MYCOBACTERIA

Introduction

- Tuberculous bacilli were discovered by R. Koch in 24-mars 1882

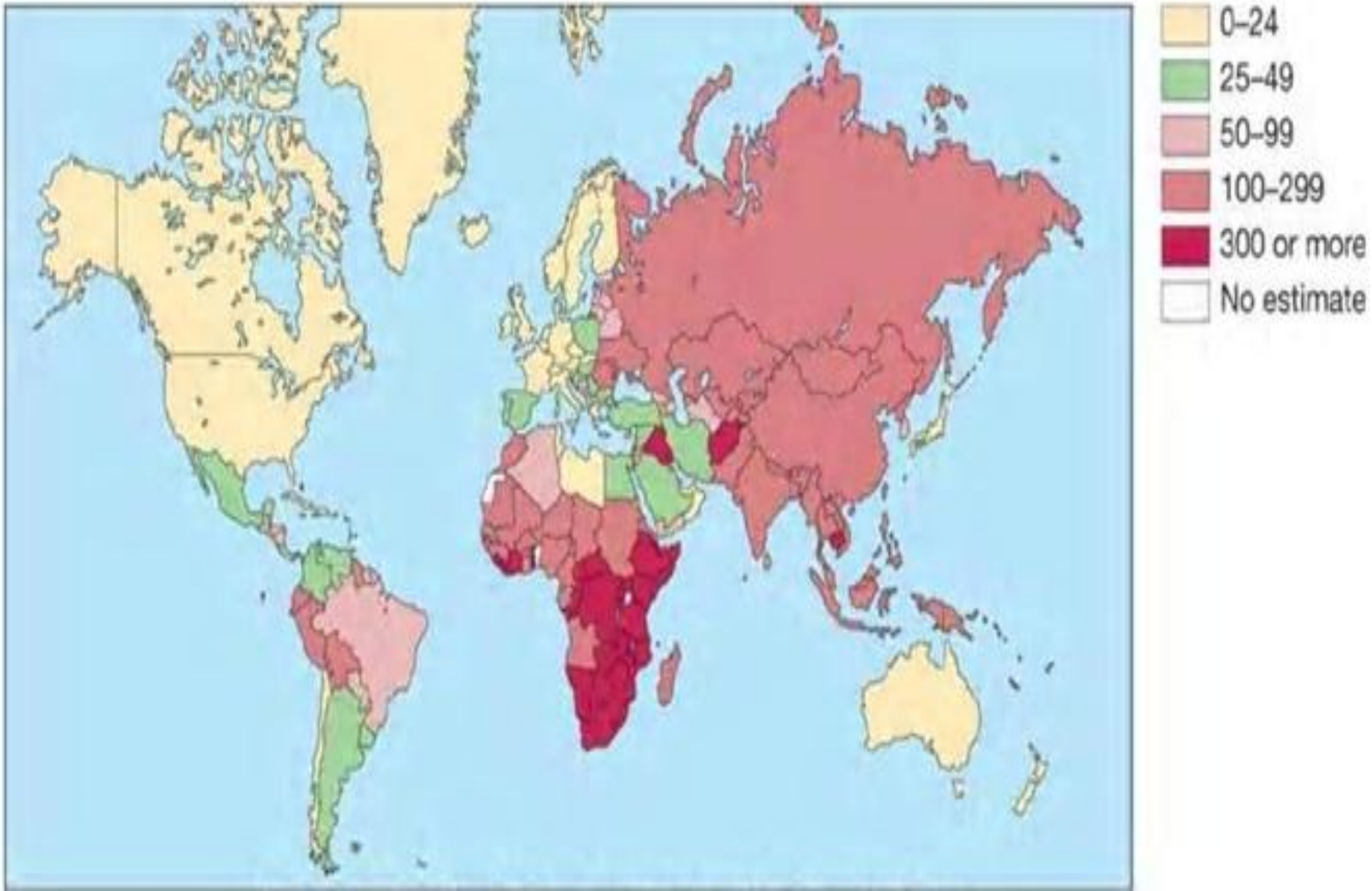
M. tuberculosis complex

- M. tuberculosis
- M. bovis
- M. africanum
- M. microti
- M. canetti
- M. caprae
- M. pinnipedii

Epidemiology

- ***M. bovis*** **(reservoir cattle) and *M. africanum* (reservoir human).**
- **in 2006 : estimated 9.2 million new cases and 1.5 million deaths attributable to TB.**
- **around one-third of the world's population has latent TB.**
- **majority of cases occur in the world's poorest nations**
- ***M. bovis*** **infection arises from drinking non-sterilised milk from infected cows.**
- ***M. tuberculosis*** **is spread by the inhalation of aerosolised droplet nuclei from other infected patients.**

World-wide incidence of tuberculosis



Factors increasing the risk of TB

Patient-related

- Age (children > young adults < elderly)
- First-generation immigrants from high-prevalence countries
- Close contacts of patients with smear-positive pulmonary TB
- Overcrowding (prisons, collective dormitories); homelessness (doss houses and hostels)
- Chest radiographic evidence of self-healed TB
- Primary infection < 1 year previously
- Smoking: cigarettes and bidis (Indian cigarettes made of tobacco wrapped in temburini leaves)

Associated diseases

- Immunosuppression: HIV, anti-TNF therapy, high-dose corticosteroids, cytotoxic agents
- Malignancy (especially lymphoma and leukaemia)
- Type 1 diabetes mellitus
- Chronic renal failure
- Silicosis
- Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption)
- Deficiency of vitamin D or A
- Recent measles: increases risk of child contracting TB

High risk

Major immunocompromising conditions

HIV infection (any stage of illness) **(TST ≥ 5 mm)**

Lymphoma, leukemia, head and neck cancer (TST > 10 mm)

Chemotherapy (TST > 5 mm)

Solid organ transplant (TST > 5 mm)

TNF-alpha inhibitors (TST > 5 mm)

Silicosis (TST > 10 mm)

Renal failure (requiring dialysis) **(TST > 10 mm)**

Moderate risk individuals are those whose risk for reactivation is three to six times higher than normal healthy individuals

Patients under age 65 should be tested

Diabetes mellitus (regardless of insulin dependence) **(TST > 10 mm)**

Systemic glucocorticoids (≥15 mg/day for ≥1 month) **(TST > 5 mm)**

Slightly increased risk :Individuals at slightly increased risk for reactivation are those whose risk is 1.5 to 3 times higher than normal healthy individuals

Patients under age 50 should be tested

Underweight (<85 percent of ideal body weight); for most individuals this is equivalent to body mass index (BMI) ≤20 (TST > 15 mm)

Cigarette smoker (1 pack/day) (TST > 15 mm)

Chest x-ray with solitary granuloma (TST > 15 mm)

Tuberculin skin test reaction size (mm)	Situation in which reaction is considered positive*
≥5	HIV infection
	Close contact of active contagious case
	Abnormal chest x-ray with fibrotic changes consistent with old TB
	Immunosuppressed patients: TNF-alpha inhibitors, chemotherapy, organ transplantation, glucocorticoid treatment (equivalent of ≥15 mg/d prednisone for ≥1 month)
≥10	Persons with clinical conditions that increase the risk of reactivation, including silicosis•, chronic renal failure requiring dialysis•, diabetes mellitus, some malignancies (leukemias, lymphomas, carcinoma of the head, neck, or lung), underweight (≥10 percent ideal body weight), jejunoileal bypass, injection drug users
	Children less than 4 years of age
	Foreign born from countries with incidence >25/100,000 Δ
	Residents and employees in high risk settings, such as prisons, jails, healthcare facilities, mycobacteriology labs, and homeless shelters
≥15	Healthy persons with low likelihood of true TB infection ◊

Mycobacterium tuberculosis

- **pathogenesis :**
  - **inhalation of aerosolized droplets from close contacts**
  - **primary TB :**

    development of granulomatous reactions in the lungs, +/− local spread to lymph nodes and hematogenously to distant organs (extrapulmonary TB, e.g. kidneys, bone)
  - **lesions usually heal and fibrose in the immunocompetent**
  - **estimated lifetime risk of developing disease after primary infection is 10%, with roughly half of this risk occurring in the first 2 years after infection.**
  - **secondary/post-primary TB:**

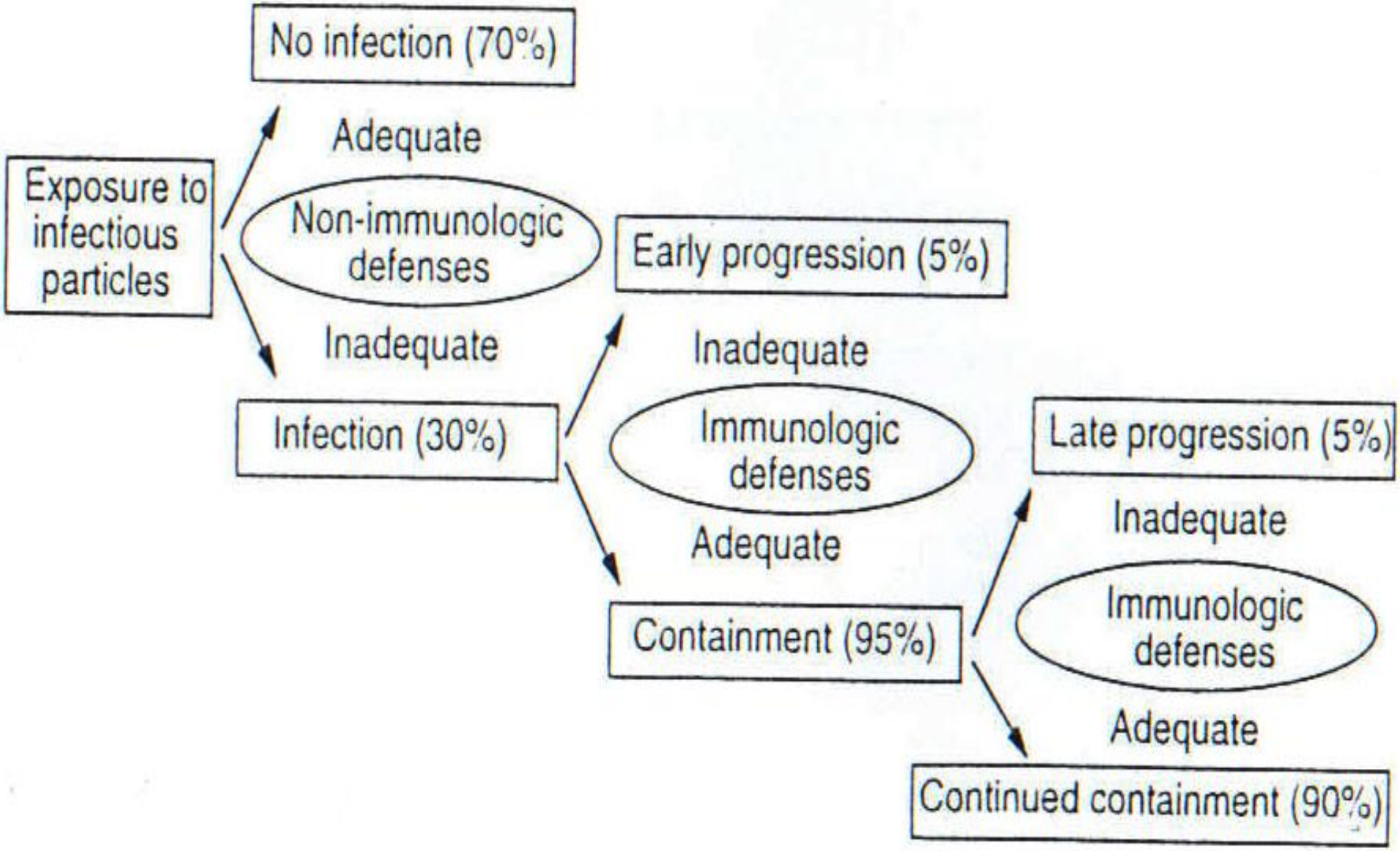
    reactivation of dormant organisms and proliferation in aging/immunocompromised patients

التدرن

قابلية تفاعل السلين الإيجابي بعد تماس مع تدرن رئوي

	نفس المسكن	الأصدقاء	تماس أحيانا
لطخ مباشر + الزرع +	%20	%4	%0.3
لطخ مباشر – الزرع +	%1,2	%0	0
لطخ مباشر – الزرع سلبي	%1	0	0

التدرن


No infection (70%)
Adequate
Exposure to infectious particles
Non-immunologic defenses
Early progression (5%)
Inadequate
Inadequate
Infection (30%)
Immunologic defenses
Late progression (5%)
Inadequate
Adequate
Immunologic defenses
Containment (95%)
Adequate
Continued containment (90%)

How is TB spread?

1.

Coughing without covering the mouth

2.

Crowded places with poor ventilation

3.

Spitting everywhere

A person may contract pulmonary tuberculosis from inhaling infected droplets from a cough or sneeze by an infected person

Granuloma in lung tissue

Timetable of TB

Time from infection	Manifestations
3-8 weeks	Primary complex, positive tuberculin skin test
3-6 months	Meningeal, miliary and pleural disease
Up to 3 years	Gastrointestinal, bone and joint, and lymph node disease
Around 8 years	Renal tract disease
From 3 years onwards	Post-primary disease due to reactivation or reinfection

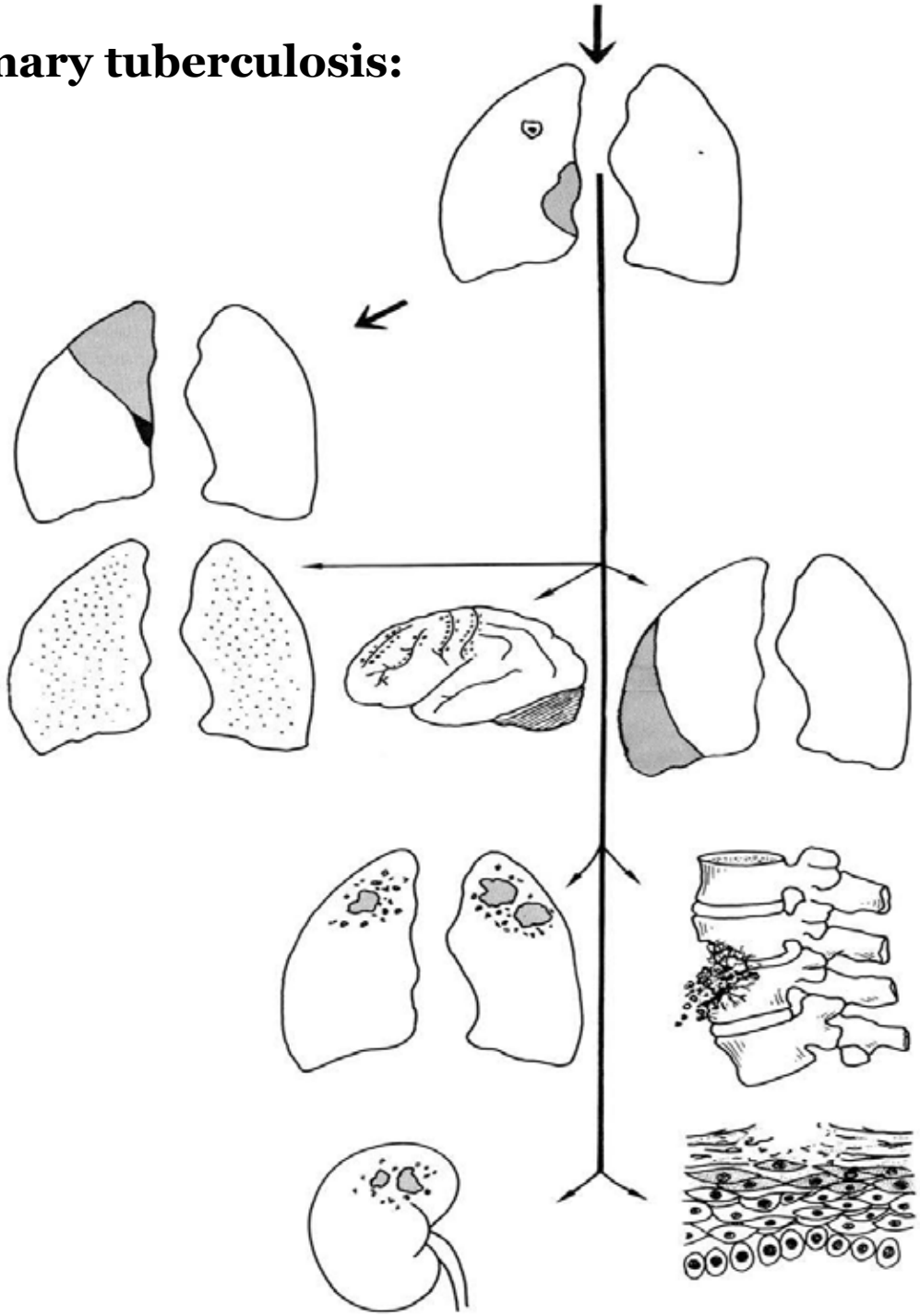
Natural history of untreated primary tuberculosis: the timetable of tuberculosis.

Tuberculin test becomes positive. Minority of those infected experience febrile illness and erythema nodosum.

Miliary and meningeal tuberculosis common in children under 5 years: pleural effusion rare in children. Usually within 6–12 months, after primary infection.

Adult (post-primary) disease and skeletal disease commonly occurs 1–5 years later.

Genito-urinary and skin lesions are late manifestations after 5–15 years.



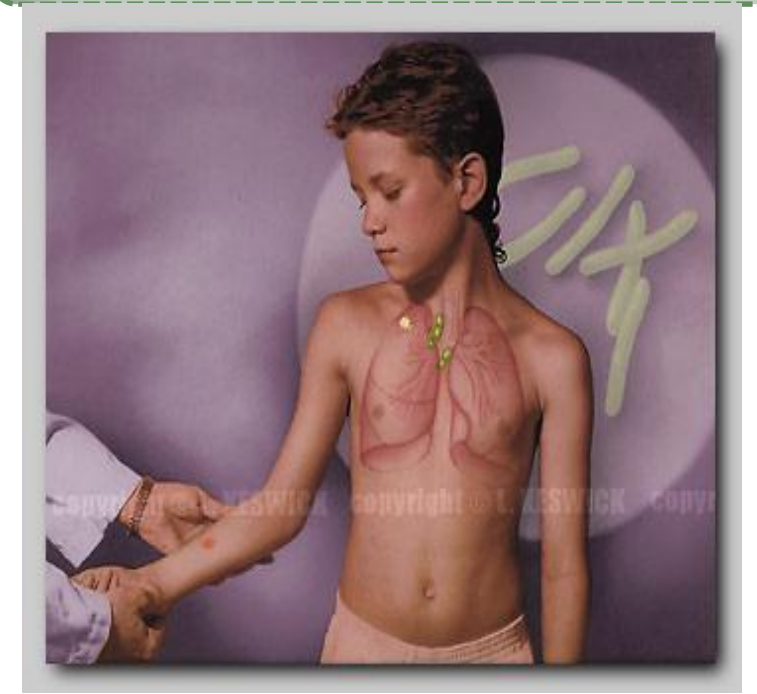
latent TB

- **the primary complex in a fibrous capsule limiting the spread of bacilli**
- **lymphatic or haematogenous spread may occur before immunity is established**
- **seeding secondary foci in other organs including lymph nodes, serous membranes, meninges, bones, liver, kidneys and lungs, which may lie dormant for years.**
- **demonstrated by tuberculin skin testing**

Latent TB

conversion TST to positive

-successful immune response to primary infection
-the organisms remain dormant



no clinical and radiological features

Tuberculosis can either be cured after healing or reactivation may occur, which results in post-primary tuberculosis

Cryptic TB

- Age over 60 years
- Intermittent low-grade pyrexia of unknown origin
- Unexplained weight loss, general debility (hepatosplenomegaly in 25-50%)
- Normal chest X-ray
- Blood dyscrasias; leukaemoid reaction, pancytopenia
- Negative tuberculin skin test
- Confirmation by biopsy (granulomas and/or acid-fast bacilli demonstrated) of liver or bone marrow

clinical presentation

- **usually asymptomatic but may have fever, lassitude, erythema nodosum, cough, sputum**

- **post-primary TB:**
  reactivation of dormant organisms in immunocompromised patients;

- **early systemic symptoms:**
  malaise, fever, sweats, anorexia, weight loss

- **late localizing symptoms:**
  dyspnea, pleuritic chest pain, cough, purulent sputum, hemoptysis

- **miliary TB (post-primary dissemination of multiple tiny granulomas in immunocompromised patients):**
  fever, anemia, splenomegaly, meningitis

Features of primary TB

Infection (4-8 weeks)

- Influenza-like illness
- Skin test conversion
- Primary complex

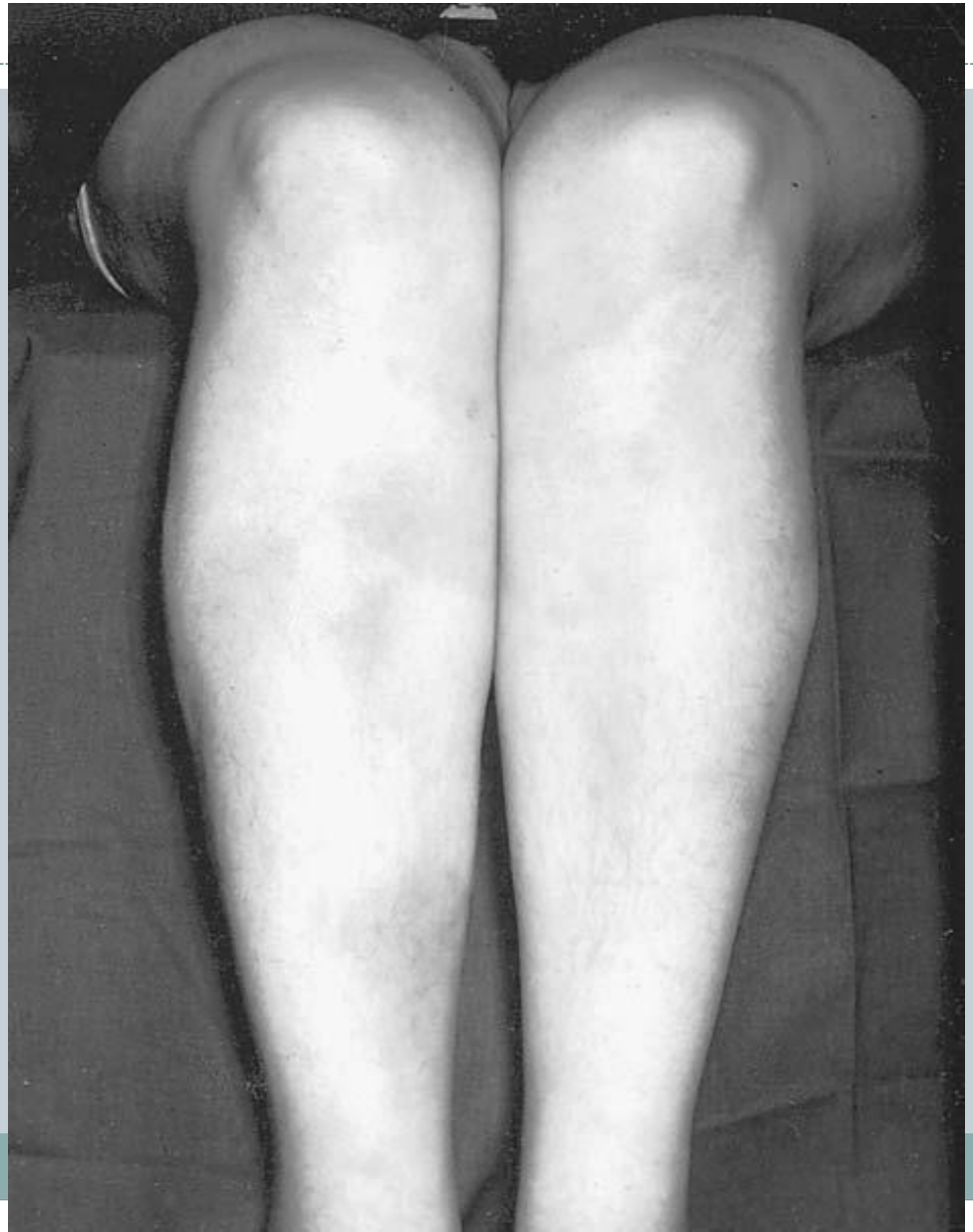
Disease

- Lymphadenopathy: hilar (often unilateral), paratracheal or mediastinal
- Collapse (especially right middle lobe)
- Consolidation (especially right middle lobe)
- Obstructive emphysema
- Cavitation (rare)
- Pleural effusion
- Endobronchial
- Miliary
- Meningitis
- Pericarditis

Hypersensitivity

- Erythema nodosum
- Phlyctenular conjunctivitis
- Dactylitis

Legs of patient with erythema nodosum.



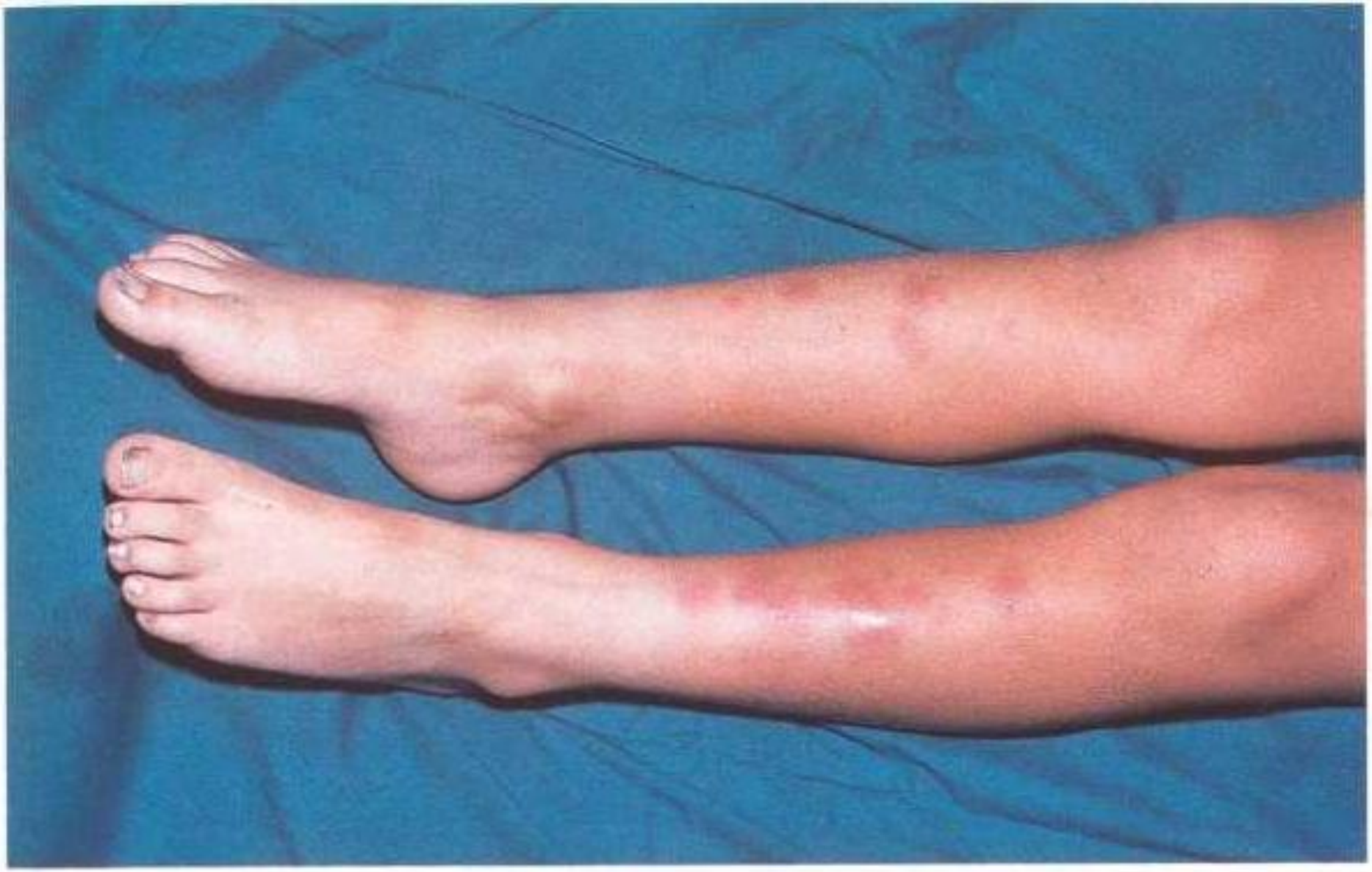


Fig. 148 Early discrete erythema nodosum (due to streptococcal disease).

Clinical presentations of pulmonary TB

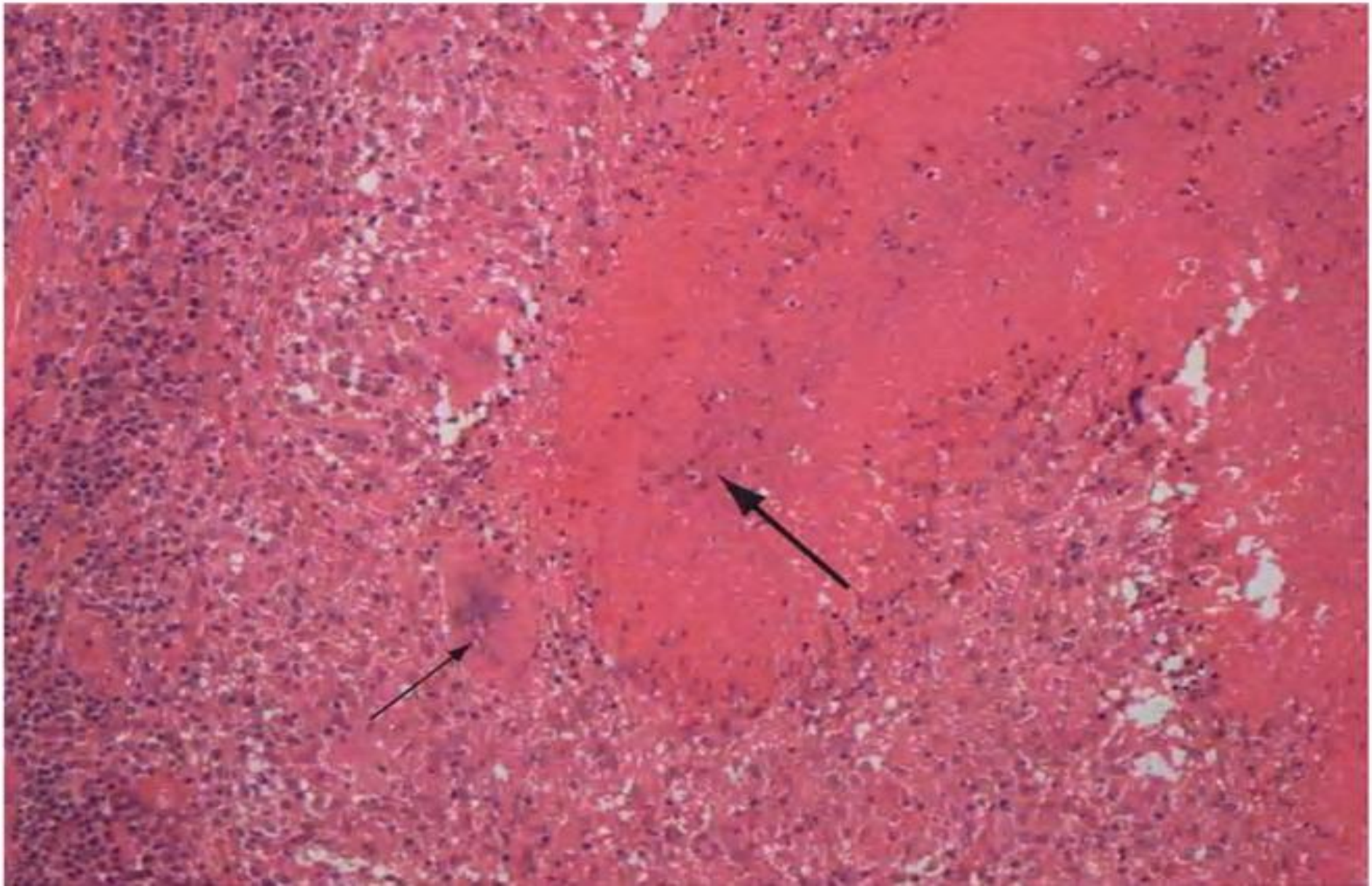
- Chronic cough, often with haemoptysis
- Pyrexia of unknown origin
- Unresolved pneumonia
- Exudative pleural effusion
- Asymptomatic (diagnosis on chest X-ray)
- Weight loss, general debility
- Spontaneous pneumothorax

pathology

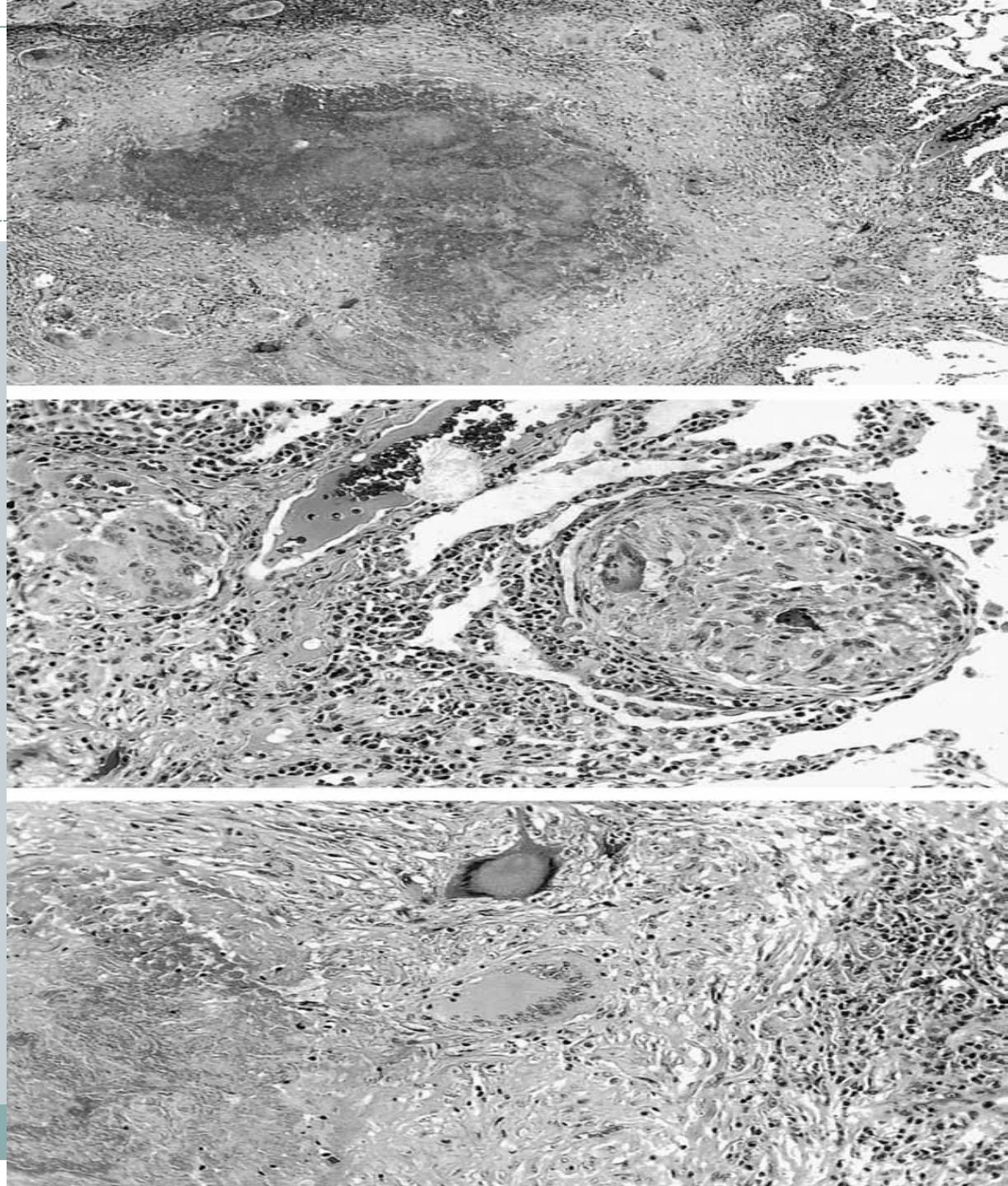
- Macrophages undergo transformation into epithelioid and Langhans cells which aggregate with the lymphocytes to form the classical tuberculous granuloma

- Numerous granulomas aggregate to form a primary lesion or 'Ghon focus'

Tuberculous granuloma



(a) Large caseous granulomatous lesion of tuberculosis showing central necrosis, a surrounding zone of epithelioid cells and giant cells, and a peripheral ring of lymphocytes and fibroblasts (haematoxylin & eosin¥35). (b) Same lesion showing small epithelioid cell granuloma with giant cells (haematoxylin & eosin ¥110). (c) Another area of the same lesion showing Langhanstype giant cells and epithelioid cells centrally, necrosis to the left and lymphocytes and fibroblasts to the right (haematoxylin & eosin ¥110).



CXR

- **primary TB:**
  nonspecific lower lobe calcified infiltrates, hilar and paratracheal node enlargement, pleural effusion

- **post-primary TB:**
  cavitation in apical regions and posterior segments of upper lobe and/or superior segment of the lower lobes +/– calcification

- **miliary TB:**
  uniformly distributed, very fine nodules (like seeds) throughout

- **presence of a miliary pattern or cavitation favours active disease.**

- **consolidation, collapse and cavitation develop to varying degrees**

Chest X-ray manifestations of TB

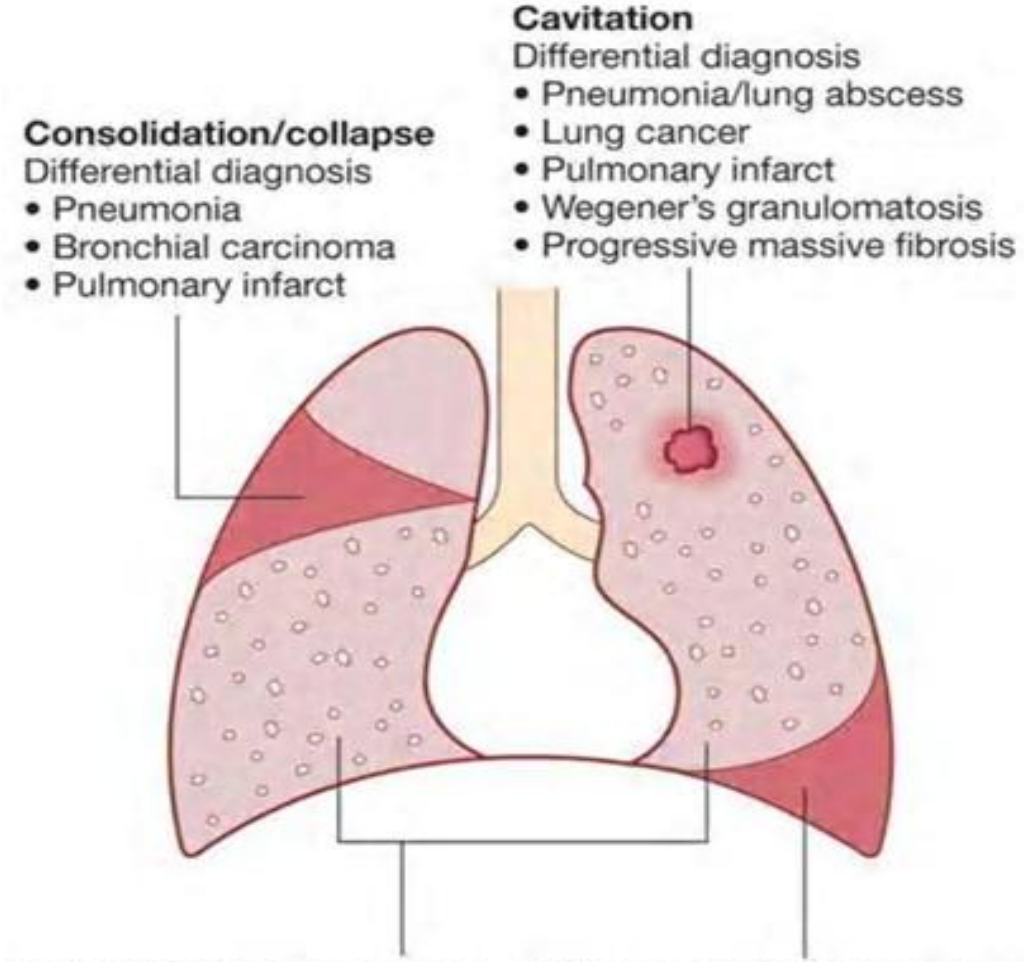
- **Primary pulmonary TB :**

- **Air space consolidation 1–7 cm diameter**
- **Lymphadenopathy: hilar, paratracheal**
- **Pleural effusion**
- **Segmental consolidation**
- **Cavitation**
- **Calcified ghon focus**
- **Calcified lymph nodes**

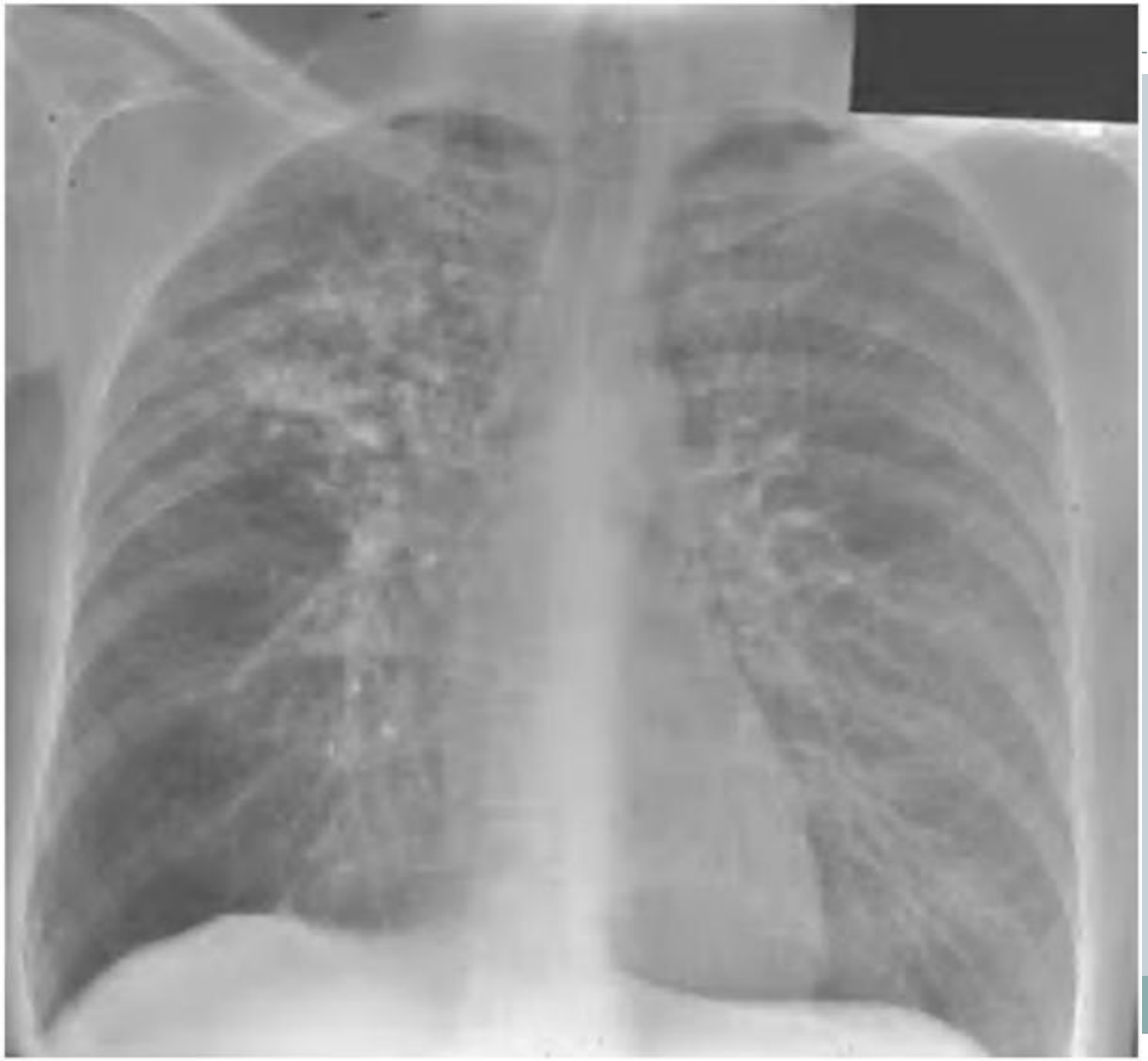
- **Post-primary TB (reactivation or initial infection or infection post-BCG):**

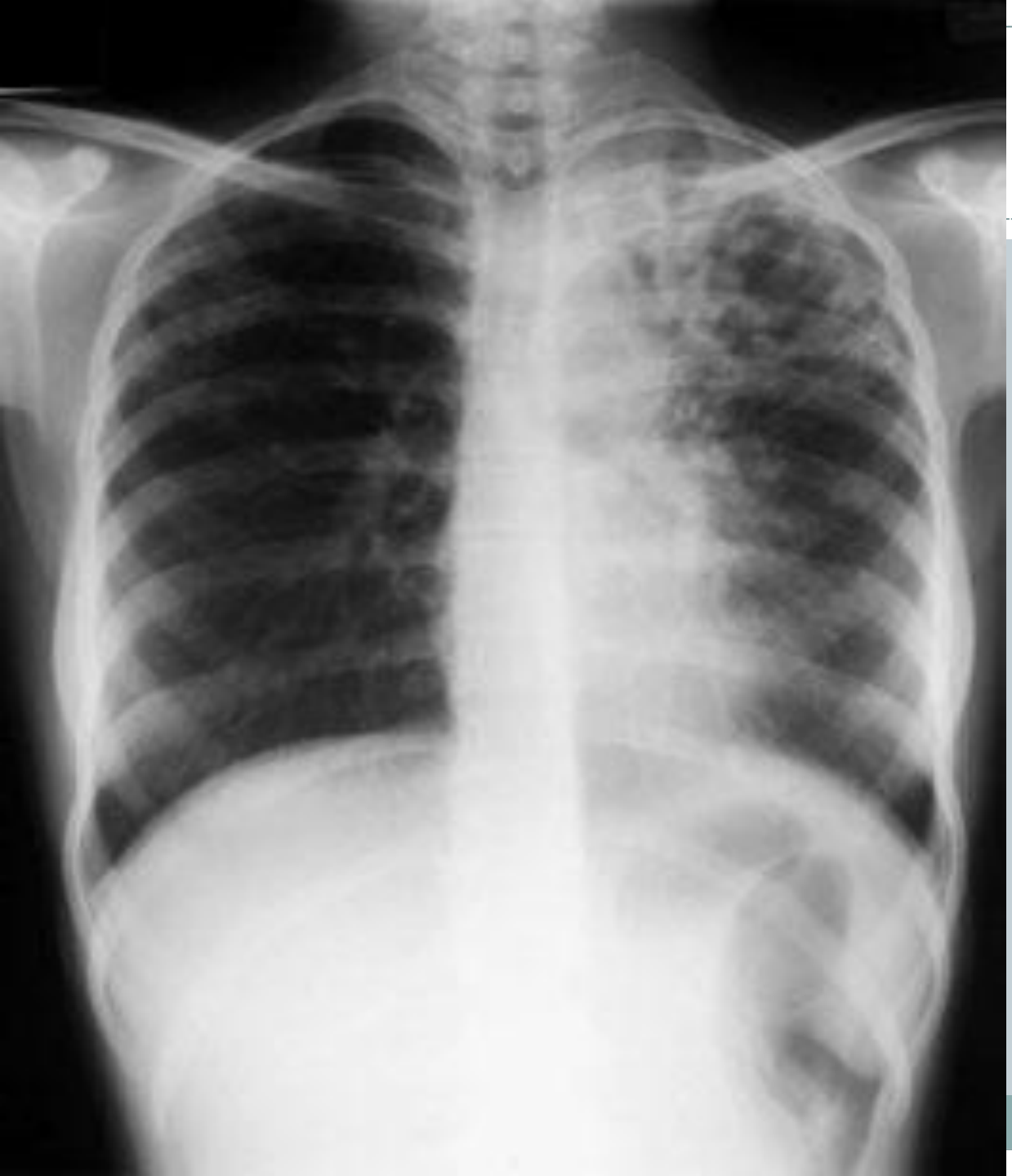
- **Apical and posterior segments of upper lobes**
- **Chronic patchy ill-defined areas of opacification**
- **Cavitation may colonise with *Aspergillus***
- **Bronchiectasis**
- **Upper lobe fibrosis**

Chest X-ray: major manifestations and differential diagnosis of pulmonary TB.

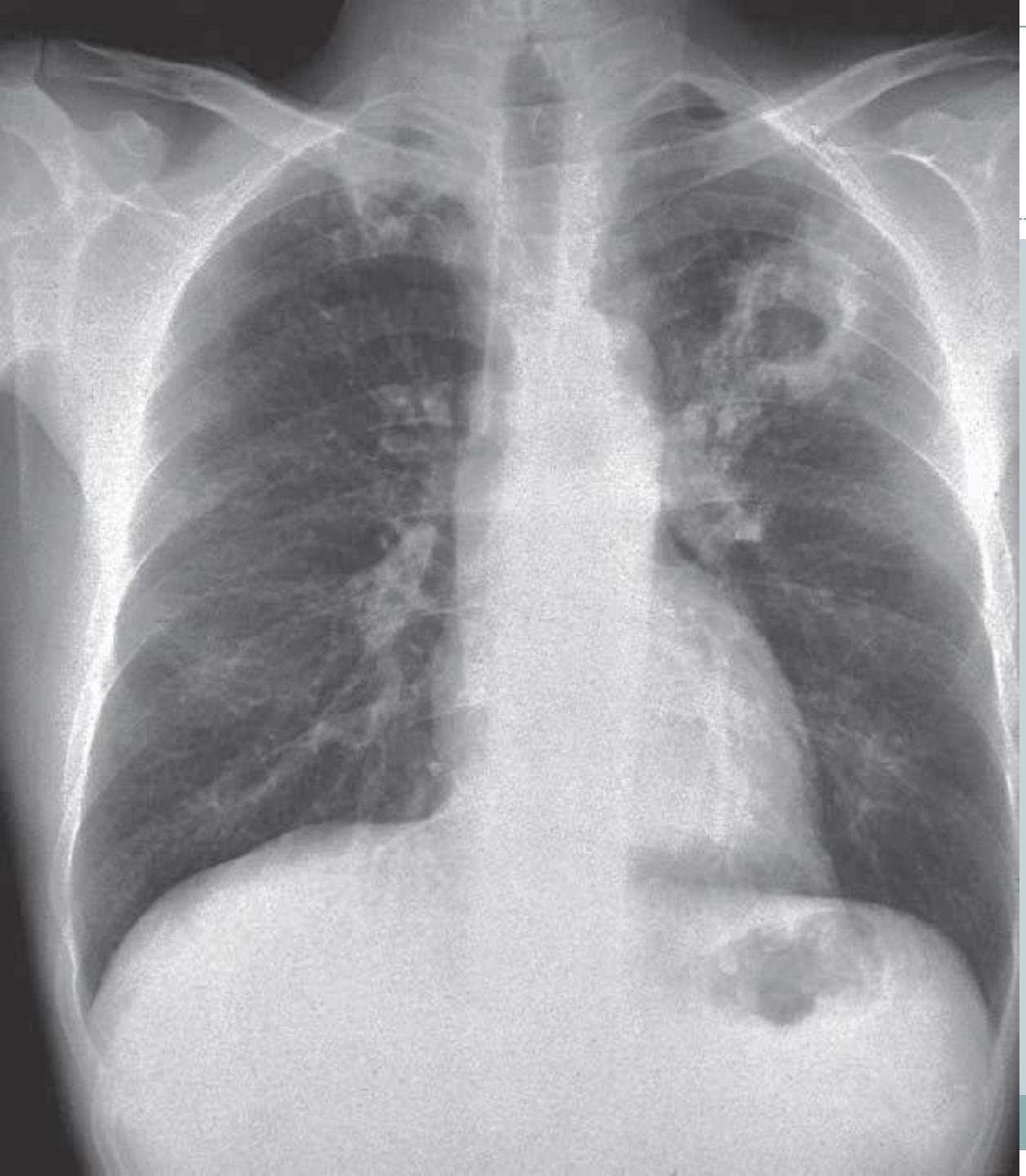


a right upper lobe cavitary process caused by *Mycobacterium tuberculosis*





cavitation left upper lobe



Tuberculous cavity in the left upper lobe in a 43-year-old man.

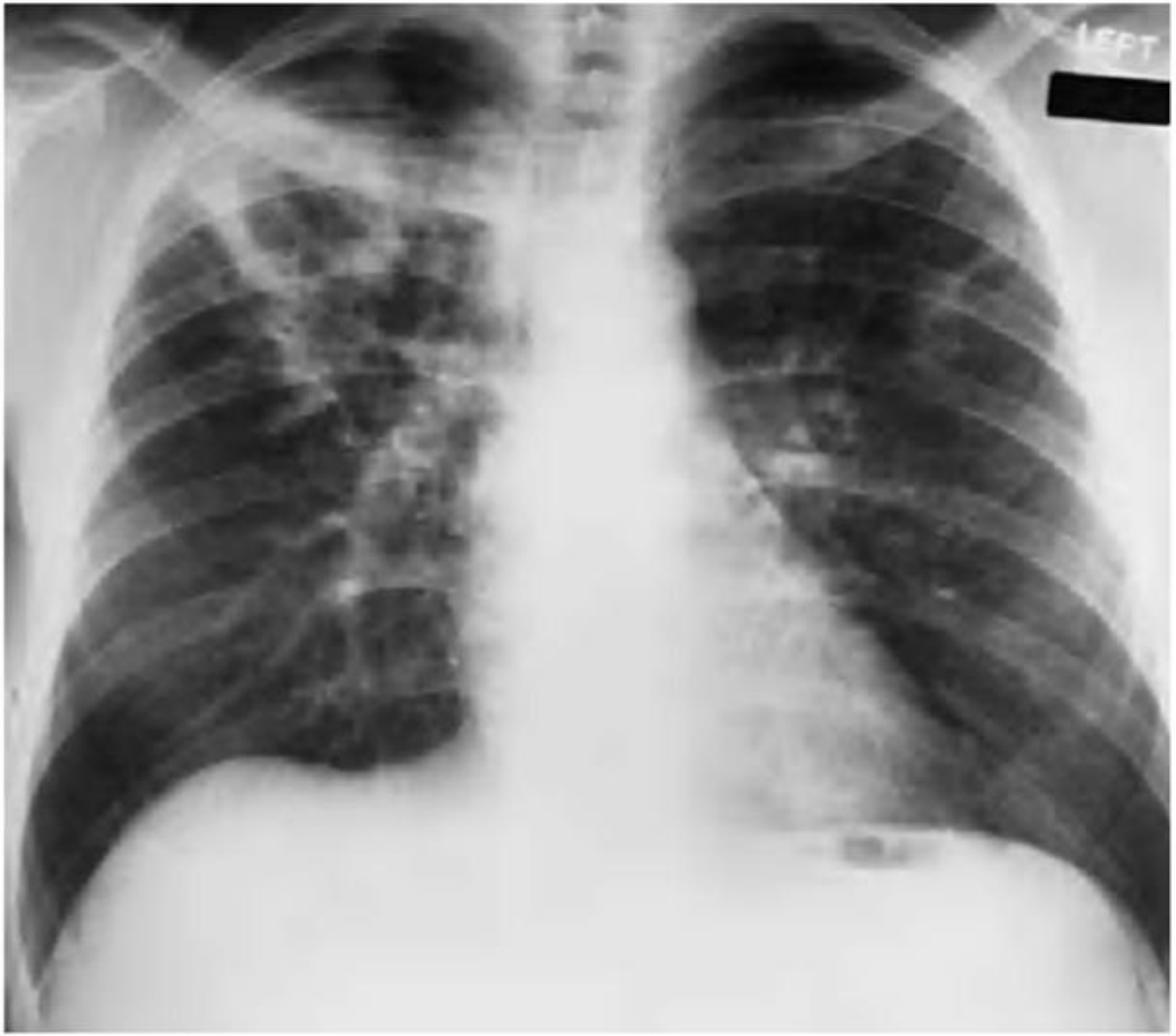
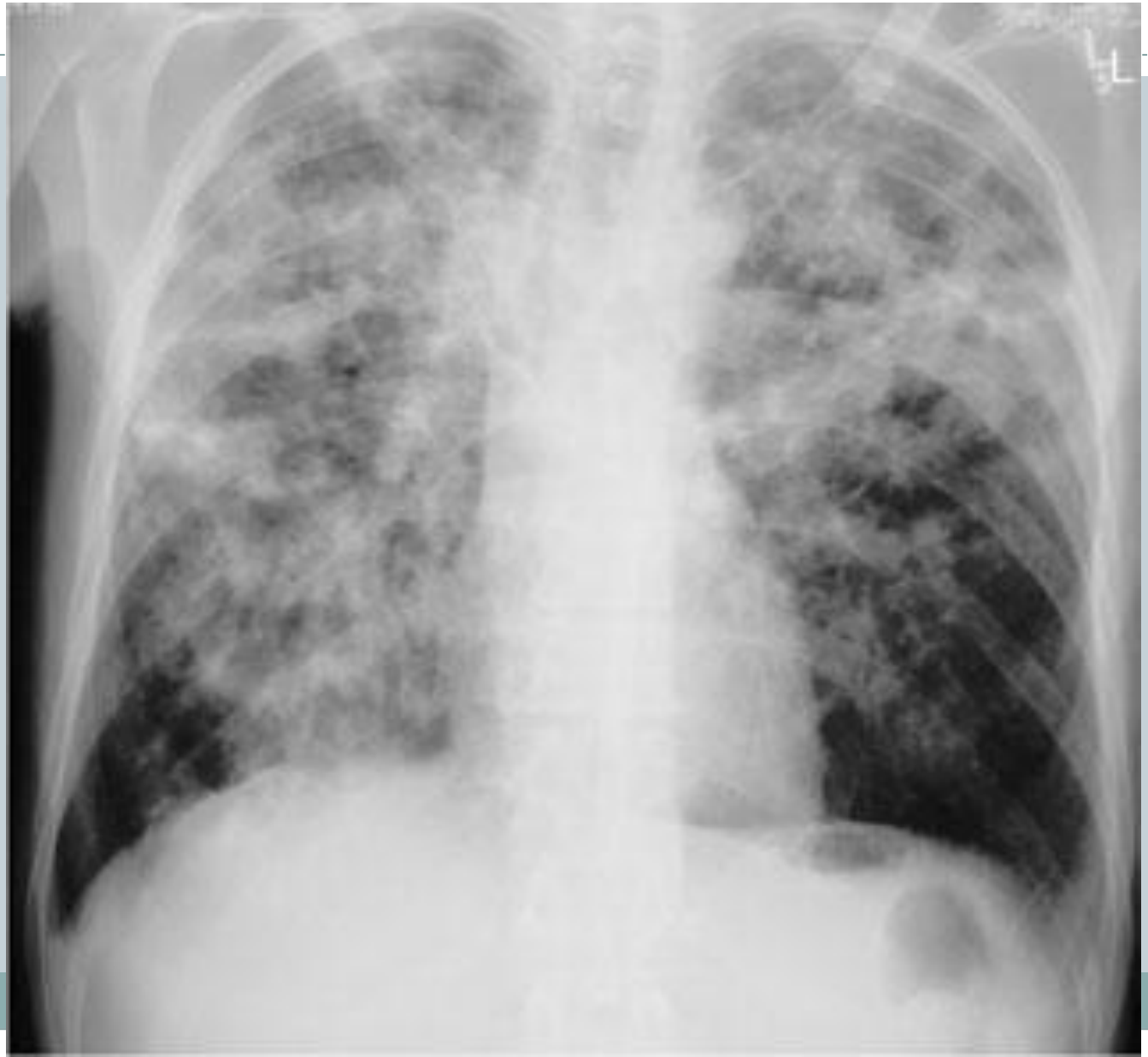
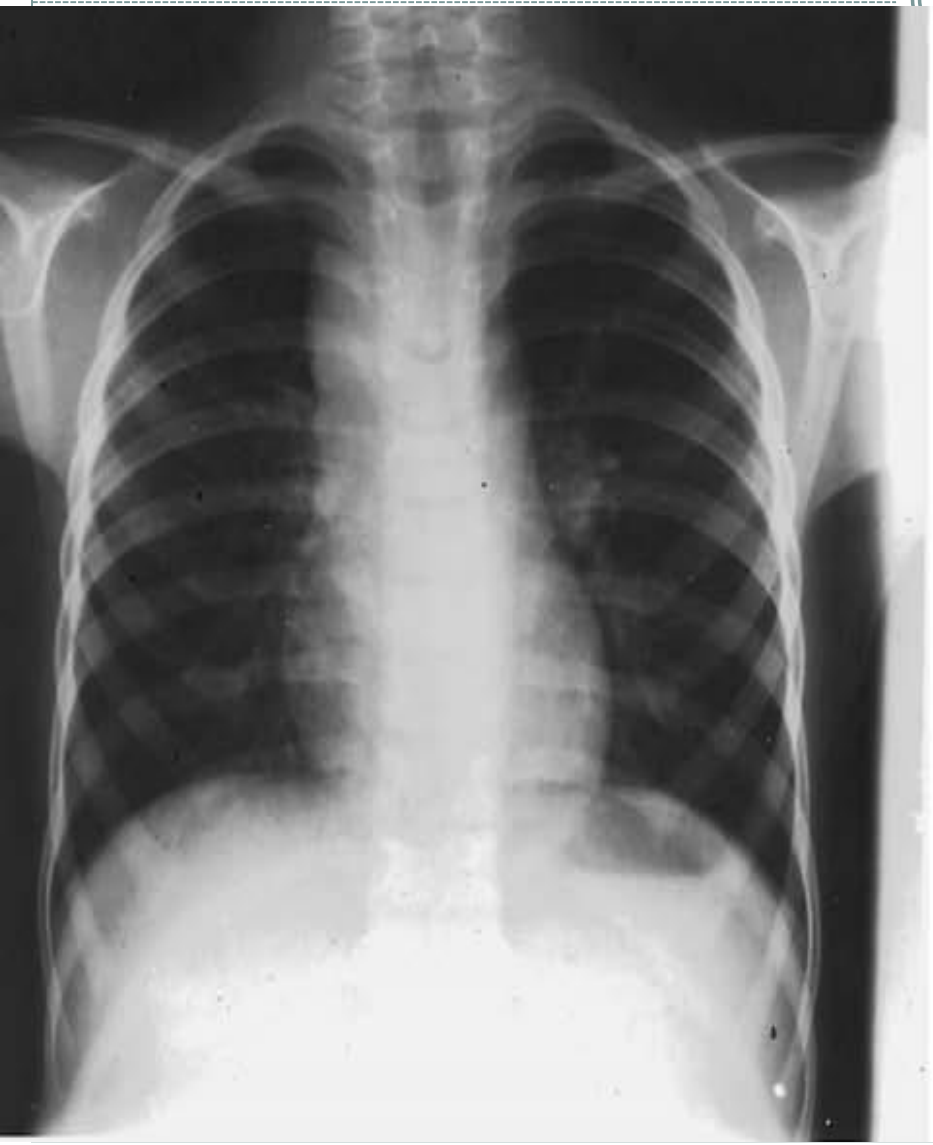


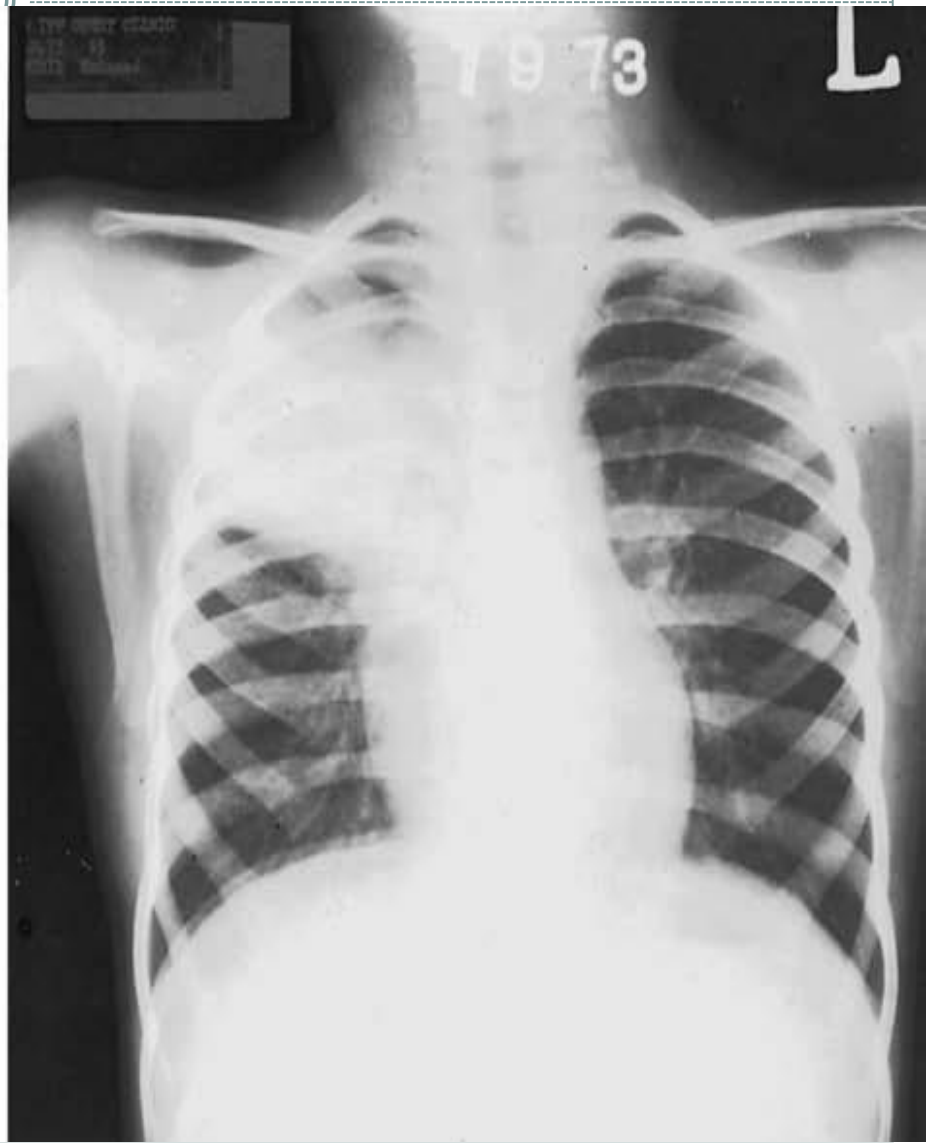
FIGURE 34-7 ▪ Frontal-view chest film showing upper lobe cavitary lesion typical of endogenous reactivation tuberculosis

pulmonary TB: ill-defined areas of consolidation in the mid- and upper zones of both lungs.

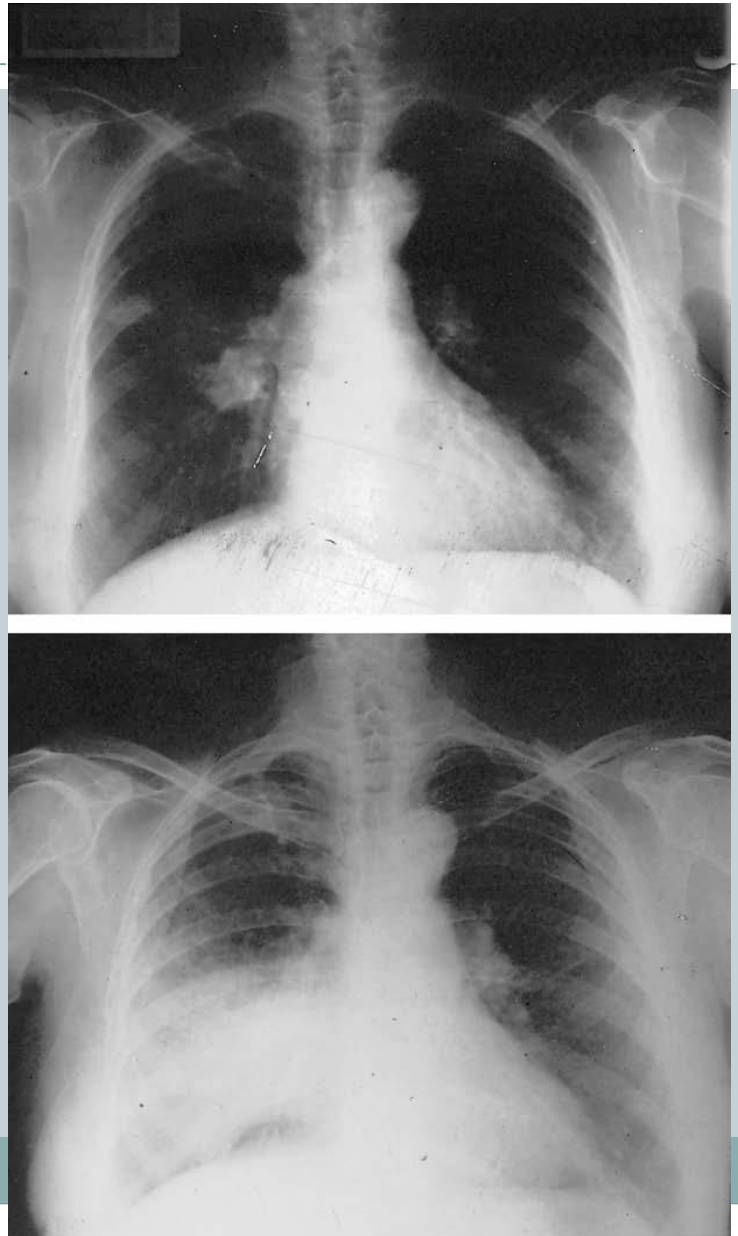


Primary tuberculosis showing hilar and paratracheal lymph gland enlargement. (b) Later film showing tuberculous consolidation of right upper lobe

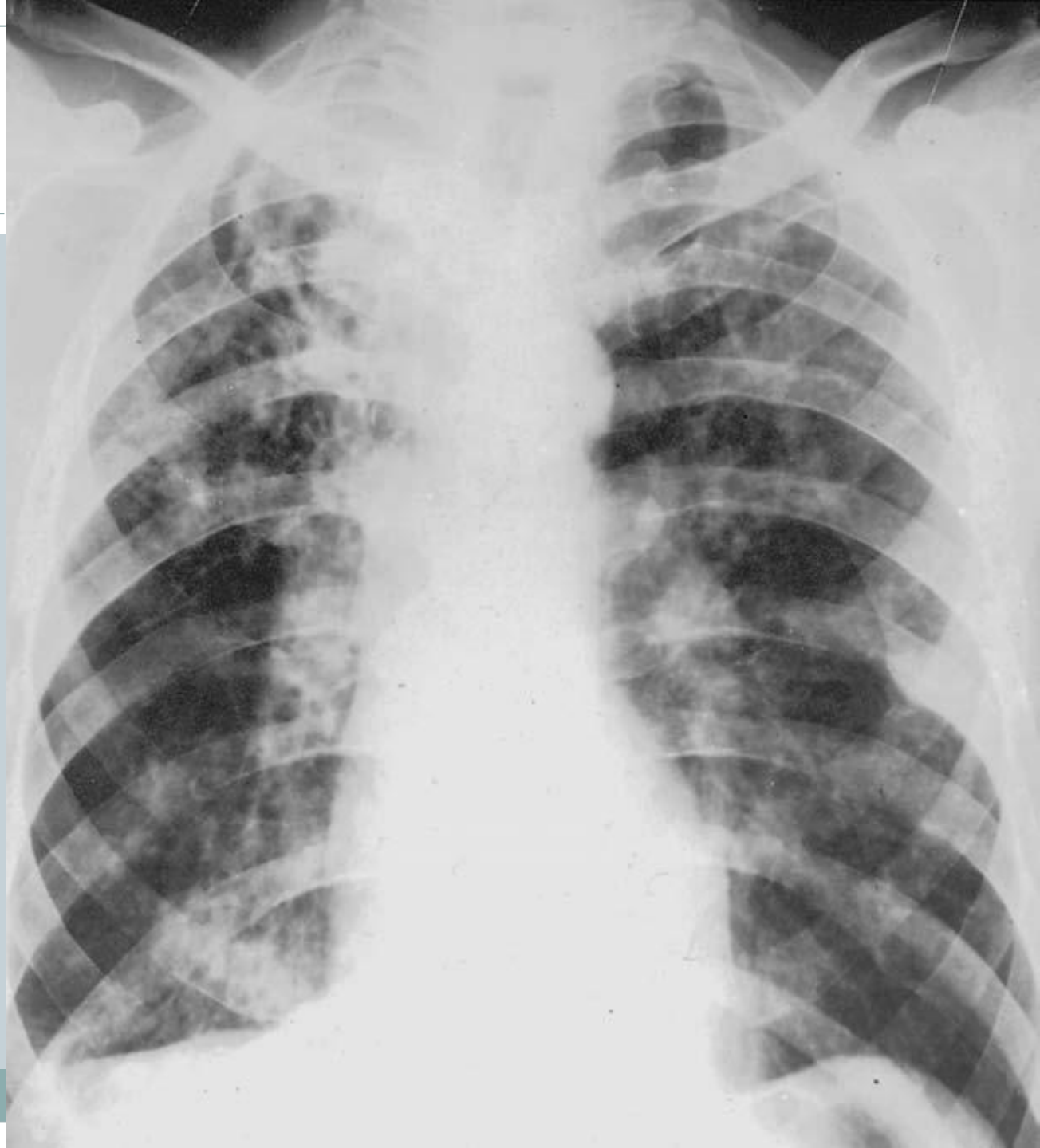




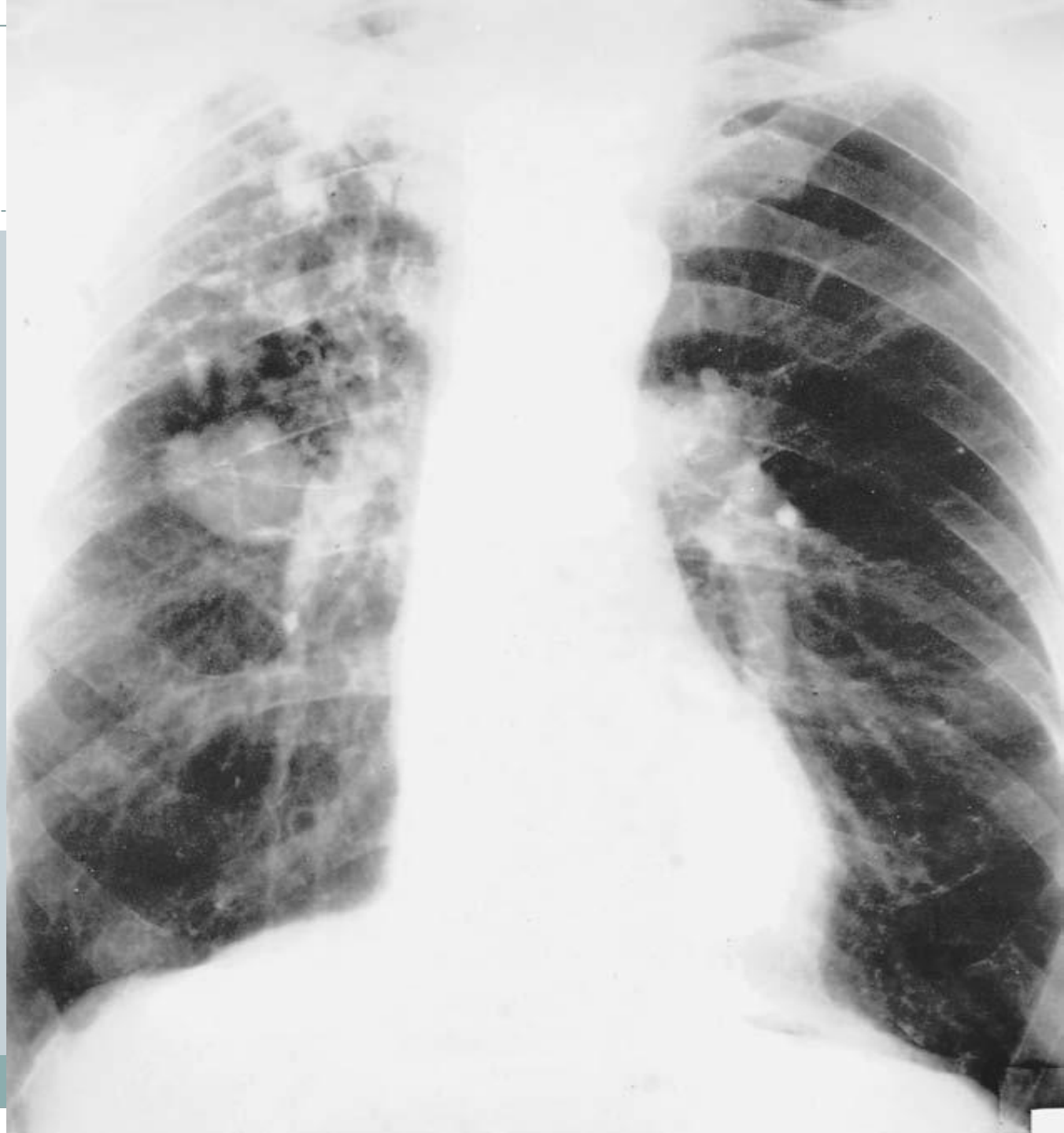
primary tuberculosis showing (a) peripheral focus and enlarged right hilar nodes and (b) consolidation of right middle lobe 1 week later.

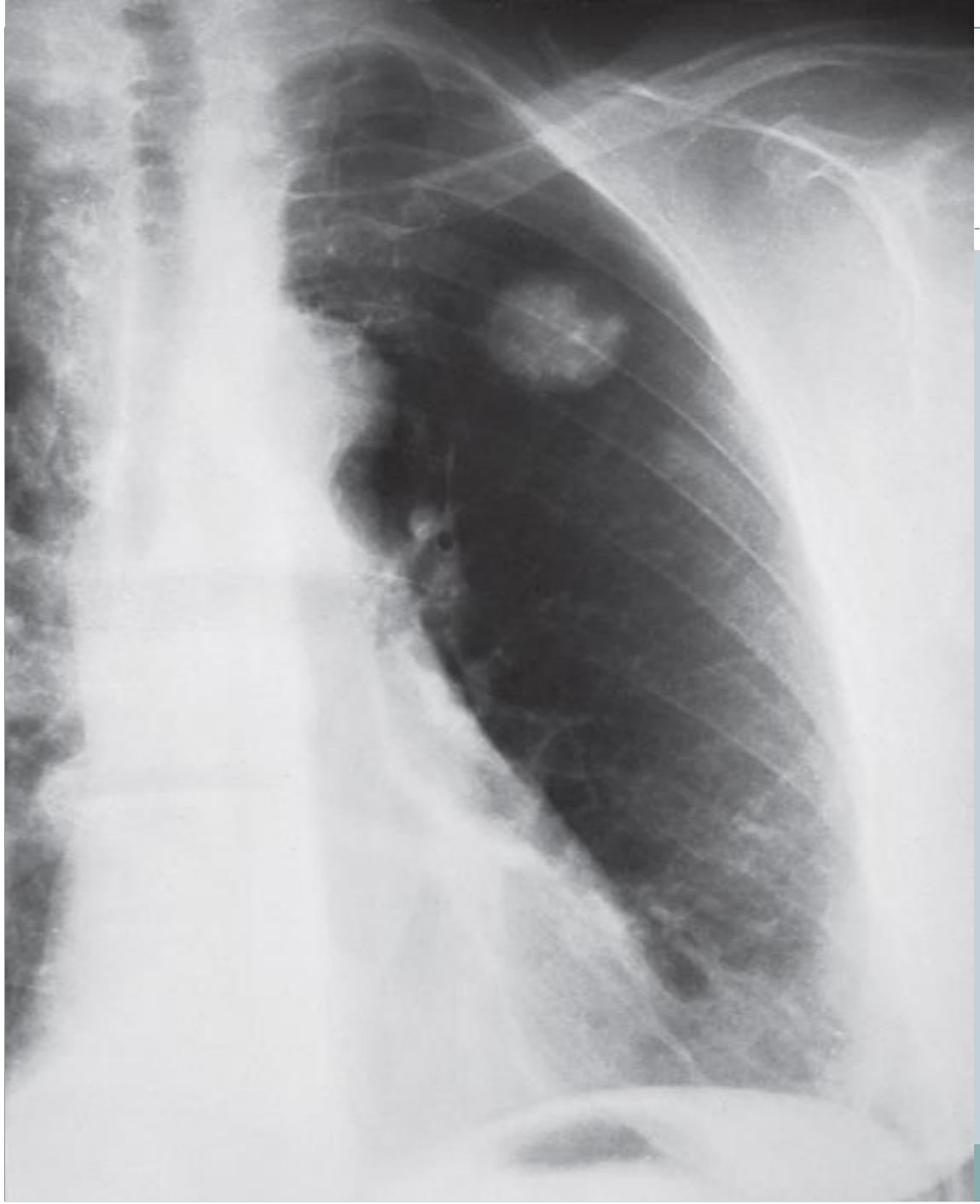


Extensive bilateral tuberculosis with cavity formation at right apex.

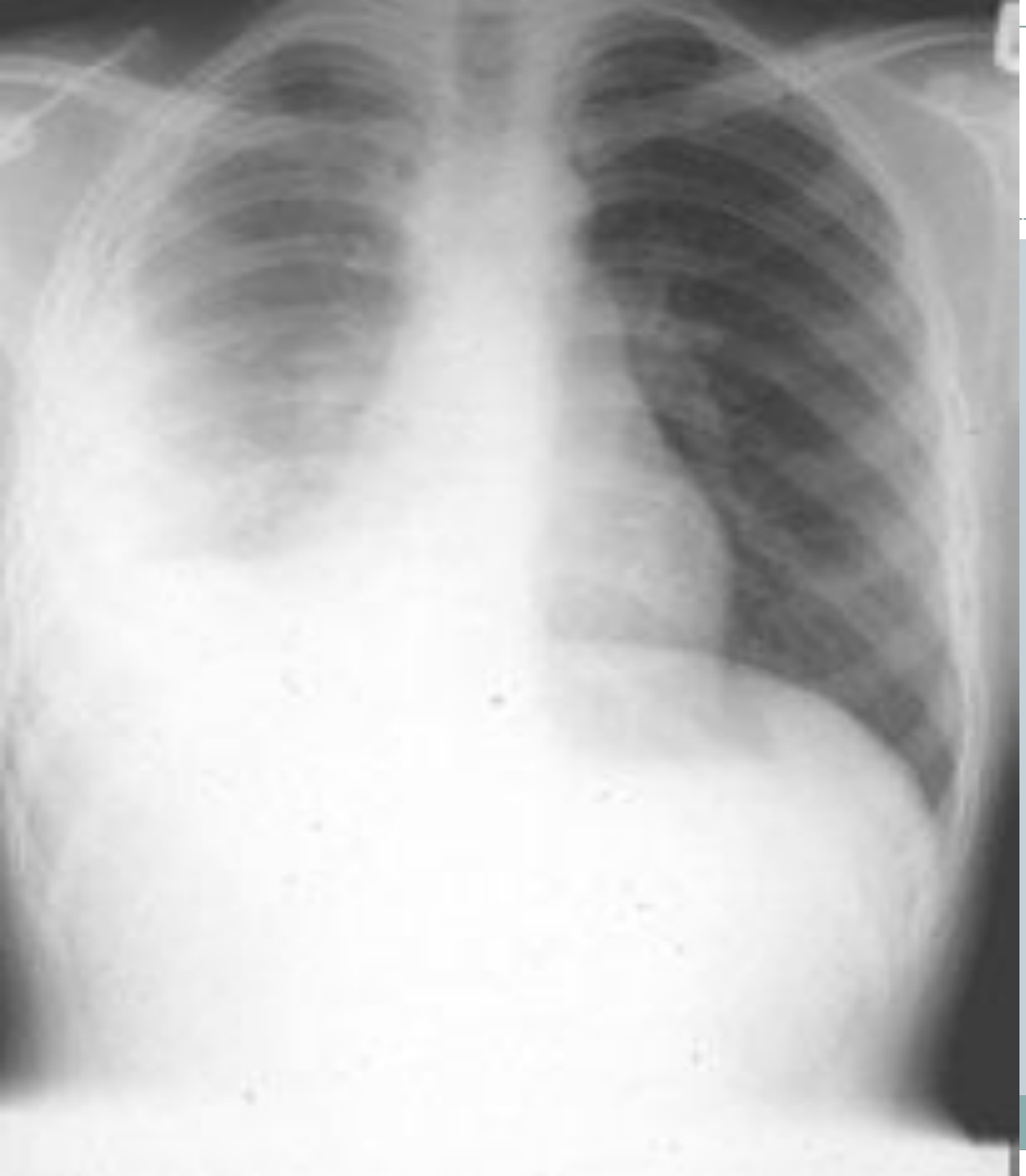


Chest radiograph showing **large tuberculoma in right mid-zone**, originally thought to be a coincidental carcinoma in patients with extensive upper lobe tuberculosis.



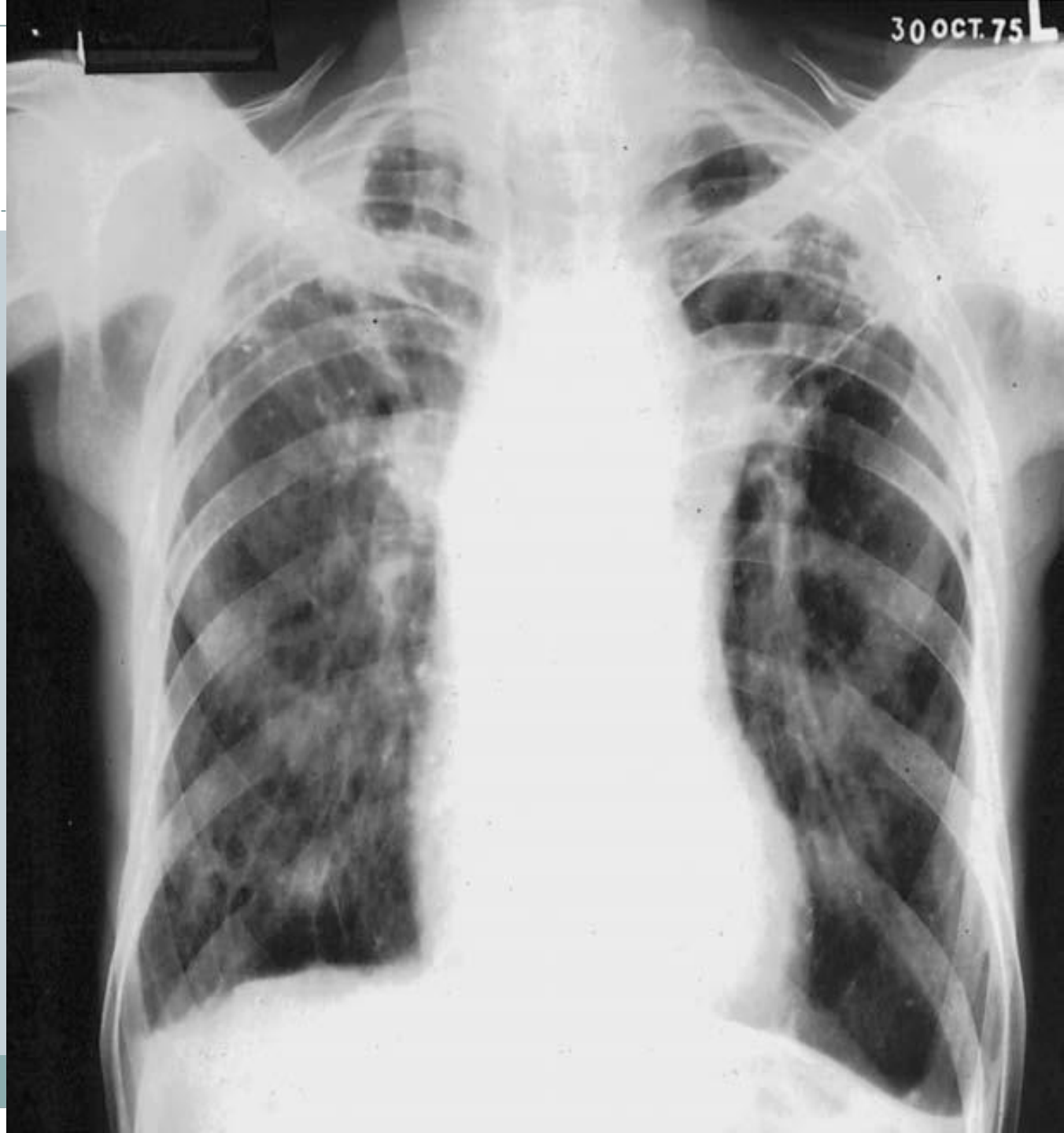


Calcified tuberculoma in a 74-year-old woman.

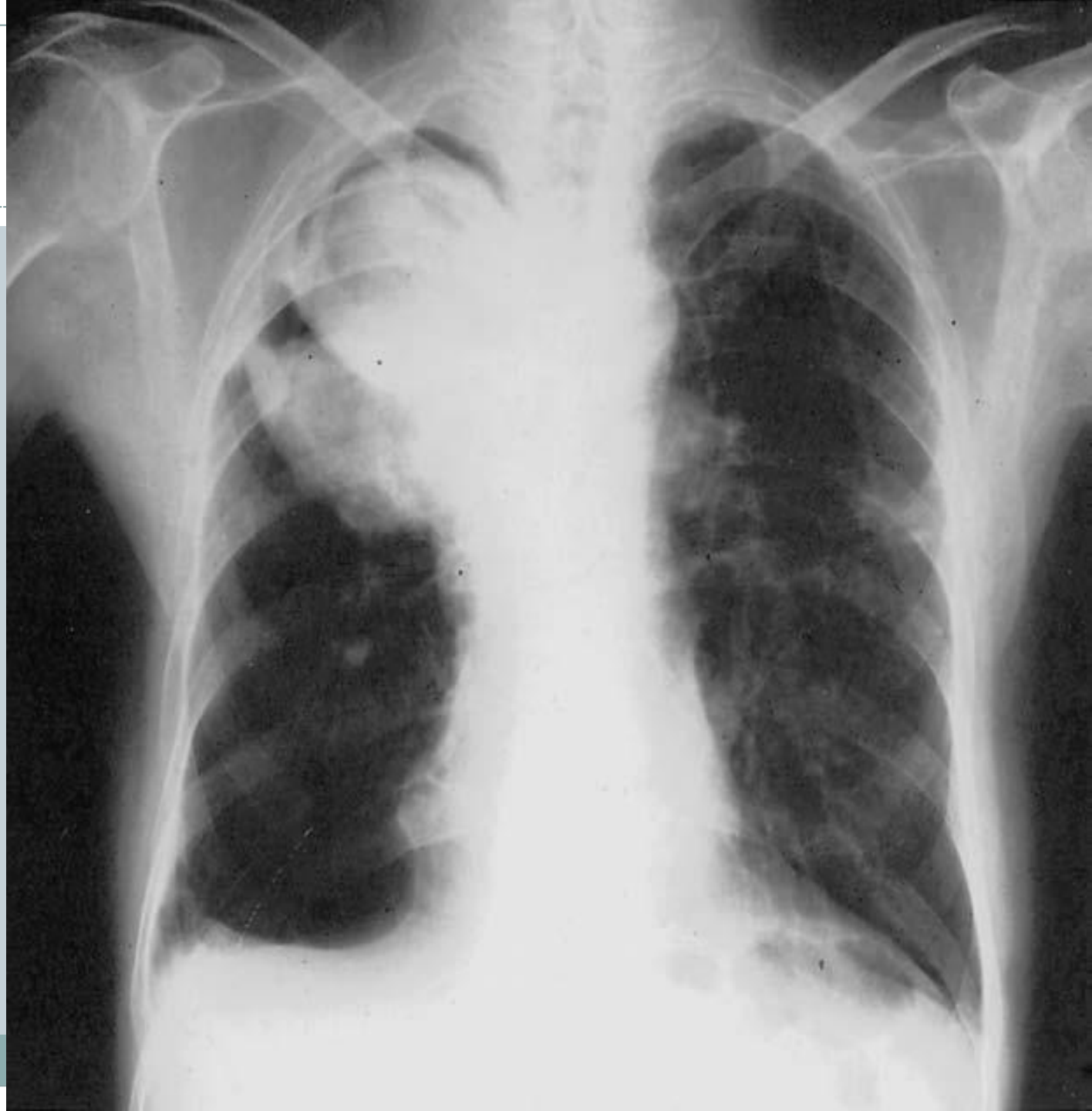


right pleural effusion

Chest radiograph showing bilateral apical fibrosis with calcification and upper lobe shrinkage with elevation of the hila.



Aspergillomas in old tuberculous cavities: the upper cavity contains an aspergilloma and shows the classical air crescent sign; the lower cavity has a fluid level with an aspergilloma protruding above it.



Ghon Complex

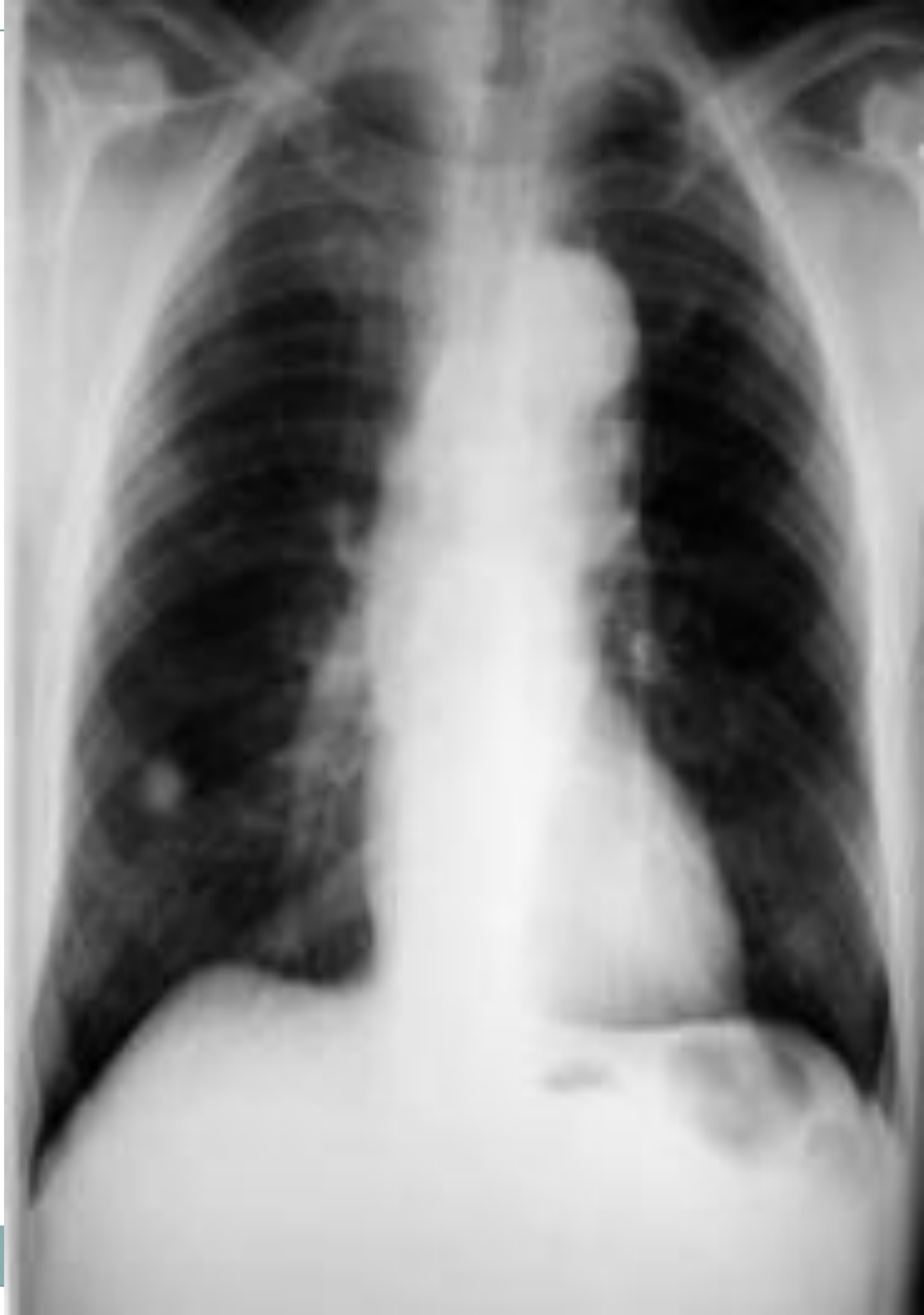
- **CXR finding of a calcified nodule plus calcified hilar/mediastianal lymphadenopathy, pathognomonic of previous primary infection by TB**

- **a pale yellow, caseous nodule, usually a few mm to 1-2 cm in diameter**

- **the combination of a primary lesion and regional lymph nodes is referred to as the 'primary complex of Ranke'**

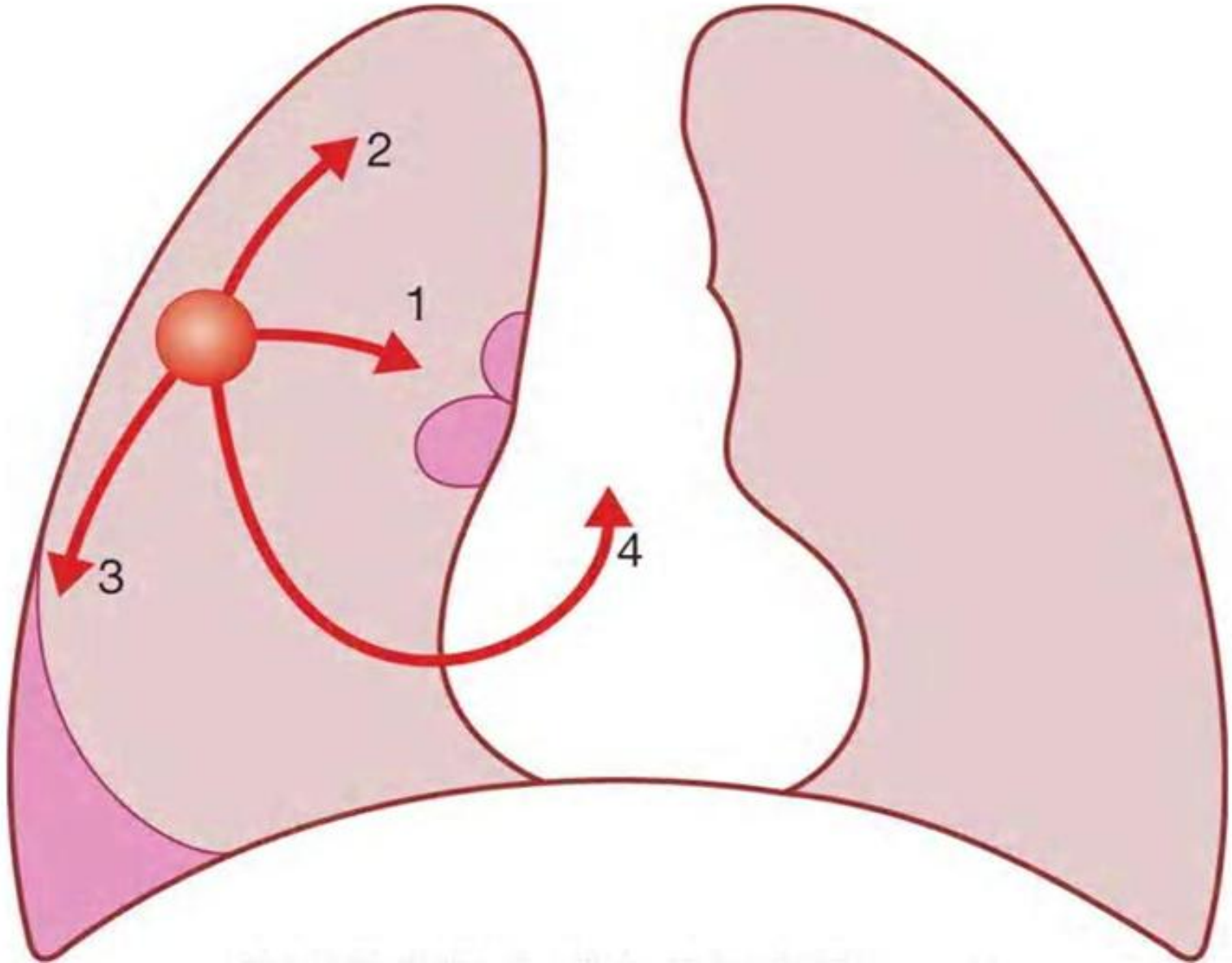
معقد غون

- بؤرة الدخول
- مع ضخامة العقد اللمفاوية السرية أو جانب رغامية أحادية الجانب



Primary pulmonary TB

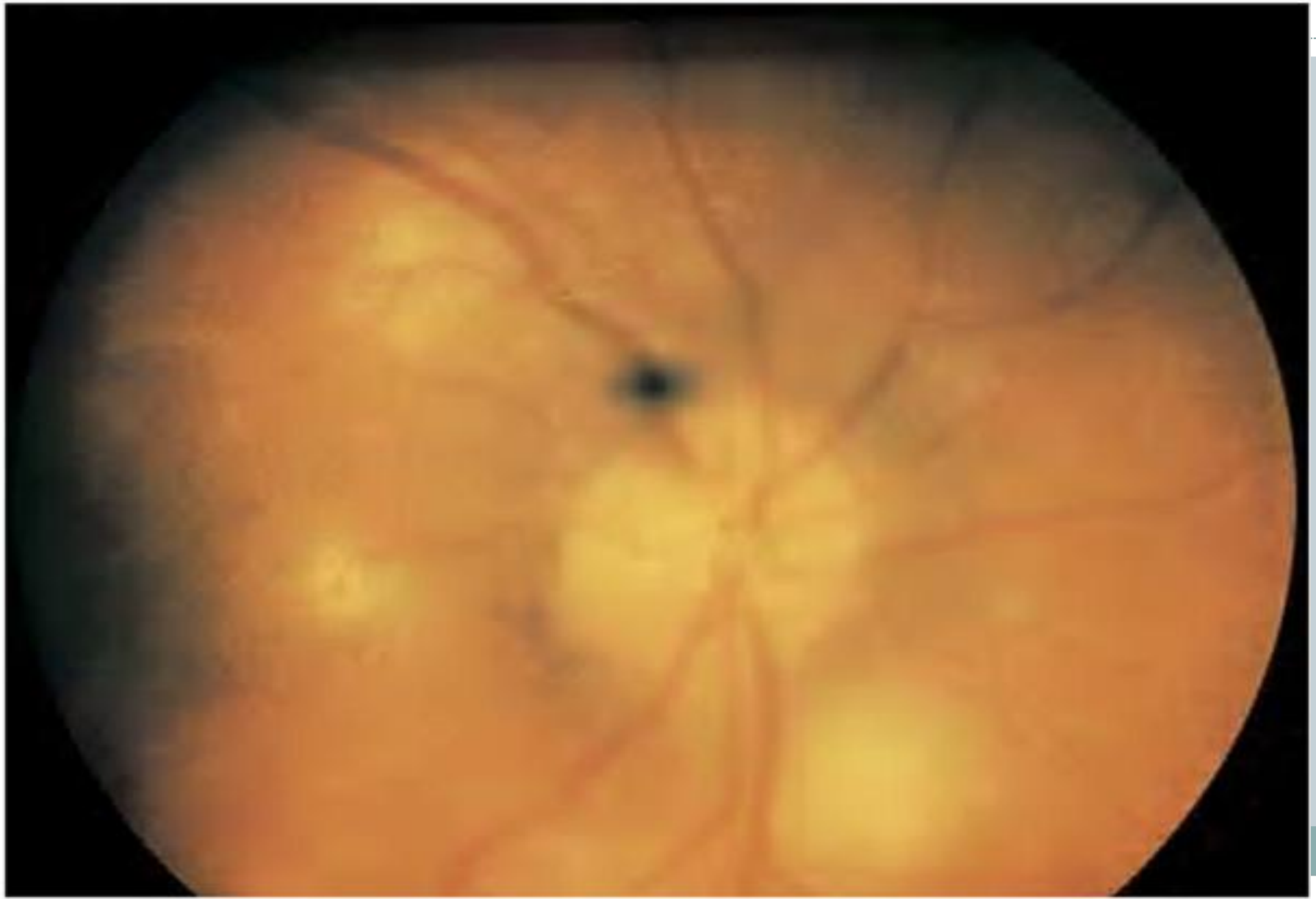
page 688
page 689



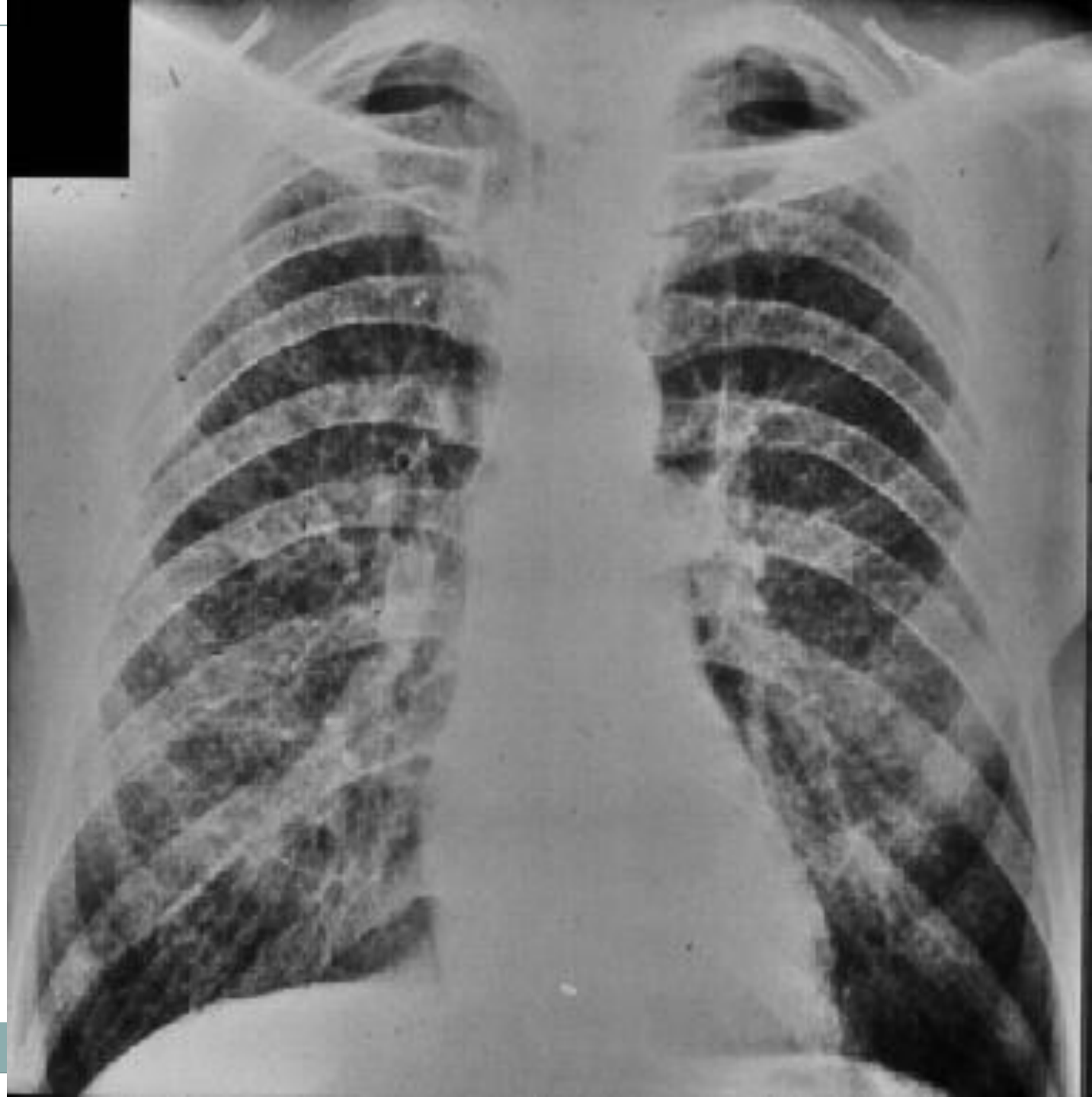
Miliary TB

- **Blood-borne dissemination**
- **fever, night sweats, anorexia, weight loss and a dry cough.**
- **Hepatosplenomegaly**
- **headache : coexistent tuberculous meningitis.**
- **Auscultation : frequently normal(more advanced disease widespread crackles).**
- **Fundoscopy : choroidal tubercles.**
- **chest X-ray : fine 1-2 mm lesions ('millet seed') distributed throughout the lung fields**
- **Anaemia and leucopenia**

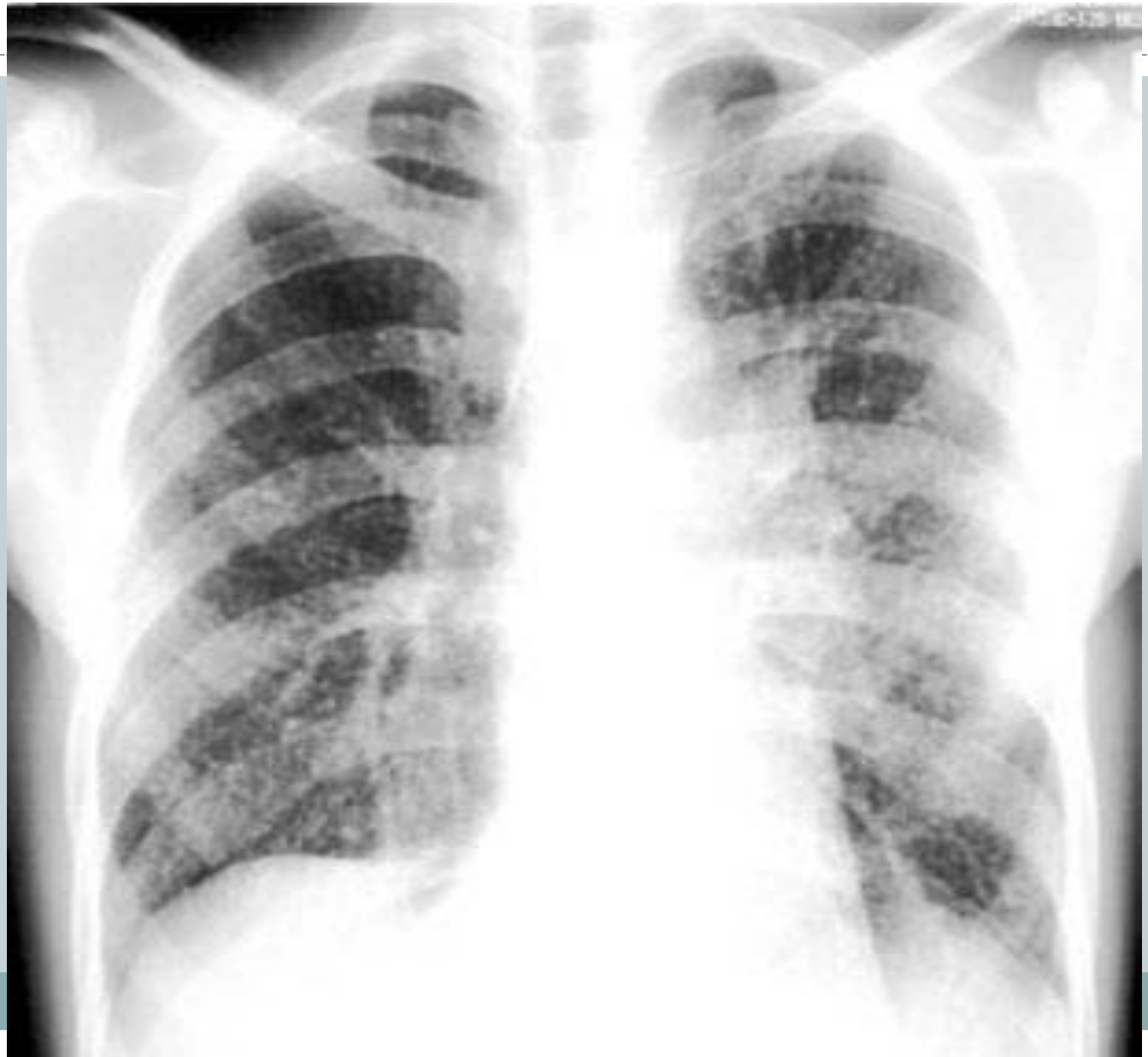
Choroidal tubercles in acute miliary tuberculosis



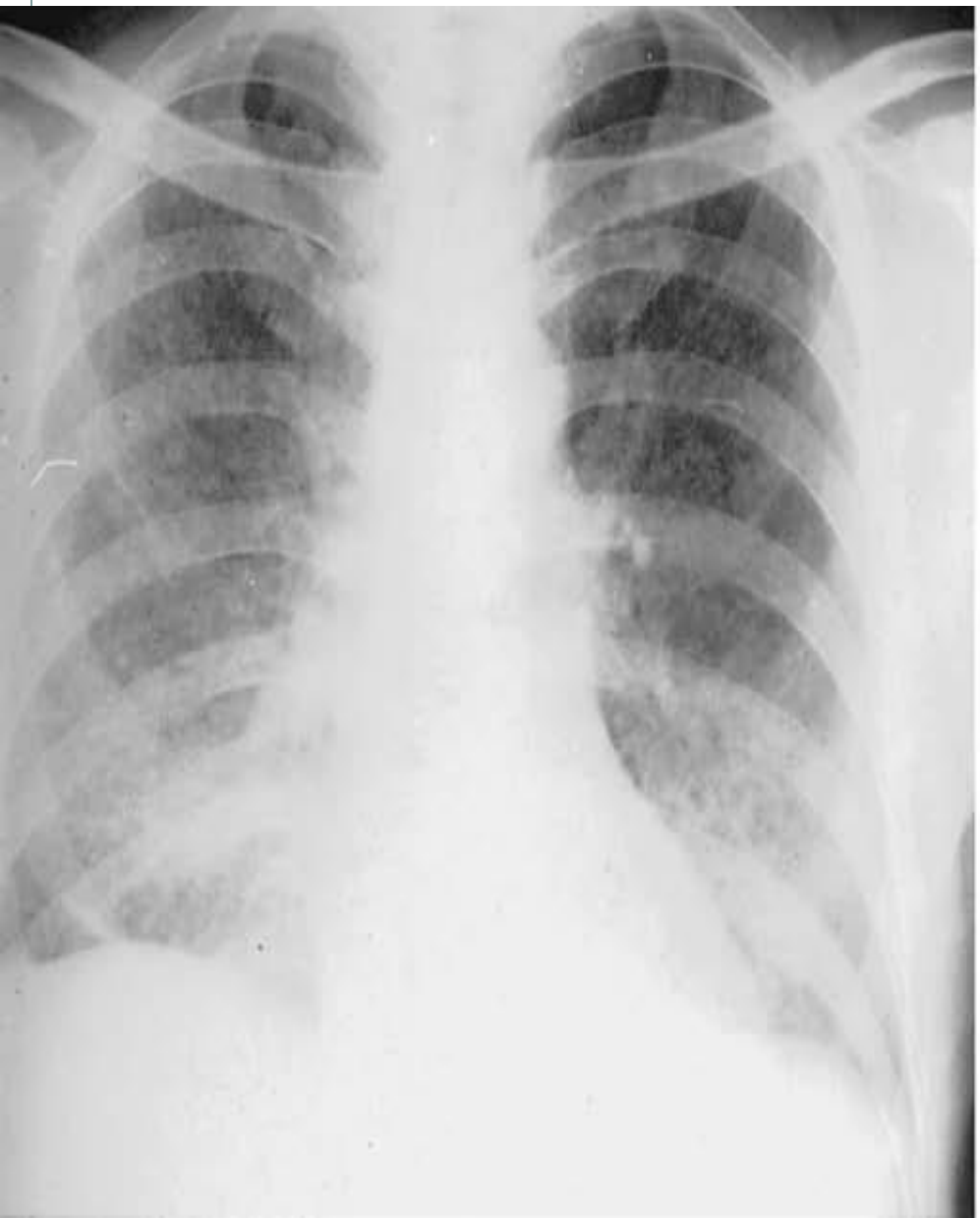
MILIARY TB

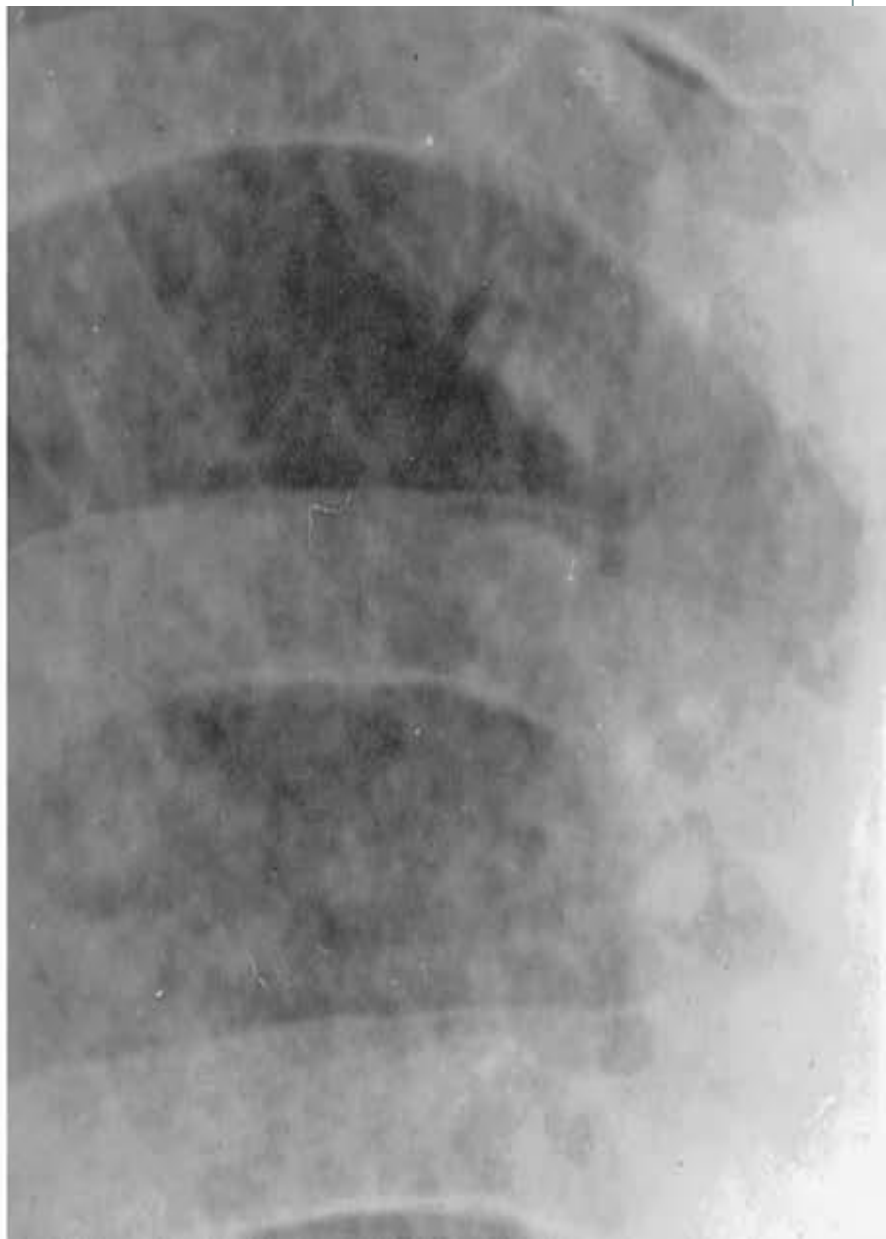


miliary TB

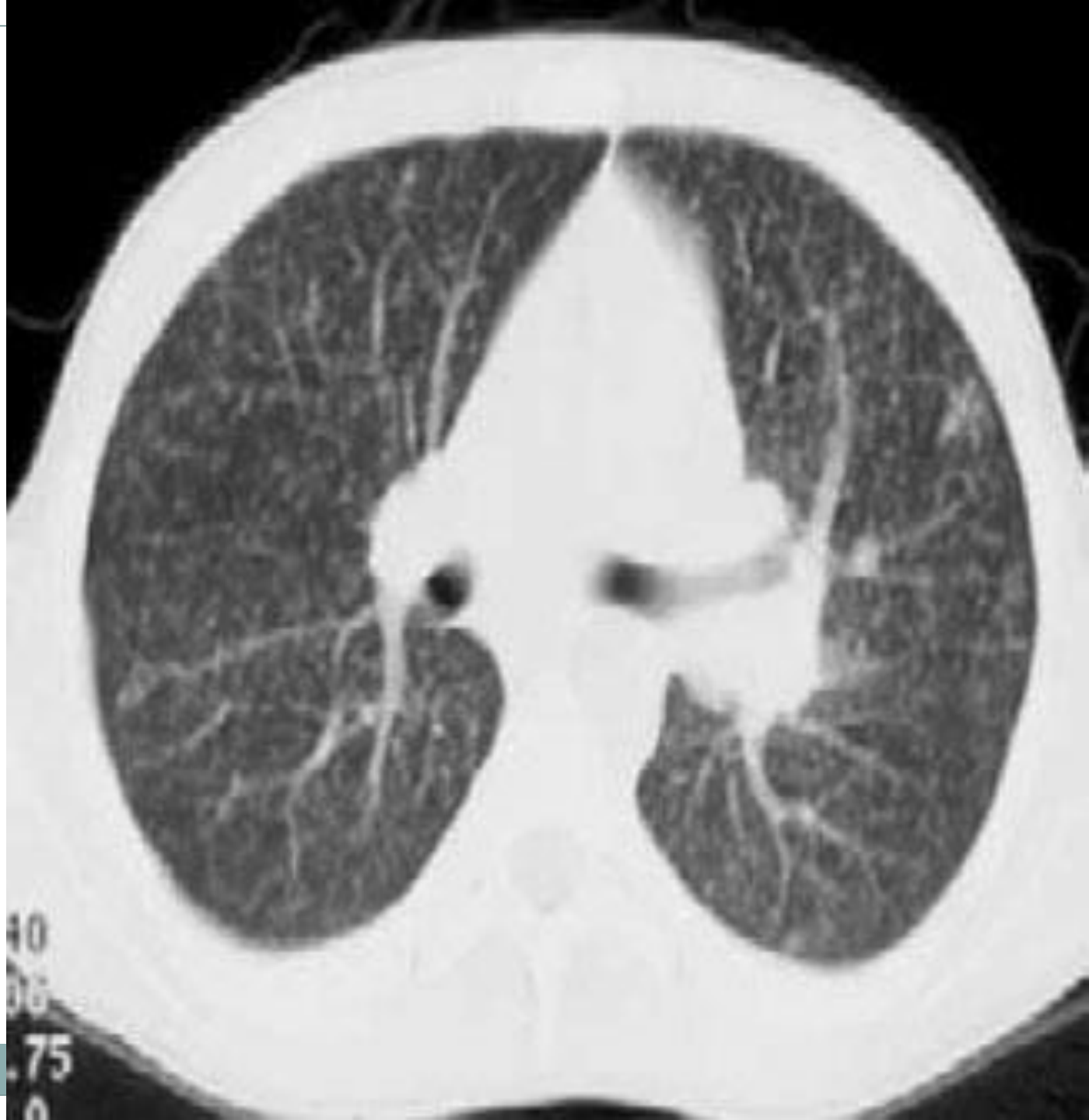


(a) Chest radiograph showing miliary tuberculosis. (b) Magnified view of the lung periphery in miliary tuberculosis.



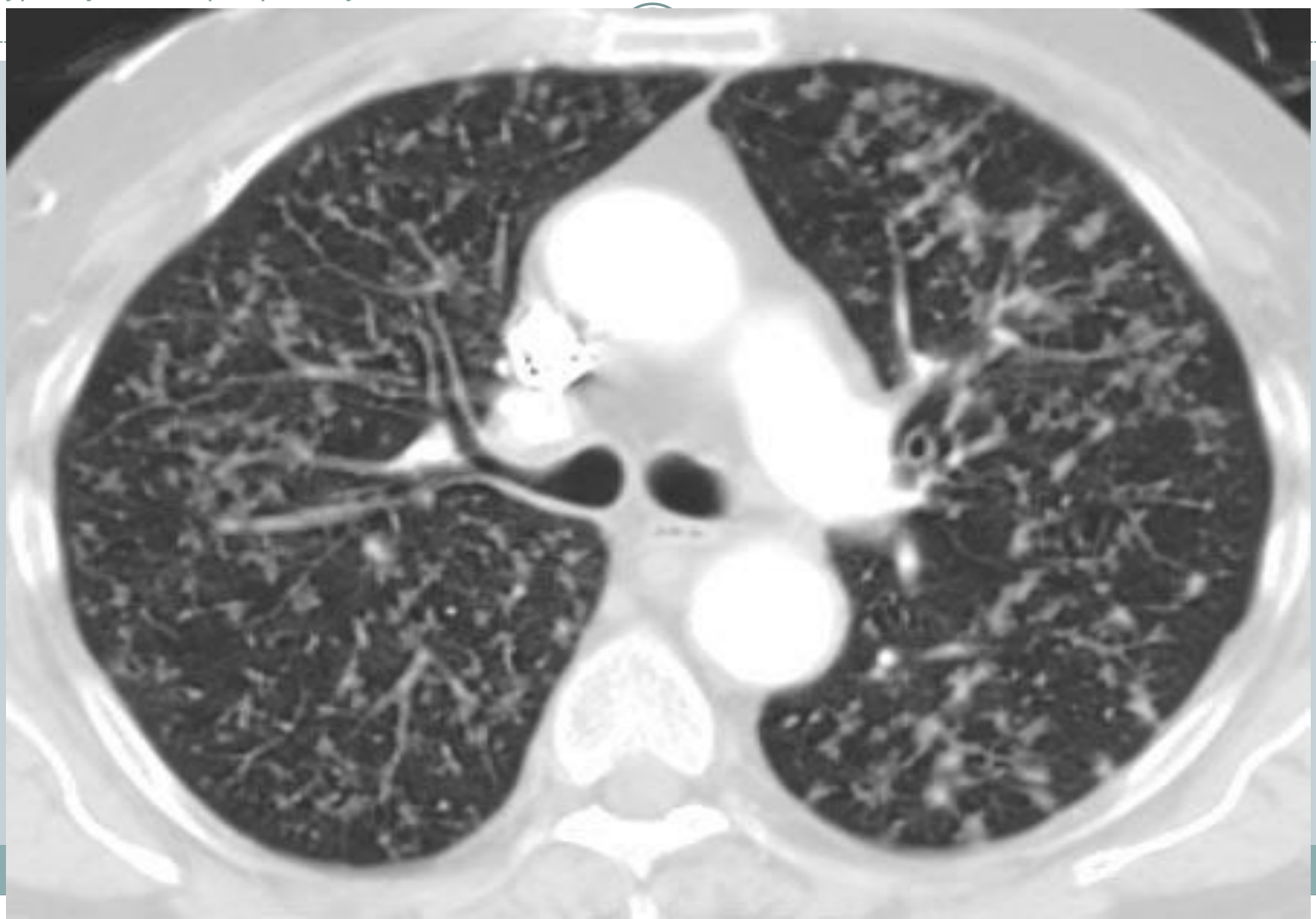


CT miliary nodules – miliary TB.



High resolution computed tomography of the chest in a patient with miliary tuberculosis

Parenchymal postprimary tuberculosis. High-resolution CT scan demonstrates multiple small, centrilobular nodules connected to linear branching opacities. This so-called tree-in-bud appearance is typically seen in postprimary tuberculosis.



Miliary nodules

- **Miliary TB**
- **Sarcoid**
- **Dust inhalation/pneumoconiosis**
- **Extrinsic allergic alveolitis**
- **Miliary metastases: thyroid, melanoma**

- **<u>Dense miliary nodule:</u>**

- **Haemosiderosis**
- **Silicosis**
- **Chicken pox**

Chronic complications of pulmonary TB

Pulmonary

- Massive haemoptysis
- Cor pulmonale
- Fibrosis/emphysema
- Atypical mycobacterial infection
- Aspergilloma
- Lung/pleural calcification
- Obstructive airways disease
- Bronchiectasis
- Bronchopleural fistula

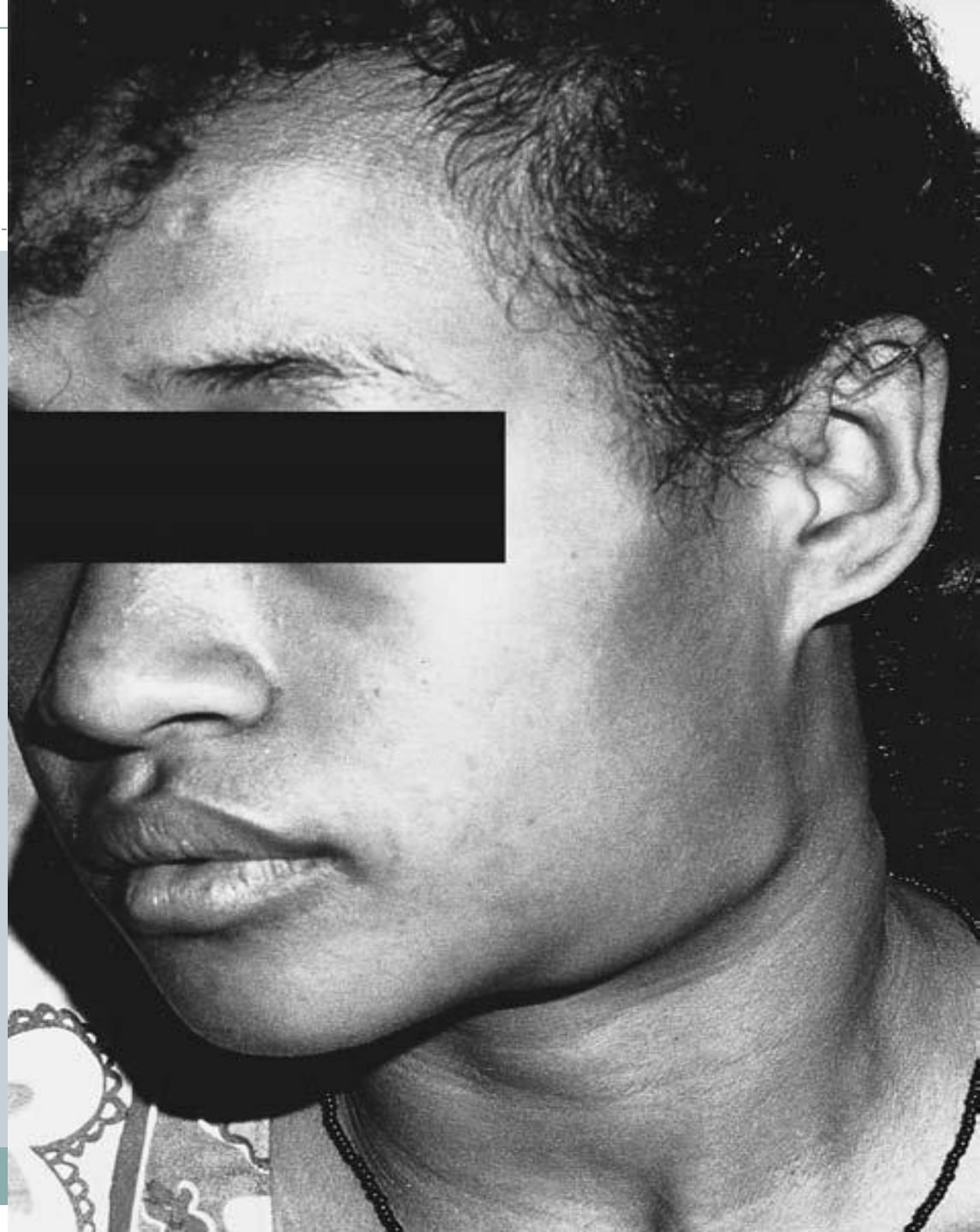
Non-pulmonary

- Empyema necessitans
- Laryngitis
- Enteritis*
- Anorectal disease*
- Amyloidosis
- Poncet's polyarthritis

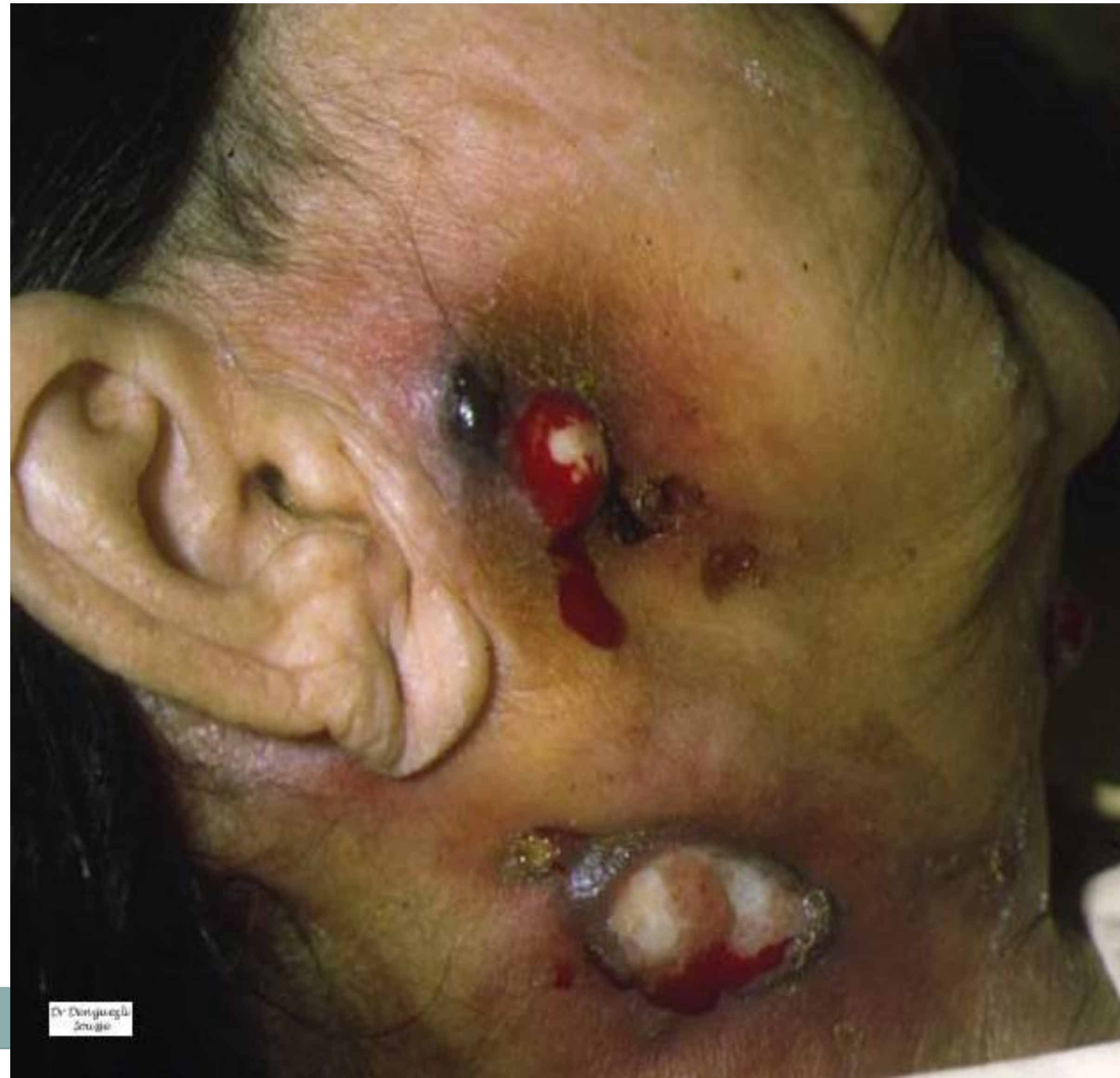
extrapulmonary disease Lymphadenitis

- **Cervical and mediastinal glands are affected most frequently**
- **may represent primary infection, spread from contiguous sites or reactivation**
- **nodes are usually painless and initially mobile**
- **the swelling becomes fluctuant and may discharge through the skin (caseation)**
- **tuberculin test : usually strongly positive.**
- **development of new nodes and suppuration may all occur but without evidence of continued infection**
- **rarely, surgical excision is necessary**

Left-sided submandibular tuberculous lymphadenitis.



المكان خارج الرئوي الأكثر شيوعاً للمرض هو العقد اللمفاوية



عقد لمفاوية رقبية صلبة
لها تدرن متنوسرة

Left-sided axillary tuberculous lymphadenitis.

Gastrointestinal disease

- **TB can affect any part of the bowel**
- **Upper gastrointestinal tract involvement : rare**
- **Ileocaecal disease : half of abdominal TB cases.**
- **Fever, night sweats, anorexia and weight loss are usually prominent**
- **right iliac fossa mass may be palpable.**
- **Up to 30% of cases present with an acute abdomen**

Gastrointestinal disease

- **Barium enema and small bowel enema :**
  - narrowing, shortening and distortion of the bowel with caecal involvement predominating.

- **Diagnosis** rests on obtaining histology by either colonoscopy or mini-laparotom

- **Tuberculous peritonitis :**
  - abdominal distension, pain and constitutional symptoms.
  - The ascitic fluid is exudative and cellular with a predominance of lymphocytes.

- **Low-grade hepatic dysfunction** is common in miliary disease when biopsy reveals **granulomas**

Pericardial disease

- **pericardial effusion and constrictive pericarditis**
- **usually insidious with breathlessness and abdominal swelling.**
- **Coexistent pulmonary disease is very rare**
- **a globular enlarged heart on chest X-ray.**
- **pericardial calcification occurs in around 25% of cases.**
- **effusion is frequently blood-stained.**
- **Open pericardial biopsy can be performed**
- **addition of corticosteroids to antituberculosis treatment:**

  beneficial for both forms of pericardial disease.

Central nervous system disease

- Meningeal disease :
  Unrecognised and untreated→ it is rapidly fatal.

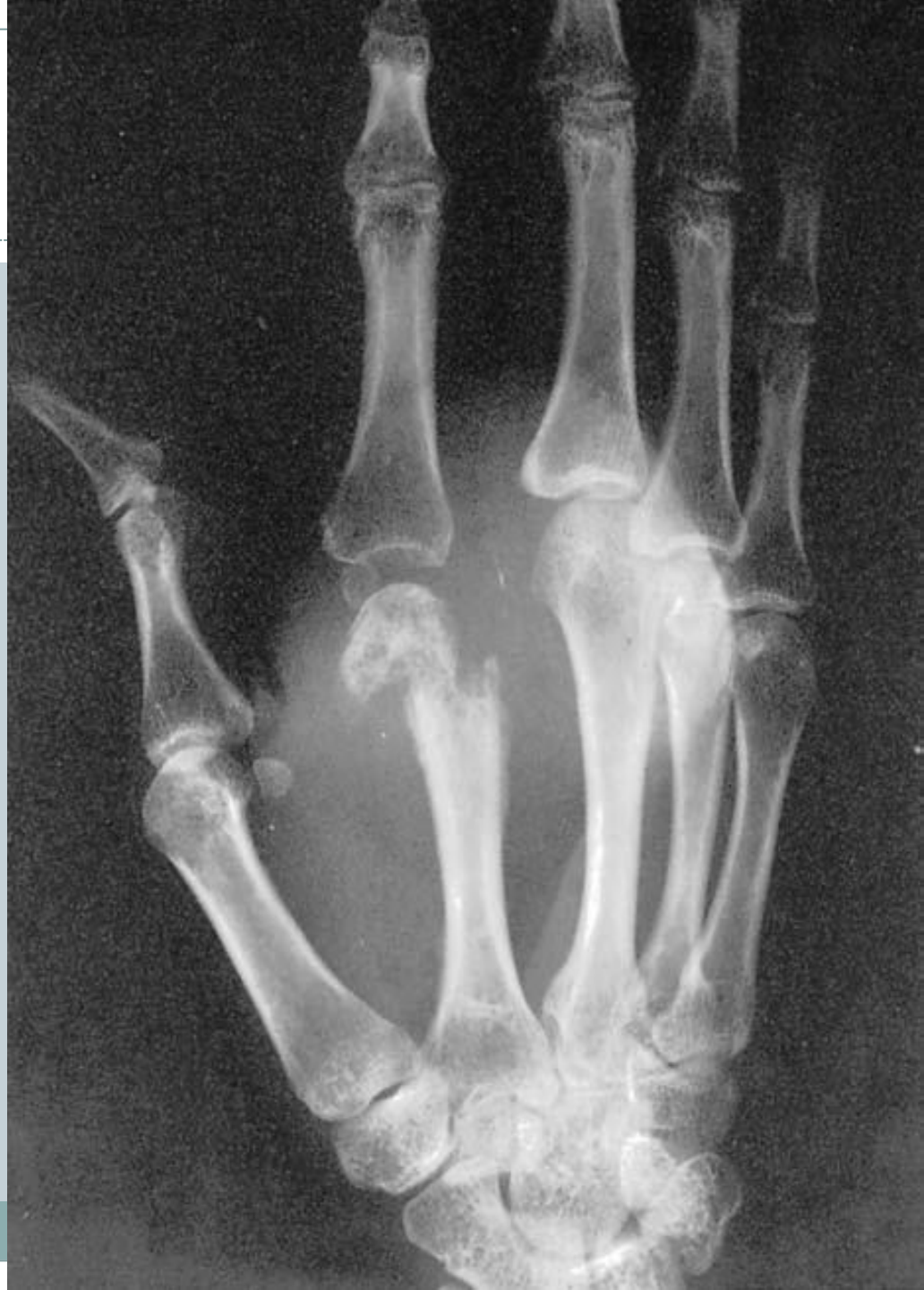
- Even when appropriate treatment is prescribed :
  mortality rates of 30%

- survivors may be left with neurological sequelae.

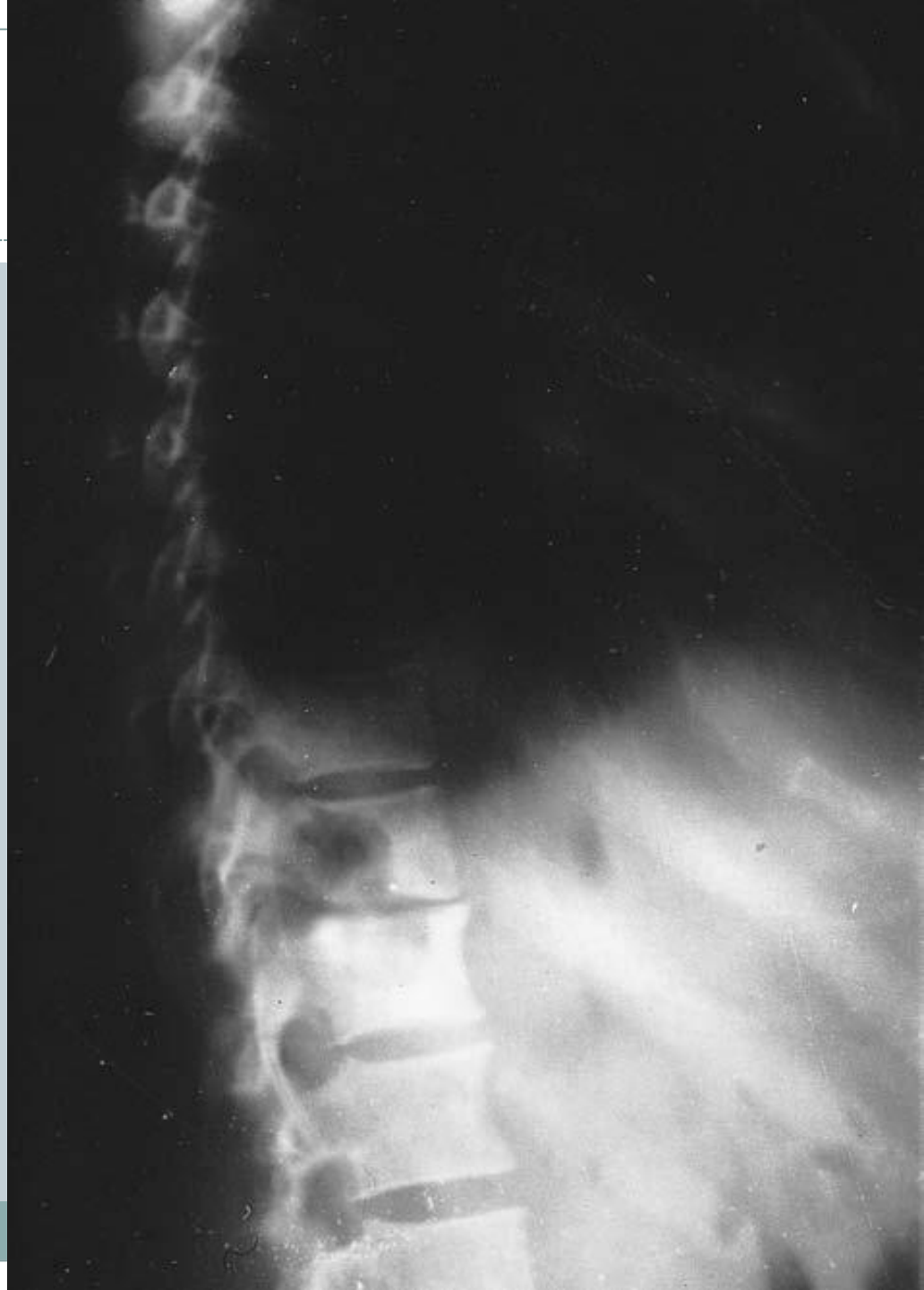
Bone and joint disease

- **spine is the most common site for bony TB (Pott's disease)**
- **usually presents with chronic back pain**
- **Paravertebral and psoas abscess formation : common**
- **may present with a large (cold) abscess in the inguinal region.**
- **complications : spinal instability or cord compression**
- **TB involves the hip or knee :**
  fever and night sweats are uncommon.
- **Poncet's arthropathy :**
  immunologically mediated polyarthritis that usually resolves within 2 months of starting treatment

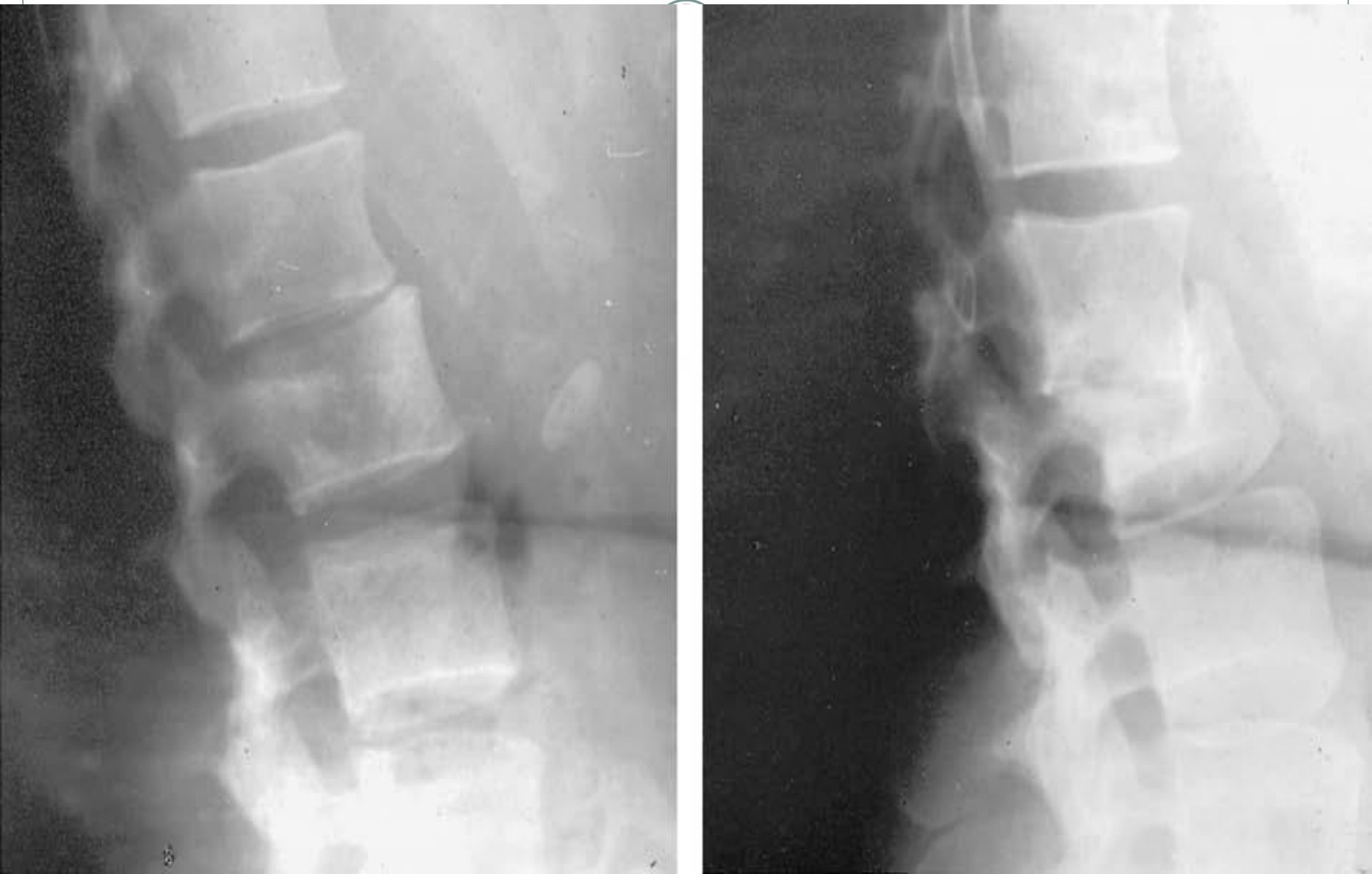
Tuberculosis of the second metacarpal with cold abscess formation in an Asian patient.



Pott's disease of the spine affecting the T12/L1 disc space and adjacent vertebrae.



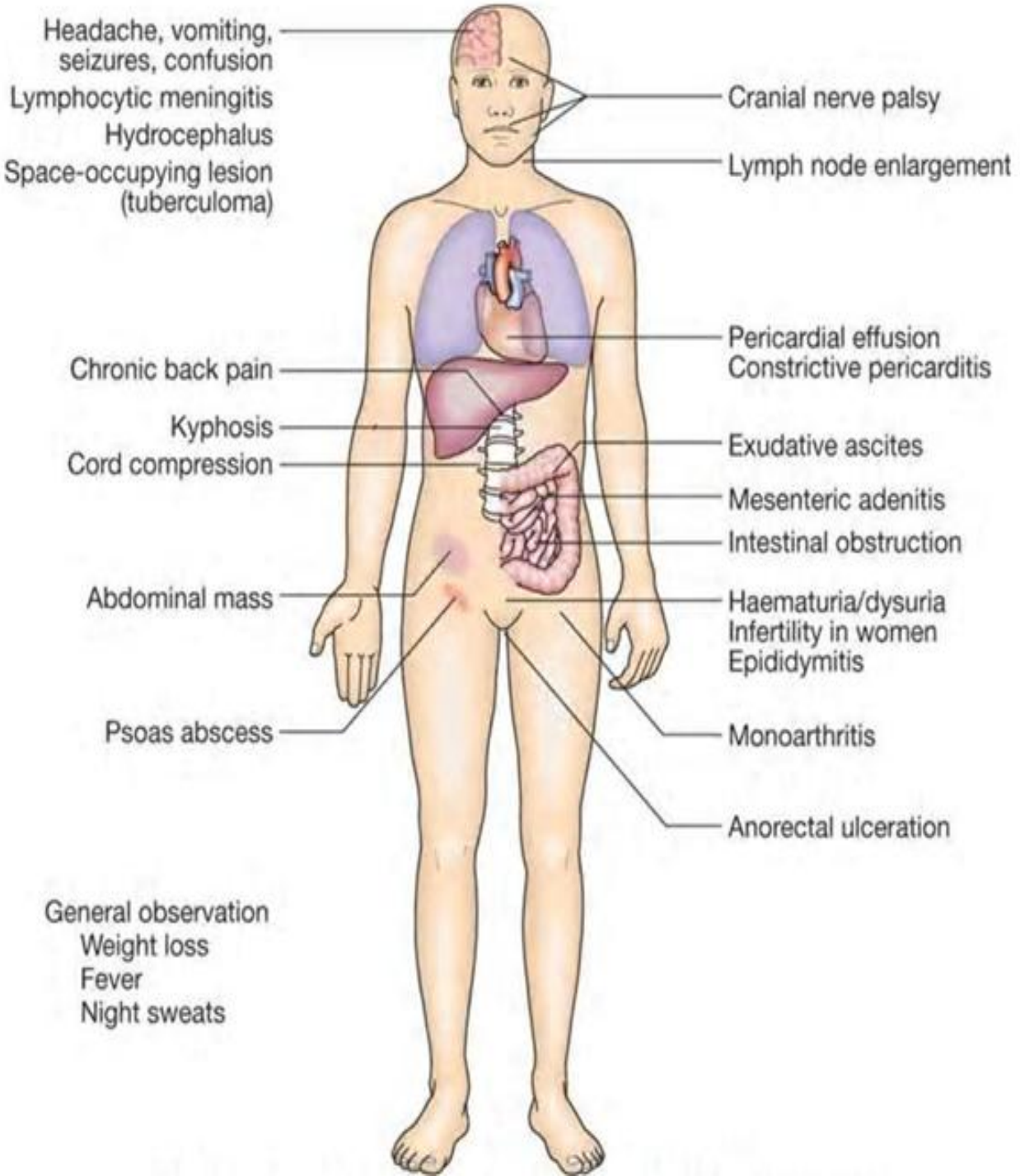
(a) Early tuberculous changes in the lumbar spine showing disc narrowing at L1/2, destruction of the body of L2 and demineralization of the adjacent end-plate. (b) The same patient 17 months later showing mild gibbous defomity resulting from extensive collapse of L2.



Genitourinary disease

- Fever and night sweats are rare
- often only mildly symptomatic for many years.
- Haematuria, frequency and dysuria are often present, with sterile pyuria
- In women: - infertility from endometritis
  - pelvic pain and swelling from salpingitis or a tubo-ovarian abscess
- In men: epididymitis or prostatitis.

Systemic presentations of extrapulmonary TB.



Tuberculosis in HIV

- **(TB) is the most common global infection**
- **affecting up to one-third of the estimated 40 million HIV patients**
- **Diagnosis may be difficult :**
  smear-positive rates are reduced in pulmonary TB
- **chest X-ray appearances may be atypical with less cavitation**
- **Standard quadruple therapy :**

  curative in the majority

Tuberculosis in HIV

Patients with HIV are at greater risk of:

- Infection after exposure
- Progressive primary disease after infection
- Reactivation of latent infection
- Reinfection with new strain
- Disseminated and extrapulmonary (e.g. meningeal and pericardial) disease
- Adverse drug reactions

Chest X-ray of pulmonary tuberculosis in HIV infection. Appearances are often atypical but in this case there are multiple cavities and focal consolidation.

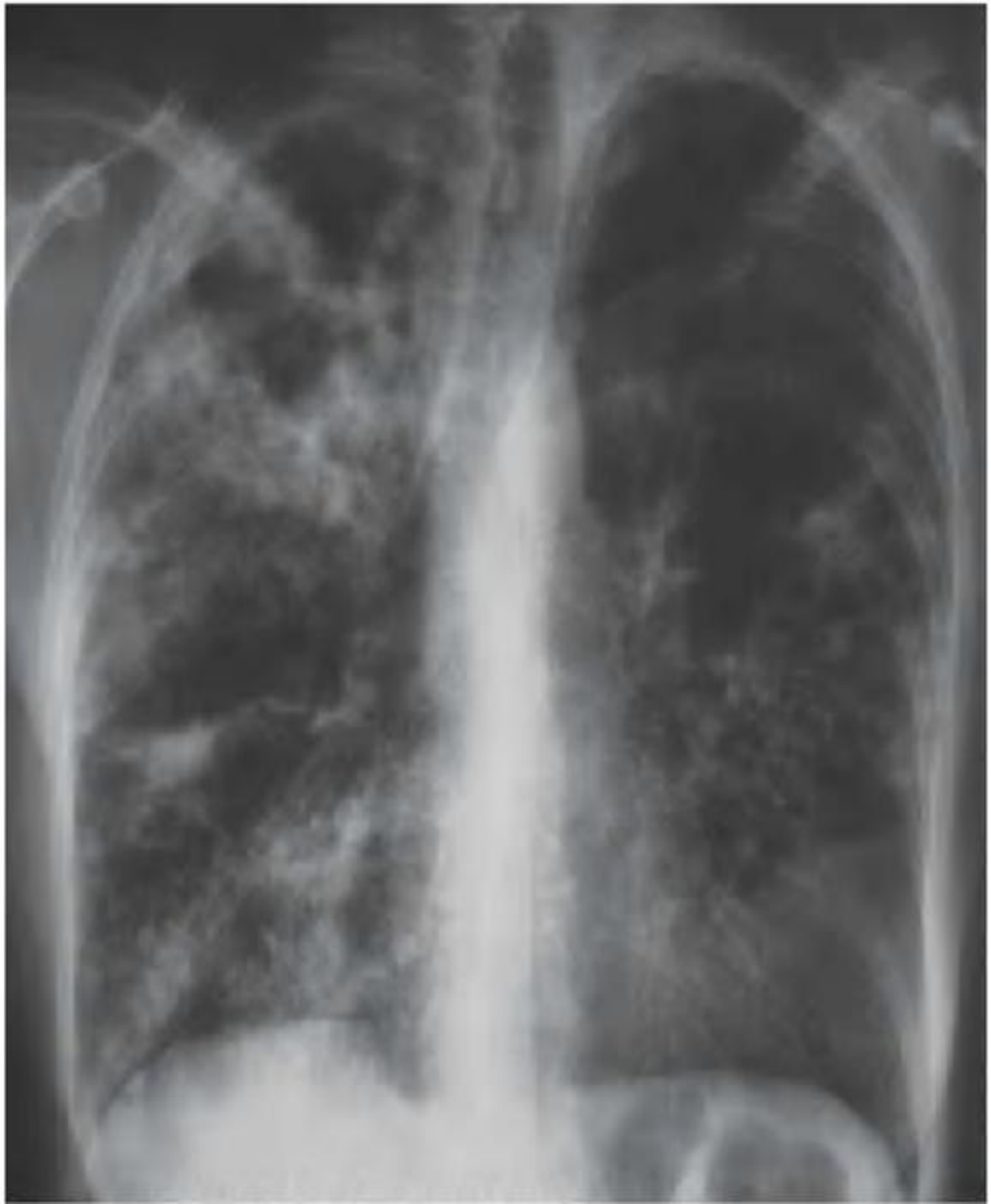


Table 4—*General Indications for a Chest Radiograph to Detect TB*

- Unexplained cough (for >3 wk)
- Unexplained cough with fever (>3 d)
- Unexplained pleuritic chest pain, hemoptysis, and/or dyspnea
- Unexplained fever, night sweats, and weight loss

Diagnosis

- unexplained cough for more **than 2-3 weeks**

- **Direct microscopy of sputum :**
  - positive when 5000-10 000 organisms are present
  - techniques :
  Ziehl-Neelsen and **rhodamine-auramine** stains

- **definitive diagnosis requires culture.**
- Smear-negative sputum should also be cultured (10-100 viable organisms are required for sputum to be culture-positive).

culture

- **4 and 6 weeks** to appear on solid medium such as **Löwenstein-Jensen or Middlebrook.**

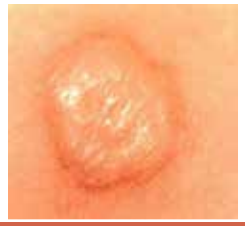
- **Faster growth (1-3 weeks) :**
  - in liquid media :
  * the radioactive **BACTEC system** :
  by measuring the liberation of $^{14}CO_2$, following metabolism of ^{14}C-labelled substrate present in the medium.

  - the non-radiometric mycobacteria growth indicator tube **(MGIT)**

- **nucleic acid amplification test (NAT) :**
  amplify nucleic acid regions specific to MTB such as IS6110, and the MPB64 skin patch test, detects active but not latent TB

Screening test

- **Tuberculin Skin Test (PPD)**
- **Interferon Gamma Releasing Assay**



IGRA	TST
Not affected by BCG	May give a false-positive result after BCG vaccination
More specific	More sensitive
More expensive	Less expensive
Results within 24 hours	At least 48 hours
No Boosting effect	Yes

A negative IGRA excludes tuberculosis in immunocompetent patients. Both of them **are not able** to differentiate between active or latent TB.

interferon-gamma release assays (IGRAs)

- measure the release of IFN-γ from sensitised T cells in response to antigens such as early secreted antigenic target (ESAT)-6 or culture filtrate protein (CFP)-10 that are encoded by genes specific to the MTB
- specificity :good

The diagnosis of extrapulmonary TB

- fewer organisms (particularly in meningeal or pleural fluid)
- culture or histopathological examination of tissue is more important.

Diagnosis of TB

Specimens required
Pulmonary

- Sputum* (induced with nebulised hypertonic saline if not expectorating)
- Bronchoscopy with washings or BAL
- Gastric washing* (mainly used for children)

Extrapulmonary

- Fluid examination (cerebrospinal, ascitic, pleural, pericardial, joint): yield classically very low
- Tissue biopsy (from affected site); also bone marrow/liver may be diagnostic in patients with disseminated disease

Diagnostic tests

- Circumstantial (ESR, CRP, anaemia etc.)
- Tuberculin skin test (low sensitivity/specificity; useful only in primary or deep-seated infection)
- Stain
  - Ziehl-Neelsen
  - Auramine fluorescence
- Nucleic acid amplification
- Culture
  - Solid media (Löwenstein-Jensen, Middlebrook)
  - Liquid media (e.g. BACTEC or MGIT)
- Response to empirical antituberculous drugs (usually seen after 5-10 days)

TECHNOLOGIES ENDORSED BY WHO

Molecular technologies

- **Xpert MTB/RIF :**
  -(automated nucleic acid amplification test) (pulmonary , extrapulmonary and paediatric samples)
  - **sensitivity and specificity** of the Xpert assay were **81 and 99 percent**
  - Line probe assays for the detection of **MTB and rifampicin resistance** conferring mutations in AFB smear positive sputum or MTB cultures

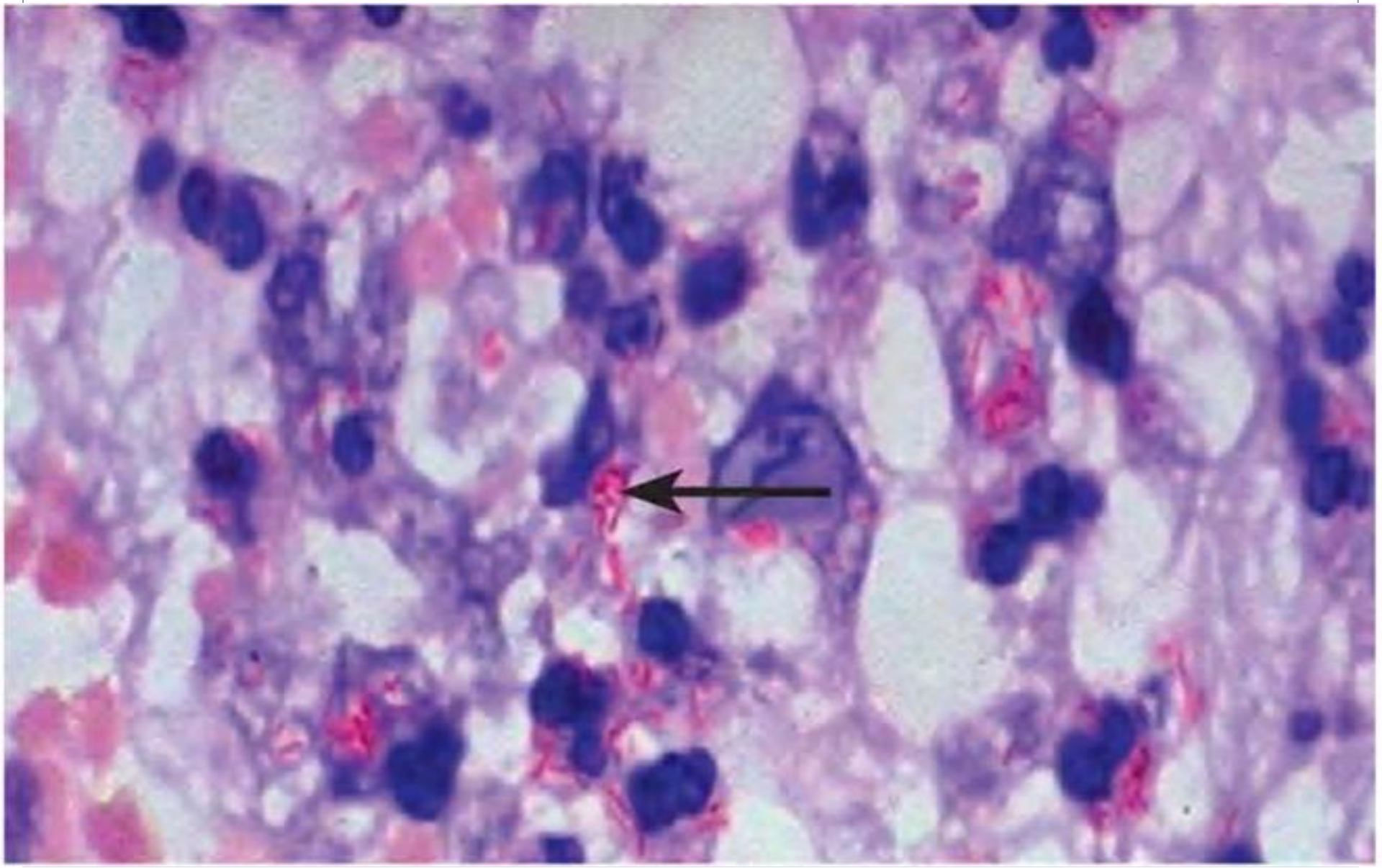
Microscopy

- Light and LED Microscopy
- Same-day diagnosis

Culture-based technologies

- Commercial liquid culture systems and rapid speciation
- Non-commercial culture and DST (MODS, NRA, CRI)

Positive Ziehl-Neelsen stain



Management

- **initial intensive phase :**
  rapidly reduces the bacterial population

- **continuation phase :** destroy any remaining bacteria.

- **Treat immediately :**
  - in any patient who is smear-positive
  - who is smear-negative but with typical chest X-ray changes and no response to standard antibiotics.

- **Six months of therapy is appropriate for all patients with new-onset, uncomplicated pulmonary disease.**

treatment

- **INH and rifampin x 6 months with pyrazinamide x the first 2 months**
- **multiple drug resistant strains (MDR-TB):**
  INH, rifampin, pyrazinamide, and ethambutol, then modified with sensitivities
- **if <u>untreated,</u> 50% will die within 5 years**
- **9-12 months of therapy :**
  - HIV-positive
  - drug intolerance occurs and a second-line agent is substituted.
- **<u>Meningitis</u>** should be treated for **a <u>minimum of 12 months</u>.**
- **Pyridoxine** should be prescribed in pregnant women and malnourished patients
- patients can be assumed to be **<u>non-infectious after 2 weeks</u> of appropriate therapy.**

Treatment schedules recommended by tuberculosis case or treatment category

TREATMENT CATEGORY	TUBERCULOSIS CASE	RECOMMENDED TREATMENT SCHEDULE	
		INITIAL PHASE	CONTINUATION PHASE
1	- New case of smear-positive PTB - Severe forms of smear-negative PTB - Severe extra-pulmonary tuberculosis	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE or 6 TH 4 HR 4 H_3R_3
2	- Smear-positivepulmonary tuberculosis: relapse failure return after interruption	2 SHRZE/1 HRZE 2 SHRZE/1 HRZE	5 $H_3R_3E_3$ 5 HRE
3	- Smear-negative PTB - Less severe extrapulmonary tuberculosis	2 HRZ 2 HRZ 2 HRZ	6 HE or 6 TH 4 HR 4 H_3R_3
4	Smear-positive pulmonary tuberculosis after re-treatment	Combinations of second-line drugs reserved for used by the reference centres	

Treatment of TB (World Health Organization recommendations)

	Category of TB	Initial phase*	Continuation phase
1	New cases of smear-positive pulmonary TB	2 months $H_3R_3Z_3E_3$ *or* 2 months $H_3R_3Z_3S_3$	4 months H_3R_3
	Severe extrapulmonary TB	2 months HRZE *or* 2 months HRZS	4 months HR
	Severe smear-negative pulmonary TB		6 months HE†
	Severe concomitant HIV disease		
2§	Previously treated smear-positive pulmonary TB	2 months $H_3R_3Z_3E_3$ *or* 1 month $H_3R_3Z_3E$	5 months $H_3R_3E_3$
	Relapse	2 months HRZES *or* 1 month HRZE	5 months HRE
	Treatment failure		
	Treatment after default		
3‡	New cases of smear-negative pulmonary TB	2 months $H_3R_3Z_3E_3$	4 months H_3R_3
	Less severe extrapulmonary TB	2 months HRZE	4 months HR
			6 months HE†

Table 4.1 DEFINITIONS OF TREATMENT OUTCOMES[a]

Outcome	Definition
Cure	A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion[b]
Treatment failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.
Died	A patient who dies for any reason during the course of treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more.
Transfer out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.
Treatment success	A sum of cured and completed treatment[c]

[a] These definitions apply to pulmonary smear-positive and smear-negative patients, and to patients with extrapulmonary disease. Outcomes in these patients need to be evaluated separately.
[b] The sputum examination may not have been done or the results may not be available.
[c] For smear- or culture-positive patients only.

Main adverse reactions of first-line antituberculous drugs

	Isoniazid	Rifampicin	Pyrazinamide	Streptomycin	Ethambutol
Mode of action	Cell wall synthesis	DNA transcription	Unknown	Protein synthesis	Cell wall synthesis
Major adverse reactions	Peripheral neuropathy[1] Hepatitis[2] Rash	Febrile reactions Hepatitis Rash Gastrointestinal disturbance	Hepatitis Gastrointestinal disturbance Hyperuricaemia	8th nerve damage Rash	Retrobulbar neuritis[3] Arthralgia
Less common adverse reactions	Lupoid reactions Seizures Psychoses	Interstitial nephritis Thrombocytopenia Haemolytic anaemia	Rash Photosensitisation Gout	Nephrotoxicity Agranulocytosis	Peripheral neuropathy Rash

Table 1. Anti-TB drugs, dosages and common adverse effects

Anti-TB drug	Recommended daily dosage	Common adverse effects (not exclusive)
Group 1: first-line oral agents		
Isoniazid	5 mg·kg^{-1} OD Should not exceed 300 mg per day Always consider co-administration of vitamin B6	Elevated transaminases Hepatitis Peripheral neuropathy GI intolerance CNS toxicity
Rifampicin	10 mg·kg^{-1} OD >50 kg: 600 mg <50 kg: 450 mg	Elevation of liver enzymes Hepatitis Hypersensitivity Fever GI disorders: anorexia, nausea, vomiting, abdominal pain Discoloration (orange or brown) of urine, tears and other body fluids Thrombopenia
Ethambutol	15–25 mg·kg^{-1} OD Maximum 2.0 g per day	Optic neuritis Hyperuricaemia Peripheral neuropathy (rare)
Pyrazinamide	30 mg·kg^{-1} OD Maximum 2.0 g per day	Arthralgia Hyperuricaemia Toxic hepatitis GI discomfort
Group 2: injectables		
Streptomycin[#]	0.75–1 g OD <50 kg: 0.75 g per day >50 kg: 1 g per day Maximum cumulative dose 50 g	Auditory and vestibular nerve damage (irreversible) Renal failure (usually reversible) Allergies Nausea Skin rash Neuromuscular blockade
Amikacin[¶]	0.75–1 g OD <50 kg: 0.75 g per day >50 kg: 1 g per day Maximum cumulative dose 50 g	Auditory and vestibular nerve damage (irreversible) Renal failure (usually reversible) Allergies Nausea Skin rash Neuromuscular blockade
Capreomycin[#]	0.75–1 g OD <50 kg: 0.75 g per day >50 kg: 1 g per day Maximum cumulative dose 50 g	Auditory and vestibular nerve damage (irreversible) Renal failure (usually reversible) Bartter-like syndrome Allergies Neuromuscular blockade

Table 1. Continued

Anti-TB drug	Recommended daily dosage	Common adverse effects (not exclusive)
Kanamycin[¶]	375–500 mg *b.i.d.* <50 kg: 0.75 g per day >50 kg: 1 g per day Maximum cumulative dose 50 g	Auditory and vestibular nerve damage (irreversible) Renal failure (usually reversible) Allergies Nausea Skin rash Neuromuscular blockade
Group 3: fluoroquinolones[+]		
Levofloxacin	500–1000 mg OD	GI discomfort CNS disorders Tendon rupture (rare) Hypersensitivity *Clostridium difficule* colitis
Ciprofloxacin	500–750 mg *b.i.d.*	GI discomfort CNS disorders Tendon rupture (rare) Hypersensitivity *Clostridium difficule* colitis
Moxifloxacin	400 mg OD	GI discomfort Headache Dizziness Hallucinations Increased transaminases QT prolongation *Clostridium difficile* colitis
Group 4: second-line oral agents		
Rifabutin	150–450 mg OD Consider monitoring drug levels	Anaemia GI discomfort Discoloration (orange or brown) of urine and other body fluids Uveitis Elevated liver enzymes
Ethionamide	0.75–1 g OD	Severe GI intolerance Nausea Vomiting Hepatitis CNS disorders
Prothionamide	0.75–1 g OD	Severe GI intolerance Nausea Vomiting Hepatitis CNS disorders

Table 1. Continued

Anti-TB drug	Recommended daily dosage	Common adverse effects (not exclusive)
Cycloserine	250 mg *t.i.d.* Maximum 1000 mg per day	CNS disorders Anxiety Confusion Dizziness Psychosis Seizures Headache
Terizidone	250 mg *t.i.d.* Maximum 1000 mg per day	CNS disorders Anxiety Confusion Dizziness Psychosis Seizures Headache
PAS	4 g *t.i.d.*	GI intolerance Nausea Diarrhoea Vomiting Hypersensitivity
Thioacetazone	50 mg *t.i.d.*	Hypersensitivity GI intolerance Vertigo Hepatitis
Group 5: oral reserve drugs with uncertain anti-TB activity		
Linezolid	600 mg OD (600 mg *b.i.d.* recommended for MRSA and VRE infections)	Thrombopenia Anaemia Neuropathy
Clofazimine	100 mg OD	Ichthiosis GI discomfort Nausea Vomiting Discoloration of the skin
Amoxicillin–clavulanate	875–125 mg *b.i.d.* or 500–250 mg *t.i.d.*	GI discomfort Diarrhoea Rash
Clarithromycin	500 mg *b.i.d.*	GI discomfort

PAS: para-aminosalicylic acid; OD: once daily; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *Enterococcus*; GI: gastrointestinal; CNS: central nervous system. #: intravenous/intramuscular administration only; ¶: intravenous administration only; +: also available from intravenous administration.

Table 4.2 SYMPTOM-BASED APPROACH TO MANAGING SIDE-EFFECTS OF ANTI-TB DRUGS

Side-effects	Drug(s) probably responsible	Management
Major		*Stop responsible drug(s) and refer to clinician urgently*
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
Minor		*Continue anti-TB drugs, check drug doses*
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily (*3*)
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration (*3*)

DOSAGE, TOXICITY, AND SPECIAL CONSIDERATIONS FOR STANDARD ANTITUBERCULOSIS MEDICATIONS

Drug	Daily Dosage	Usual Adult Dose, Thrice/Twice Weekly	Toxicity	Special Considerations	Comments
Isoniazid (INH)	300 mg PO	600 mg II 900 mg	Hepatitis, neuritis, mood/cognition, lupus reaction	Pregnancy: safe Liver disease: caution Renal impairment: ↓ dose if severe	Monitor liver function test results monthly in most patients; clinically significant interactions with phenytoin and antifungal agents (azoles)
Rifampin (RIF)[*]	600 mg PO 450 mg in persons < 50 kg body weight	600 mg II (same)	Hepatitis, thrombopenia, nephritis, flu syndrome	Pregnancy: acceptable Liver disease: caution Renal impairment: safe	Key: multiple, profound drug interactions possible (see later); turns urine and fluids red
Rifapentine (RPT)	Not recommended	Not recommended (600 mg PO once weekly)	Similar to RIF	Similar to RIF	The primary role for RPT is in *once-weekly* continuation therapy given with INH. Not indicated for persons with AIDS
Rifabutin (RBU)	150–300 mg/kg PO	300 mg II (same)	Similar to RIF; modestly more neutropenia and thrombopenia than with RIF	Similar to RIF	The primary role for RBU is for tuberculosis in persons with AIDS to lessen drug-drug interactions
Pyrazinamide (PZA)	20–30 mg/kg PO	30–40 mg/kg II	Hepatitis, arthralgias, and arthritis from hyperuricemia, gastrointestinal distress, rash	Pregnancy: unknown (avoid)	Urate levels always rise; do not treat or stop PZA unless unmanageable gout develops
		40–50 mg/kg		Liver disease: caution Renal impairment: caution	
Ethambutol (EMB)	15–20 mg/kg PO	30–35 mg/kg II	Optic neuritis, rare peripheral neuritis gastrointestinal distress,	Pregnancy: safe Liver disease: safe Renal impairment: ↓ dose/frequency	Monitor visual acuity and color vision regularly
		40–50 mg/kg			
Streptomycin (SM)	12–15 mg/kg IM	15 mg/kg II (same)	Vestibular and auditory, cation depletion	Pregnancy: high-risk (avoid) Liver disease: safe Renal impairment: ↓dose/frequency	Reduce dose and/or frequency in case of renal impairment

treatment

- **Most patients can be treated at home.**

- **Admission to a hospital unit with appropriate isolation facilities :**
  - uncertainty about the diagnosis
  - intolerance of medication
  - questionable compliance
  - adverse social conditions
  - significant risk of **multidrug-resistant TB** (MDR-TB: **culture-positive after 2 months** on treatment, or contact with known MDR-TB).

treatment

- **Baseline liver function and regular monitoring**
- **rifampicin, isoniazid and pyrazinamide, as all of these agents are potentially hepatotoxic.**
- **Mild asymptomatic increases in transaminases are common but serious liver damage is rare.**
- **rifampicin :**
  urine, tears and other secretions will develop a bright **orange/red** coloration
- **oral contraceptive pill:** its efficacy will be reduced
- **Ethambutol : patients with renal failure: appropriate dose reduction**
- **Adverse drug reactions occur in about 10% of patients (more common in the presence of HIV co-infection)**

The effectiveness of therapy for pulmonary TB

- further sputum smear at 2 months and at 5 months.
- A positive sputum smear at 5 months defines treatment failure.

Figure 4.1 SPUTUM MONITORING BY SMEAR MICROSCOPY IN NEW PULMONARY TB PATIENTS

Note: If a patient is found to harbour a multidrug-resistant strain of TB at any time during therapy, treatment is declared a failure and the patient is re-registered and should be referred to an MDR-TB treatment programme.

Months of treatment					
1	2	3	4	5	6
[========	========]	[----------	----------	----------	----------]
	•			• [a] if sm +, obtain culture, DST[b]	• [a] if sm +, obtain culture, DST[b]

If smear-positive at month 2, obtain sputum again at month 3. If smear-positive at month 3, obtain culture and DST.

[========	========]	[----------	----------	----------	----------]
	• (sm +)	• if sm +, obtain culture, DST		• if sm +, obtain culture, DST[b]	• if sm +, obtain culture, DST[b]

Key:

[========] Intensive phase of treatment (HRZE)
[----------] Continuation phase (HR)
• Sputum smear examination
sm + Smear-positive

Drug-resistant TB

- **presence of resistance to any first-line agent.**
- **Multidrug-resistant (MDR) TB :**
  resistance to at least **rifampicin and isoniazid**, **with or without** other drug resistance.
- **Extensively drug-resistant (XDR) TB :**
  resistance to at least **rifampicin** and **isoniazid**, in addition to **any quinolone** and at least **one injectable second-line agent.**
- **more common in :**
  - **a prior history of TB**
  - **if treatment has been inadequate**
  - **those with HIV infection**

- it requires **prolonged treatment** with less effective, more toxic and more expensive therapies.
- **Mortality rate** from MDR-TB is **high** and that from XDR-TB higher still.

Factors contributing to emergence of drug-resistant TB

- Drug shortages
- Poor-quality drugs
- Lack of appropriate supervision
- Transmission of drug-resistant strains
- Prior anti-tuberculosis treatment
- Treatment failure (smear-positive at 5 months)

Corticosteroids

- **treating pericardial or meningeal disease**
- **children with endobronchial disease.**
- **TB of the ureter, pleural effusions and extensive pulmonary disease**
- **suppress hypersensitivity drug reactions.**

Surgery

- **massive haemoptysis**
- **loculated empyema**
- **constrictive pericarditis**
- **lymph node suppuration**
- **spinal disease with cord compression**

*** usually only after a full course of antituberculosis treatment.**

Prognosis

- **cure should be anticipated in the majority of patients.**
- **(< 5%)** unavoidable risk of **relapse,** which usually occurs within **5 months**
- **In the absence of treatment :**
  - a patient with smear-positive TB will remain infectious for an average of 2 years
  - in 1 year, 25% of untreated cases will die.
- **Death is** more likely in those who are **smear-positive** and those who **smoke.**
- **HIV-positive patients have higher mortality rates and a modestly increased risk of relapse.**

Detection of latent TB

- identified using the tuberculin skin test
- 10-20% of close contacts of patients with smear-positive pulmonary TB and 2-5% of those with smear-negative, culture-positive disease have evidence of TB infection.

prophylaxis

- **Rifampicin plus isoniazid for 3 months or isoniazid for 6 months for patients with skin test conversion within the last two years**

- **with positive skin test:**
  < 35 years old, abnormal CXR,
  immunocompromised or predisposed to TB

- **recommended for**
  - **children aged less than 16 years identified during contact tracing to have a strongly positive tuberculin test**
  - **children aged less than 2 years in close contact with smear-positive pulmonary disease**

- **who are close contacts of someone with active TB**

- **HIV contact of infected person**

- **rifampin for contacts of INH-resistant TB carriers**

- **the risk of developing TB in immunocompetent patients after skin test conversion is 1% per year for the first 5 years and 0.1% per year subsequently (10% lifelong risk)**

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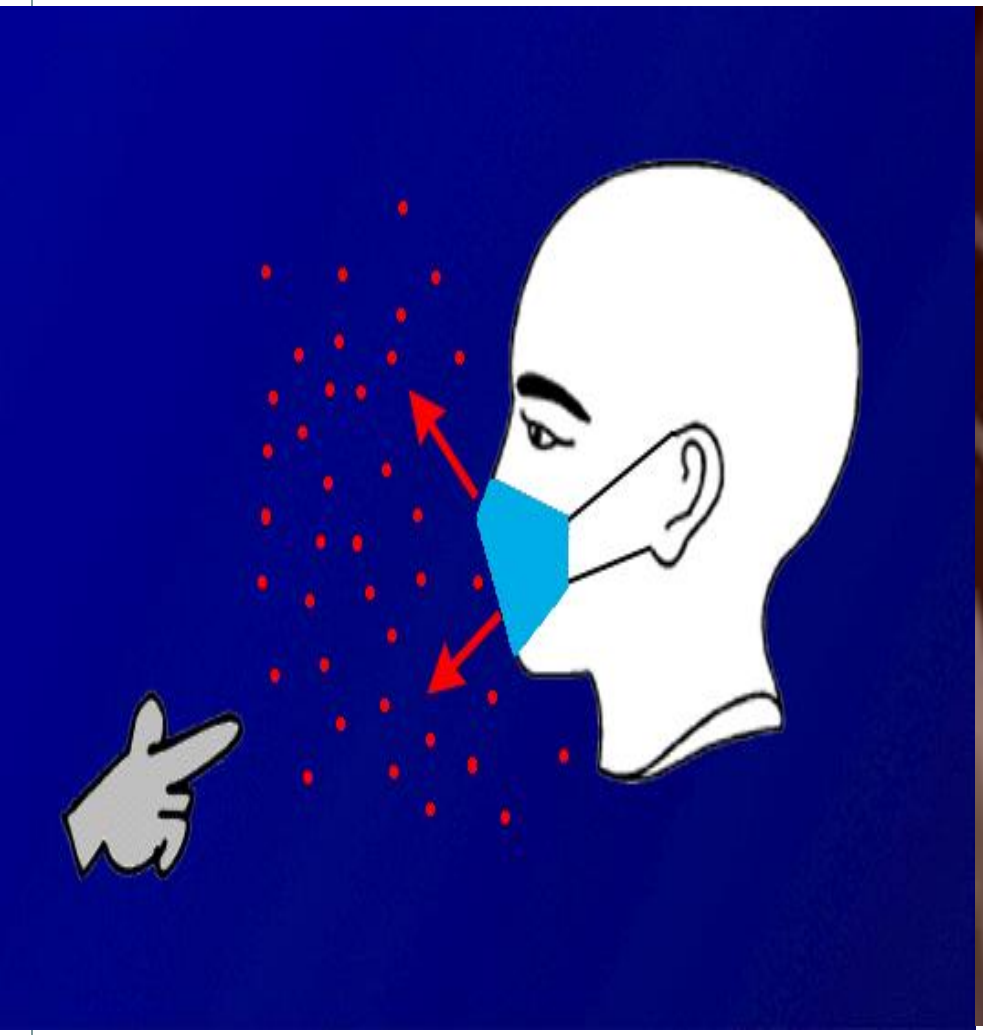


BCG (the Calmette-Guérin bacillus),

- **a live attenuated vaccine derived from *M. bovis***
- **administered by intradermal injection**
- **effective in :**
  - preventing **disseminated disease**, including tuberculous meningitis in children
  - its efficacy in adults is inconsistent
- **very safe** with the occasional complication of local abscess formation.
- **It <u>should not be</u> administered to those who are <u>immunocompromised</u> (e.g. by HIV) or <u>pregnant</u>.**

Atypical Mycobacteria

- **etiology:**

  M. *avium intracellulare, kansasii, and xenopi*

  ***M. avium* complex (MAC) :**
  in severe HIV disease (CD4 count < 50 cells/mL)

- **at risk:**
  immunocompromised, elderly, chronic lung disease (COPD, bronchiectasis, pneumoconiosis, old TB, or cystic fibrosis), malnutrition

- **clinical presentation: similar to TB**

Site-specific opportunistic mycobacterial disease

Pulmonary

- *M. xenopi*
- *M. kansasii*
- *M. malmoense*
- MAC

Lymph node

- MAC
- *M. malmoense*
- *M. fortuitum*
- *M. chelonei*

Soft tissue/skin

- *M. leprae*
- *M. ulcerans* (prevalent in Africa, northern Australia and South-east Asia)
- *M. marinum*
- *M. fortuitum*
- *M. chelonei*

Disseminated

- MAC (HIV-associated)
- *M. haemophilum*
- *M. genavense*
- *M. fortuitum*
- *M. chelonei*
- BCG

treatment

- **none without evidence of progression**
- **usually multiple**
- **<u>resistance to conventional antituberculous</u> drugs, but new agents like macrolides, quinolones, and rifabutin in combination may be effective**

The Tuberculosis Skin Test (Mantoux Test)

- performed by intradermal injection of 0.1 ml of PPD (purified protein derivative) tuberculin containing 5 TU (tuberculin units)

- check 48-72 hours later for amount of induration

The Tuberculosis Skin Test (Mantoux Test)

Skin testing in TB: tests using purified protein derivative (PPD)

Heaf test

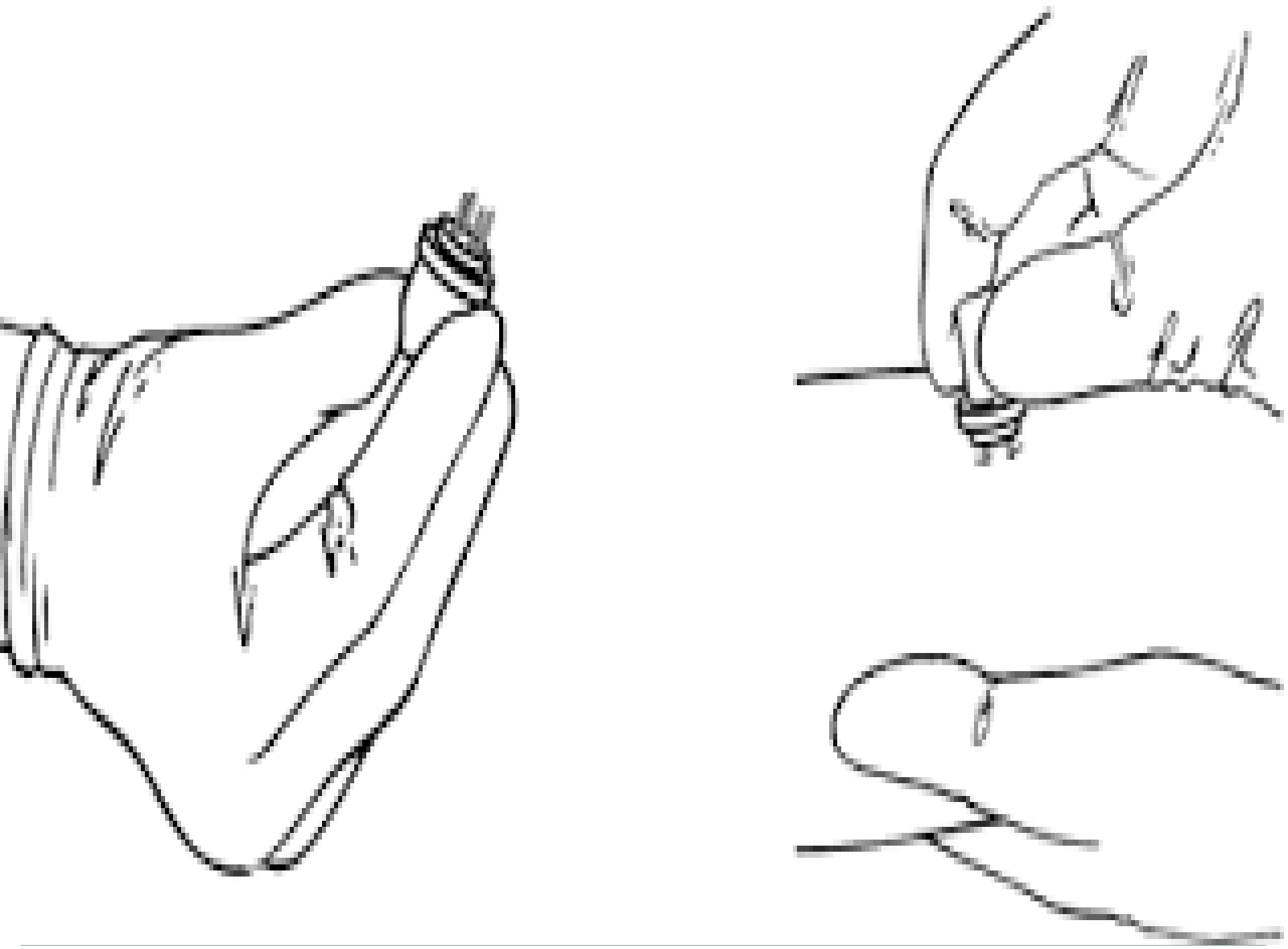
- Read at 3-7 days
- Multipuncture method
  - Grade 1: 4-6 papules
  - Grade 2: Confluent papules forming ring
  - Grade 3: Central induration
  - Grade 4: > 10 mm induration

Mantoux test

- Read at 2-4 days
- Using 10 tuberculin units
  - Positive when induration 5-14 mm (equivalent to Heaf grade 2) and > 15 mm (Heaf grade 3-4)

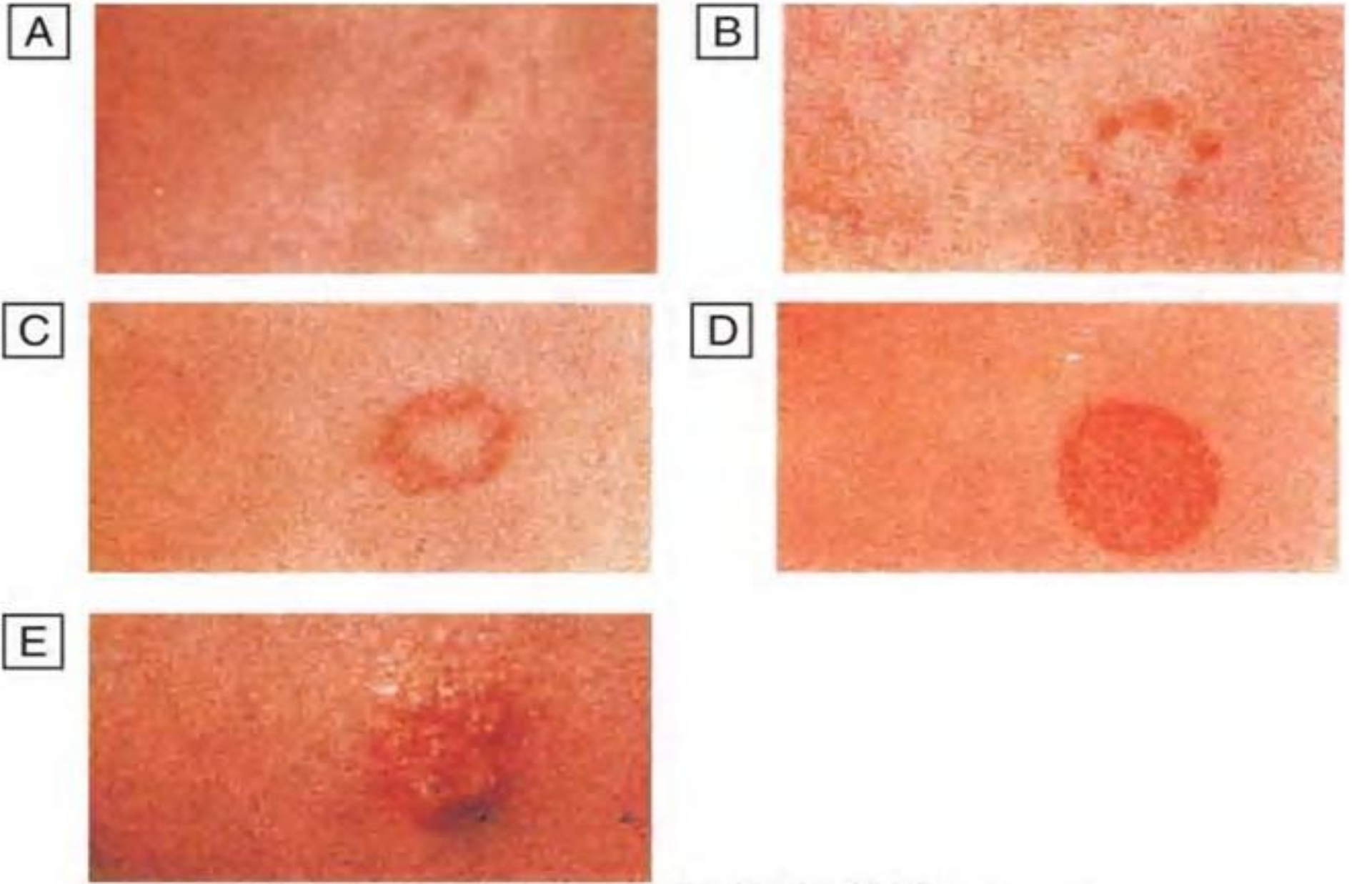
False negatives

- Severe TB (25% of cases negative)
- Newborn and elderly
- HIV (if CD4 count < 200 cells/mL)
- Malnutrition
- Recent infection (e.g. measles) or immunisation
- Immunosuppressive drugs
- Malignancy
- Sarcoidosis



Gradings of the Heaf test response.

A: Negative. B: Grade 1. C :Grade 2. D : Grade 3. E :Grade 4.



Typical Heaf test reactions, grades I–IV

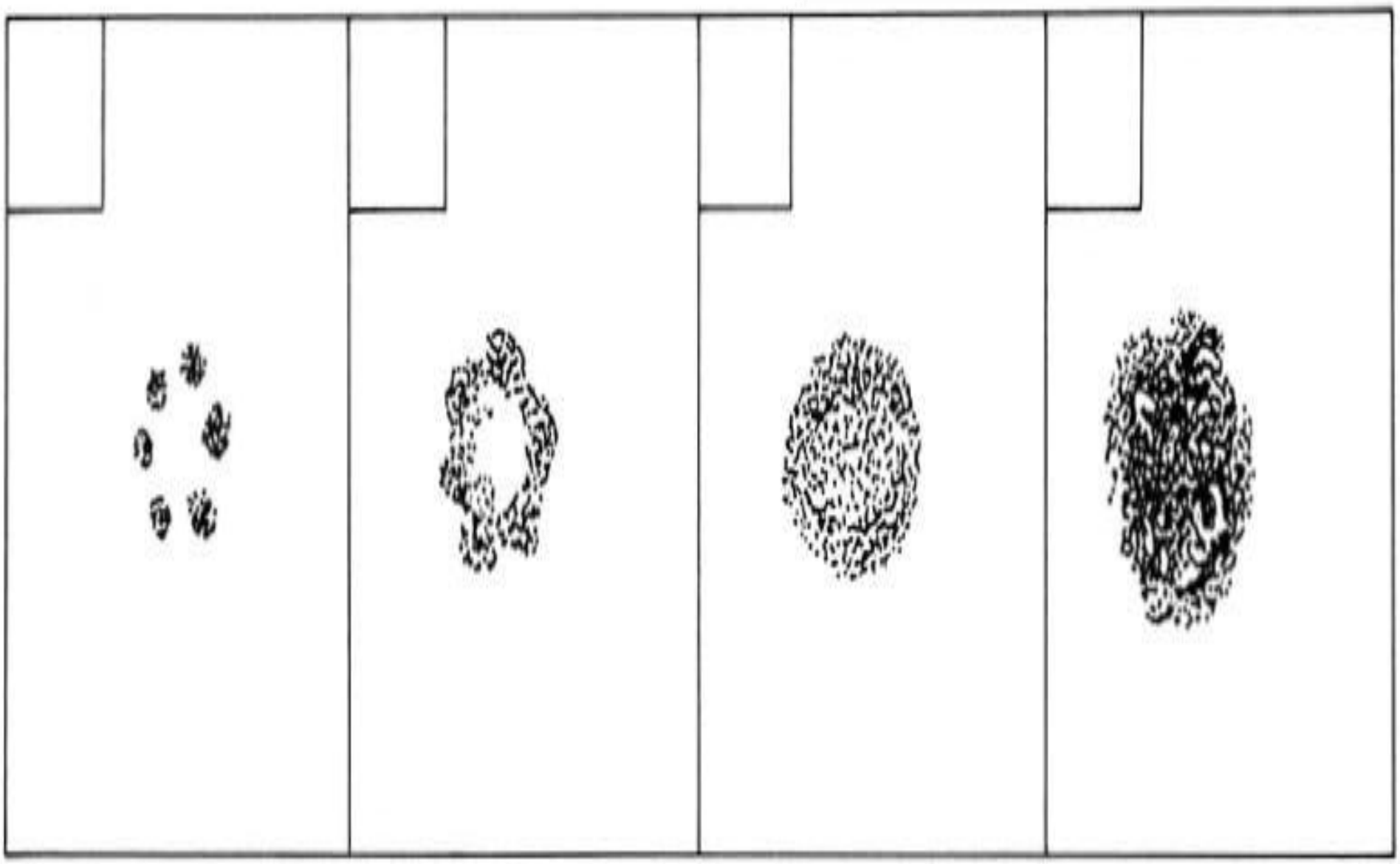


Table 3-8: Positive PPD Determination based on Preexisting Conditions

Treatment of Latent Tuberculosis Infection	
Certain groups are at high risk of developing TB ***disease*** once ***infected***. These people are candidates for treatment ***regardless*** of their age -- after ensuring active infection is ***not*** present. The current optimum treatment regimen for ***all*** patients is 9 months of daily INH. See text for treatment of drug-resistant organisms. Treat ALL the following (ALL ages!):	
PPD Result (induration)	**In People with the Following Conditions**
≥ 5 mm is positive in this high-risk group	Known/suspected HIV infection Close contacts of active cases Chest radiograph suggests previous inactive tuberculosis Organ transplants and other immunosuppressed pts with greater than 1 month of equivalent prednisone use (> 15 mg/d)
≥ 10 mm is positive in these intermediate-risk groups	IV drug user known to be HIV-negative
	Immunosuppressive illness or therapy < 15 mg/d equivalent prednisone. Diabetes, Renal failure, or Hematologic malignancy.
	Immigrants from high-prevalence countries Residents of long-term care or correctional facilities Locally identified high-prevalence groups: migrant workers, homeless
≥ 15 mm is positive in this low-risk group	NO known risk factors
PPD negative but HIGH RISK	High risk contacts of ACTIVE cases

Conversion of TB Skin Test

change in TB skin test :

within 2 years from < 10 mm to > 10 mm or an increase of 6 mm from previous skin test

Booster Phenomenon (Two-step testing)

- in persons infected with TB many years ago, **skin reactivity** to TB skin test **may have waned**, leading to false negative results
- however, in such previously infected persons, this first TB skin test boosts the reaction to **a second test** administered **within 1-3 weeks of the first one**
- if initial **test negative**, second TB skin test is given :

  *if **second test** also **negative**, = no previous infection

  * if second test **positive**, = previous infection with TB