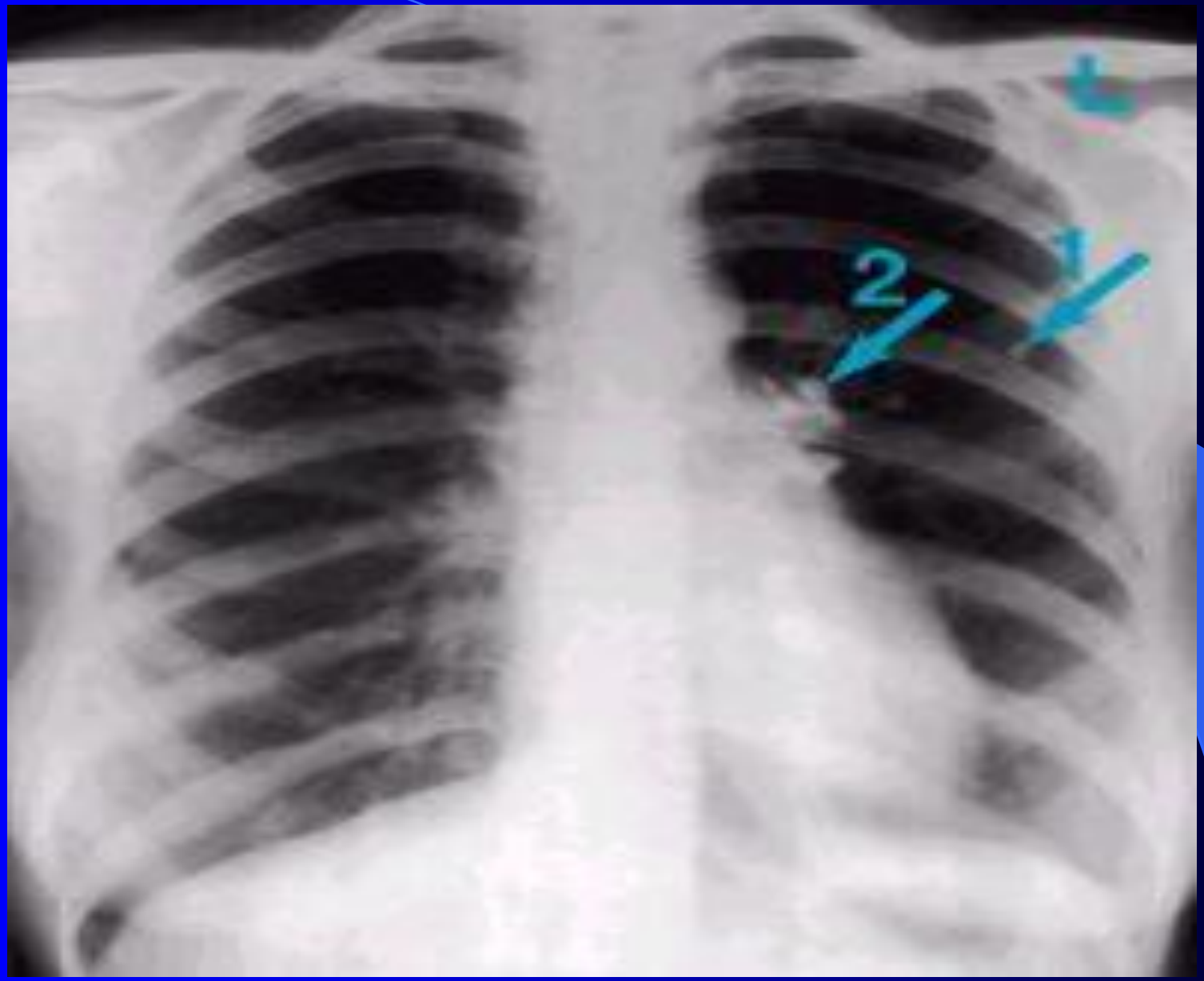
Occurs in patients not previously infected.

Inhalation of bacilli → Phagocytosis →
lymph nodes calcify to produce **GHON focus** (or **Primary Complex**) at the periphery of mid zone of lung.

Pathogenesis of TB




Nose
Mouth
Larynx
Trachea
Bronchioles
Bronchi
Pleural space
Alveoli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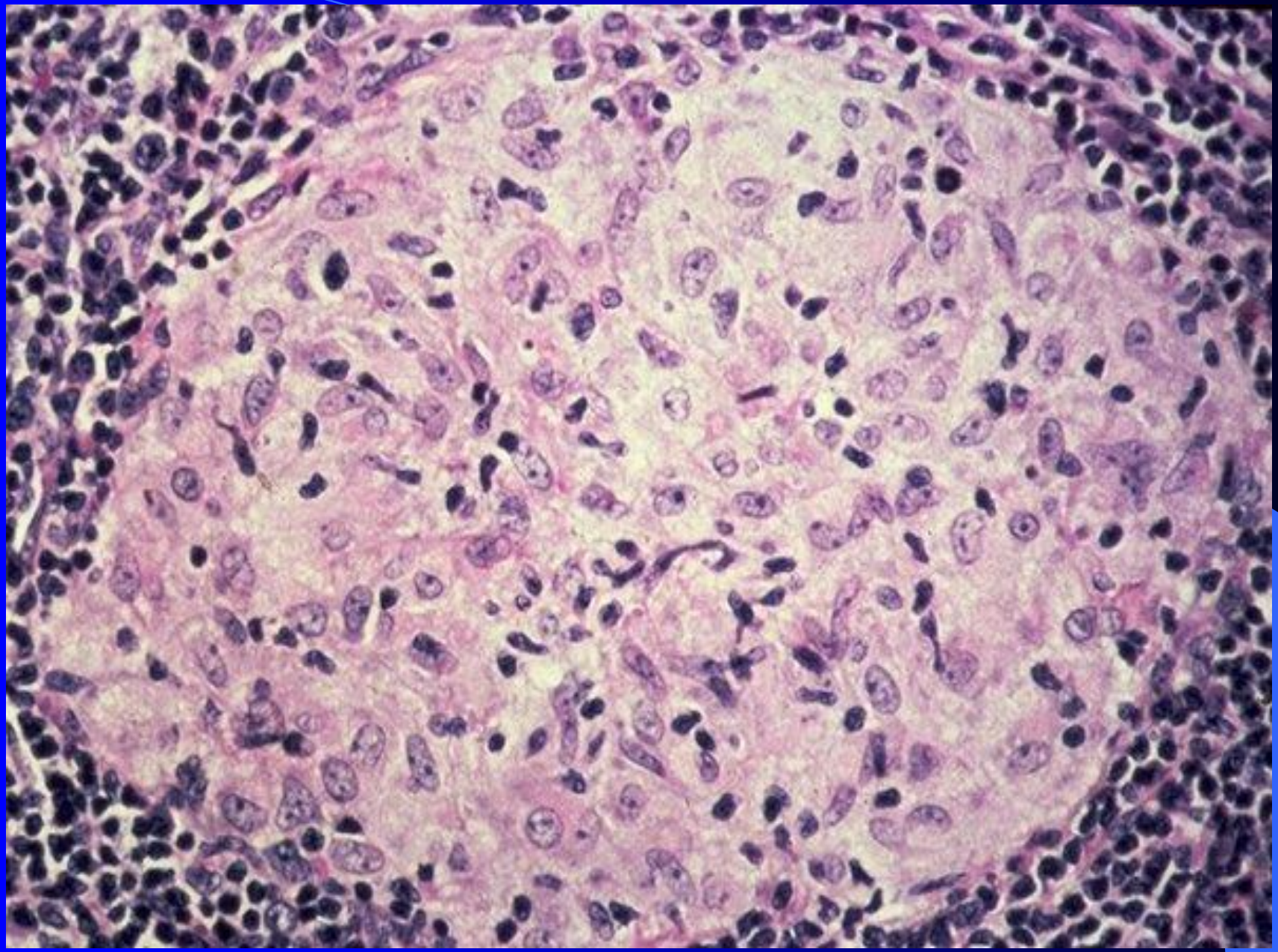
2

Primary Tuberculosis

- Microscopy of lesion shows Granuloma.
- **Clinically**: primary TB usually asymptomatic or / minor illness.
- **Non-pulmonary TB**: may spreads from pulmonary infections to other organs eg.:
  - TB of lymph nodes (cervical, mesenteric).
  - TB meningitis
  - TB bone & joint

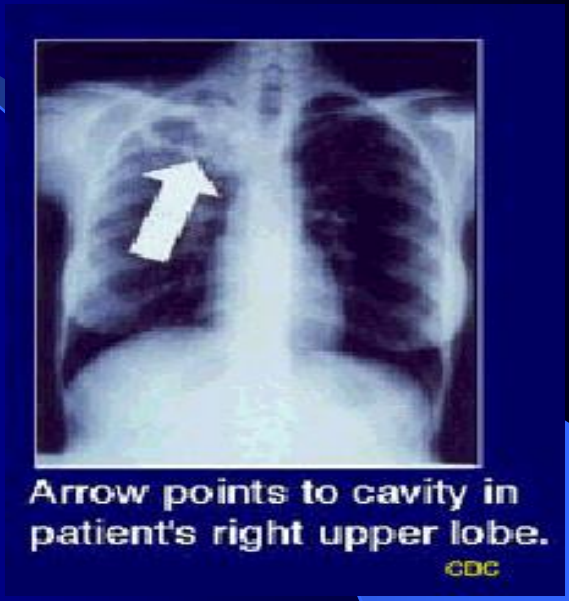


Primary Tuberculosis

- Genitourinary TB
- Miliary TB → (blood and other organs)
- Soft tissue **(cold abscess)**: lack of inflammation with caseation.
- **Caseation**: due to delayed hypersensitivity reaction. Contains many bacilli ,enzymes, O_2,N_2 intermediates, → necrotic centre of granuloma → cheezy material.

Secondary TB (reactivation)

- Occurs later in life
- Lung more common site
- Immunocompromised patients.
- Lesion localized in apices
- **Infectious & symptomatic**
- Microscopy: many bacilli, large area of caseous necrosis → **cavity (open TB) with granuloma and caseation.**



Secondary TB

- Clinically: fever, cough, hemoptysis ,weight loss & weakness.
- **Source of secondary TB :**

- Endogenous (reactivation of an old TB) or

- Exogenous (re-infection in a previously sensitized patient who has previous infection with the organism**).**

Immunity to Tuberculosis

- Cell-mediated immunity associated with delayed hypersensitivity reaction.
- Detected by **tuberculin skin test**.
- Tuberculin test takes 2-10 weeks to react to tuberculin and becomes positive.

Tuberculin Skin Test

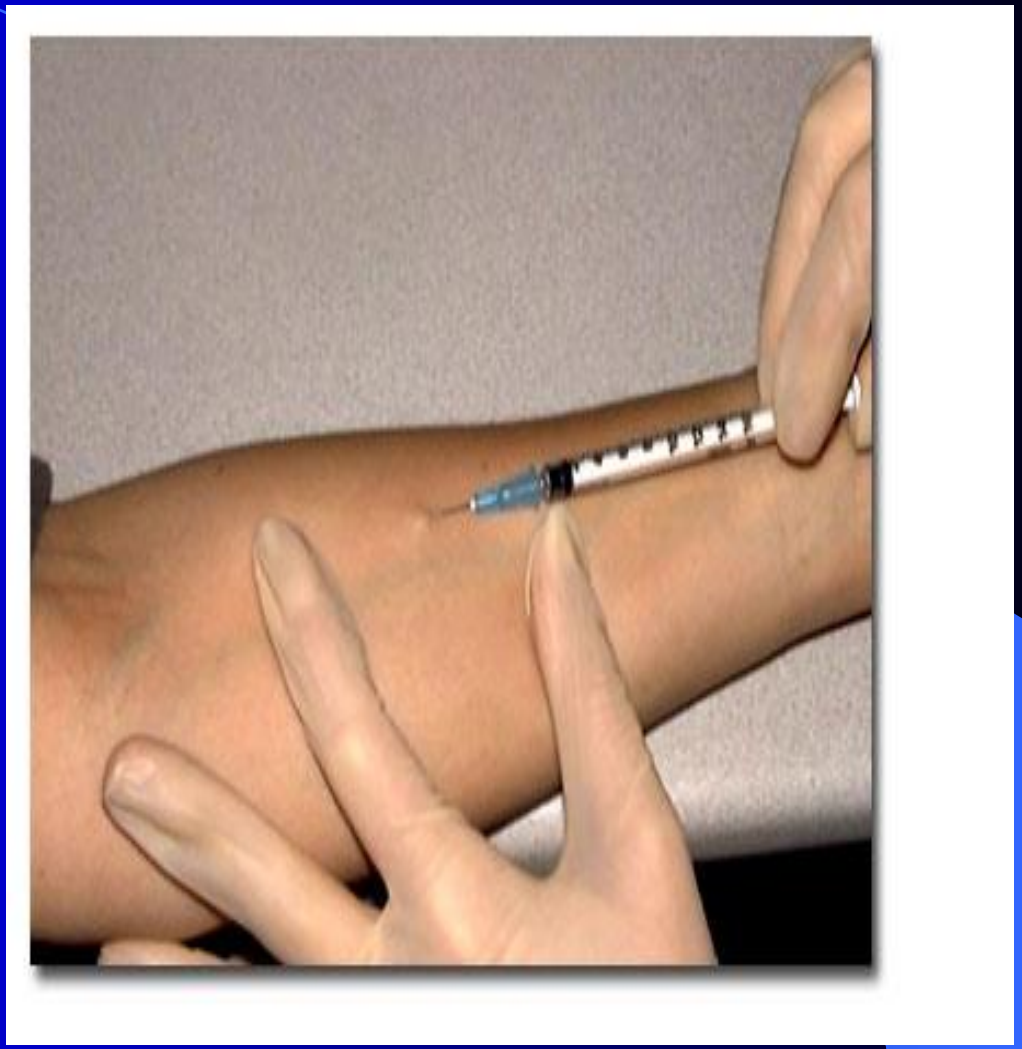
- Uses purified protein derivative (**PPD**).
- Activity expressed by Tuberculin unit .
- Activates synthesized lymphocytes to produce CMI which appear as skin induration.
- May not distinguish between active and past infection except in an individual with recent contact with infected case.
- Low level activity induced by environmental mycobacteria , previous vaccination.

Methods of Tuberculin Skin Test

- Intradermal inoculation of 0.1 ml of PPD , 5TU.
- Read after 48-72hrs.
- ***Methods of tuberculin skin test*** **:**

1- **Mantoux test.**

2- **Heaf test** (for screening, rarely used).



Positive Tuberculin Skin Test

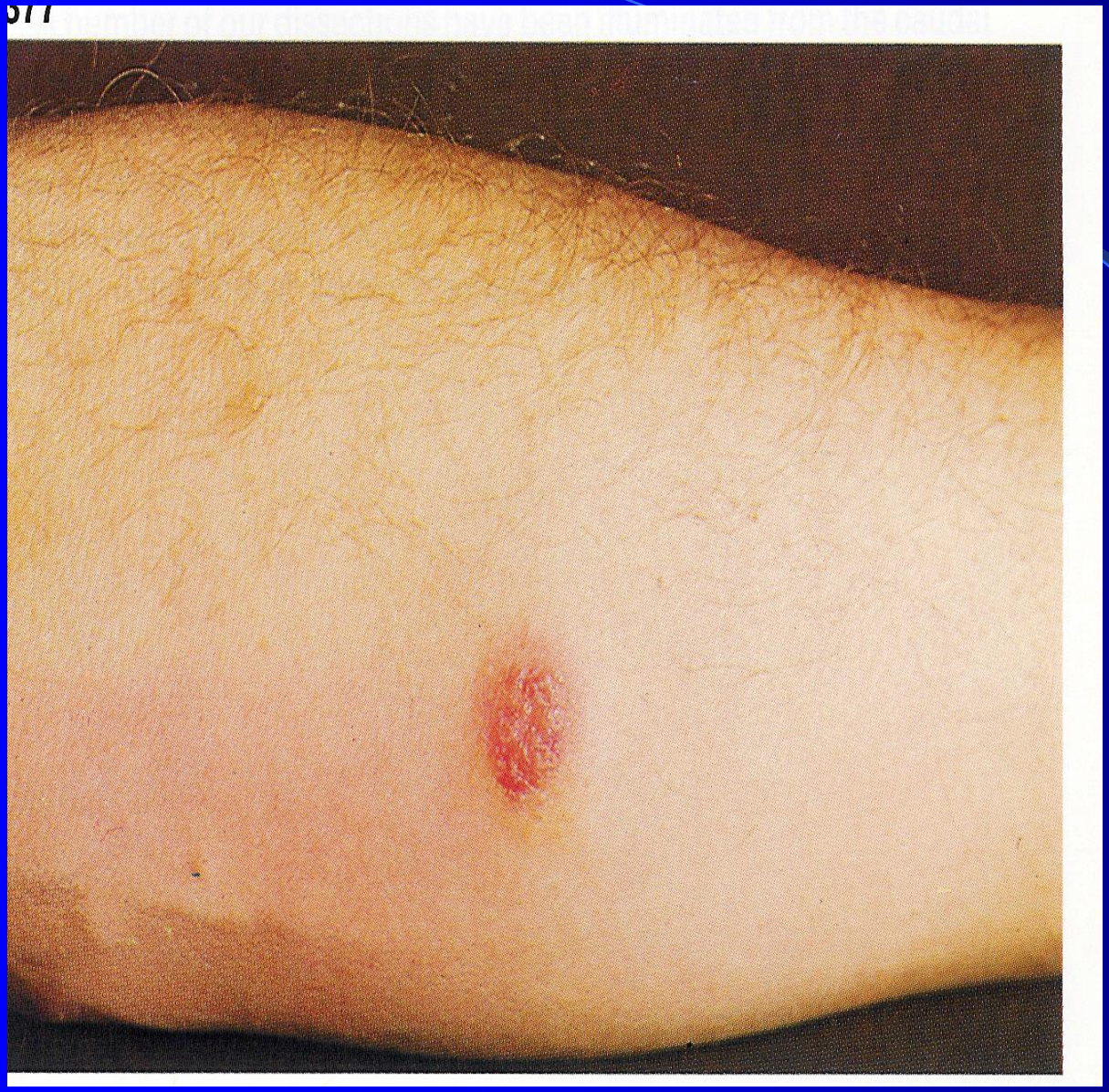
- 1- **>5mm** induration positive in :
  - Recent contact with active TB.
  - HIV or high risk for HIV
  - Chest X-ray consistent with healed TB.
- 2- **> 10mm** induration positive in:
  - IV drugs user, HIV seronegative patient.
  - Medical conditions eg. *diabetes , malignancy*.

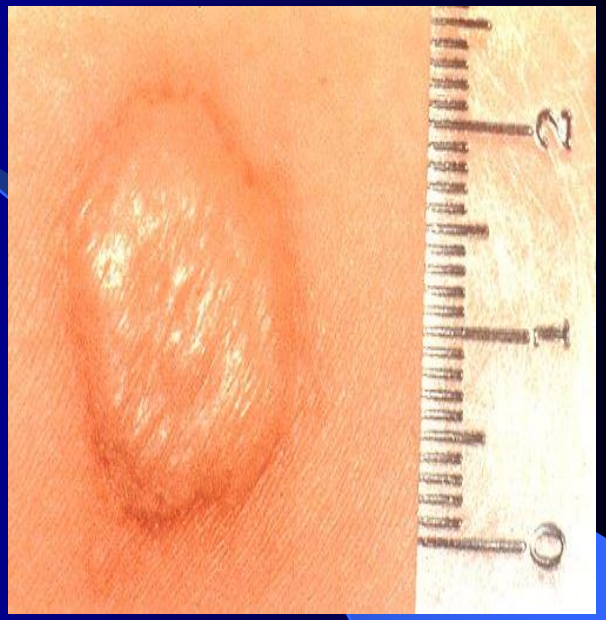
Positive Tuberculin Test

- Residents & employee at high risk
- Patients from country with high incidence.
- Children < 4yrs or exposed to adult high risk group.
- Mycobacteriology lab. personnel.

➢ **3-** **>15 mm** induration positive in :

- any persons including those with no risk factors for TB.

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Negative Tuberculin Skin Test

- No induration , either due to:
  - No previous infection
  - Pre-hypersensitivity stage
  - Lost TB sensitivity with loss of antigen.
- AIDS patients are anergic and susceptible to infection.

Laboratory Diagnosis of TB

- **1- Specimens:**
  - Pulmonary TB: 3 **early morning sputum samples** (or induced cough**),or** bronchial lavage, or gastric washing (infants) ,…etc.
- Cerebrospinal fluid (CSF) (TB meningitis)
- 3 early morning urine
- Bone , joint aspirate
- Lymph nodes, pus or tissues **NOT swab.**
- Repeat sample .

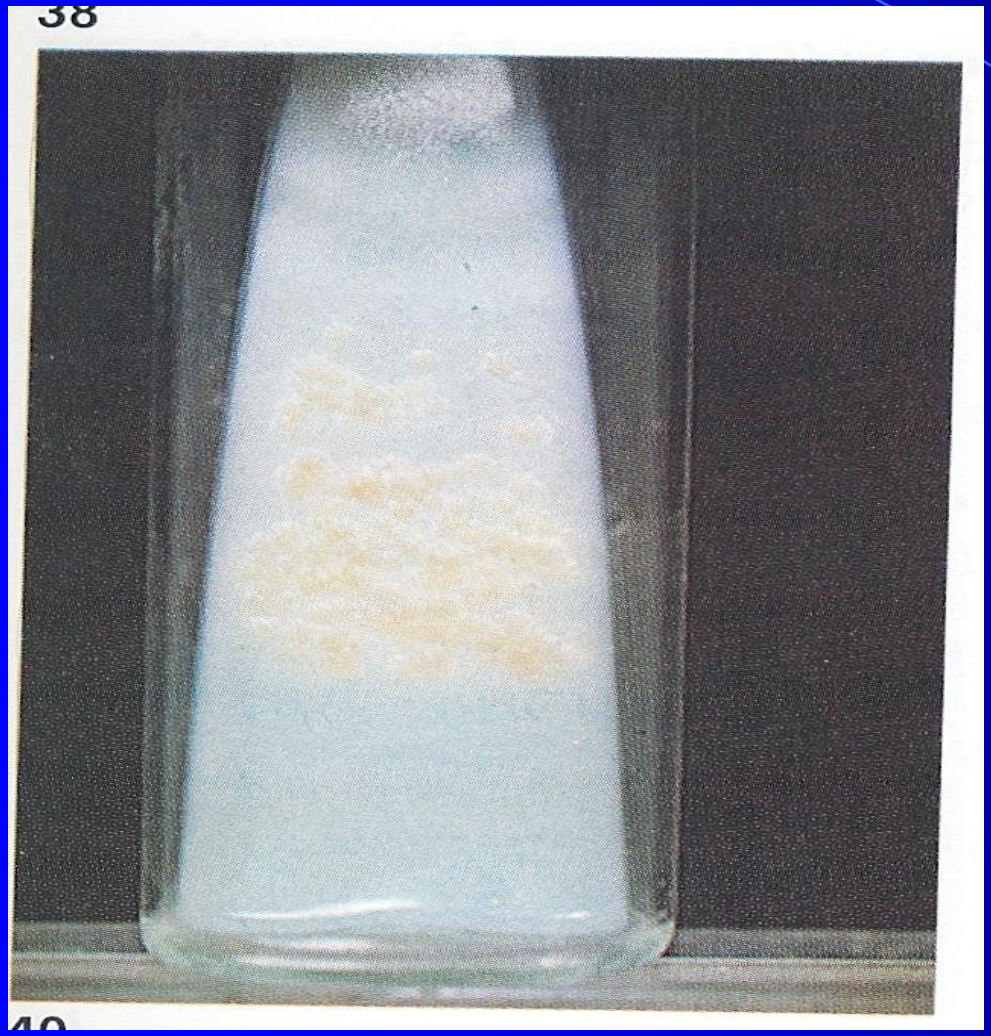
Laboratory Diagnosis of TB

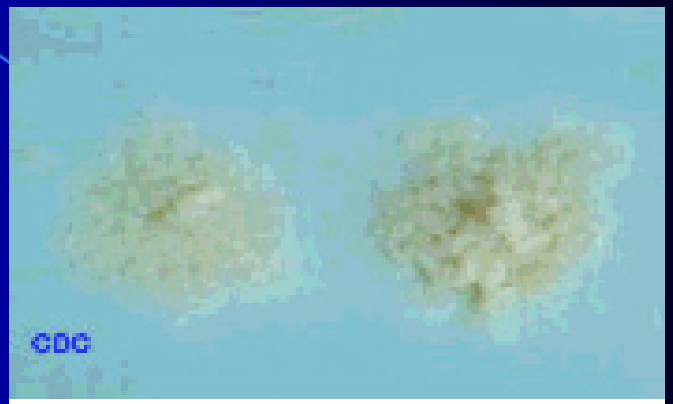
- 2- **Direct microscopy of specimen :**
  - **Z-N** or (Auramine) stain.
- 3- **Culture:** the gold standard test for identification and sensitivity.
  - **Media used:** Lowenstein-Jensen media (L J).

  Media contains: eggs, asparagin, glycerol, pyruvate/ malachite green.

Laboratory Diagnosis of TB

- Colonies appear in LJ media after 2-8 weeks as eugenic, raised,buff,adherent growth enhanced by glycerol (*MTB*) or by pyruvate (*M.bovis*).
- Other media **plus** LJ media may be used:
  - Fluid media (middle Brook)
  - MGIT (mycobacteria growth indicator test)
  - Automated methods :- eg. Bactec MGIT.
  - Measurement of interferon –gamma **(IF-γ)** secreted from sensitized lymphocytes challenged by the same mycobacterial proteins in a patient previously exposed to disease, will produce interferon gamma. Has a specific significance than tuberculin skin test.
  - **PCR**: molecular test directly from specimen (CSF) and ProbTech directly from respiratory samples..





Crumbly, buff colored *M. tuberculosis* colonies

Identification

- Morphology , growth at 37C + 5 -10 % CO_2
- Biochemical tests : Niacin production & Nitrate test.
- Sensitivity testing
- Guinea pig inoculation: rarely done.

Management of a TB case

- 1- Isolation for 10-14 days (for smear positive cases i.e. > 1000 organisms / ml of sputum considered infectious case).
- Triple regimen of therapy .Why ?
  - To prevent resistant mutants
  - To cover strains located at different sites of the lung .
  - To prevent relapse
- 2- Treatment must be guided by sensitivity testing.

First Line Treatment

- Isoniazide (INH)
- Rifampicin (RIF)
- Ethmbutol (E)
- Pyrazinamide (P)
- Streptomycin (S) (sometimes added to first line)

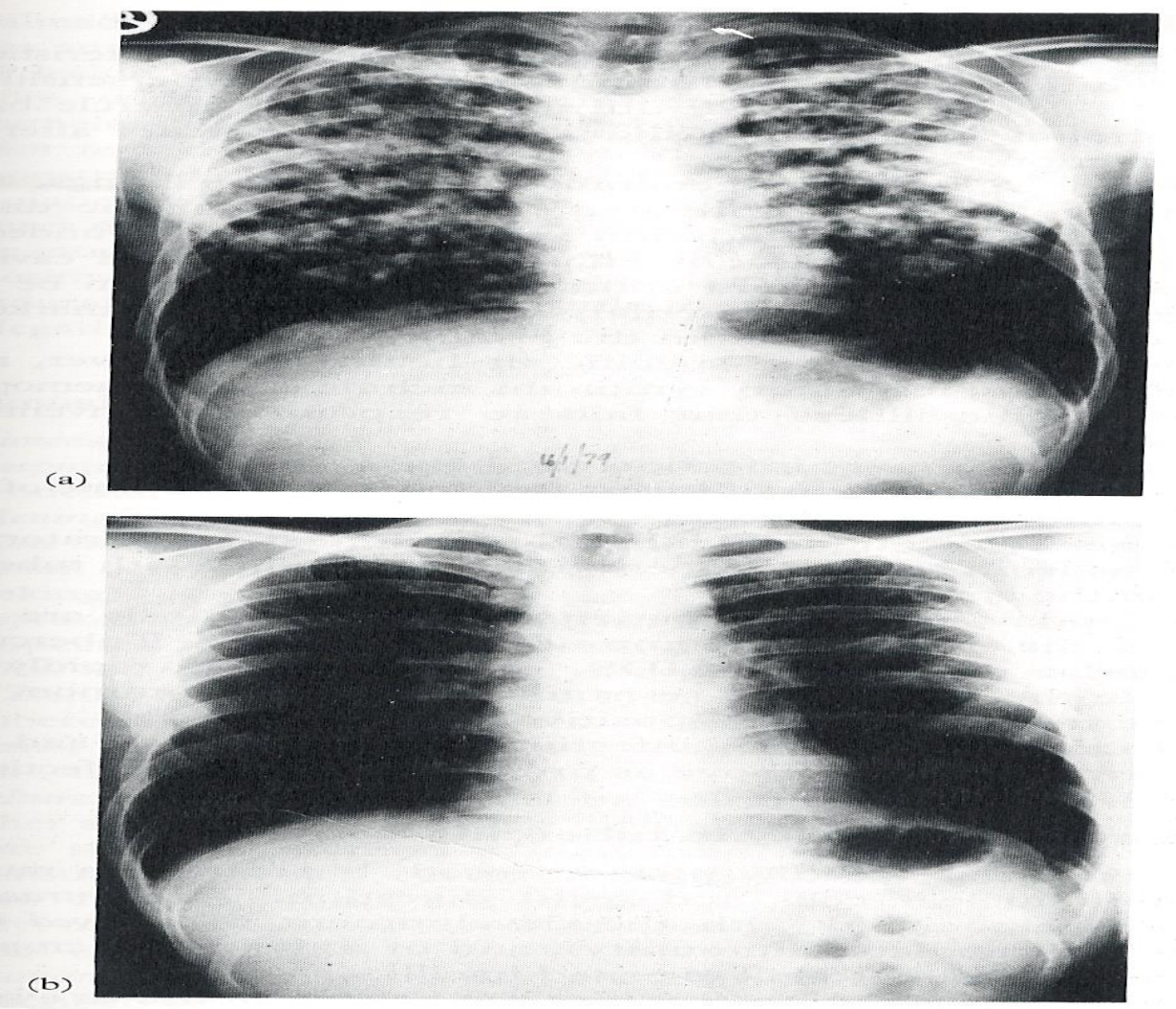
INH+ RIF +P for 2 months then continue with INH+RIF for **4-6 months**. **Multidrug resistant TB is resistance to INH & RIF.**

- Directly Observed Therapy (DOT).

Second Line

Used if the bacteria was resistant to first line drugs. More toxic than the first line drugs.

- PASA (Para-Amino Salicylic acid)
- Ethionamide
- Cycloserine,
- Kanamycin,
- Fluroquiolones



Tuberculosis: (a) Chest X-ray of a patient with tuberculosis bronchopneumonia. (b) Chest X-ray of the same patient 10 months after antituberculous therapy. (Courtesy of Dr. R.S.Kennedy)

Prevention of TB

- Tuberculin testing of herds.
- Slaughter of infected animals.
- Pasteurization of milk to prevent bovine TB
- Recognition of new cases.
- Prophylaxis with INH of contacts.
- Follow up cases .
- Immunization with BCG to all new borne.