Undiagnosed Tuberculosis in a General Hospital*

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Tuberculosis occasionally appears in an obscure form. Six patients are presented in whom the diagnosis was made either at autopsy or after an exploratory laparotomy. The disease had remained undiagnosed because of the paucity of clinical and roentgenologic findings referable to the lungs, an indeterminate tuberculin skin reaction and the misinterpretation of the so-called “inactive fibrotic scars.” To improve the diagnostic accuracy, repeated skin testing, cultures of liver and bone marrow biopsies and surgical specimens should be more widely used. A therapeutic trial with antituberculosis drugs is a useful diagnostic test in prolonged unexplained fevers.

With the introduction of effective and relatively safe drugs, tuberculosis became a medically curable disease and its infectiousness promptly controllable. As the need for prolonged isolation in specialized hospitals is not now required, the care of the tuberculous patient is becoming the concern of the general hospitals and general physicians. This trend has been the subject of committee reports from the NTRDA in recent years expressing the view that the general hospitals have the same responsibility to the tuberculous patients as to any sick person.1,2

The clinician will usually encounter the disease in an above middle-age patient who presents with symptoms, an abnormal chest x-ray film, a positive tuberculin skin reaction with or without isolation of M tuberculosis. Tuberculosis may, however, appear in an obscure form and becomes a diagnostic challenge; it also presents a serious threat, spreading the infection to the community and hospital population. Six such cases are presented to point out the difficulties in recognizing tuberculosis in some clinical settings and to emphasize the importance of pursuing the diagnostic work-up even if it requires a surgical procedure since the disease is curable and almost always fatal if not treated. In cases 1 to 4 the disease was recognized only at autopsy and in cases 5 and 6 the diagnosis was established during an exploratory laparotomy.

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Case Reports

Case 1

A 66-year-old alcoholic man presented with a history of weight loss and fever for three months. He was a heavy smoker and had symptoms of chronic bronchitis. Physical examination showed an enlarged tender liver. A chest roentgenogram revealed clear lung fields and possible widening of the upper mediastinum (Fig 1A). Results of laboratory tests were normal with the exception of liver function tests; plasma thromboplastin antecedent (PTA) 68 percent, alkaline phosphatase 15 King Armstrong units, bromsulphalaine (BSF) 25 percent at 45 minutes. Bronchoscopy showed extrinsic compression of the left main stem bronchus but bronchial washings and biopsy specimens were negative for malignancy. On liver scan an area of decreased uptake suggested liver metastasis or hepatoma. Liver biopsy showed changes consistent with alcoholic hepatitis. Peritoneoscopy revealed a large nodule in the liver but attempts to take a biopsy specimen from it were unsuccessful. Upper gastrointestinal series, barium enema, and intravenous pyelogram gave normal results. The possibility of tuberculosis was not seriously considered because the PPD was negative on admission but was not repeated later. The patient was discharged with the diagnosis of occult malignancy with liver metastases. He was readmitted two weeks later, extremely dyspneic and moribund. A portable chest film showed bilateral upper lobe infiltrates (Fig 1B). The patient died the following day. Autopsy disclosed miliary tuberculosis of the lungs, spleen, liver, adrenal and lymph nodes. Acid-fast bacilli were recognized on microscopy and M tuberculosis grown from the lungs, spleen and bone marrow. In a few microscopic sections of the spleen and lymph nodes, Reed-Sternberg cells were found, suggesting also the presence of Hodgkin's granuloma.

Case 2

A 58-year-old woman with a history of renal failure secondary to biopsy-proved chronic interstitial granulomatous nephritis was admitted because of fever, vomiting and weak-
ness. She had been on prednisone for one year. On physical examination the lungs were clear and the pulse irregular. Hemoglobin was 9.4 gm percent, white blood cell count was 14,500 with 81 percent polymorphonuclear leukocytes, 3 percent lymphocytes, and 10 percent monocytes. Serum creatine 8.6 mg percent and blood urea nitrogen (BUN) 284 mg percent. Intermediate strength PPD (5 TU) was negative. ECG showed atrial fibrillation and left ventricular hypertrophy with strain. A chest x-ray picture showed cardiomegaly and clear lung fields. The patient died suddenly on the fifth hospital day. The clinical diagnosis was interstitial nephritis, digitalis toxicity, and pulmonary embolism. Autopsy revealed caseating granulomas in the lungs, spleen, and liver; *Mycobacterium tuberculosis* was grown from the liver. The kidneys showed extensive interstitial fibrosis suggestive of a burned-out inflammatory process. The granulomatous lesions in the kidneys previously described were found only in the premortem kidney biopsy specimen.

**Case 3**

A 58-year-old white man with severe chronic obstructive airway disease developed acute respiratory failure precipitated by a spontaneous left pneumothorax. The lung expanded rapidly following placement of a chest tube under suction. He remained in respiratory failure and required a tracheostomy and assisted ventilation. Sputum cultures during his hospitalization showed *Staphylococcus aureus*, *E. coli* and Pseudomonas, for which the appropriate antibiotics were given. Six sputum smears and three cultures for AFB were negative.

Bilateral pulmonary infiltrates which appeared on the 134th hospital day were attributed to a Gram-negative pneumonia (Fig 2A). Shortly before his death, blood cultures yielded *Staphylococcus aureus* and *E. coli*. The autopsy results showed changes of severe bilateral chronic bronchitis, bronchiectasis, fibrosis and emphysema and a Gram-negative pneumonia. There was also active cavitory tuberculosis in the left upper lobe from which tubercle bacilli were grown, although AFB were not recognized on microscopy. A review of his admission chest x-ray film (Fig 2B) revealed a calcified lesion in the left hilum which had been reported as an "old inactive calcified tuberculous lesion."

**Case 4**

The patient, an 84-year-old white man, known to have arteriosclerotic heart disease, was admitted because of weakness, anorexia, and fever. Examination disclosed an enlarged liver and edema of the lower extremities. The heart and lungs were unremarkable. Roentgenograms showed slight cardiomegaly and fibrotic streaking in the right apex, attributed to an old "inactive" tuberculous lesion (Fig 3). Hemoglobin was 9.5 gm percent and the WBC count was 8,450 per mm³ with 61 percent polymorphonuclear cells, 28 percent lymphocytes, 8 percent monocytes, and 5 percent eosinophils; red cells were hypochromic; SGOT 38, alkaline phosphatase 29, LDH 1400.

On the eighth hospital day his temperature was 39.4° C; a chest film revealed a right lower lobe infiltrate. Sputum cultures grew out beta hemolytic streptococci, Pneumococcus, and a yeast-like organism. He was treated with ampicillin, then cephalothin (Keflin). He remained febrile and pursued a downhill course and died on the 21st hospital day. The clinical diagnosis was pneumonia complicating congestive heart failure. Autopsy revealed miliary tuberculosis of the lungs, liver, spleen, lymph nodes, bone marrow, and intestines; and reticulum cell sarcoma of the liver and spleen. Acid-fast bacilli were recognized on microscopic examination of the lung and the liver, but the results of cultures were negative.

**Case 5**

A 43-year-old alcoholic man presented with dyspnea, fever, nonproductive cough, weight loss, and left-sided chest pain of two months' duration. A chest film showed a left
pleural effusion, but no parenchymal lesions. Thoracentesis yielded a sterile, yellow exudate with 98 percent lymphocytes. The PPD test (5 TU) was negative. Liver function tests showed an elevated gamma globulin (1.9 gm percent), alkaline phosphatase 4.7 BU, SGOT 43, PTA 77 percent, BSP at 45 minutes 16 percent. The presumptive diagnosis of tuberculosis was made and the patient began a therapeutic trial of INH 300 mg daily and streptomycin 1 gm daily. His fever persisted, the pleural effusion reaccumulated, and the liver became enlarged and tender. Liver biopsy showed changes consistent with Laennec's cirrhosis. Right-sided pleural effusion developed while the patient was on antituberculosis medications. Thoracentesis yielded a sterile exudate; smears were negative for acid-fast bacilli and other organisms. Because the patient's fever persisted and the right pleural effusion reaccumulated following numerous thoracenteses, the antituberculosis drugs were discontinued. An extensive search for collagen diseases, systemic mycoses, and malignancy gave negative results. The liver function tests deteriorated: (SGOT 202; alkaline phosphatase 7.1 BU; PTA 53 percent; BSP at 45 minutes 32 percent and the patient developed tenderness and a mass in the right upper quadrant of the abdomen and generalized abdominal guarding. The diagnoses of hepatic abscess or hepatoma were entertained.

At exploratory laparotomy the peritoneal surface was studded with small tubercles 2 mm in size which on frozen section were granulomatous in nature. The liver was greatly enlarged and a biopsy showed acid-fast bacilli but the culture was negative; there was no caseation and no granuloma formation, but occasional Langhan's type giant cells and chronic inflammatory changes were seen. He was started immediately on streptomycin and INH. A remarkable subjective improvement was noted. The fever persisted at a lower range of 37.4° to 38° C for two weeks followed by defervescence. Before discharge, the liver function tests reverted to normal and a repeat PPD (5 TU) was strongly positive. All cultures of blood, sputum, gastric washings, urine, pleural fluid and bone marrow did not grow acid-fast organisms.

**Case 6**

A 48-year-old nurse entered the hospital complaining of fever, weight loss and abdominal pain for six weeks. An extensive work-up prior to admission was nonrevealing. She had a 20-year history of rheumatoid arthritis for which she was treated with aspirin, but she was not given steroids. Many years previously she had had cervical lymph node enlargement and a biopsy performed at that time showed nonspecific chronic inflammation. She was also known to react strongly against the first strength PPD.

The physical examination gave negative results except for small firm lymph nodes palpable in the neck. Hemoglobin was 9.8 mg percent, WBC count was 3,600 per mm³ with 82 percent neutrophils and 16 percent lymphocytes. Result of an extensive work-up for her fever was negative. Smears and cultures of sputum, urine, bone marrow were negative for acid-fast bacilli. All liver function tests were normal on admission. By the 14th hospital day the BSP was 40 percent at 45 minutes, SGOT 740, alkaline phosphatase 40, King Armstrong units. Liver scan was normal. Needle biopsy of the liver was consistent with mild hepatitis; chest x-ray films were normal. The diagnosis of Hodgkin's disease was considered because abdominal lymph nodes showed filling defects on lymphangiography.

At exploratory laparotomy the spleen and para-aortic lymph nodes were biopsied and microscopic examination showed...
chronic granulomatous inflammation and acid-fast bacilli. A culture of splenic tissue grew *Mycobacterium tuberculosis*. Triple therapy was begun with INH, PAS, and streptomycin. The liver and liver function tests returned to high-normal range at the time of discharge on the 53rd hospital day.

Discussion

The difficulty in reaching a diagnosis of tuberculosis in some cases is due to the fact that the chest x-ray picture may be nonrevealing, symptoms that refer to the lungs may be minimal or absent, the tuberculin skin test is either negative or not determined, and the patient has no history of exposure to tuberculosis. Numerous cases wherein the diagnosis was made only at autopsy have been described in the literature.*6 In a series of 40 adults with miliary tuberculosis, the disease was termed “cryptic” in 40 percent because its usual clinical and radiologic manifestations were absent and only 18 percent had symptoms referable to the lungs.*6 Tuberculosis has also been emphasized as the most common infectious cause of prolonged unexplained fever.*3

The six patients in this series were above middle age and presented with fever, weight loss and weakness. Only one (case 5) had cough and chest pain, and in four patients the chest x-ray film on admission was clear. Case 5 had a left pleural effusion, but the lung fields were clear on a postthoracentesis chest film. The chest roentgenogram in case 4 showed fibrotic streaks in the right apex which were attributed to an inactive tuberculous process, and so tuberculosis was considered an unlikely possibility.

To add to the confusion, the tuberculin reaction is often suppressed due to various reasons. For years it was thought that 99 percent of patients with active tuberculosis would react positively to tuberculin, and that false negatives were rare.*7 However, it is now evident that temporary or permanent anergy may be caused by a number of conditions including sarcoidosis, lymphomas, chronic leukemia, amyloidosis, carcinomatosis, acute exanthematous diseases, overwhelming cavitary or miliary tuberculosis, and administration of corticosteroids. Skin reactivity to tuberculin may also decrease with age, usually in patients over 50 years old.*8

Skin anergy was also reported in 38 percent of cases of disseminated tuberculosis in adults in contrast to only 10 percent of childhood cases.*9 This high rate of tuberculin anergy is not clearly understood since adult miliary tuberculosis is usually a manifestation of late tuberculosis and sufficient time has elapsed for the establishment of positive reactivity. Stead*10 pointed out that 30 percent of patients with subsequently proved active tuberculosis fail to react to an intermediate strength of PPD on admission to the hospital. Some of them do not react even to the second strength PPD. As the general health improves and infection comes under control 98 percent of the patients have a positive tuberculin reaction. In a clinical situation suggestive of tuberculosis, a false negative tuberculin reaction may cause the physician to exclude tuberculosis from the differential diagnosis erroneously. It is therefore recommended to repeat the tuberculin skin test on three different occasions, at intervals, before accepting a result as negative.

In our patients, three were not tested for tuberculin sensitivity, one had history of a positive reaction, and two were negative to 5 TU; one of the two, however, reacted to 5 TU ten weeks later after the diagnosis was made at laparotomy.

The presence of concomitant diseases, to which the entire clinical picture may be attributed, may also complicate diagnoses of the tuberculous patient. Case 2, 3, and 4 developed manifestations of tuberculosis while under treatment for interstitial nephritis, Gram-negative septicemia, and congestive heart failure respectively. In a study comparing the deaths from tuberculosis in a general hospital in two consecutive five year periods, the incidence of tuberculosis was reduced in the second period, yet 75 percent of the cases were undiagnosed before autopsy. The large number of missed diagnoses was partly explained by the high incidence of other fatal conditions.*4

A chest x-ray film cannot be presumed to suggest with accuracy the type of tuberculous infection one...
is dealing with. Radiologists reporting on chest x-ray pictures showing a fibrotic apical scar frequently add a reassuring statement that it is "due to an old tuberculous process with no evidence of active disease." Such old inactive lesions can flare up into a tuberculous bronchopneumonia during conditions of diminished resistance or during administration of corticosteroids. If APB are not found on routine sputum examinations and some other pathogens are recovered, tuberculosis is erroneously ruled out. The situation where an individual shows a "fibrous scar" on a chest x-ray film with either a positive or undetermined tuberculin reaction represents a common pattern of tuberculosis that is too often so demonstrated only in retrospect. The contention is that the minimal inactive lesion is often either active now or will be active soon.

When all attempts at laboratory diagnosis are unrewarding and there is reason to suspect disseminated tuberculosis, culture of a needle biopsy specimen from the spleen, liver or bone marrow may be diagnostic. In the present series, Mycobacterium tuberculosis was isolated from the liver in three cases, from the spleen in two other cases and from the bone marrow in one. In 163 cases of miliary tuberculosis from the literature, the liver biopsy was a valuable diagnostic procedure in 75 percent of the cases.

Finally, in patients with prolonged obscure fevers, one is justified to institute trial therapy with isoniazid, alone or combined with PAS or ethambutol. These agents act presumably on Mycobacteria only and therefore a remission of the fever and improvement in the patient's condition within two to four weeks after therapy is considered a useful diagnostic test.

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REFERENCES
5 Bottiger LE, Nordenstam HI, Wester PO: Disseminated tuberculosis as a cause of fever of obscure origin. Lancet 1:19, 1962

Comments on Hegel

Hegel (1770-1831) was a Platonist (or rather a Neo-Platonist) of sorts and, like Plato, a Heracledian of sorts. He was a Platonist whose world of "Ideas" was changing, evolving. Plato's "Forms" or "Ideas" were objective and had nothing to do with conscious ideas in a subjective mind; they inhabited a divine, an unchanging, heavenly world (superhuman in Aristotle's sense). By contrast Hegel's "Ideas", like those of Plutinus, were conscious phenomena: thoughts thinking themselves and inhabiting some kind of consciousness, some kind of mind or "Spirit"; and together with this "Spirit" they were changing and evolving. According to Hegel, though the "Objective Spirit" (comprising artistic creation) and "Absolute Spirit" (comprising philosophy) both consist of human productions, man is not creative. It is the hypostatized "Objective Spirit", it is the divine self-consciousness of the Universe, that moves men: "individuals . . . . . . . are instruments", instruments of the Spirit of Epoch, and their work, their "substantial business", is "prepared and appointed independently of them".