

Update in Tuberculosis: Diagnosis and Management of LTBI in the Workplace



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Learning objectives



- Apply evidence-based practice guidelines in screening patients with suspected Tuberculosis.
- Appropriately initiate screening and appropriately interpret PPD skin tests.
- Implement evidence-based practice guidelines for the treatment of latent TB infection (LTBI).

Case of DPH



- DPH is a 62 year old woman who has been hired to work in your institution's housekeeping department
 - She has a Green Card and moved here from Columbia three years ago to live with her children
 - She says she never had a PPD before
 - She denies symptoms of TB
- What are your institution's practices?
 - Who is screened? PPD? One stage, two stage, etc? Symptom review only?
 - Chest x-ray?

Do we still need to be worried about TB?



- In the year 2000, globally:
 - 8.3 million new cases of TB occurred
 - 1.84 million people died from TB
 - In sub-Saharan Africa, TB increased by 6.4% per year in the past decade (*NEJM 1993; 328:1137*)
 - 53% of all cases in the U.S. were in foreign-born individuals (5 countries of greatest incidence: Mexico; Philippines; India; Vietnam; China;)
 - If the incidence of TB is to truly decrease, efforts must be global, given the increasing numbers of immigrants to the U.S.

Environments with outbreaks of TB



- Correctional facilities
- Homeless shelters
- Bars
- Newly recognized social settings:
 - Persons in an East coast network of gay, transvestite and transsexual HIV infected men
 - Persons frequenting an abandoned junkyard for drug use and prostitution
 - Dancers in adult entertainment clubs and their contacts, including children

Factors determining transmission of TB



- Characteristics of source case
 - Cavitory disease? Concentration of organisms in sputum; frequency/strength of cough
- Characteristics of exposed person
 - Previous infection with MTB; genetic susceptibility to TB; innate resistance to MTB
- Characteristics of exposure
 - Frequency/duration of exposure; concentration of exposure; turnover of aeration; exposure to sunlight/UV rays
- Virulence of infecting *M. tuberculosis* strain

TB incidence among racial and ethnic minorities in US, 2003

| Race/ethnicity | Rate/100,000 (risk vs. whites) |
|--------------------------------|--------------------------------|
| White, non-Hispanic | 1.4 |
| American Indian/Alaskan native | 8.0 (5.7) |
| Hispanic | 10.5 (7.5) |
| Black, non-Hispanic | 11.5 (8.2) |
| Asian, Pacific Islander | 29.4 (21.0) |

Challenges to successful control of TB



- Prevalence of TB among foreign-born persons residing in the U.S.
- Delays in detecting and reporting cases of pulmonary TB
- Delays in protecting contacts of active TB cases and in preventing and responding to TB outbreaks
- Presence of a substantial number of people with LTBI who are at risk to develop active TB
- Maintaining clinical and public health knowledge of TB in the era of declining TB

A definition of importance.....



- **LTBI: *latent* TB infection (AKA Stage II TB)**
 - “Infected” with TB
 - ✦ PPD positive
 - ✦ Normal chest x-ray
 - ✦ No symptoms of TB
 - ✦ Cultures, if obtained, are negative
 - ✦ NOT infectious or contagious to others
 - *Represents the largest group of patients in which to ‘prevent’ future cases of TB*
 - *Estimated that 9.5-14.7 million cases of LTBI exist in the US*

Progression from LTBI to TB disease



- Human immune response is fairly effective; all organisms may not be killed
- For the majority, only evidence of LTBI is positive skin test or positive whole blood, antigen stimulated gamma interferon release assay result (Quanti-FERON TB Gold test)
- Greatest risk for progression from LTBI to TB is greatest in the *first two years* following infection (when half of the 5-10% lifetime risk of progression occurs)

Progression from LTBI to TB disease



- Persons at the greatest risk for progression of LTBI to TB disease are:
 - HIV infected persons
 - Patients with Diabetes mellitus
 - Acquisition of LTBI during early childhood
 - Apical fibronodular chest x-ray abnormalities
 - Other conditions:
 - ✦ Silicosis
 - ✦ Chronic renal disease
 - ✦ Immunosuppression
 - ✦ Anti-TNF alpha agent administration (RA; Crohn's Disease)

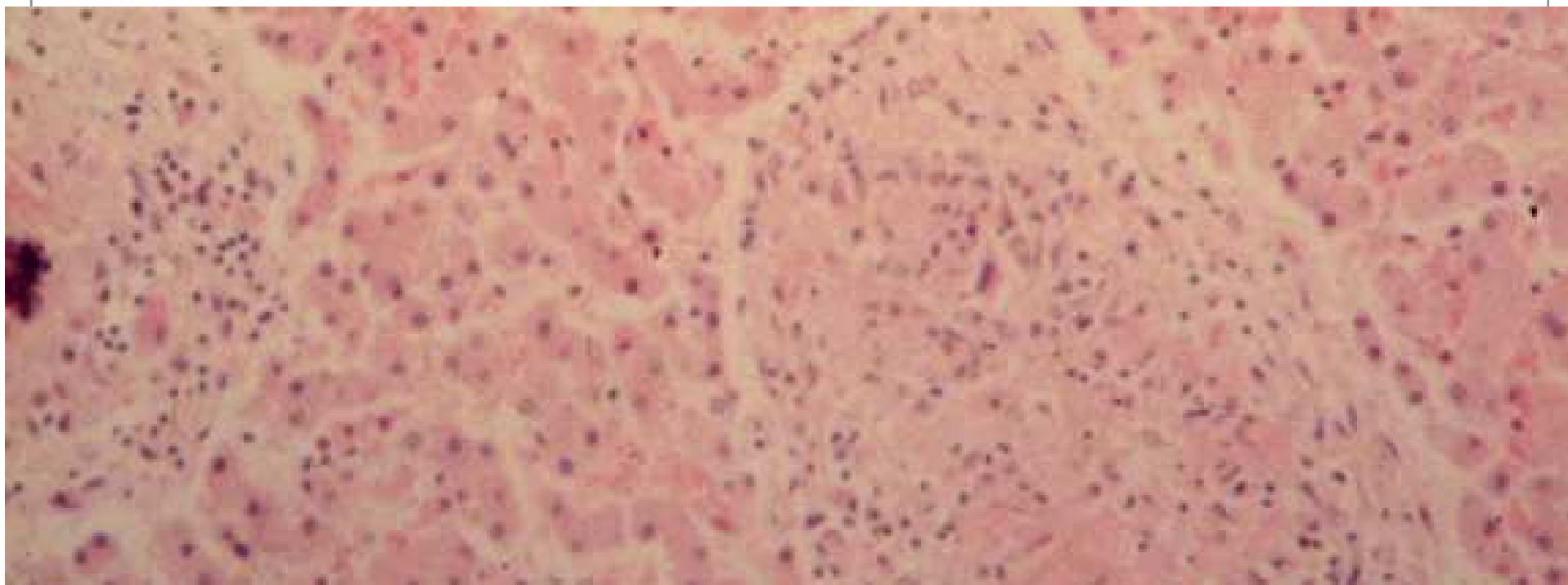
Risks of developing active TB

Table 3. Relative risk* for developing active tuberculosis (TB), by selected clinical conditions

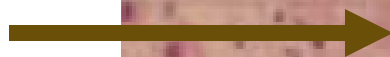
| Clinical condition | Relative risk |
|------------------------------------|-------------------------|
| Silicosis | 30 (37,38) [†] |
| Diabetes mellitus | 2.0-4.1 (42-44) |
| Chronic renal failure/hemodialysis | 10.0-25.3 (39-41) |
| Gastrectomy | 2-5 (45-47) |
| Jejunioileal bypass | 27-63 (48-49) |
| Solid organ transplantation | |
| Renal | 37 (50) |
| Cardiac | 20-74 (51,52) |
| Carcinoma of head or neck | 16 (53) |

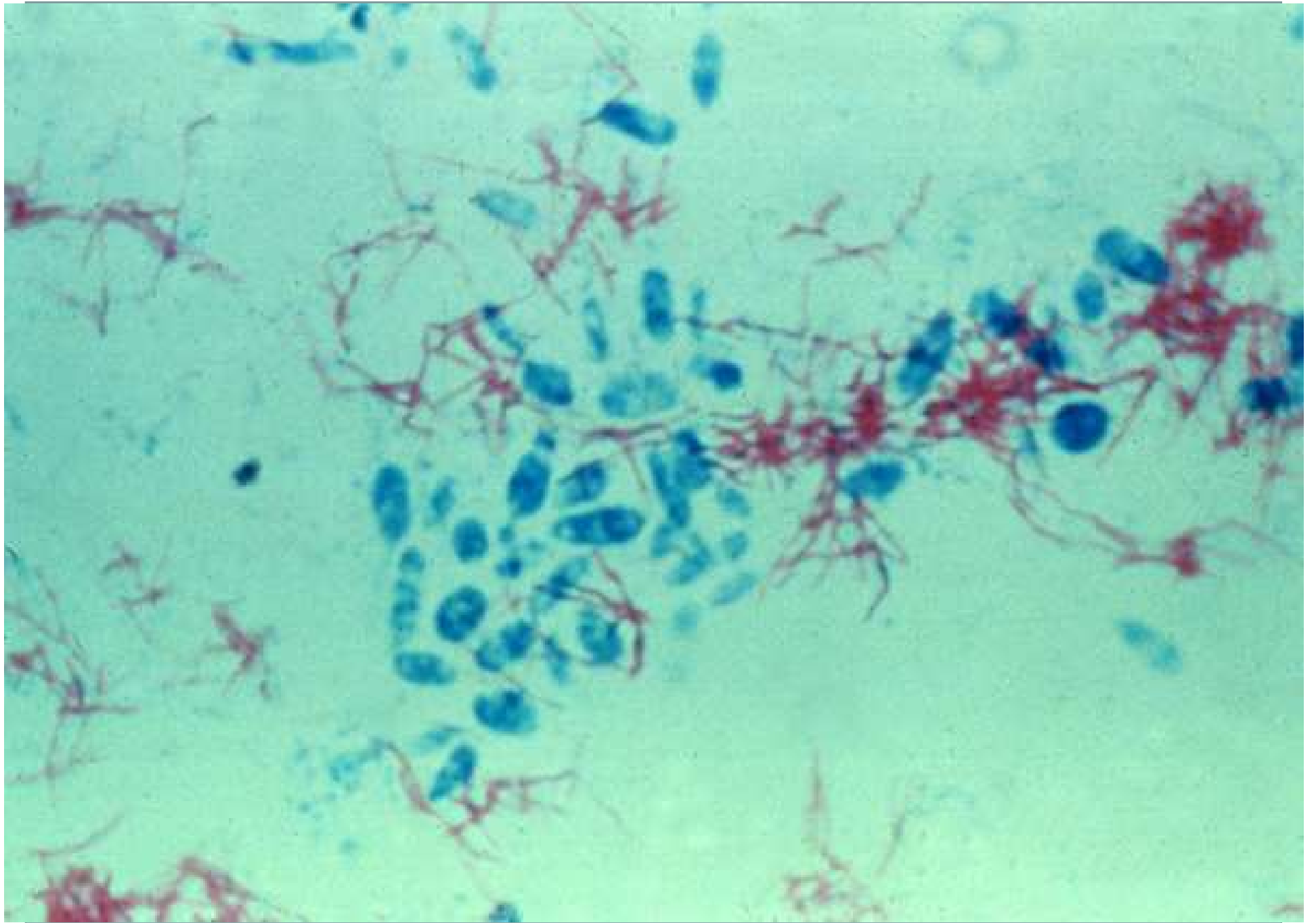
*Relative to control population; independent of tuberculin-test status.

[†] Numbers in parentheses are reference numbers.



Multinucleated giant cell within
Granuloma; on special staining, AFB are
present





Pathophysiology of Tuberculosis



- Tubercle bacilli are inhaled via droplet nuclei, reaching the alveoli (2-3 microns)
 - Engulfed by nonimmune alveolar Macrophages (MO)
- TB bacilli multiply intracellularly, killing MO; chemokines are released, attracting new MO
- Transported to hilar lymphatics, and spread systemically
- T lymphocytes respond to TB Agns which limit proliferation and/or kill bacilli
 - Cell mediated immunity results

Pathophysiology of Tuberculosis



- The host may fail to mount effective immune response and develop primary TB in the lung or at distant site OR
- Primary focus can later reactivate, undergo liquefaction with cavity formation
 - Extracellular bacilli multiply exponentially during this accelerated proliferation
 - Patient expectorates bacilli in secretions
 - Another individual inhales bacilli; cycle completed

Screening for TB



WHO, WHY, WHEN, HOW

Populations and Subpopulations to be screened for LTBI (AKA 'Targeted testing')

- **Tier 1:**

- Persons working in or served by community care clinics caring for HIV infected; prisoners; legal immigrants and refugees with B1 or B2 TB notification status; recently arrived refugees; other well-defined groups in congregate living settings; persons enrolled in substance abuse programs

- **Tier 2:**

- Jail detainees; persons living or working in homeless shelters; immigrants reporting for adjustment in status;

- **Tier 3:**

- Other foreign born persons at high risk, who immigrated \leq 5 years ago from countries with a high incidence of TB or US residents of racial/ethnic minorities with increased incidence of TB

Risks of developing active TB

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Skin testing for TB



- **Delayed hypersensitivity testing:**
 - Intradermal injection of PPD
 - Test is read 48-72* hours after placement
 - INDURATION is evaluated when considering whether or not test is positive
 - ✦ Erythema does NOT COUNT!!!!
 - ✦ Beware the patient who refuses testing stating that they are "allergic" to PPD skin test
 - Usually indicates prior positivity
- **A word about the 'new test'.....**
 - Quanti-FERON TB Gold test *MMWR 2005; Vol 54, RR-15*

Quanti-FERON TB Gold test

- FDA approved in 2005 for the testing of people at risk for TB infection;
- Can be used in place of, not in addition to PPD
 - Positive QFT-G should prompt the same investigation as a positive PPD
- If tested soon after exposure, and negative, should repeat later to confirm
 - Is not positive in cases of BCG vaccination (difference in proteins)
- Cost may be an issue as well as collection and transfer of specimens (requires 12 hour window)

Table 1. Changes from prior recommendations on tuberculin testing and treatment of latent tuberculosis infection (LTBI)

Tuberculin testing

Emphasis on targeted tuberculin testing among persons at high risk for recent LTBI or with clinical conditions that increase the risk for tuberculosis (TB), regardless of age; testing is discouraged among persons at lower risk

For patients with organ transplants and other immunosuppressed patients (e.g., persons receiving the equivalent of ≥ 15 mg/d prednisone for 1 mo or more), 5 mm of induration rather than 10 mm of induration as a cut-off level for tuberculin positivity

A tuberculin skin test conversion is defined as an increase of ≥ 10 mm of induration within a 2-yr period, regardless of age

Treatment of latent tuberculosis infection

For human immunodeficiency virus (HIV)-negative persons, isoniazid given for 9 mo is preferred over 6-mo regimens

For HIV-positive persons and those with fibrotic lesions on chest X-ray consistent with previous TB, isoniazid should be given for 9 mo instead of 12 mo

For HIV-negative and HIV-positive persons, rifampin and pyrazinamide should be given for 2 mo

For HIV-negative and HIV-positive persons, rifampin should be given for 4 mo

Clinical and laboratory monitoring

Routine baseline and follow-up laboratory monitoring can be eliminated in most persons with LTBI, except for those with HIV infection, pregnant women (or those in the immediate postpartum period), and persons with chronic liver disease or those who use alcohol regularly

Emphasis on clinical monitoring for signs and symptoms of possible adverse effects, with prompt evaluation and changes in treatment, as indicated

Table 7. Criteria for tuberculin positivity, by risk group

| Reaction ≥ 5 mm of induration | Reaction ≥ 10 mm of induration | Reaction ≥ 15 mm of induration |
|---|--|-------------------------------------|
| Human immunodeficiency virus (HIV)-positive persons | Recent immigrants (i.e., within the last 5 yr) from high prevalence countries | Persons with no risk factors for TB |
| Recent contacts of tuberculosis (TB) case patients | Injection drug users | |
| Fibrotic changes on chest radiograph consistent with prior TB | Residents and employees [†] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters | |
| Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/d of prednisone for 1 mo or more)* | Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of $\geq 10\%$ of ideal body weight, gastrectomy, and jejunioileal bypass Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk | |

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

[†] For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥ 15 mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19-34.

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection
ATS/CDC Statement Committee on Latent Tuberculosis Infection, June 2000

Table 10. Recommended drug regimens for treatment of latent tuberculosis (TB) infection in adults

| Drug | Interval and duration | Comments | Rating* (Evidence) [†] | |
|----------------------------|------------------------------------|---|---------------------------------|------------------|
| | | | HIV ⁻ | HIV ⁺ |
| Isoniazid | Daily for 9 mo [§] | In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs) | A (II) | A (II) |
| | Twice weekly for 9 mo [§] | Directly observed therapy (DOT) must be used with twice-weekly dosing | B (II) | B (II) |
| Isoniazid | Daily for 6 mo [§] | Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children | B (I) | C (I) |
| | Twice weekly for 6 mo [§] | DOT must be used with twice-weekly dosing | B (II) | C (I) |
| Rifampin plus pyrazinamide | Daily for 2 mo | May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible TB In HIV-infected patients, protease inhibitors or NNRTIs should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenavir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir [¶] | B (II) | A (I) |
| | Twice weekly for 2–3 mo | DOT must be used with twice-weekly dosing | C (II) | C (I) |
| Rifampin | Daily for 4 mo | For persons who cannot tolerate pyrazinamide For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide | B (II) | B (III) |

*Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given.

[†] Quality of evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion.

[‡] Recommended regimen for children younger than 18 yr of age.

[§] Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 mo as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

[¶] Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see Table 8).

| Drugs | Duration (mo) | Interval | Rating* (Evidence) [†] | |
|-----------------------|------------------|--------------|---------------------------------|---------|
| | | | HIV- | HIV+ |
| Isoniazid | 9 | Daily | A (II) | A (II) |
| | | Twice weekly | B (II) | B (II) |
| Isoniazid | 6 | Daily | B (I) | C (I) |
| | | Twice weekly | B (II) | C (I) |
| Rifampin-pyrazinamide | 2 | Daily | B (II) | A (I) |
| | 2-3 | Twice weekly | C (II) | C (I) |
| Rifampin | 4 | Daily | B (II) | B (III) |

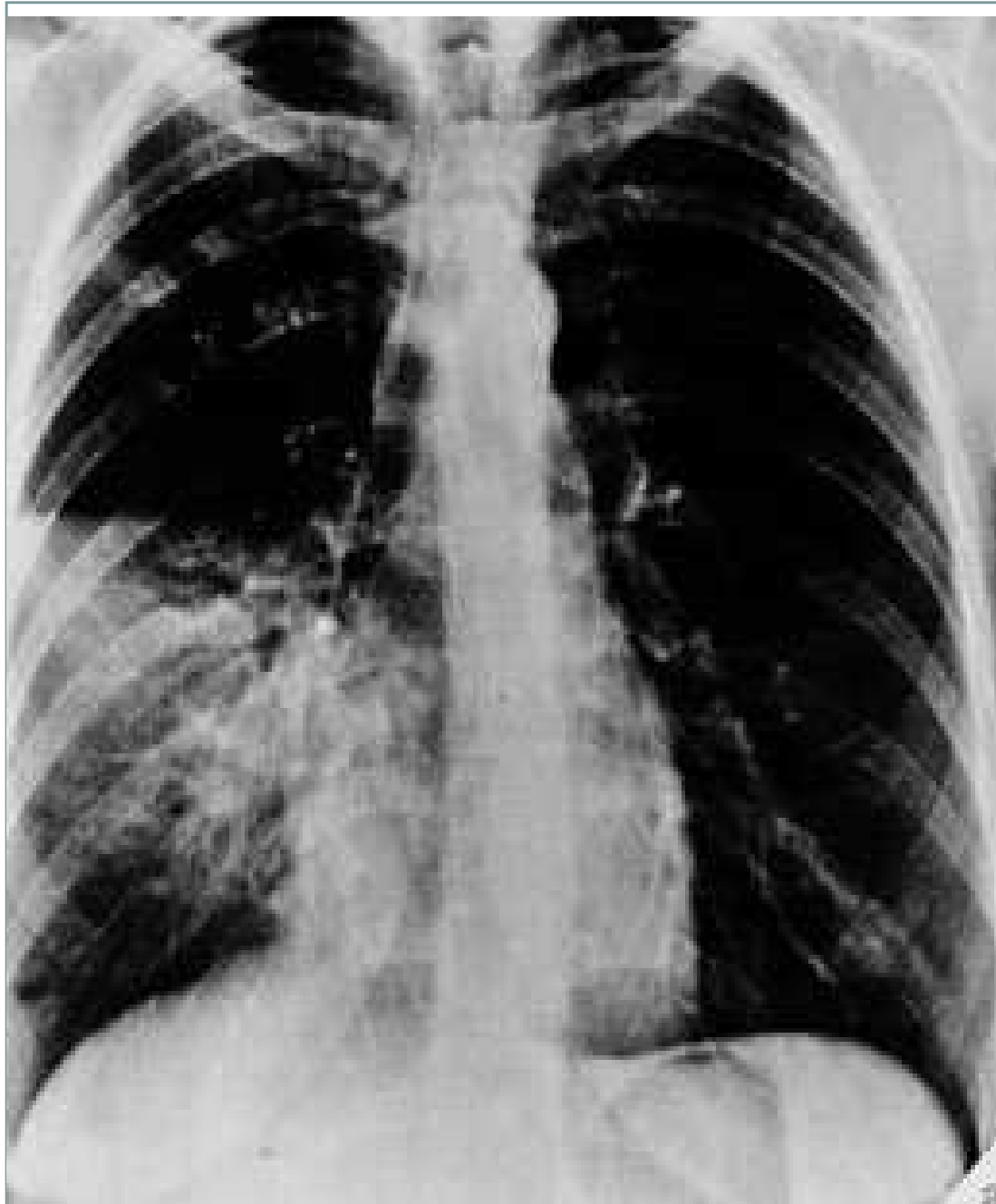
* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.

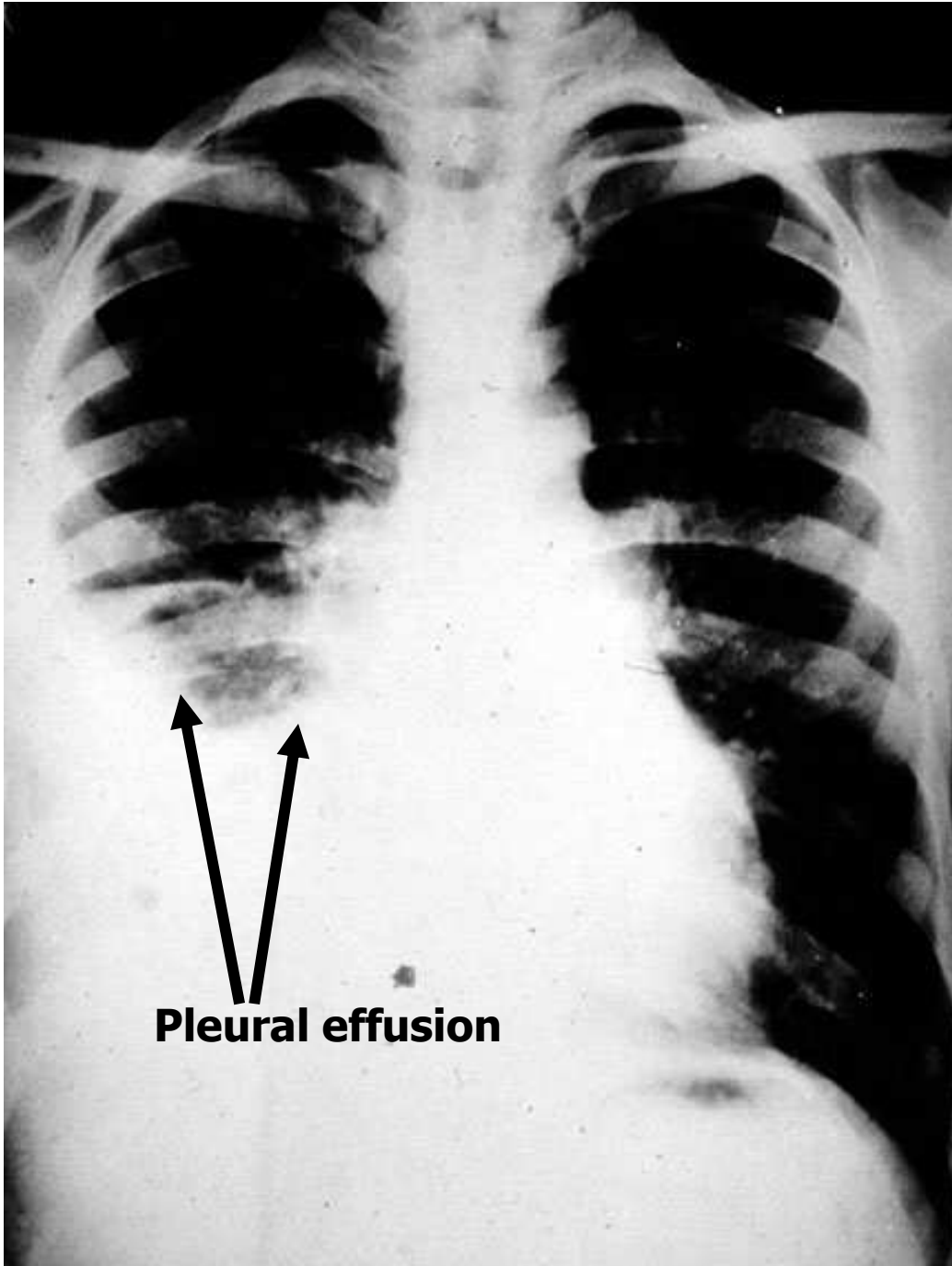
[†] I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.

The alternative.....



**WHEN WE ARE NOT SUCCESSFUL IN
TREATING LTBI**





Pleural effusion

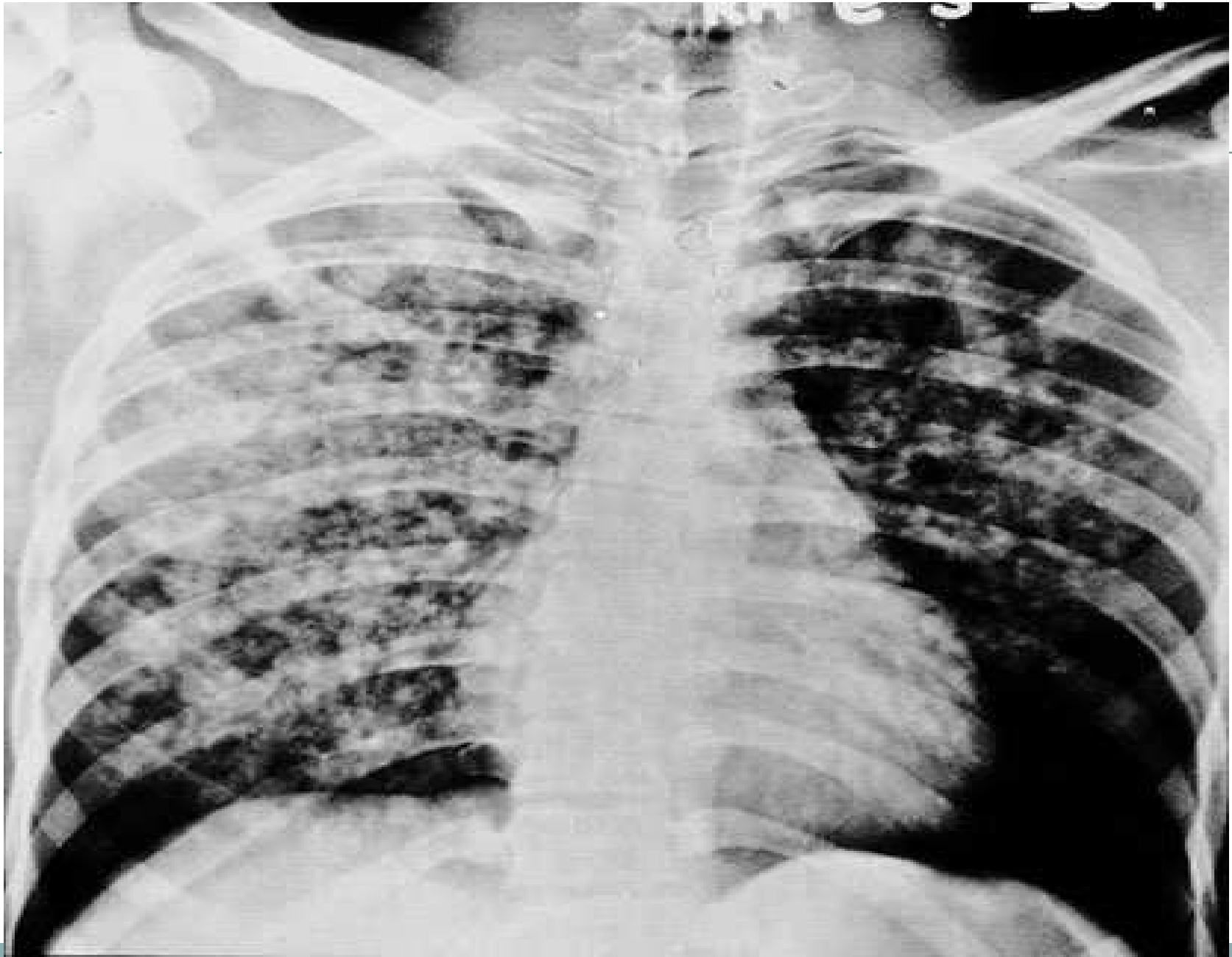
Typical pleural effusion
Seen in TB:

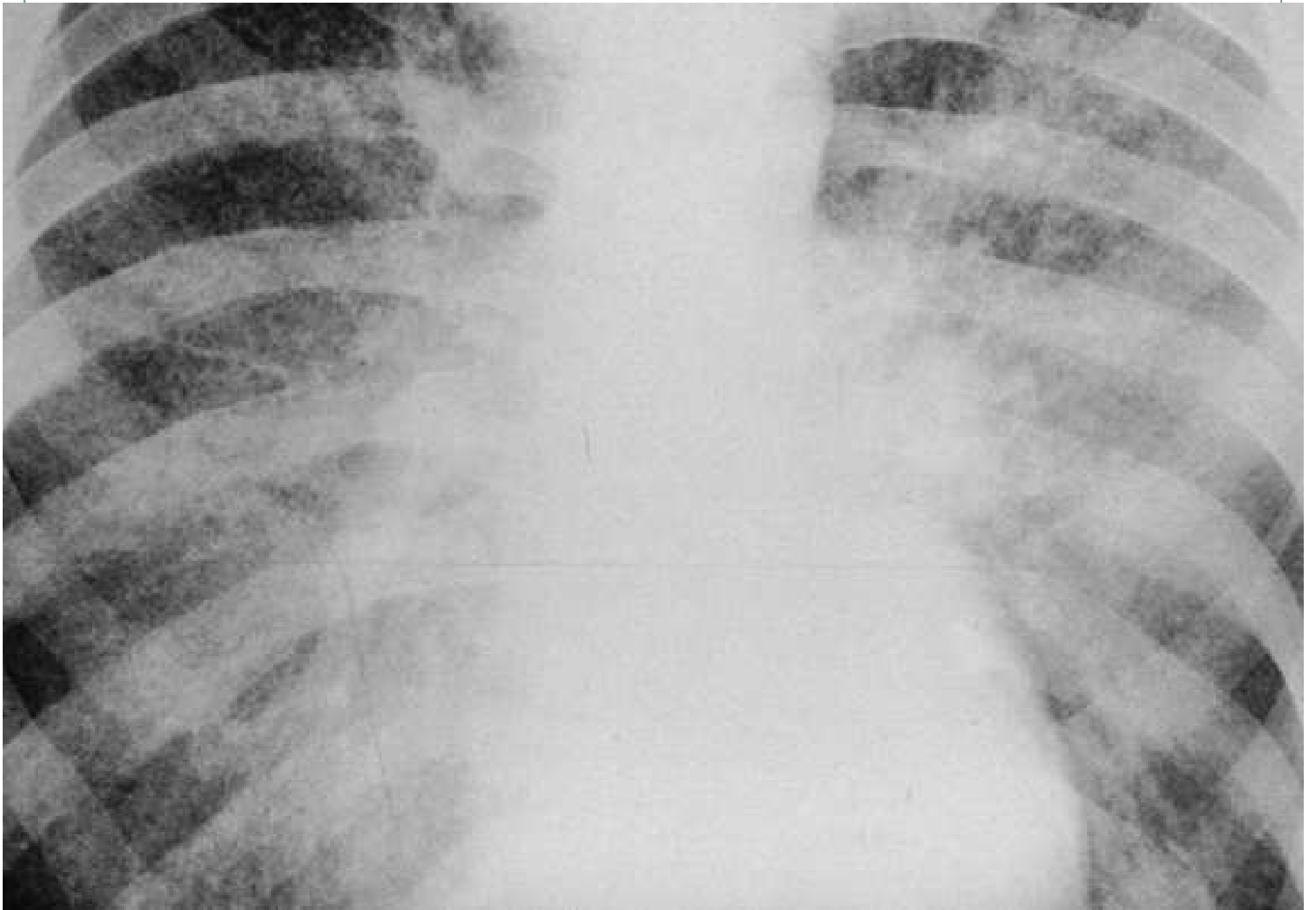
- Bloody
- Exudate
- Lymphocytic infiltrate
- pH: 7.3-7.4

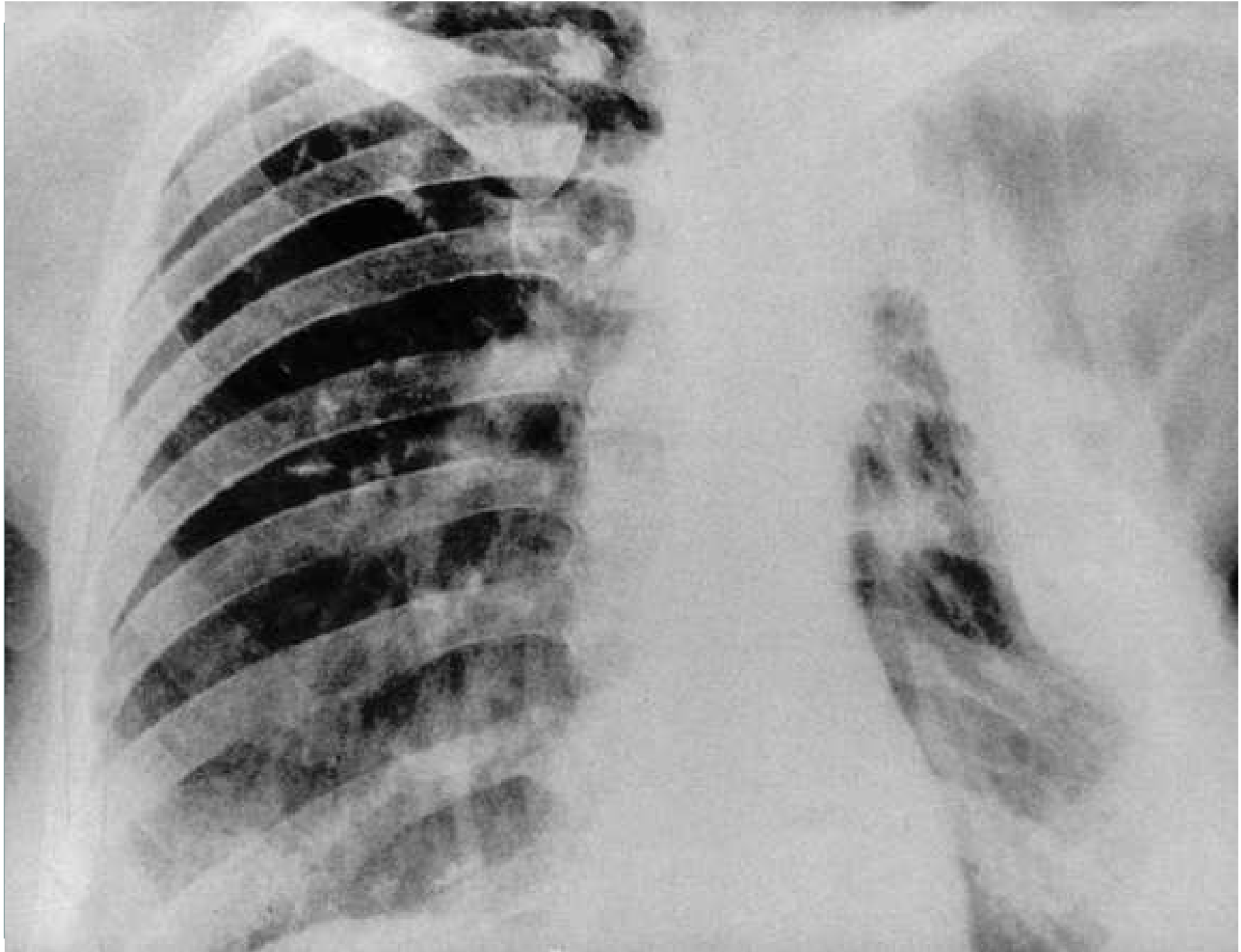


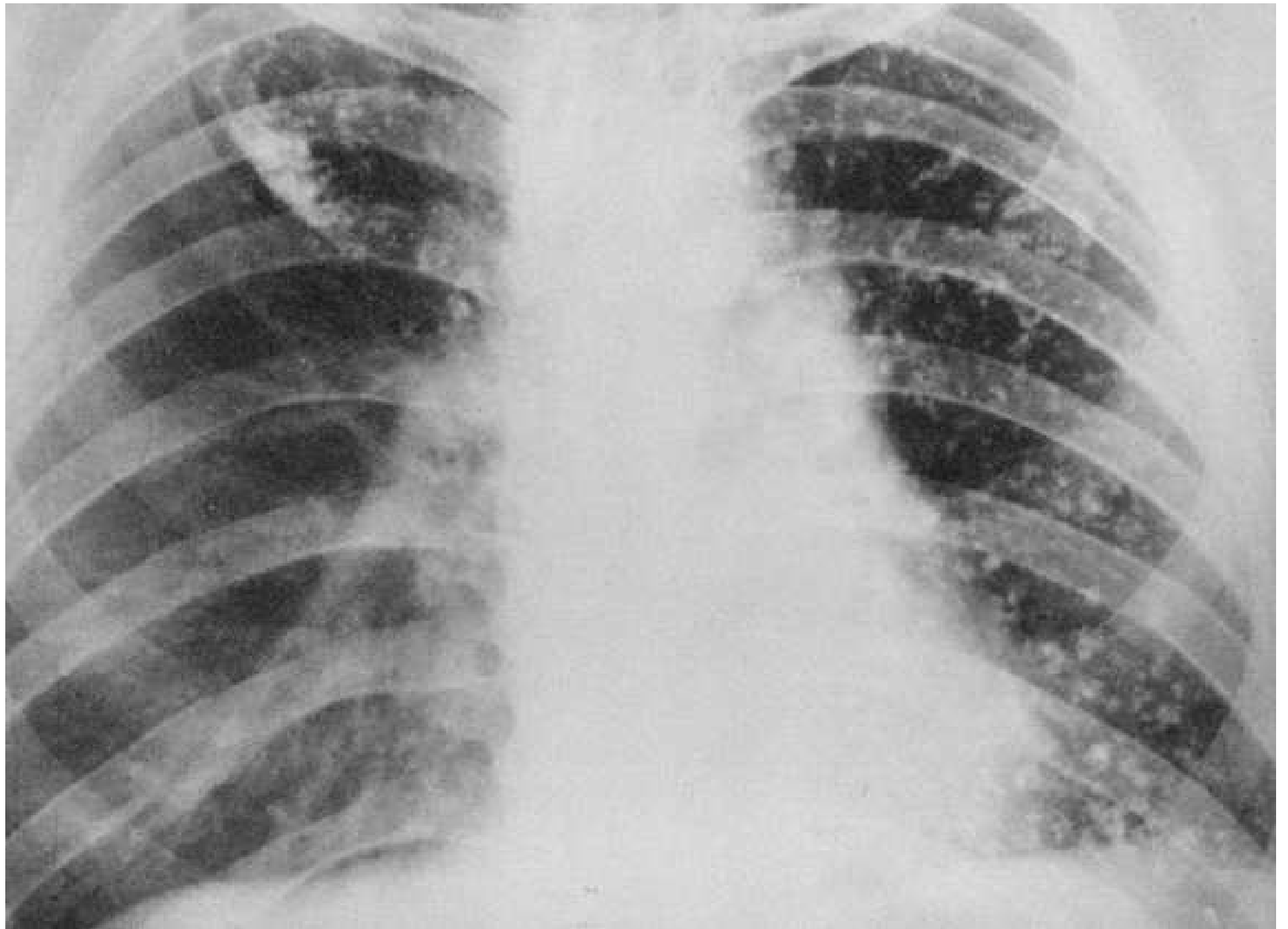
Mediastinal
lymphadenopathy

A black and white chest X-ray showing the rib cage and the mediastinal region. The text 'Mediastinal lymphadenopathy' is overlaid in a white box with blue text. Two horizontal black lines are positioned above and below the text box. The X-ray shows the ribs and the central mediastinal area, which appears slightly widened, consistent with the diagnosis of lymphadenopathy.



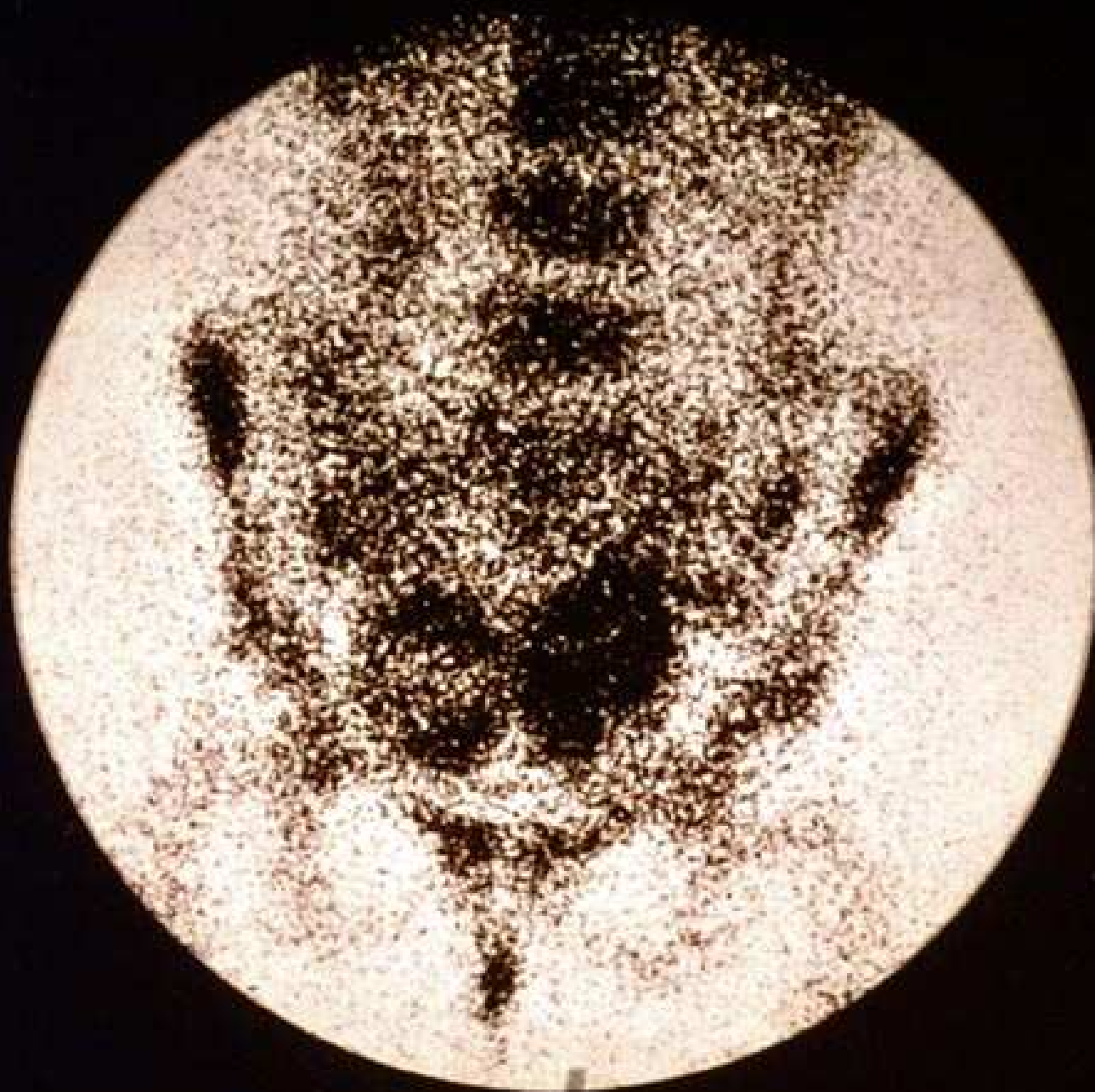
















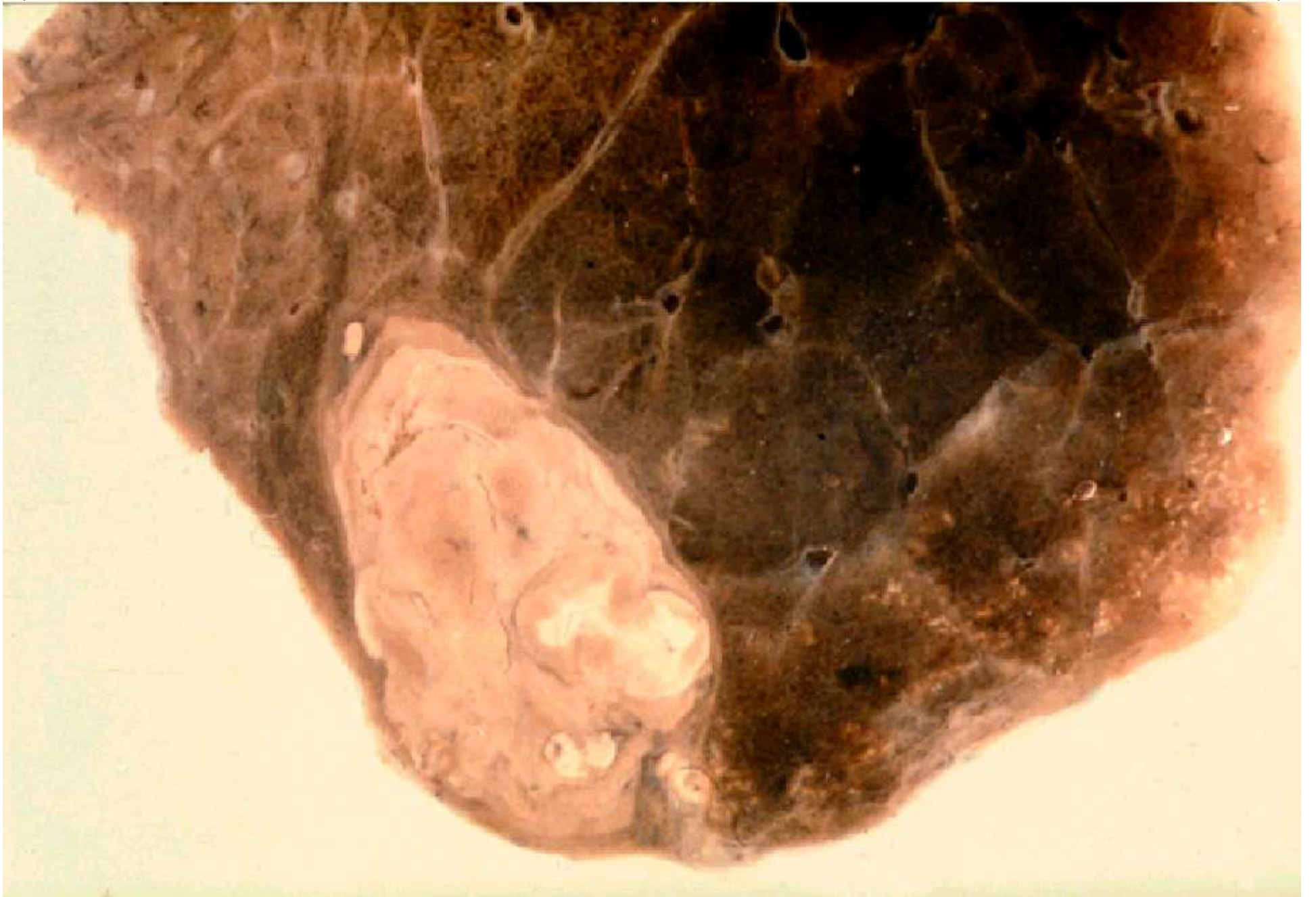


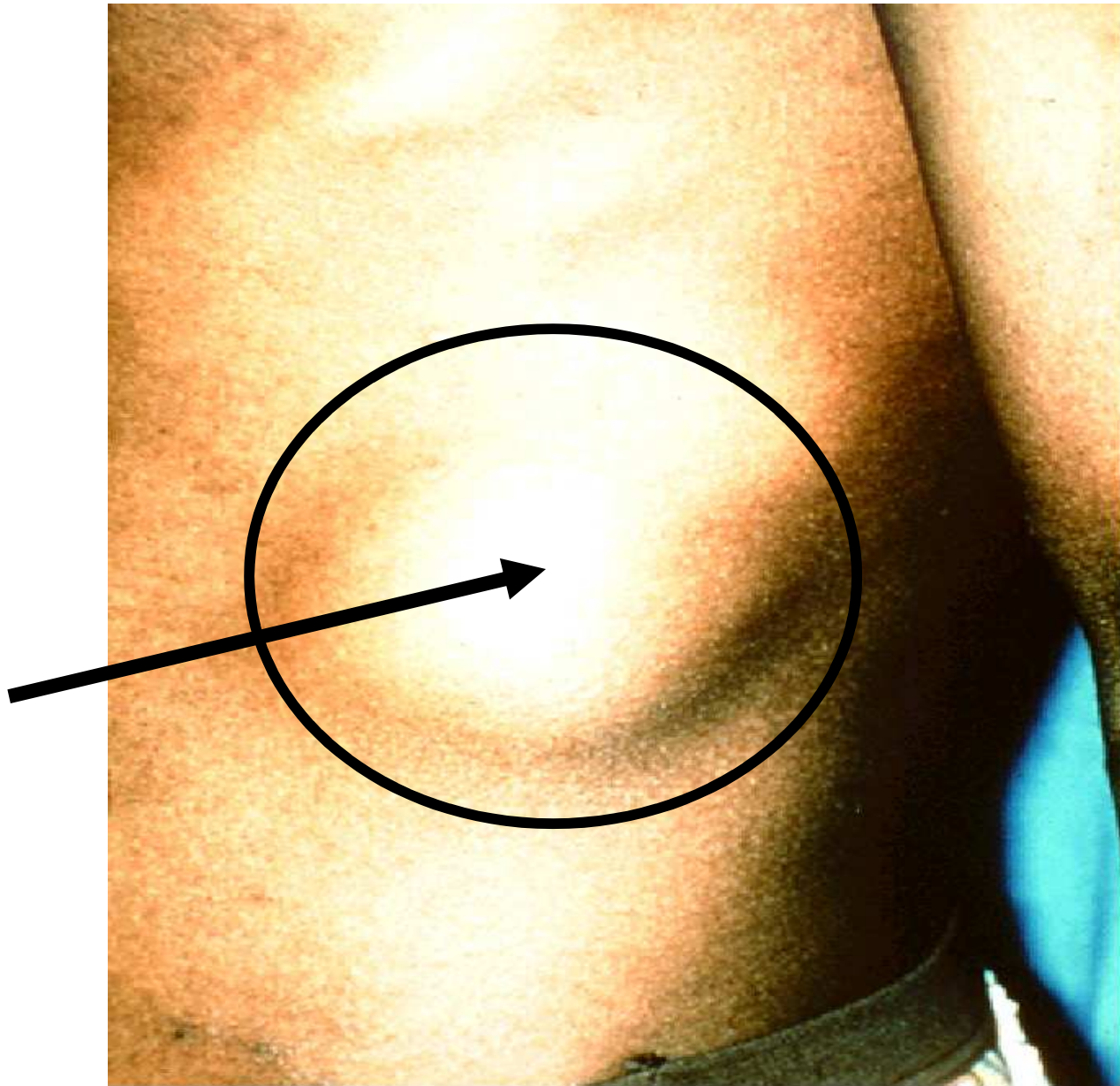




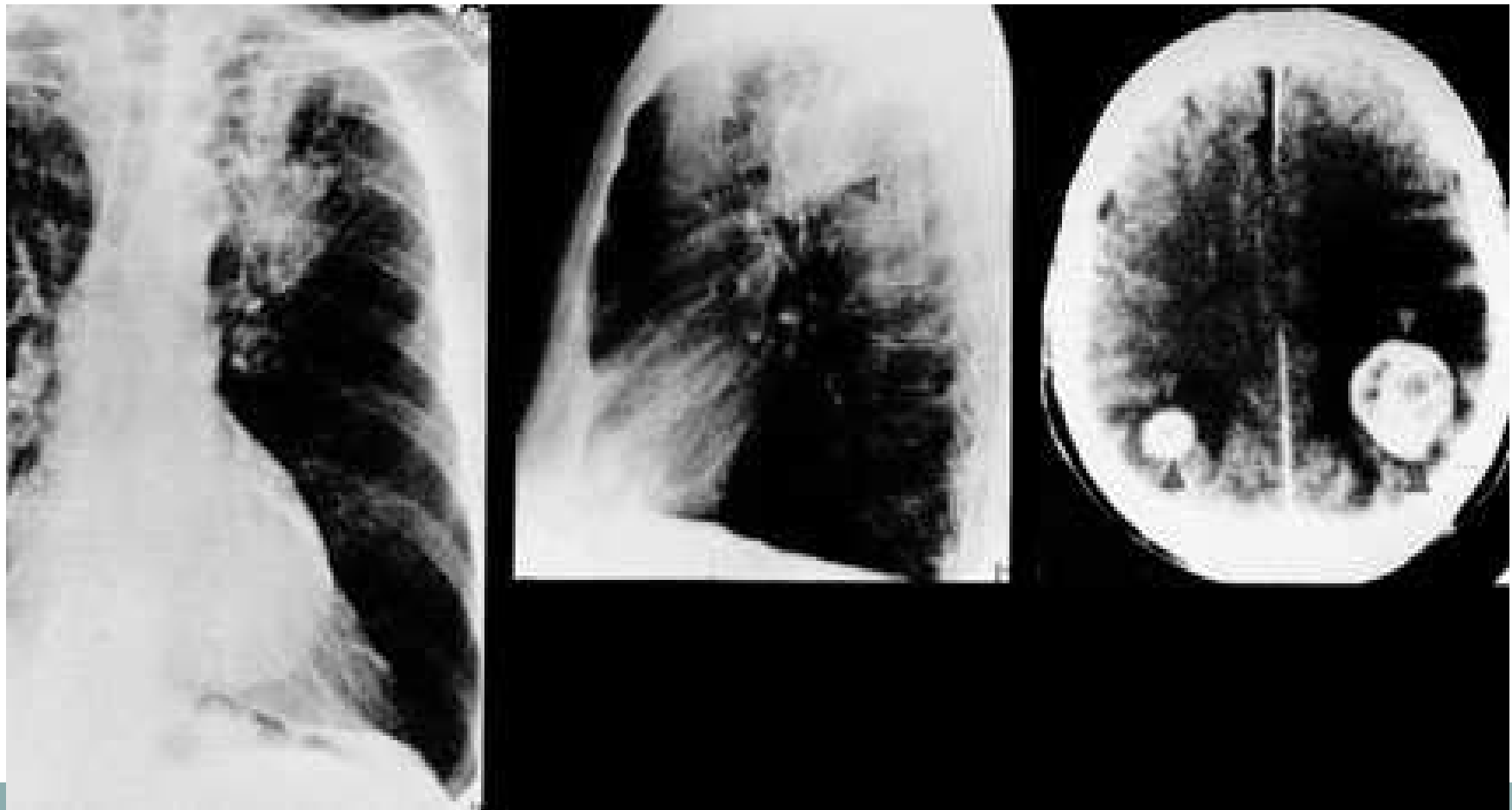




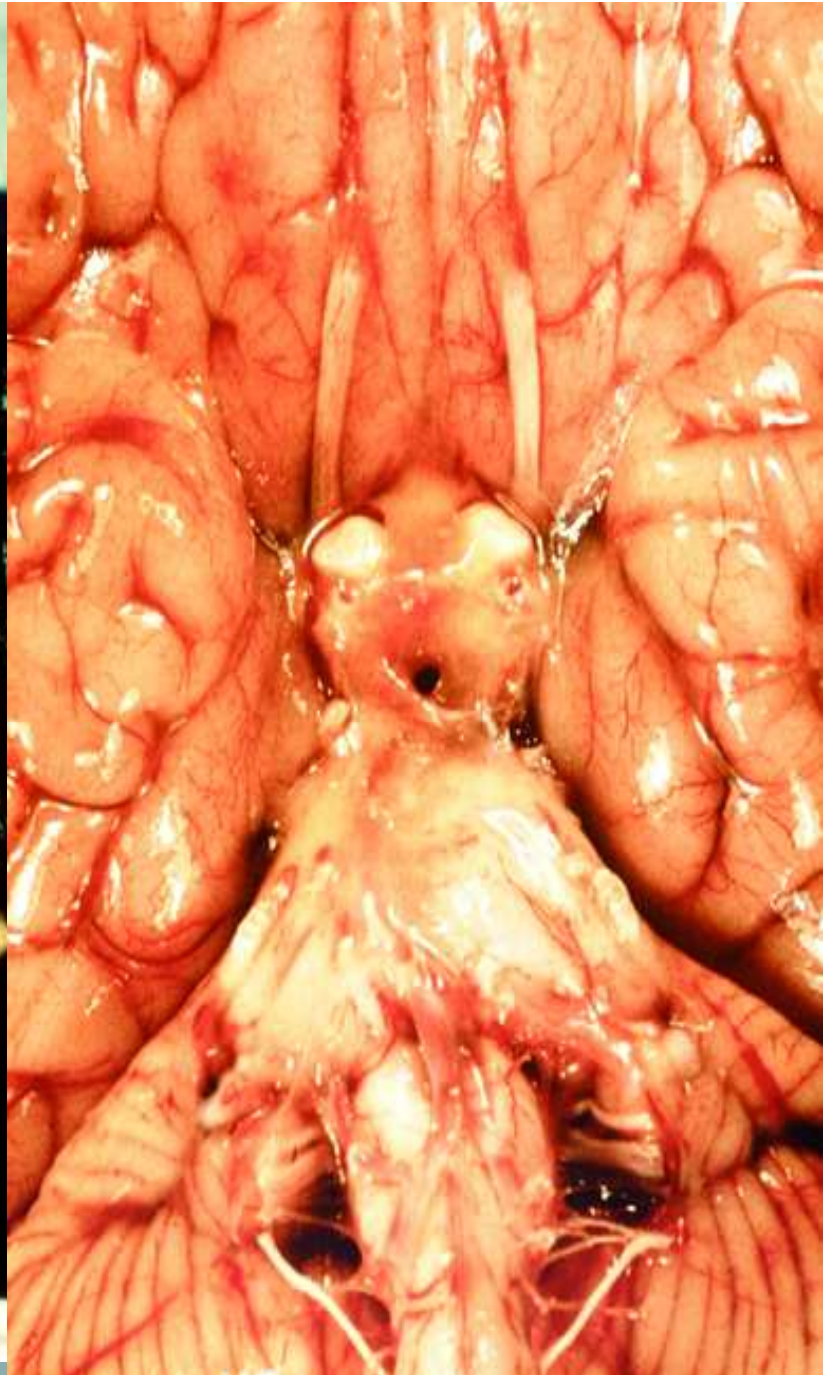




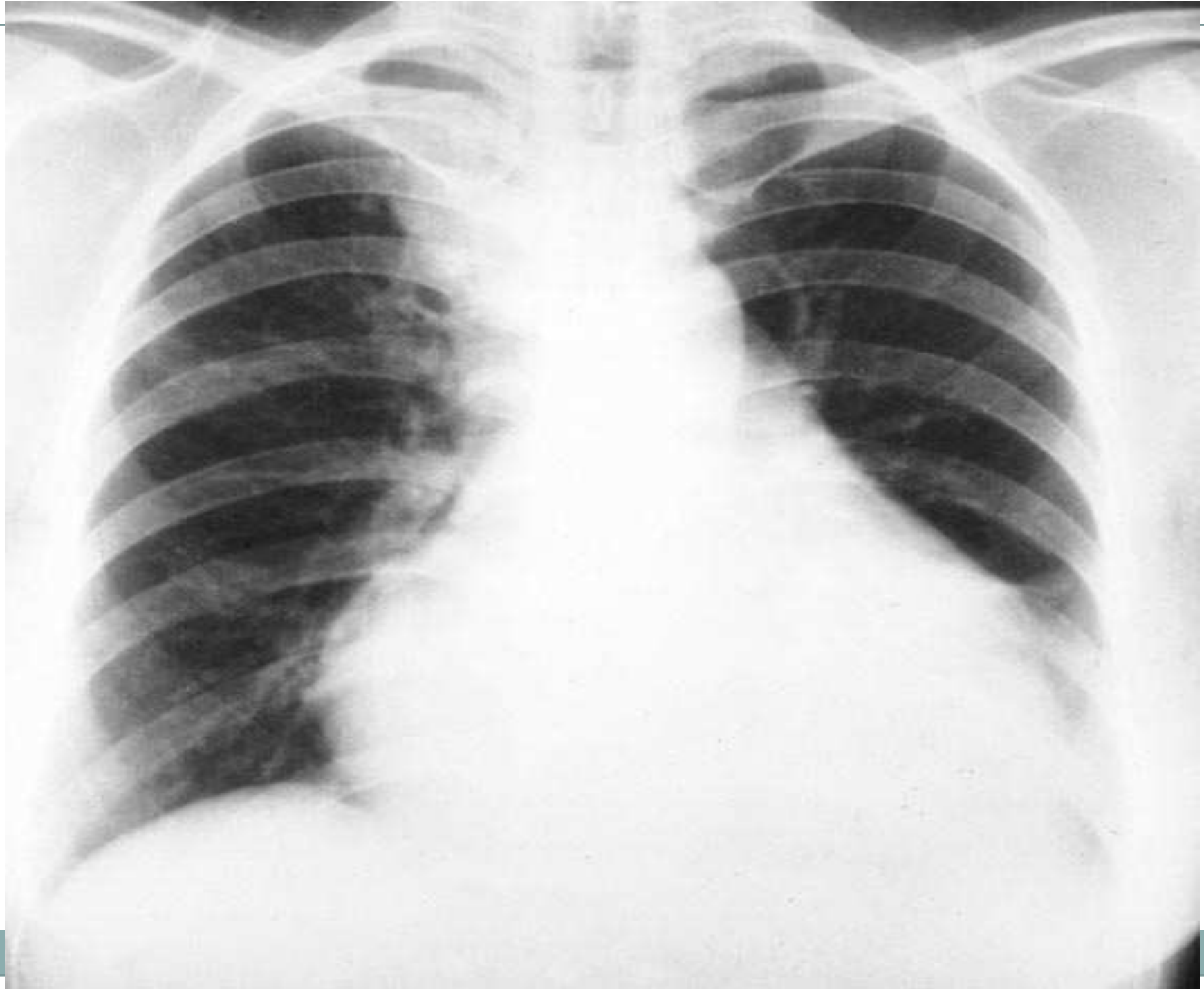
Tuberculosis-Multisystem Disease

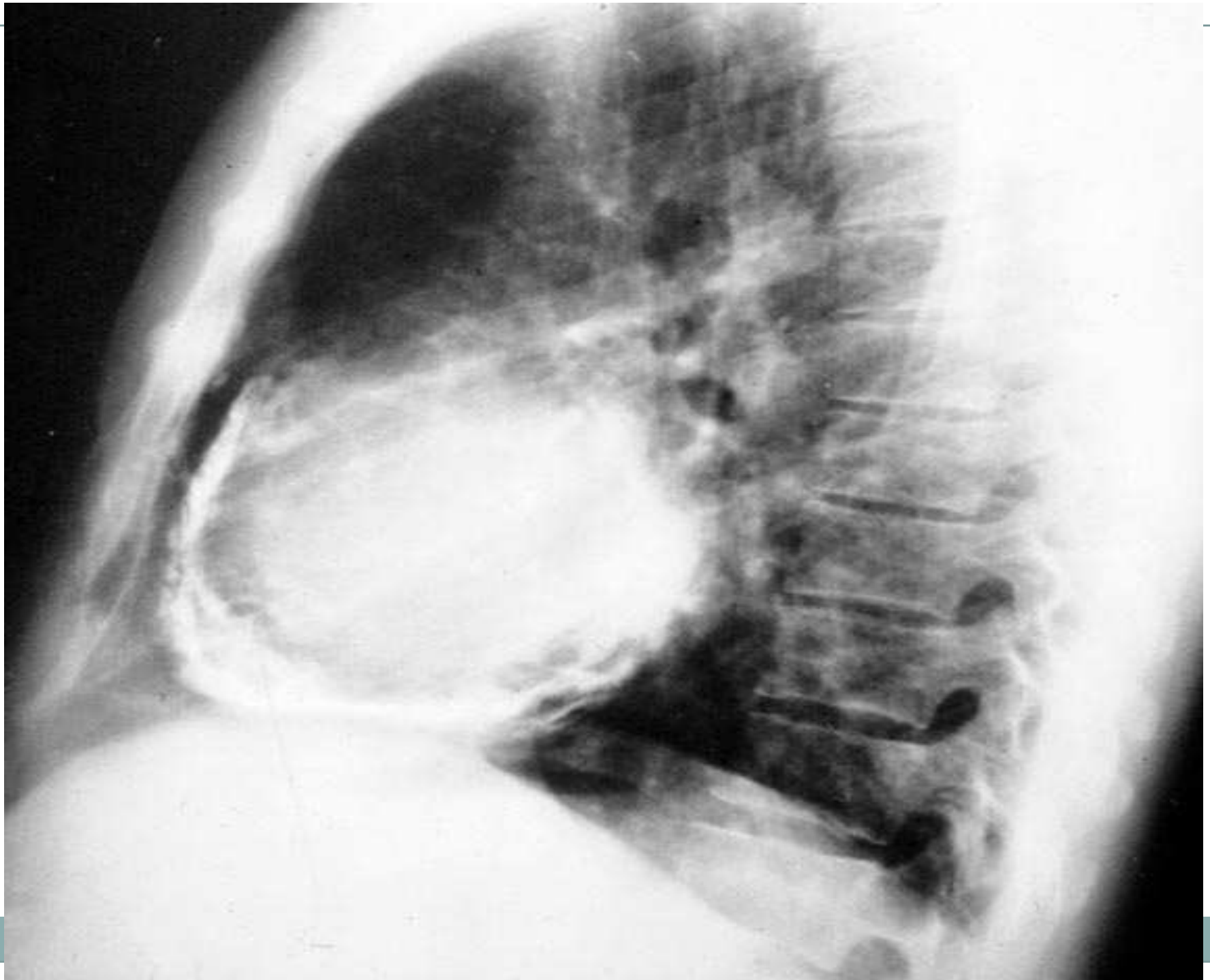


32 yr old
immigrant
with chronic
headaches











Diagnosis of Tuberculosis



- **Suspicion:**
 - If pulmonary disease is obvious on CXR or is suspected, order:
 - ✦ **Sputum for AFB smear and culture (X3)**
 - Early morning specimens are optimal
 - Can Induce sputum specimen IF necessary
 - **ISOLATION**
 - Otherwise, AFB smear and culture on relevant suspicious tissue or fluid

Diagnosis of Tuberculosis



- **Cultures:**
 - *M. tuberculosis* grows very slowly.....
 - ✦ Cultures are 'held' for 6 weeks before they are called Negative
 - IF culture is positive, then susceptibility testing is performed
 - ✦ In Missouri, sent to State TB laboratory in Mt. Vernon, Missouri

Treatment for active TB 2008



- Currently, four drug regimen is indicated:
 - Isoniazid +
 - Rifampin +
 - Pyrazinamide +
 - Ethambutol OR Streptomycin

***CONSIDERATION SHOULD BE GIVEN IN ALL
CASES FOR DIRECTLY OBSERVED
THERAPY (DOT)***

Summary



- TB is a global disease
- We must be vigilant in identifying cases of active TB and collaborating with our Health Departments for active quarantine and contact investigations when appropriate
- LTBI can be effectively treated
 - Requires identification of LTBI cases
 - Requires application of EBM based treatment for LTBI

Helpful websites



- LTBI treatment:
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm>
- Diagnosis and management of TB
<http://www.cdc.gov/MMWR/PDF/rr/rr5211.pdf>