MYCOBACTERIA

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

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

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

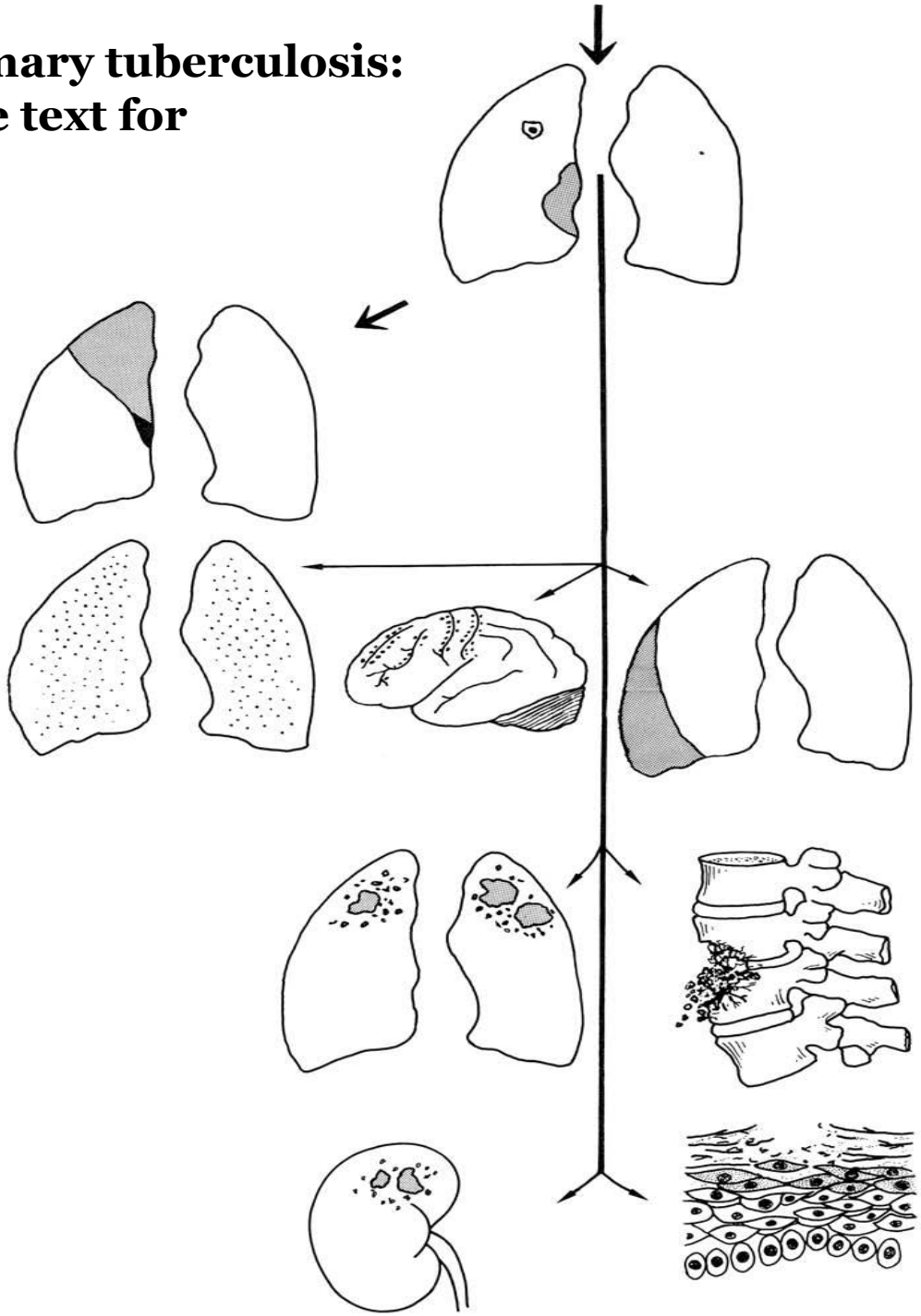
Natural history of untreated primary tuberculosis: the timetable of tuberculosis. See text for explanation.

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**

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

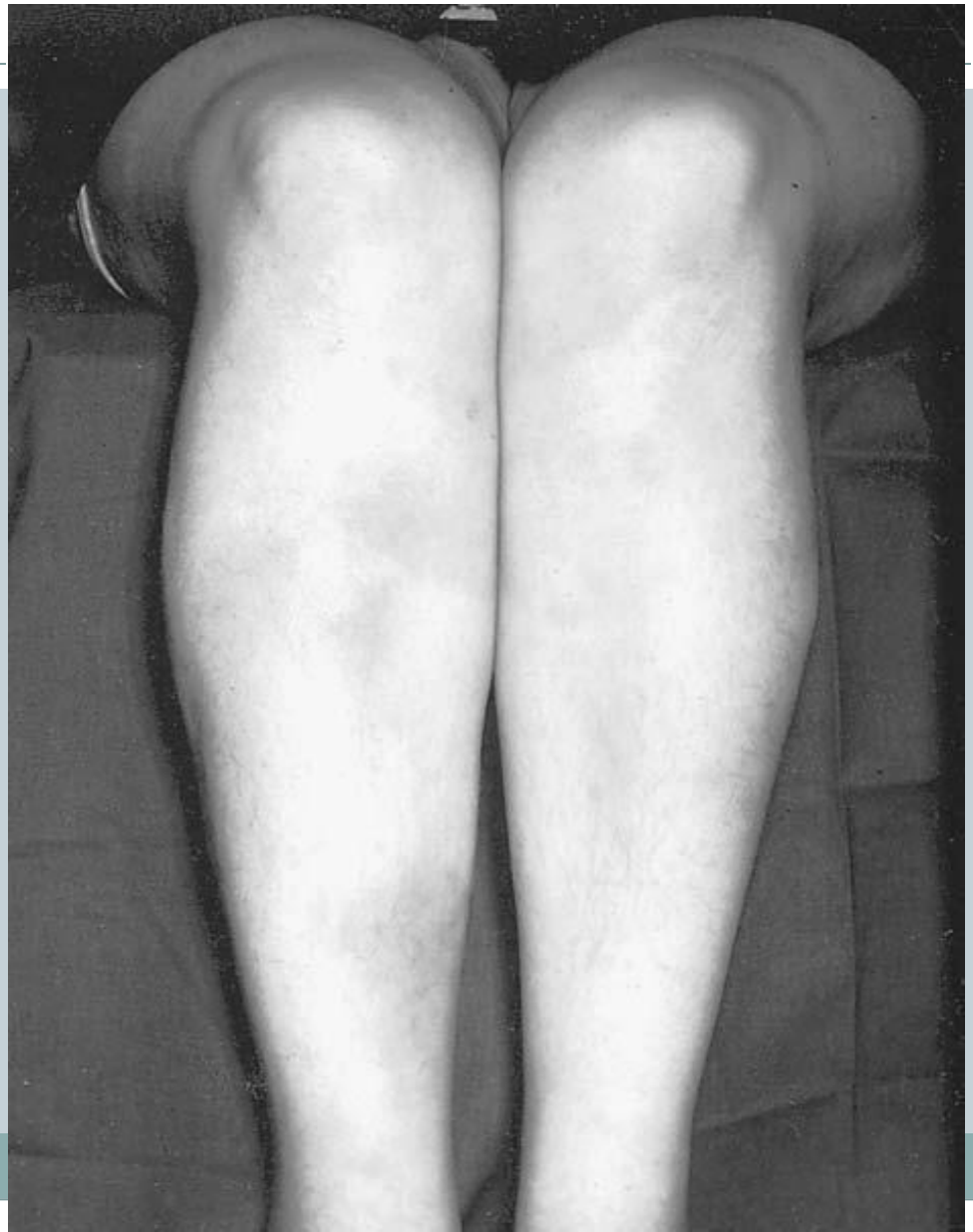
Disease

- 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.



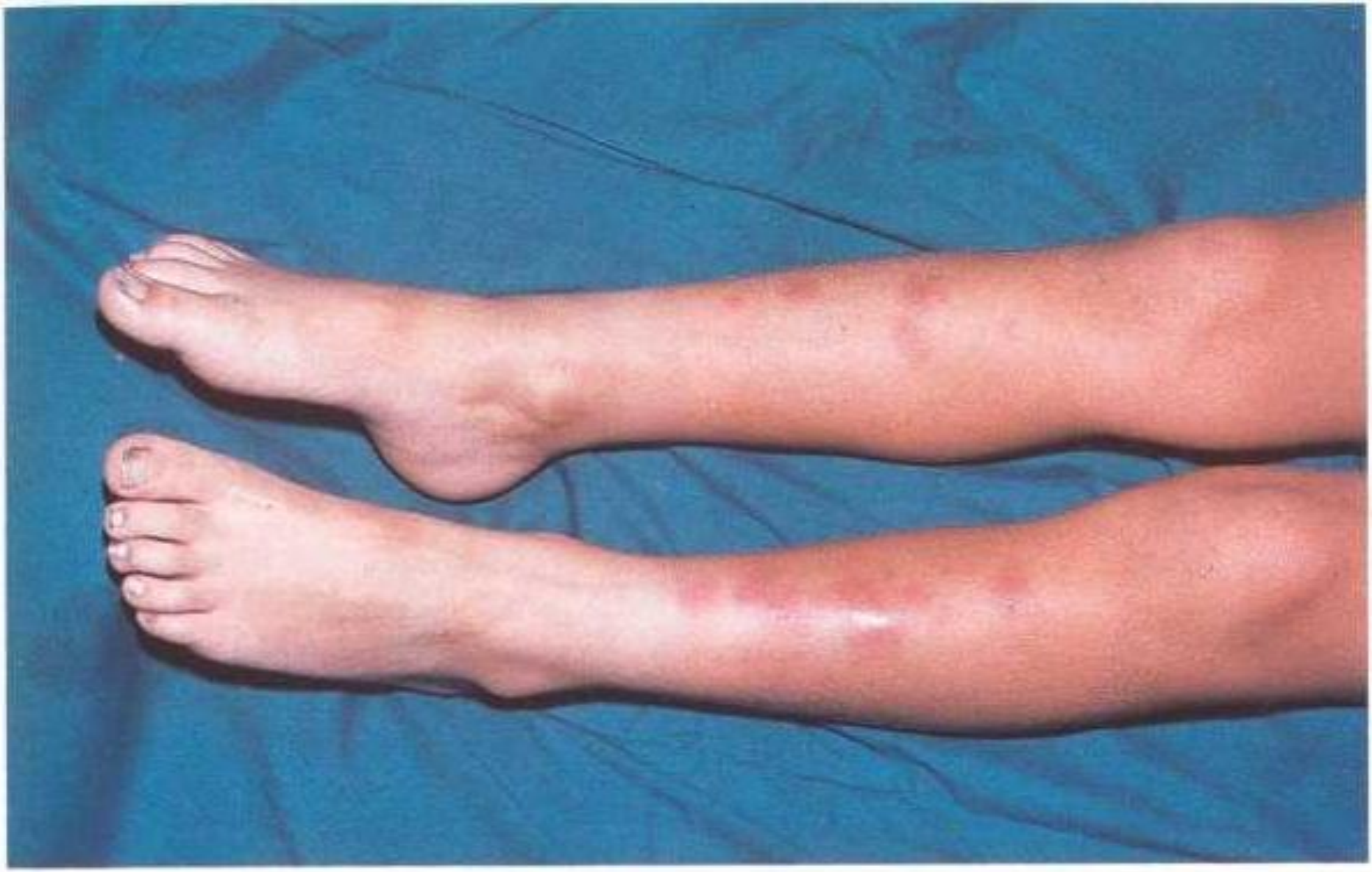


Fig. 148 Early discrete erythema nodosum (due to streptococcal disease).

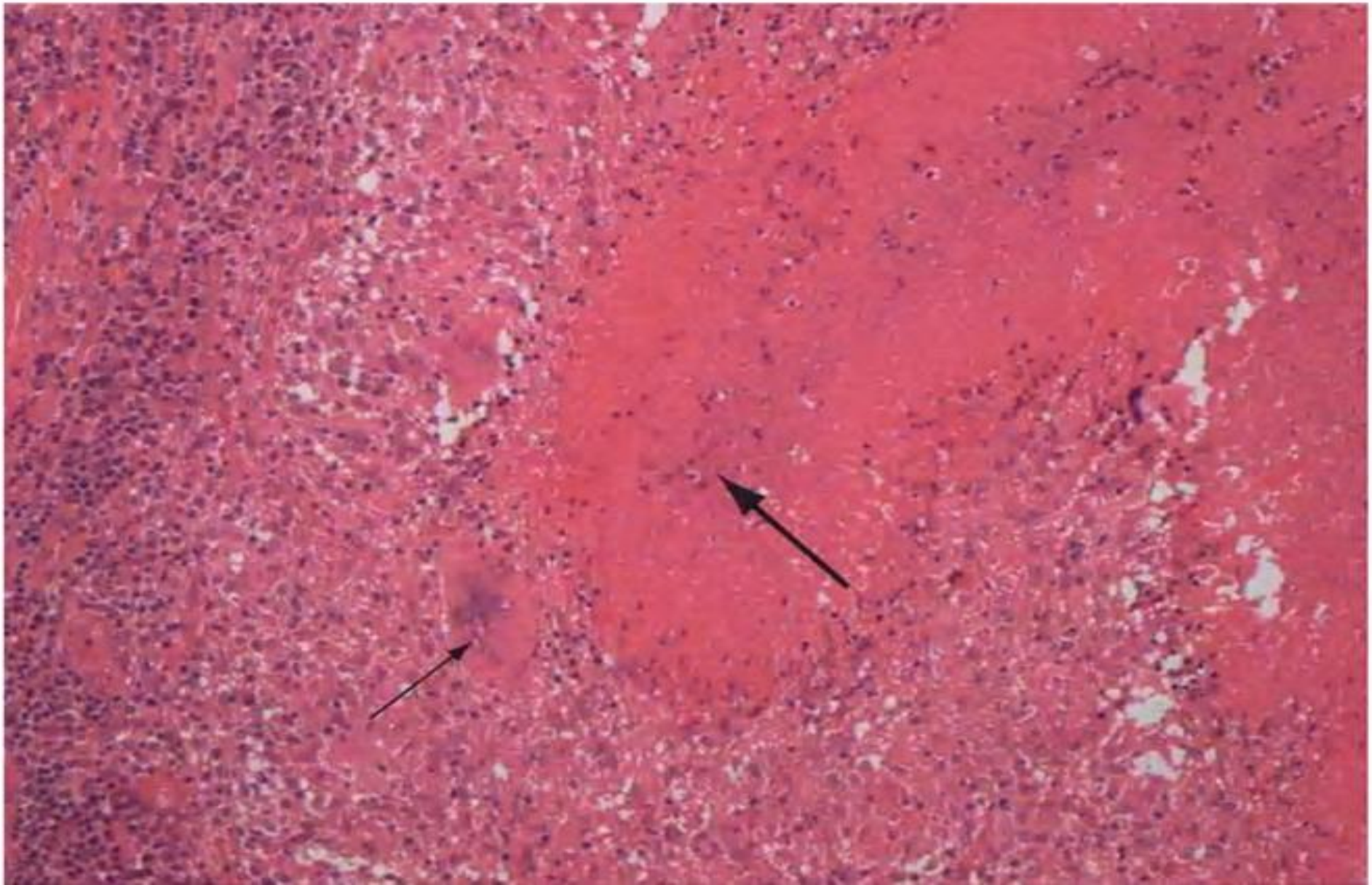
Clinical presentations of pulmonary TB

- 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

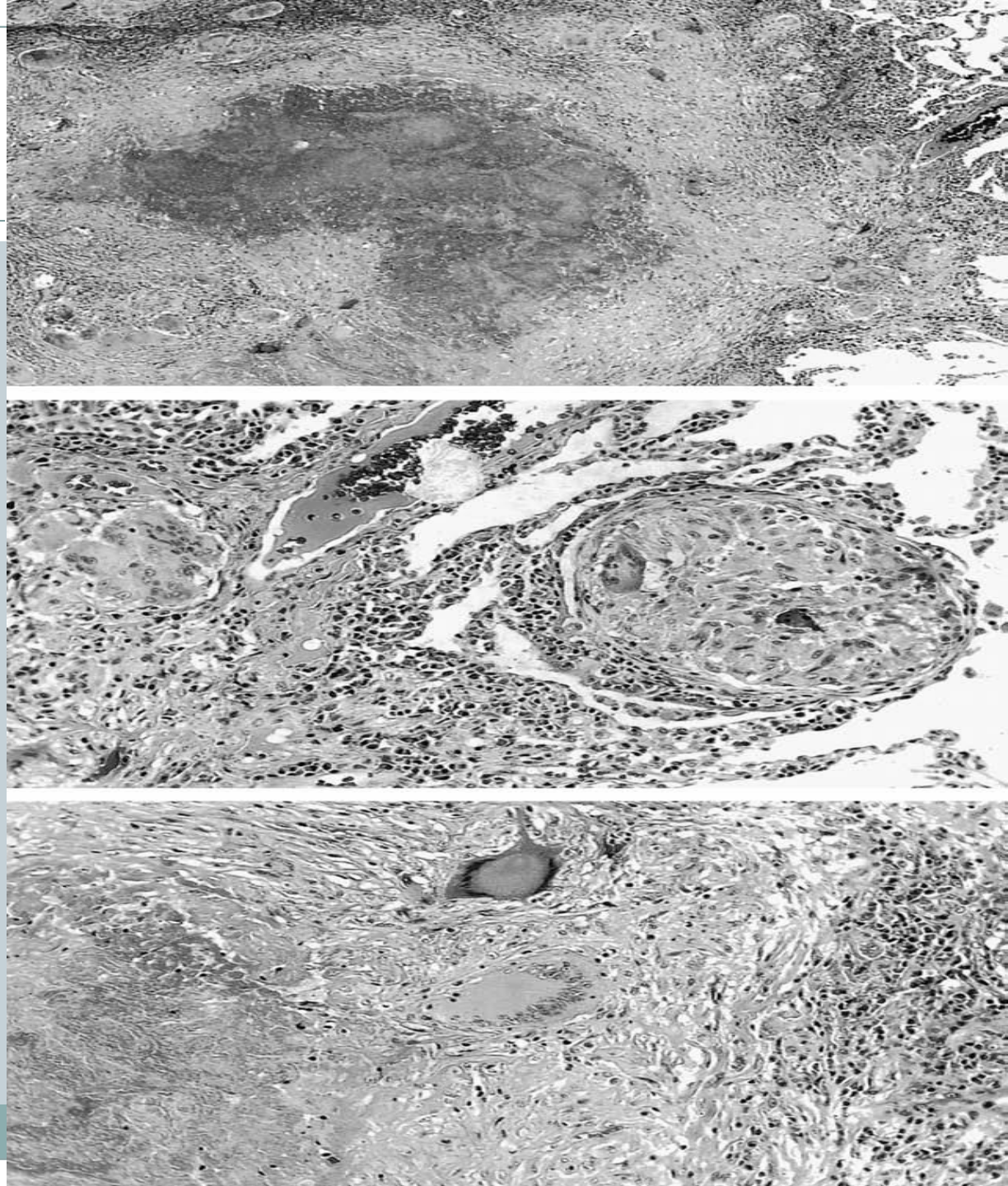
pathology

- 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

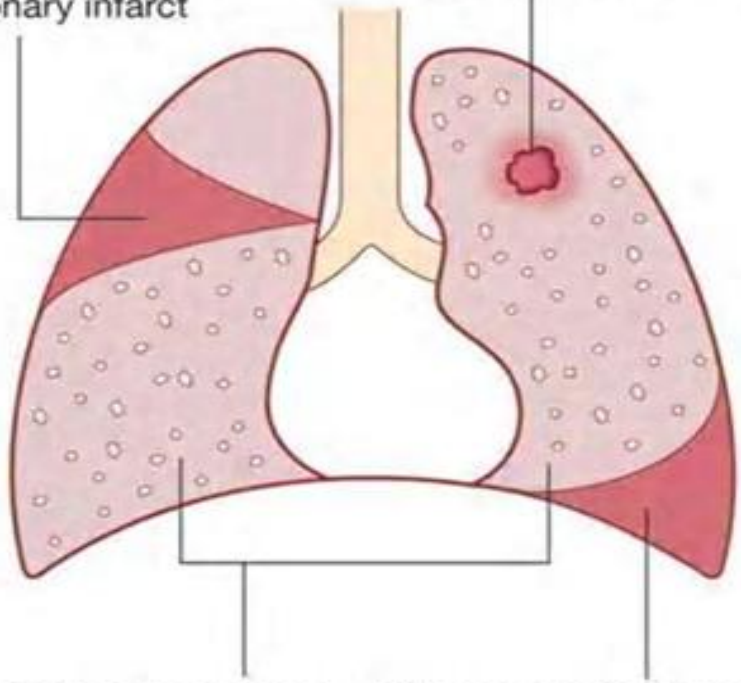
- **Primary pulmonary TB :**

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

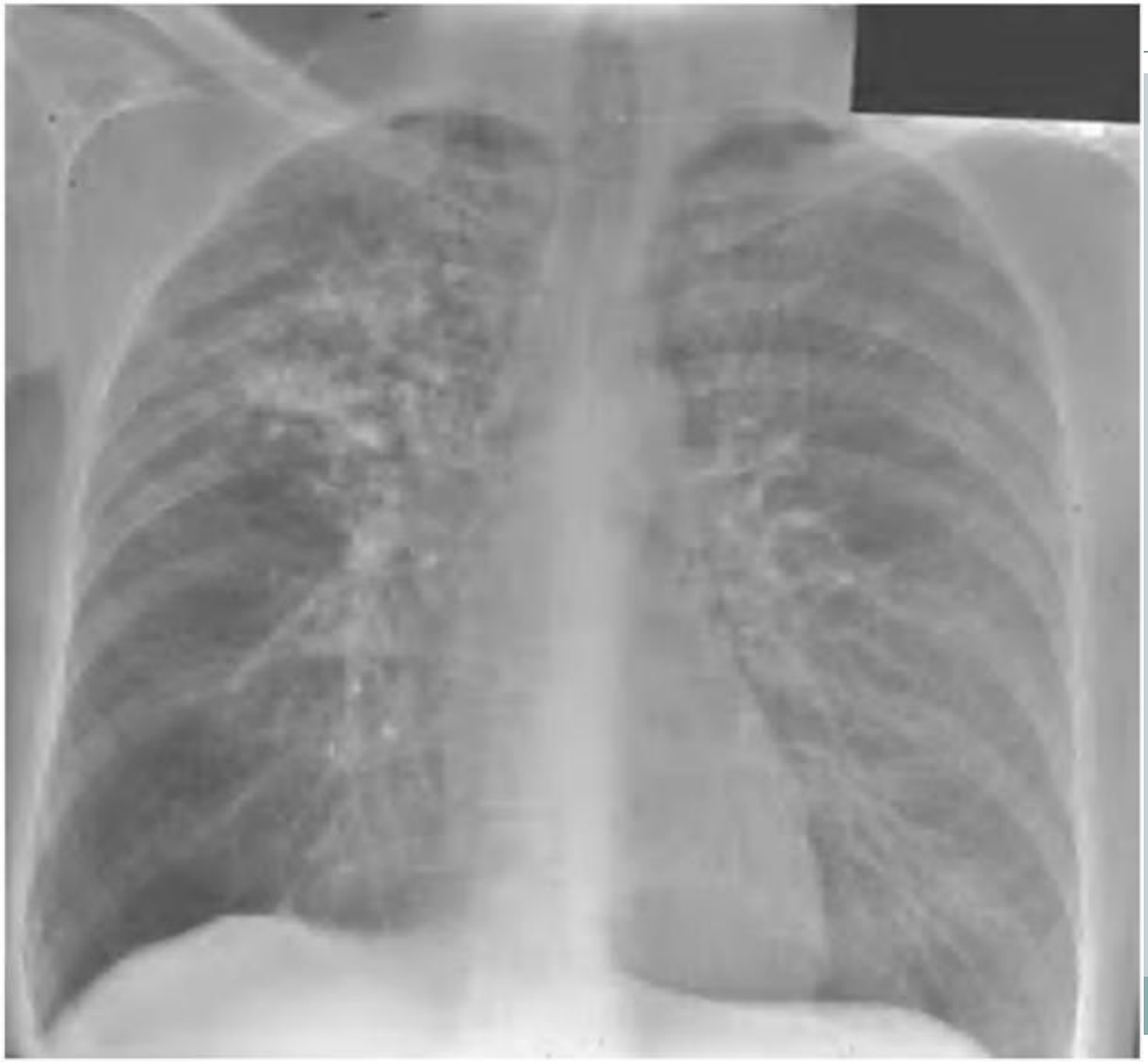
- **Post-primary TB (reactivation or initial infection or infection post-BCG):**

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

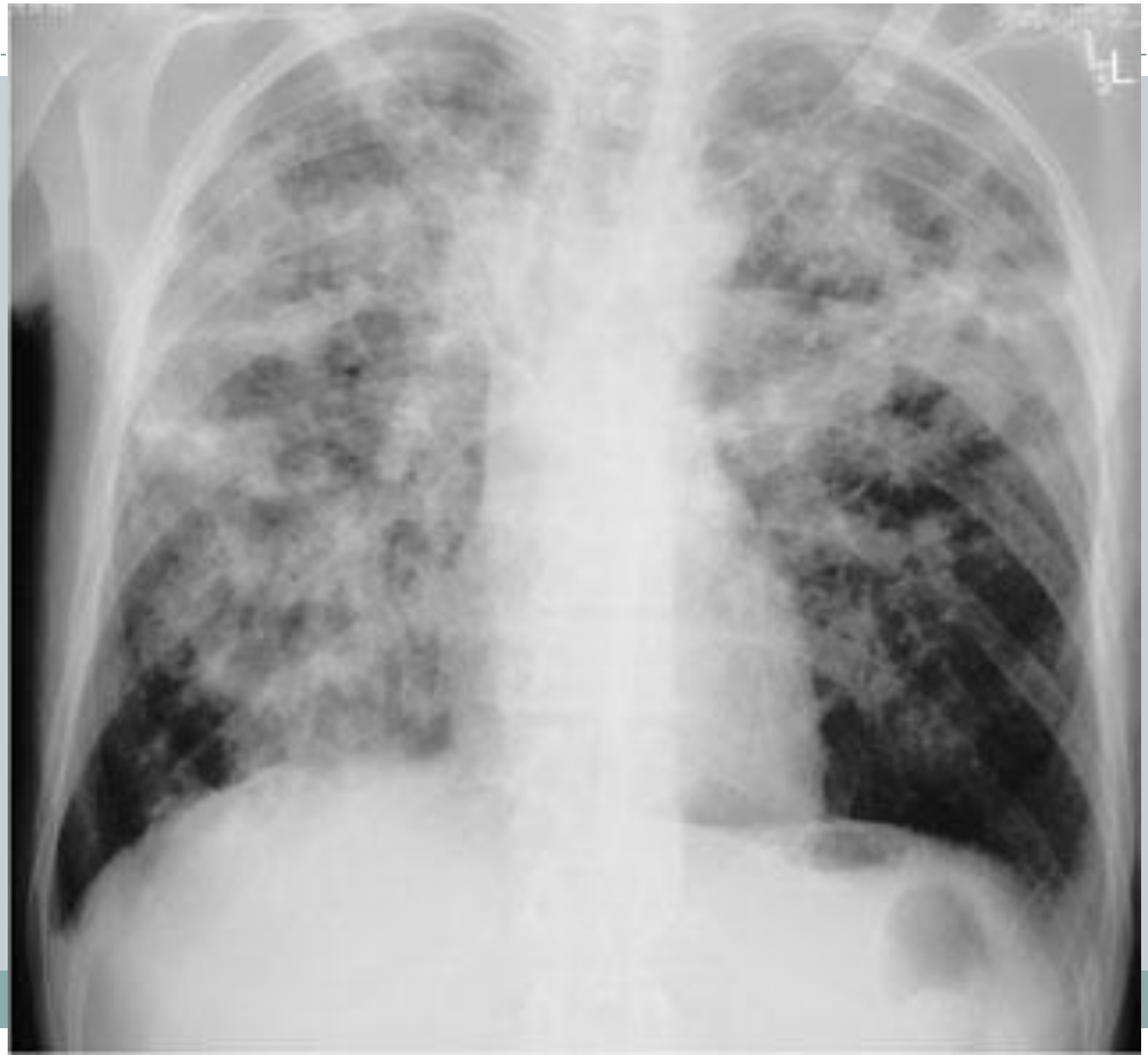
Chest X-ray: major manifestations and differential diagnosis of pulmonary TB.



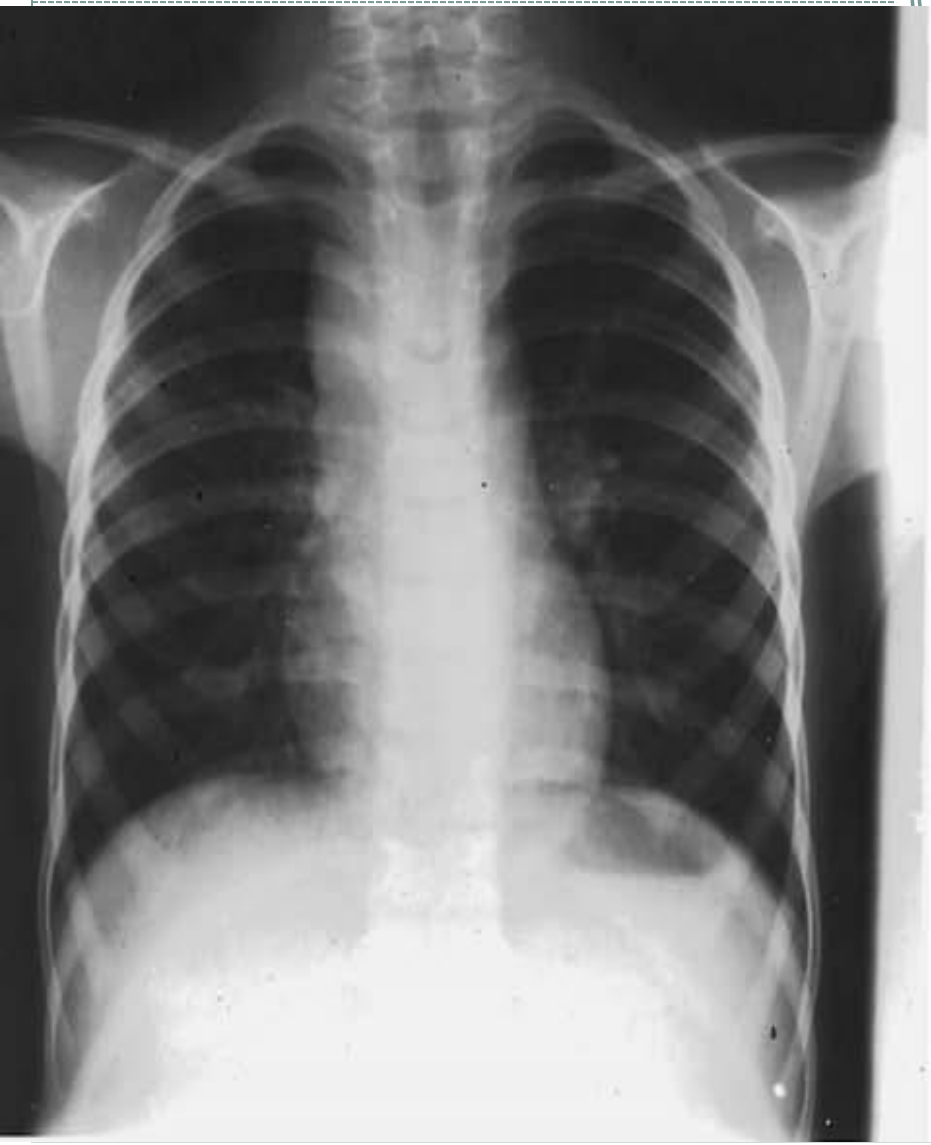
a right upper lobe cavitary process caused by *Mycobacterium tuberculosis*

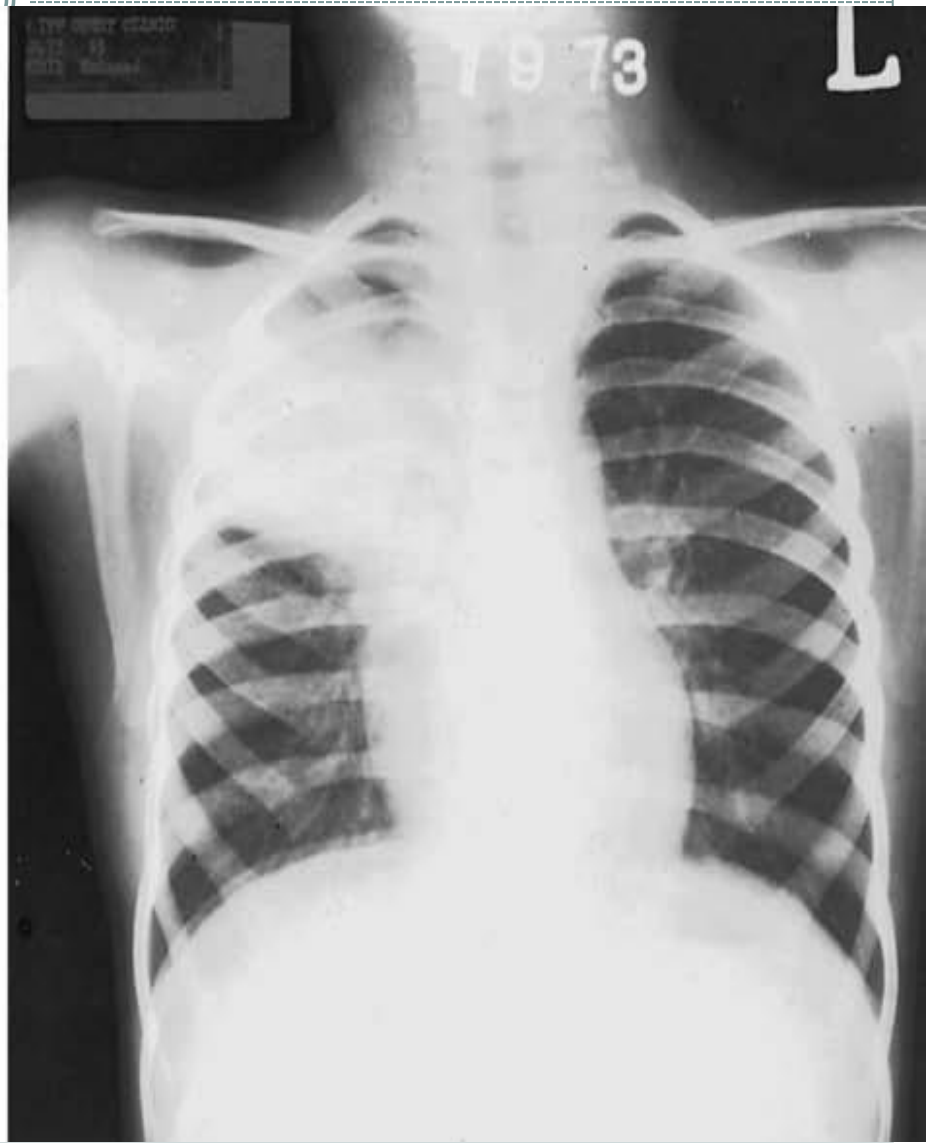


pulmonary TB: ill-defined areas of consolidation in the mid- and upper zones of both lungs.

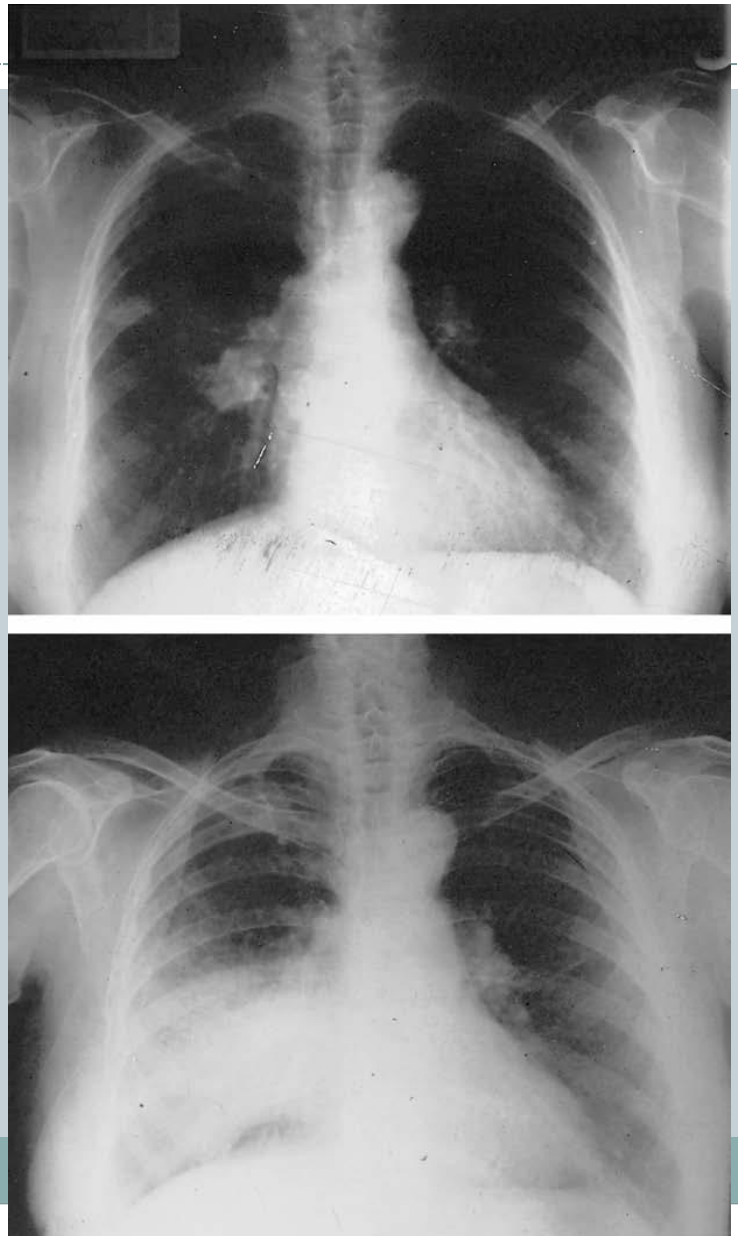


Primary tuberculosis showing hilar and paratracheal lymph gland enlargement. (b) Later film showing tuberculous consolidation of right upper lobe

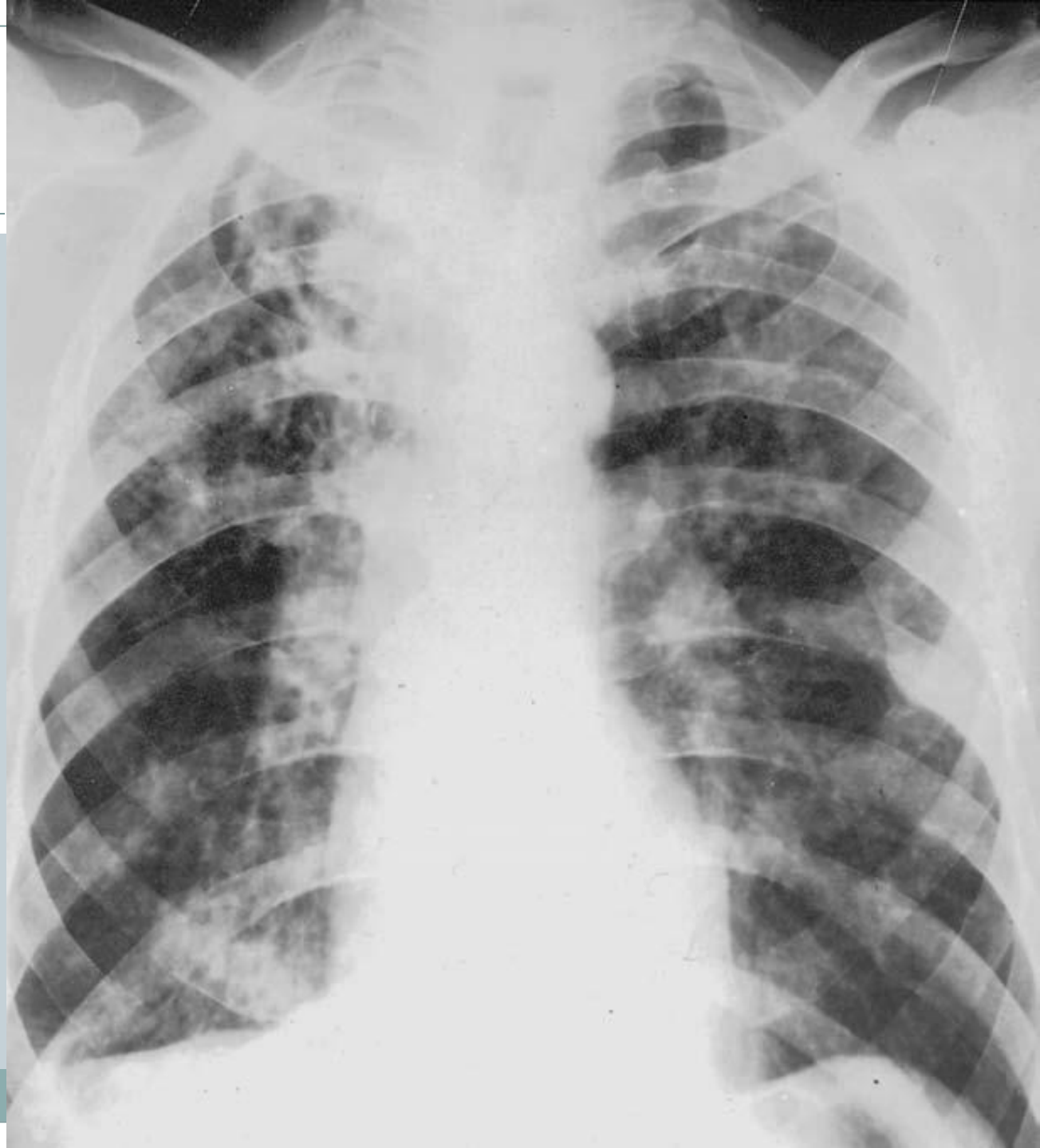




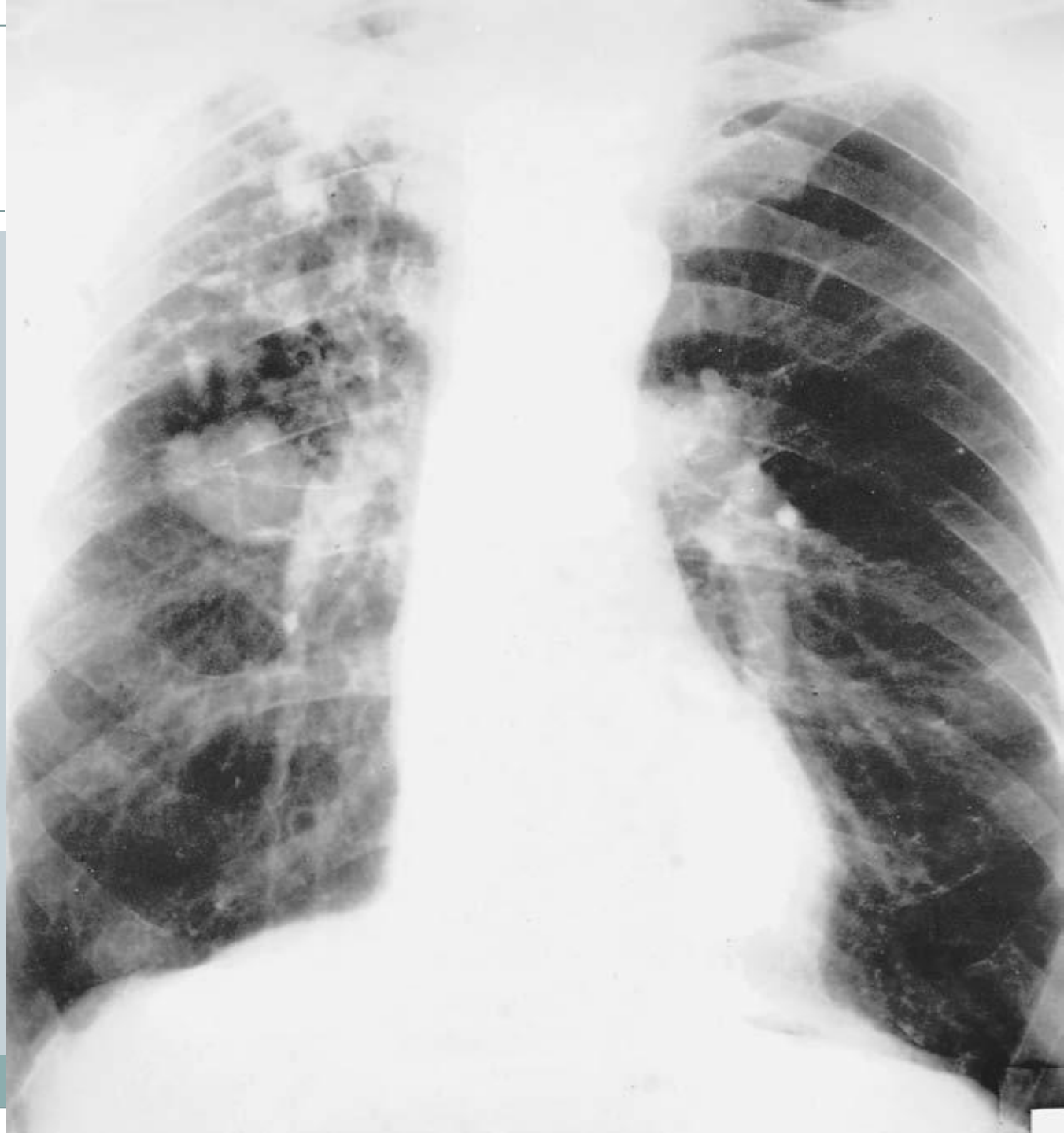
primary tuberculosis showing (a) peripheral focus and enlarged right hilar nodes and (b) consolidation of right middle lobe 1 week later.



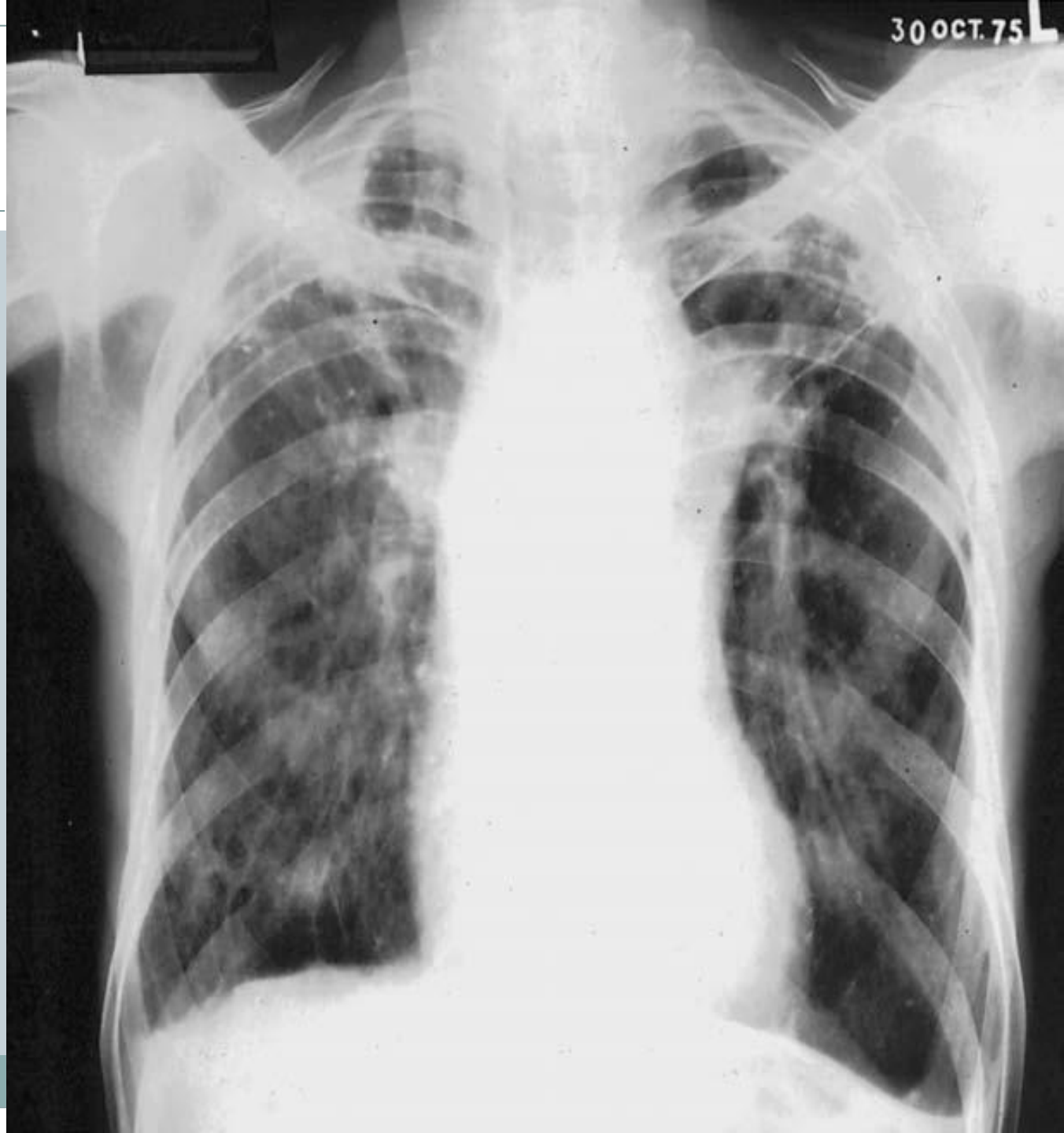
Extensive bilateral tuberculosis with cavity formation at right apex.



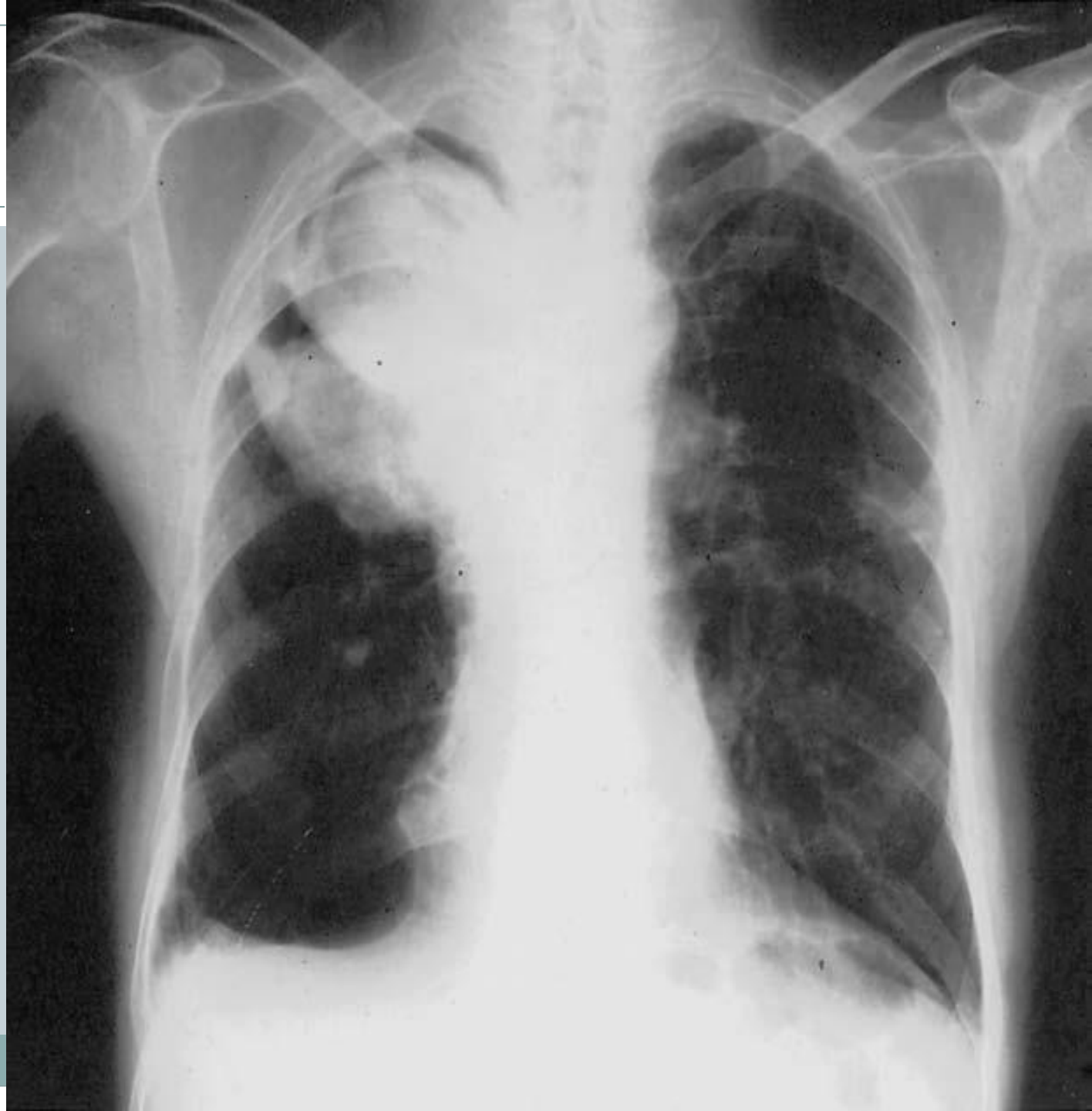
Chest radiograph showing **large tuberculoma in right mid-zone**, originally thought to be a coincidental carcinoma in patients with extensive upper lobe tuberculosis.



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'

Primary pulmonary TB

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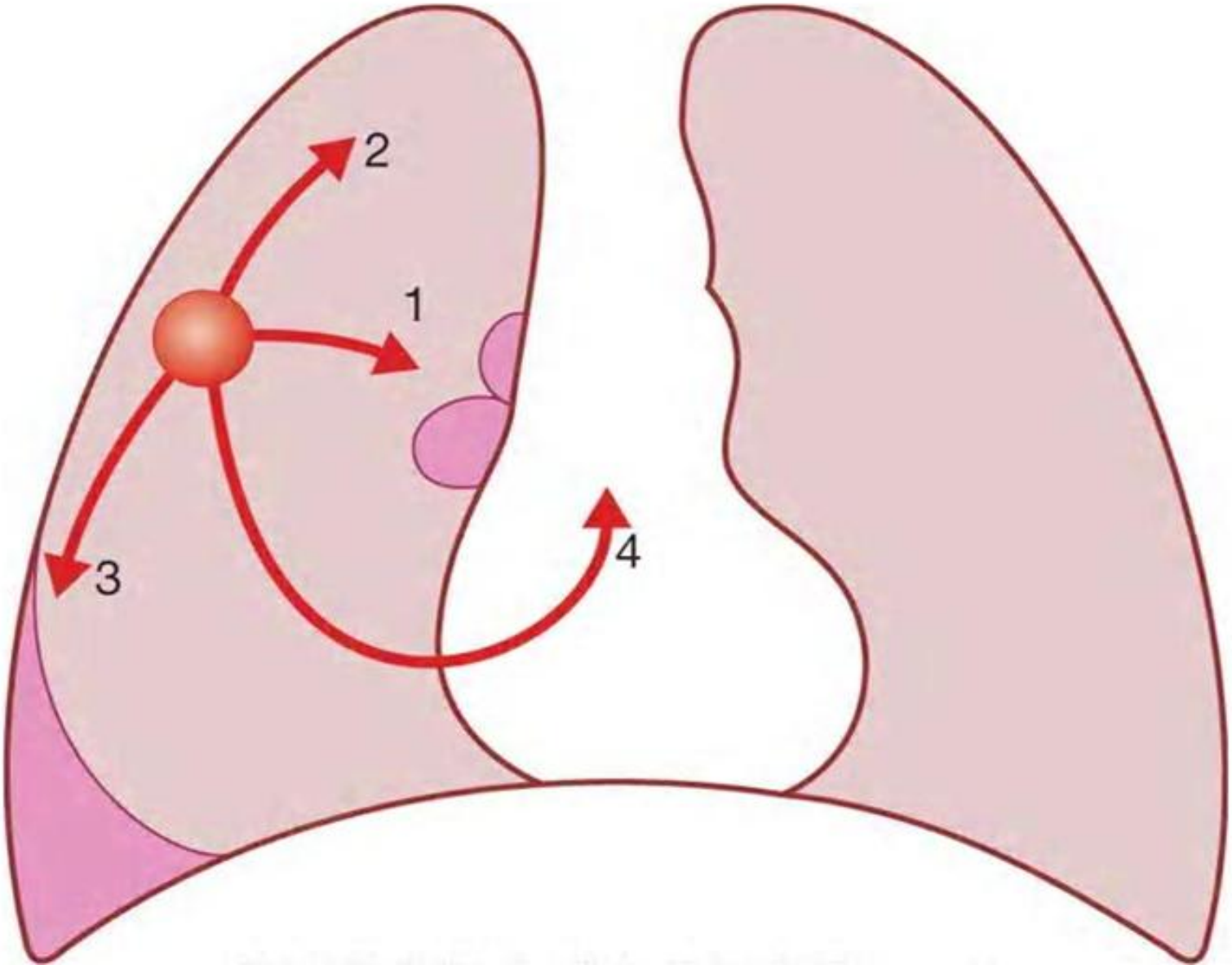
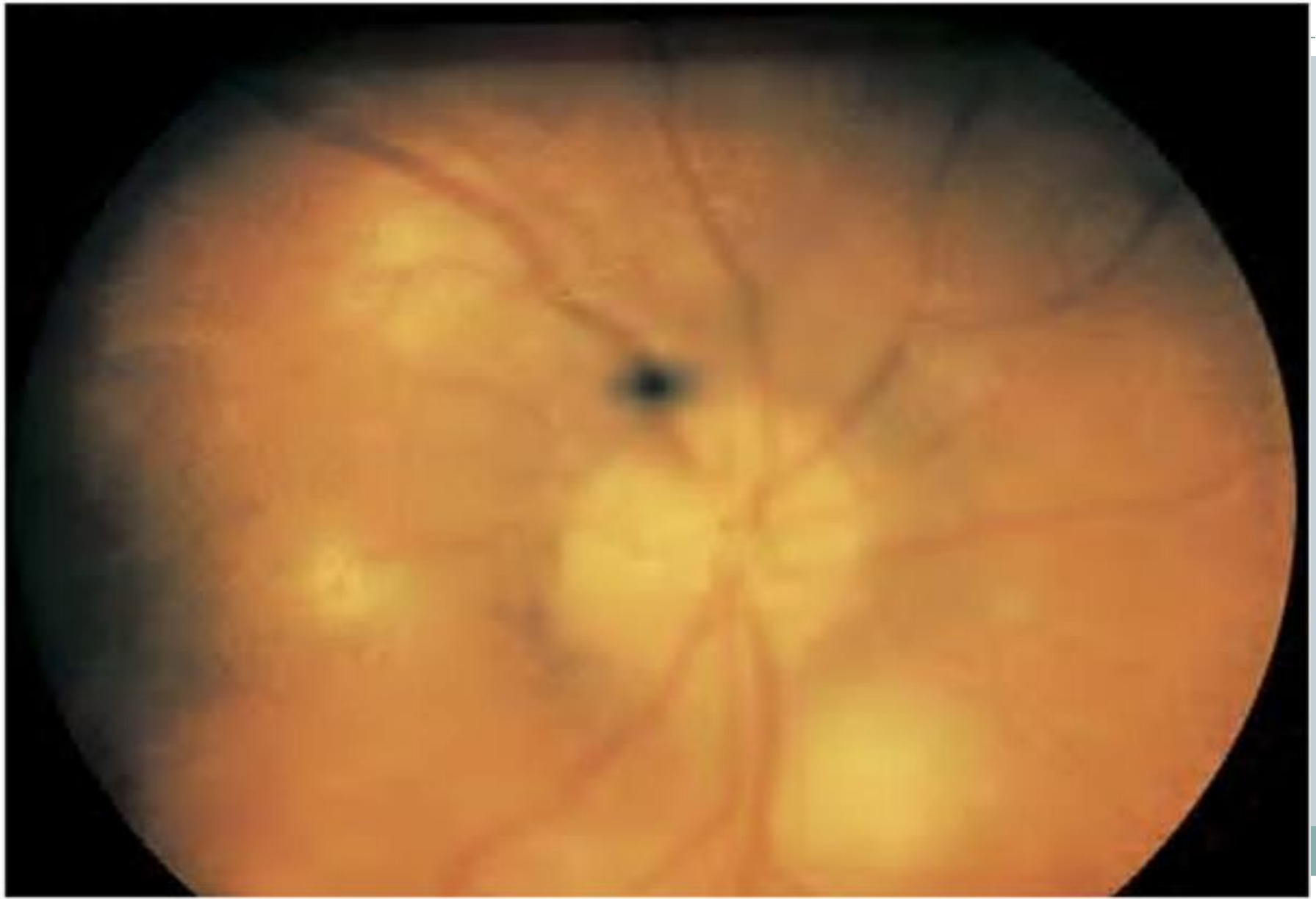


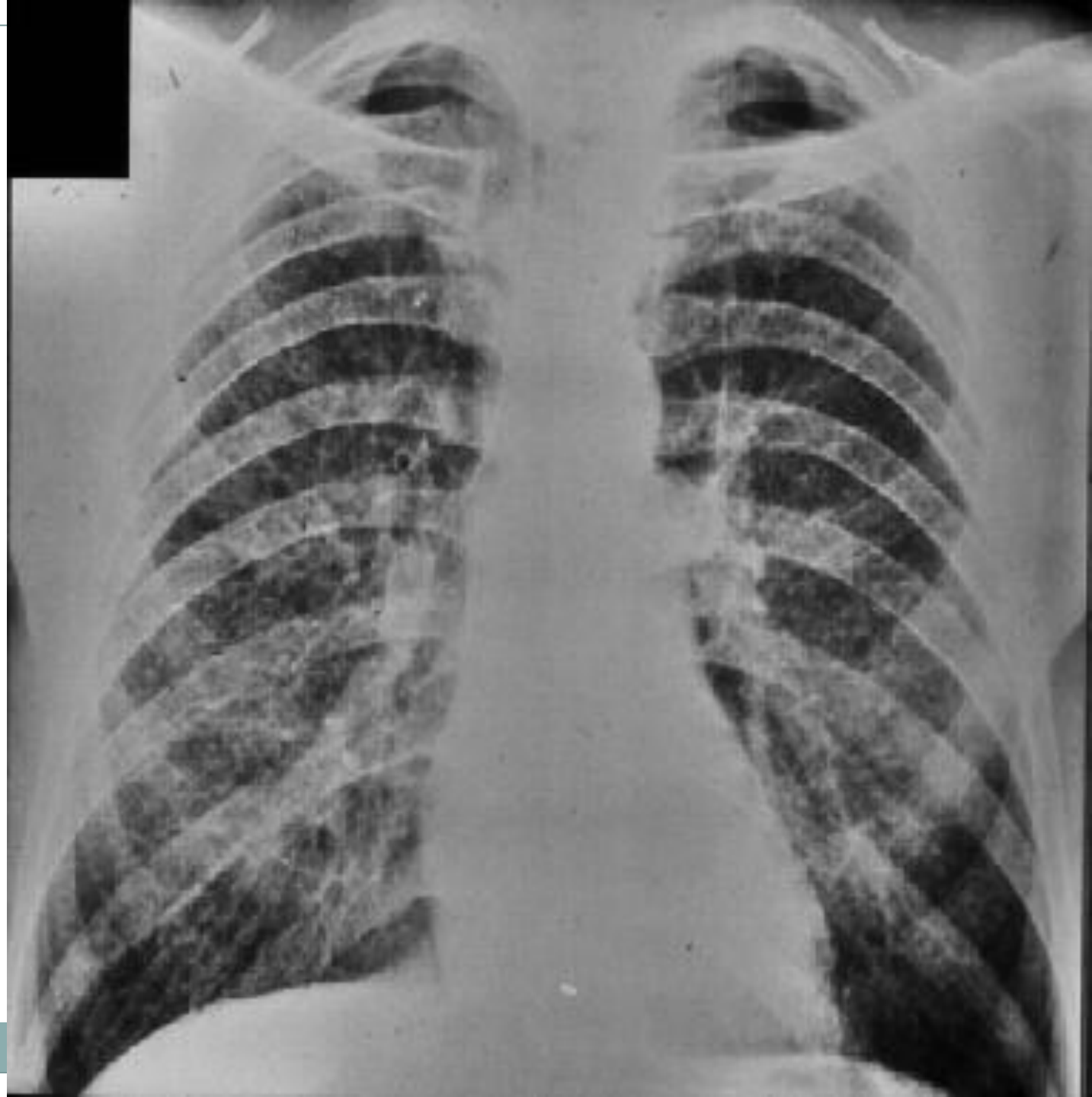
Miliary TB

- **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**

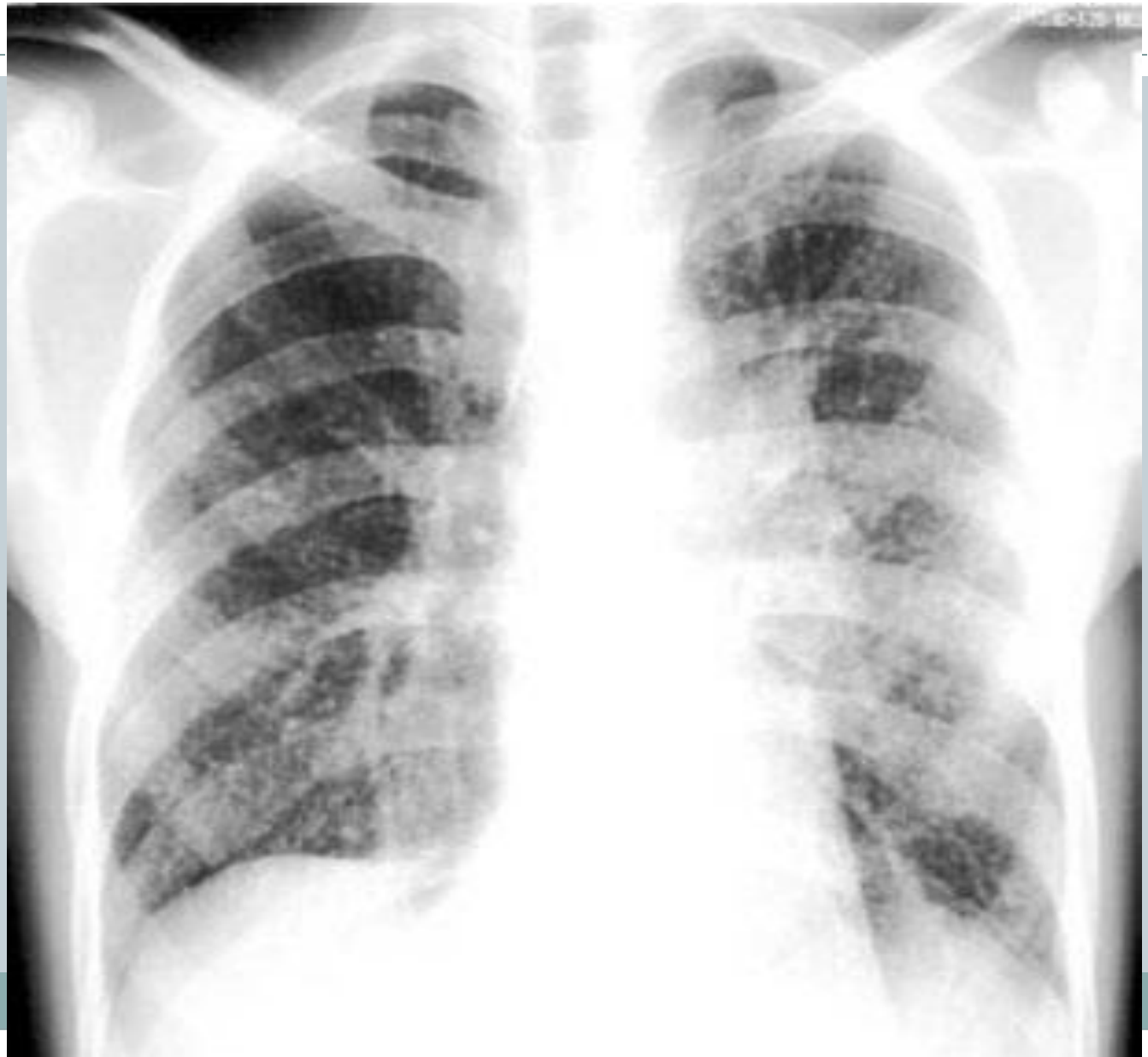
Choroidal tubercles in acute miliary tuberculosis



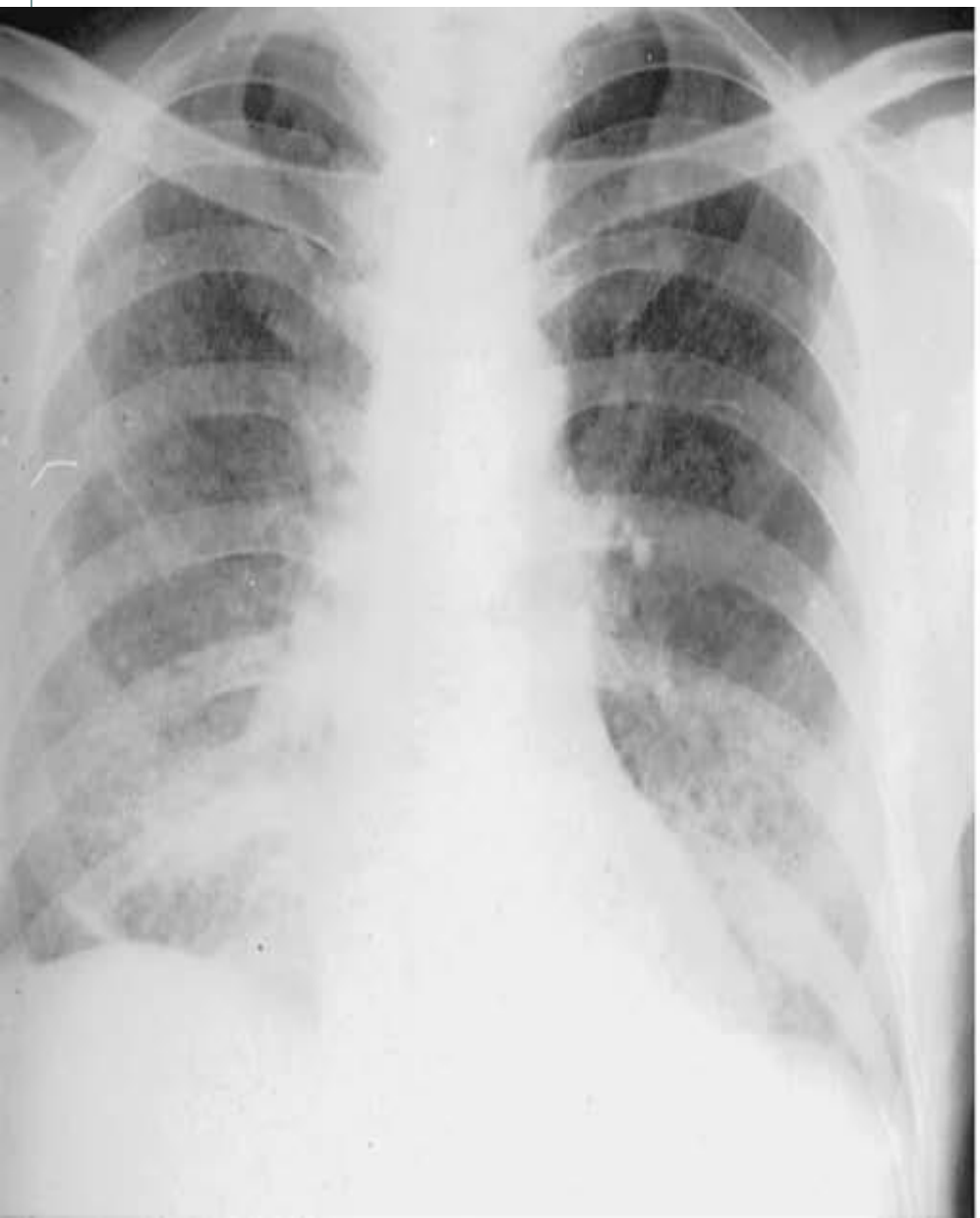
MILIARY TB

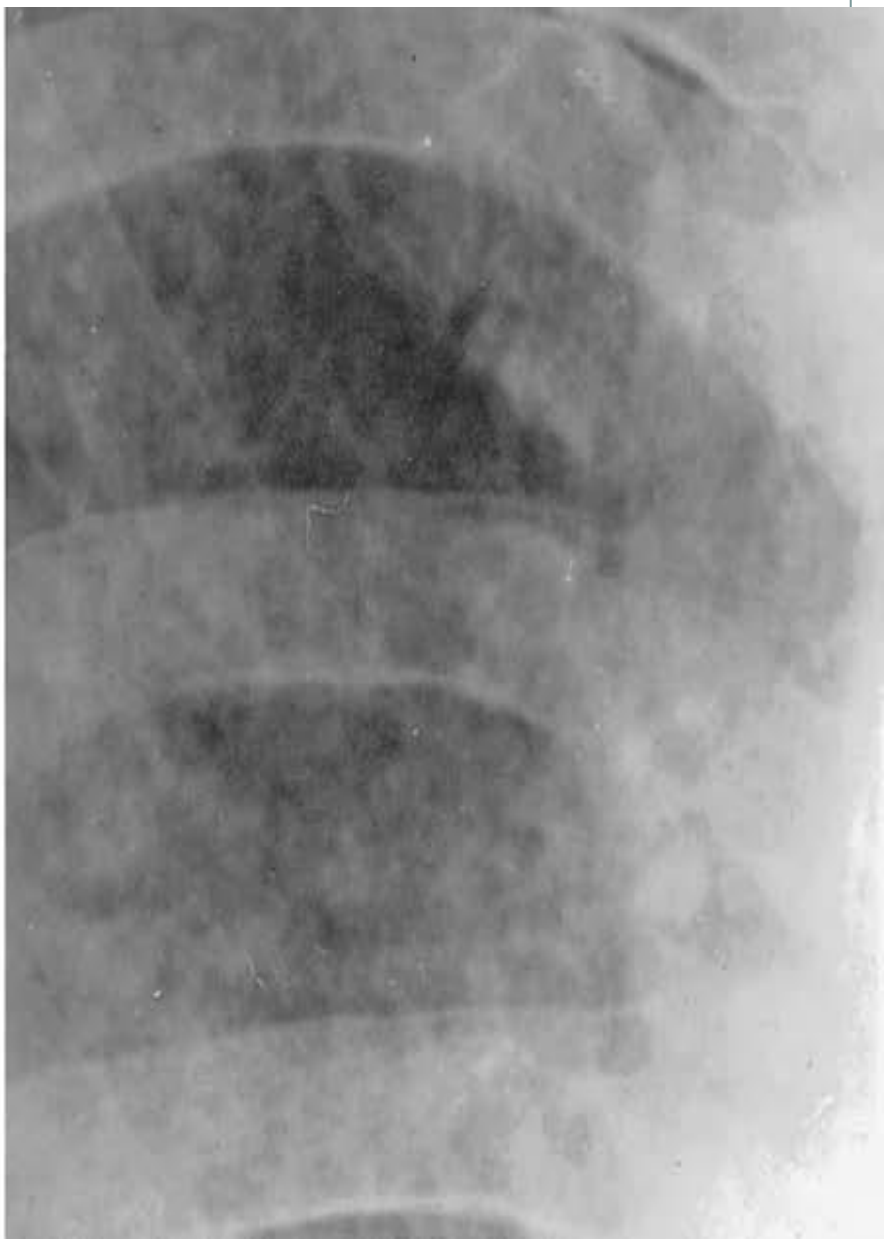


miliary TB

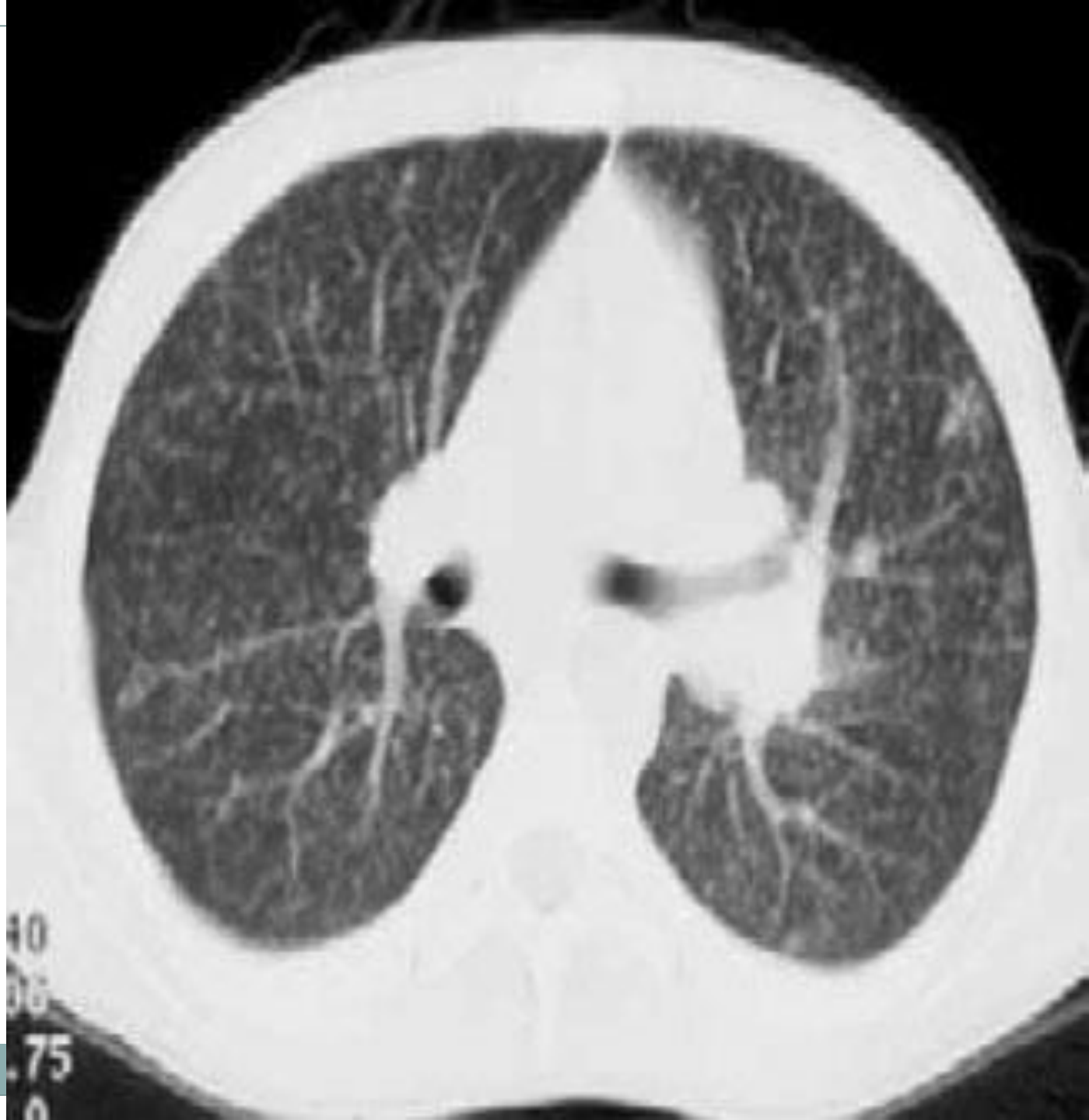


(a) Chest radiograph showing miliary tuberculosis. (b) Magnified view of the lung periphery in miliary tuberculosis.





CT miliary nodules – miliary TB.



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

Miliary nodules

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

- **Dense miliary nodule:**

- **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

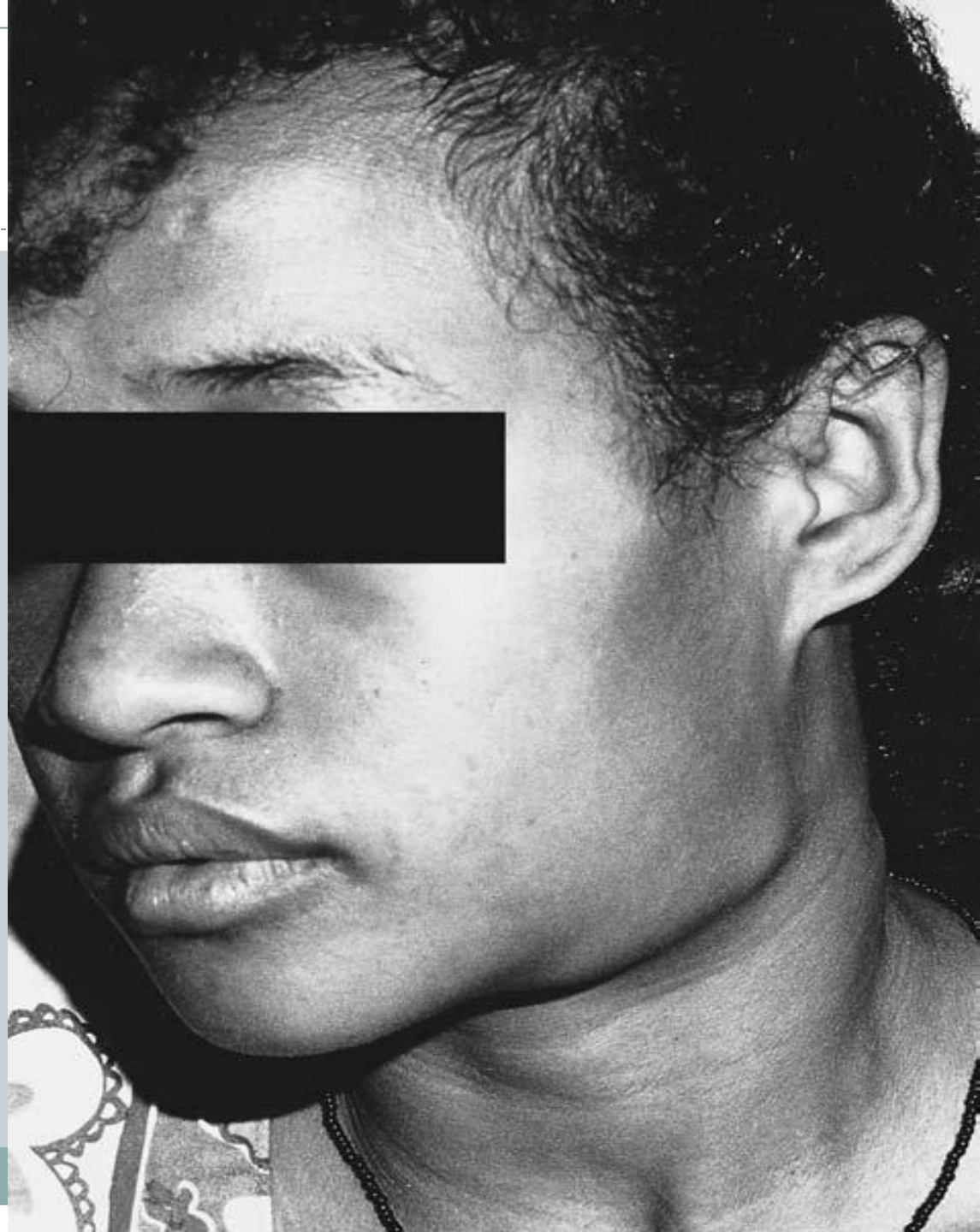
- Empyema necessitans
- Laryngitis
- Enteritis*

- 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.



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**
- **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.

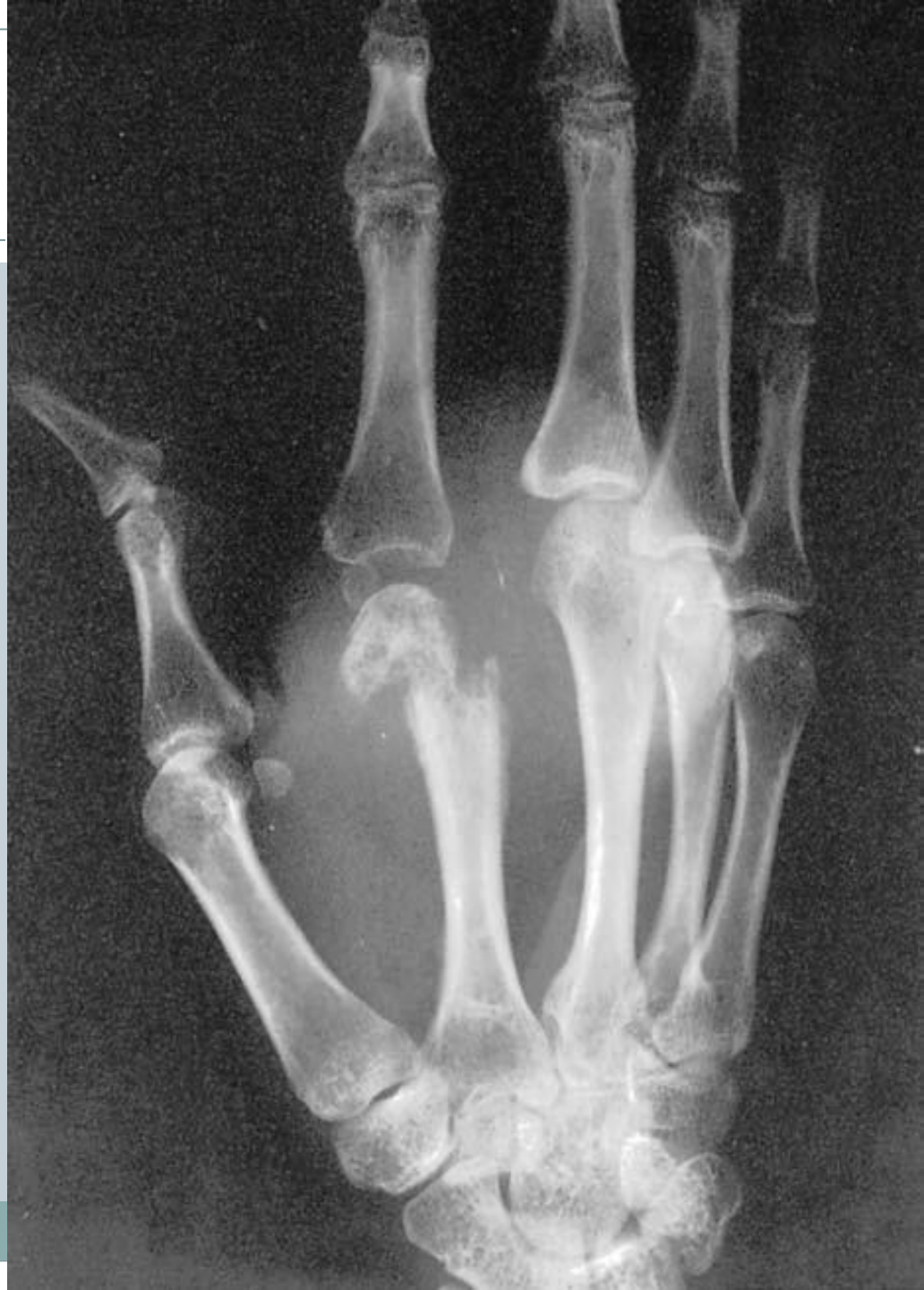
- Even when appropriate treatment is prescribed : mortality rates of 30%

- survivors may be left with neurological sequelae.

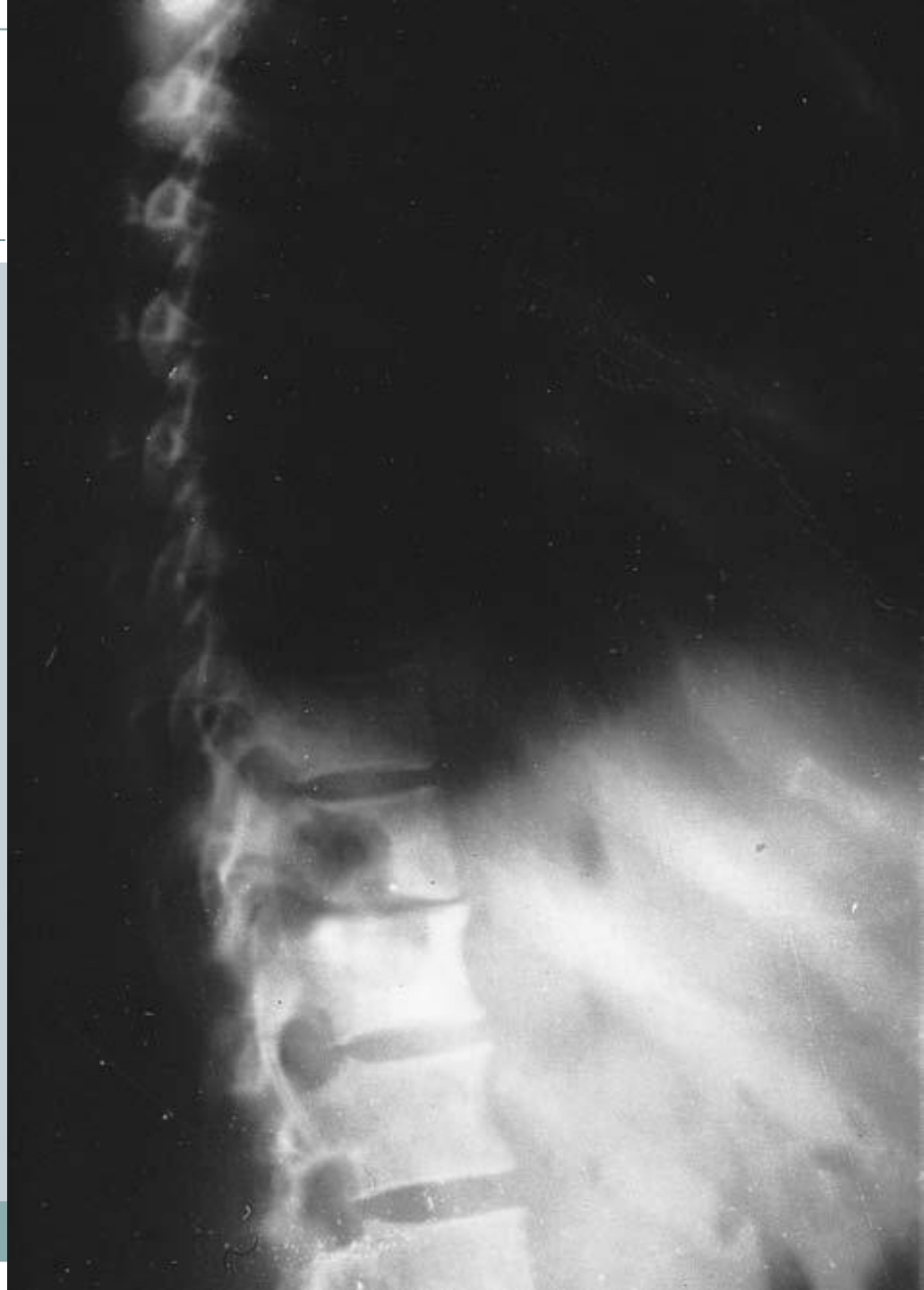
Bone and joint disease

- **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**

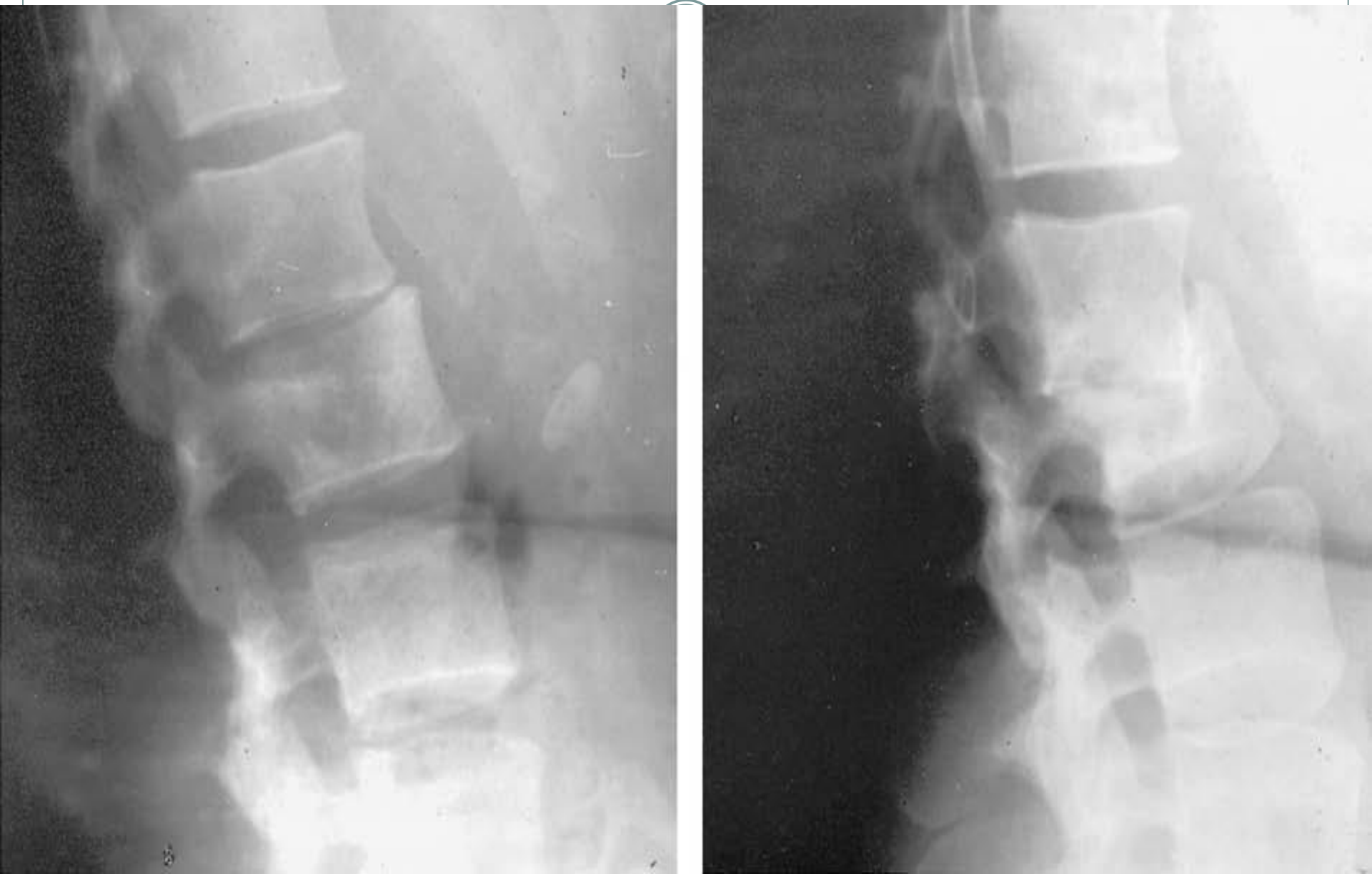
Tuberculosis of the second metacarpal with cold abscess formation in an Asian patient.



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



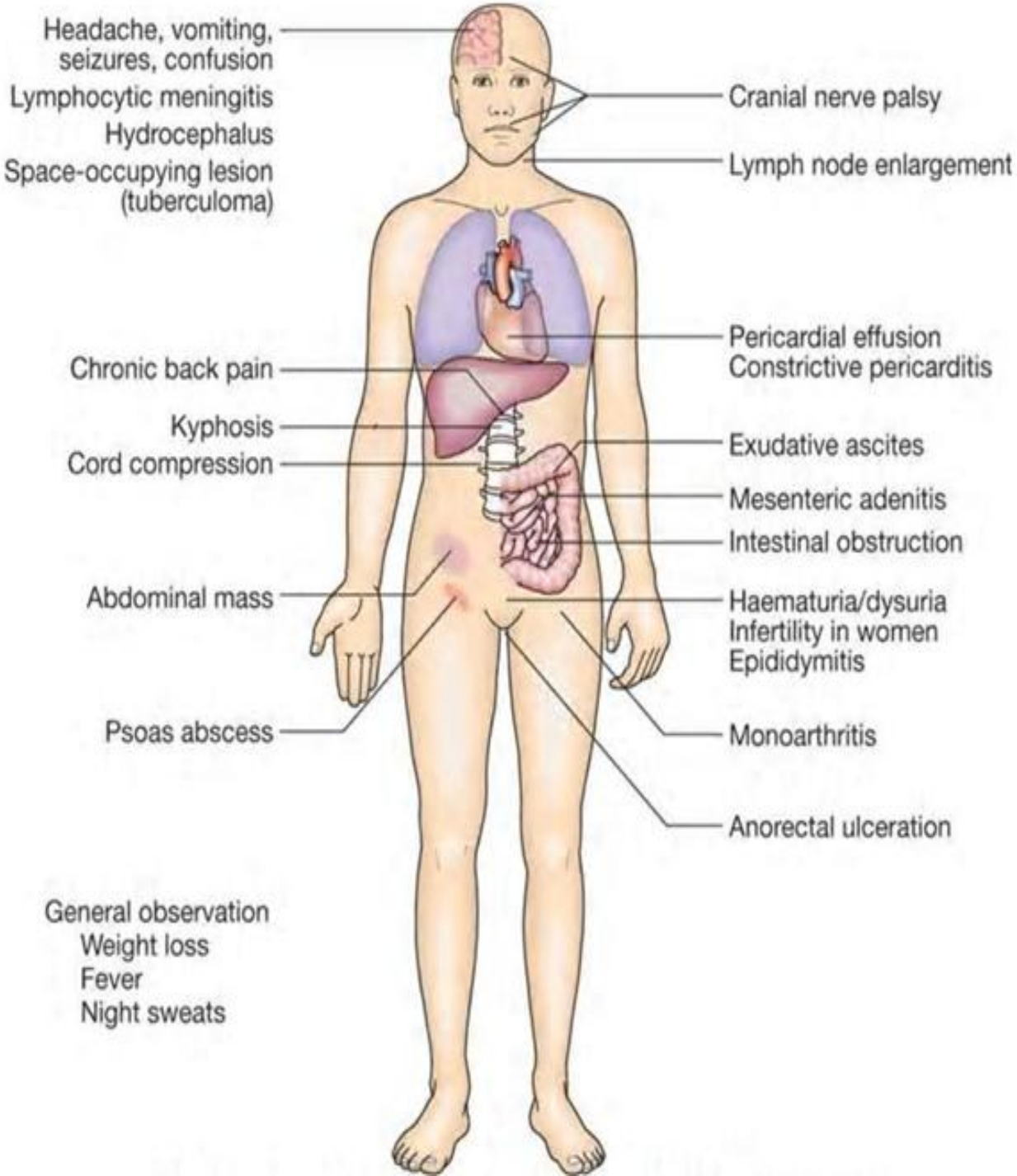
(a) Early tuberculous changes in the lumbar spine showing disc narrowing at L1/2, destruction of the body of L2 and demineralization of the adjacent end-plate. (b) The same patient 17 months later showing mild gibbous defomity resulting from extensive collapse of L2.



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

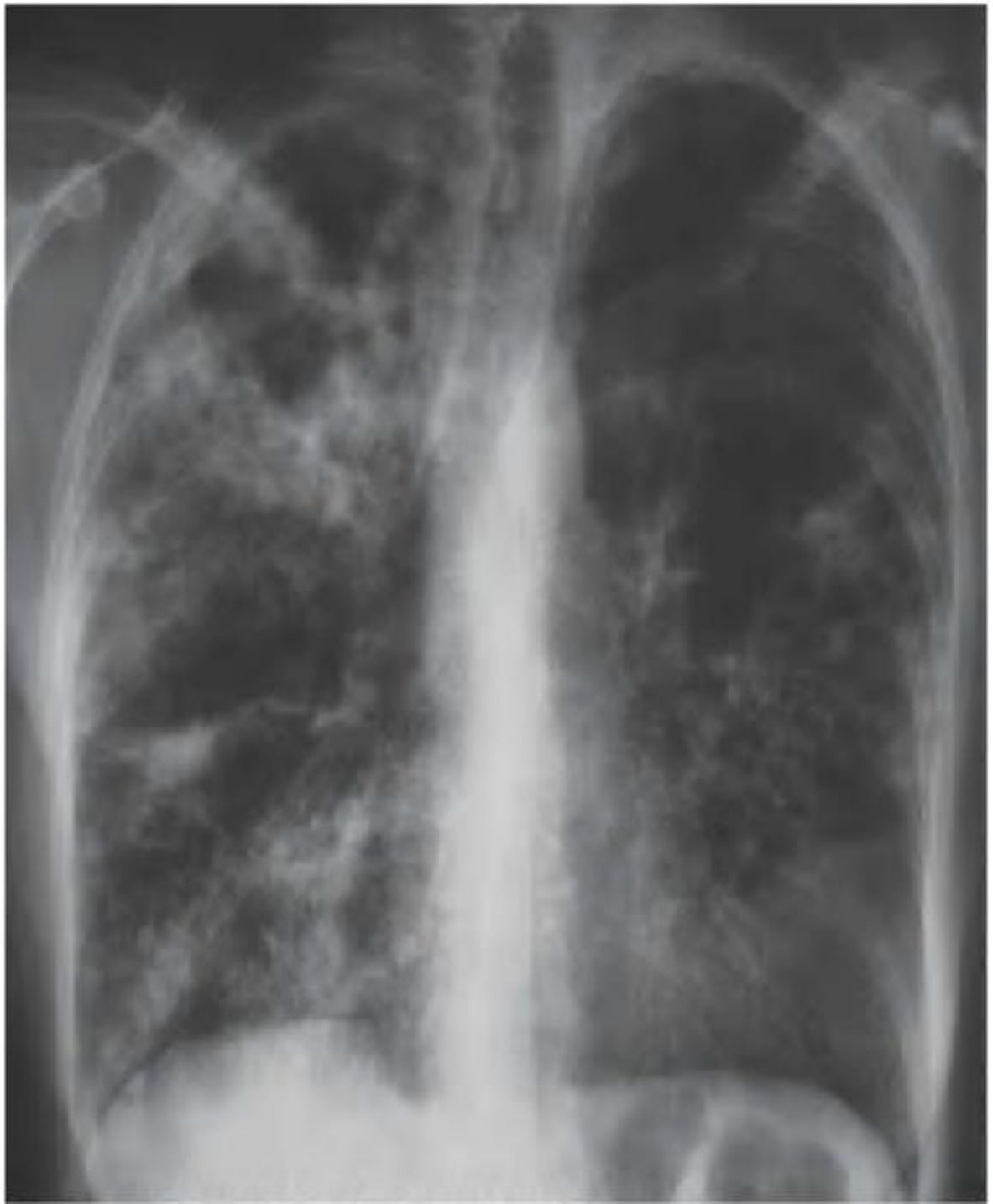
Patients with HIV are at greater risk of:

- 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

14.15 Pulmonary tuberculosis

Epidemiology	Due to *M. tuberculosis*, *M. bovis* or *M. africanum*
	Mycobacterium enhances HIV replication and acceleration of the disease; HIV causes immunosuppression and increases risk of reactivation and susceptibility to infection
At-risk CD4 count	Any, with risk increasing as count falls
Pathology	Granulomas and caseating necrosis
Clinical features	
Presentation	History over weeks to months
	Fever, night sweats and weight loss
	CD4 count > 200 cells/mm^3: reactivated upper-lobe cavitatory disease is more likely with cough and haemoptysis
	CD4 count ≤ 200 cells/mm^3: miliary, atypical pulmonary and extrapulmonary TB become more common
Suspect if	PUO, pneumonia failing to respond to antibiotics, exudative pleural effusion, unexplained weight loss, or TB is endemic in patient's country of origin
Differential diagnosis	PCP, Kaposi's sarcoma, unusual fungi (*Histoplasma*, *Penicillium*, *Cryptococcus*, *Coccidioides*), atypical pneumonia, *Nocardia* and lymphoma
Complications	Massive haemoptysis, empyema, acute respiratory distress syndrome (ARDS), cor pulmonale, aspergilloma
Key investigations and diagnosis	
Chest X-ray	Cavities, miliary shadowing, pleural effusion, mediastinal lymphadenopathy, collapse and consolidation (see Fig. 14.8)
	5% with smear-positive disease have a normal chest X-ray
Sputum	Organisms seen on Ziehl-Neelsen and auramine stains, and grown by radiometric culture
	Nucleic acid amplification allows rapid speciation and identification of rifampicin resistance; also used in smear-negative samples to increase diagnostic yield
Other	Positive mycobacterial cultures from blood identified in 50% of those with CD4 < 200 cells/mm^3
Management	
Treatment	*First-line*: rifampicin, isoniazid, ethambutol and pyrazinamide for 2 mths, then rifampicin and isoniazid for 4 mths. Drug reactions more common
	Consider steroids for moderate to severe disease
	Commence/optimise HAART. Efavirenz (with two NRTIs) first line because metabolism of protease inhibitors (PIs) is induced by rifampicin (p. 404)
	Stop therapy when complete
Immune restoration syndrome	Occurs in 10-15%. Most common in those with a nadir CD4 < 50 cells/mm^3 and a brisk CD4 response to HAART. Commonly presents as focal disease
	Treatment: NSAIDS or steroids
Prophylaxis	Isoniazid (with or without rifampicin) reduces the risk of TB by 60% in patients with positive tuberculin skin tests (less in those with negative tests)
	Protection limited to 2-4 yrs probably because of reinfection
Prognosis	Mortality 5%

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



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.

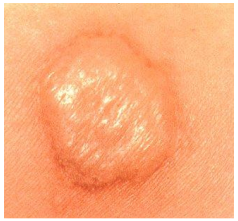
  - the non-radiometric mycobacteria growth indicator tube (MGIT)

  - 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 <u>immunocompetent</u> patients. Both of them **<u>are not able</u>** to differentiate between active or latent TB.

2007;20(6):540-547 Medscape from WebMD

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)

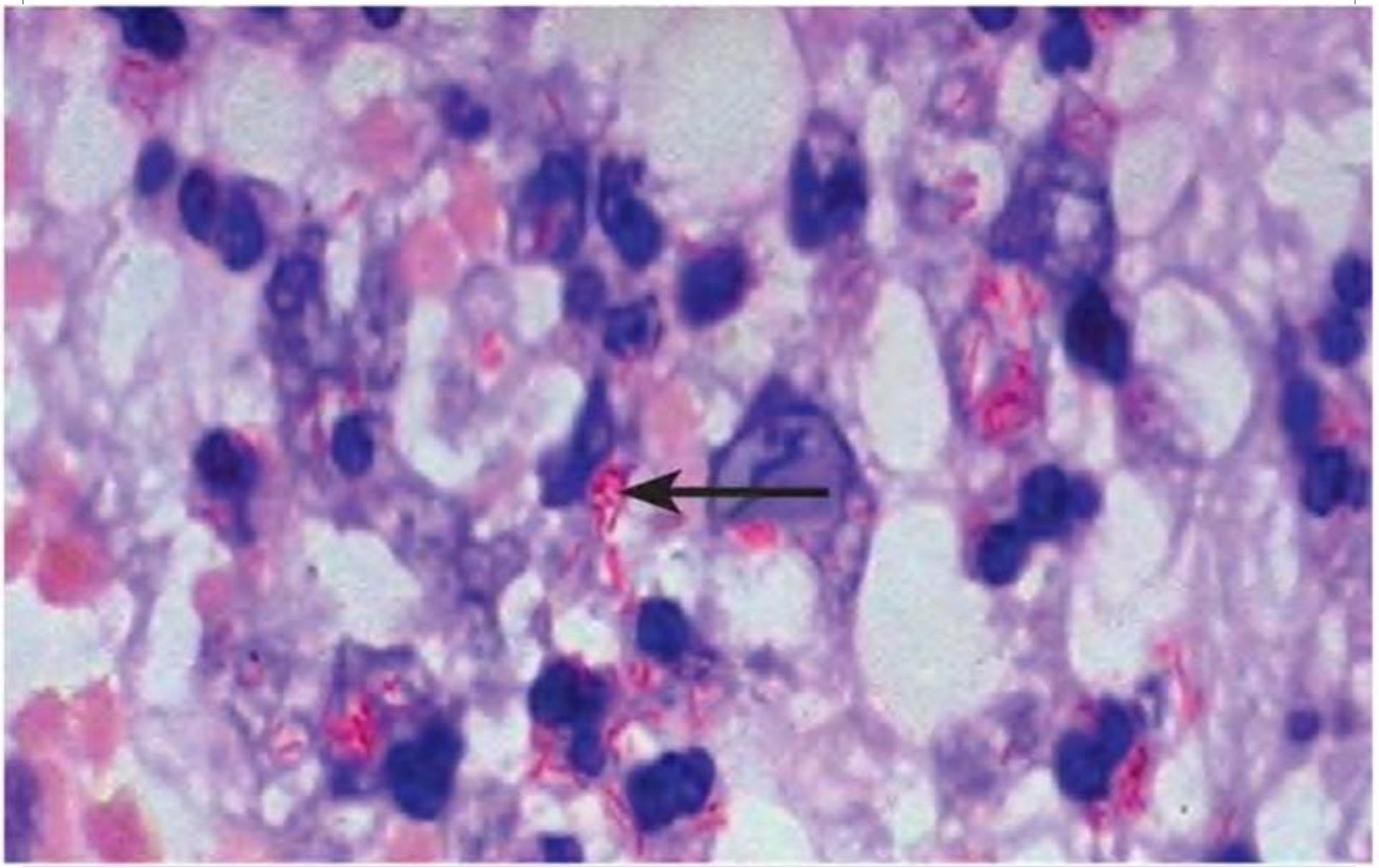
Extrapulmonary

- 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)

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 untreated, 50% will die within 5 years**
- **9-12 months of therapy :**
  - HIV-positive
  - drug intolerance occurs and a second-line agent is substituted.
- **Meningitis should be treated for a minimum of 12 months.**
- **Pyridoxine should be prescribed in pregnant women and malnourished patients**
- **patients can be assumed to be non-infectious after 2 weeks 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†

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

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.

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)**

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 should not be administered to those who are immunocompromised (e.g. by HIV) or pregnant.**

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**
- **resistance to conventional antituberculous 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

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

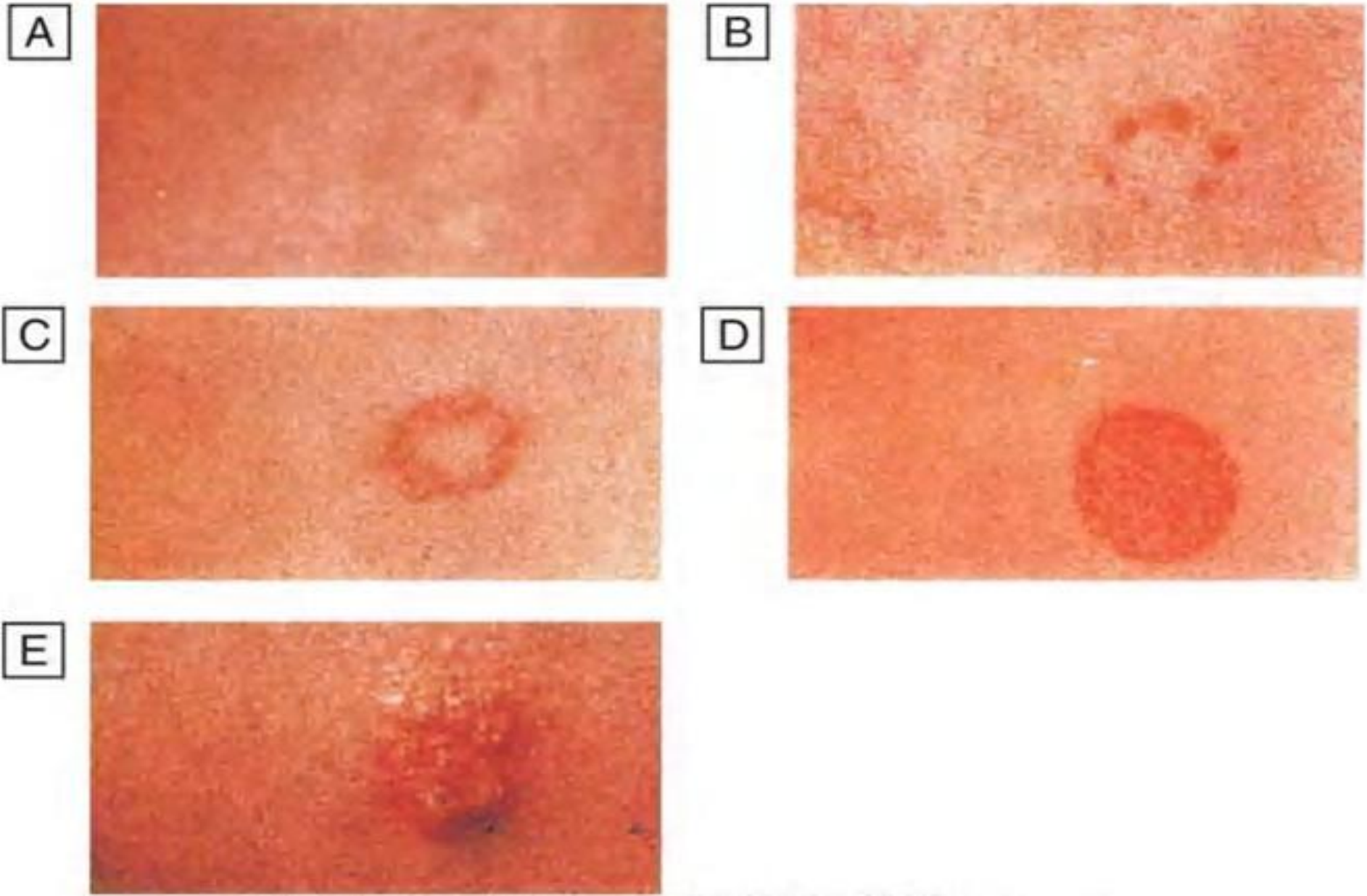
- Read at 2-4 days
- Using 10 tuberculin units
  - Positive when induration 5-14 mm (equivalent to Heaf grade 2) and > 15 mm (Heaf grade 3-4)

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

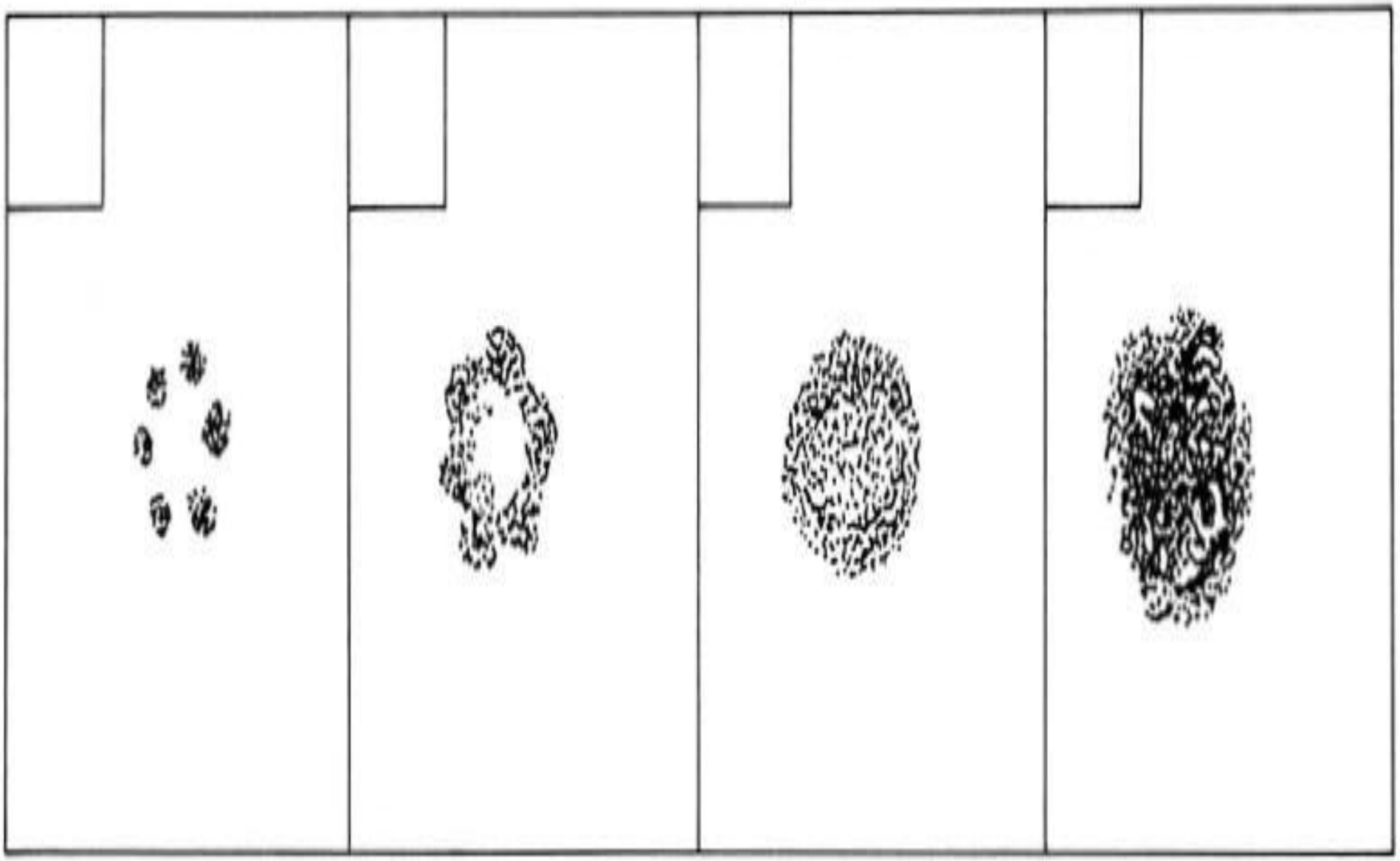


Table 3-8: Positive PPD Determination based on Preexisting Conditions

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