The Prognostic Significance of Idiopathic Pleural Effusion*

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The practicing physician, despite mass chest x-ray surveys and similar programs, must still remain the most important single factor in tuberculosis case finding. Early case finding and treatment are the major tenets of effective tuberculosis control, as they are in any communicable disease, and have been practiced most diligently in many areas. The presence of parenchymal pulmonary lesions by x-ray, symptomatology and bacteriologic study of the sputum or gastric expressions are frequently in themselves diagnostic of tuberculosis or prompt continued study and observation of the patient to evaluate the presumptive diagnosis. Unfortunately, however, the role of the so-called "idiopathic" pleural effusion as one of the important early manifestations of tuberculous infection is less readily recognized by many physicians and the opportunity for control of the tuberculous process in its minimal phase is not infrequently lost. The lack of positive diagnostic etiologic findings, either laboratory or x-ray, has undoubtedly in most instances contributed to this difficulty. It is the purpose of this paper to emphasize the basic importance of this entity as a clinical manifestation of active tuberculous infection and the necessity for early treatment to avoid its known and varied complications.

Pleural effusions occur as complications in many diseases, chiefly the bacterial or viral pneumonitides, rheumatic fever, invasion of the pleura by neoplastic tissue or lymphoma, congestive heart failure, renal disease and tuberculosis. The differential diagnosis of the underlying disease in these instances and the characteristics of complicating pleural effusion have been described extensively in standard textbooks and the literature, and need not be elaborated here. The age of the patient, symptoms, bacteriologic studies, response to drug or antibiotic therapy will frequently substantiate or narrow the clinical impressions within a short time. It is the

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group whose clinical course and findings suggest a tuberculous etiology, but in whom it cannot be proven, that are usually relegated to the "idiopathic" category. It is this group that requires the most careful consideration by the physician and has the highest incidence of subsequent tuberculous manifestations.

The incidence of patients with idiopathic pleural effusion reaches its peak at about age 20, and the majority are age 30 or under (Fig. 1). The distribution indicates that it is usually found in late adolescence and early adulthood, and comparison with the curve for the age distribution of pulmonary tuberculosis indicates a very significant dissimilarity. A recent study of 1365 cases by Eberle¹ notes a peak incidence at the age of 16 in males and a wider distribution at age 17 to 22 in females. Males predominate in the adolescent and adult groups, but not in children. Its major incidence in this important economic and social age group further stresses the need for its clinical recognition as a tuberculous process.

Adequate studies of the racial incidence of primary pleural effusion are not available, although it is generally accepted that Negroes have a higher incidence of tuberculous disease and a less favorable course and prognosis than the white race. Kraft² found a 14 per cent incidence among Negroes in a series of 100 cases of primary pleural effusion in Army personnel, and Karron and Purves³ an incidence of 22 per cent among non-whites (chiefly Negroes) in a similar series of 215 cases at an Army Tuberculosis Center. Jones and Dooley⁴ in a study primarily of Negro patients consider tuberculous pleurisy with effusion a more frequent manifestation of widespread extrapulmonary disease than among white patients, with a much higher (16 per cent) mortality. More fre-

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21200/)
quent and widespread pulmonary disease, as well as extrapulmonary dissemination, secondary to primary pleural effusion in the Negro is reported, with earlier appearance, poorer prognosis and higher mortality of these complications following the inadequately treated initial manifestations.

The frequency of pleural effusion as a manifestation of tuberculosis in the age group cited has been considered by many investigators to be a reaction subsequent to the development of tuberculin sensitivity during a primary tuberculous infection. The increase of these effusions in England during the war years, as well as in our own military forces, has been attributed to the entry of young male adults who have escaped their first tuberculous infection in childhood into industrial or military life where they may be exposed to sudden massive doses of tubercle bacilli. Similar transitions resulting from population movements from protected tuberculin negative environments to those less well controlled, such as leaving for schooling or employment in larger cities and towns, may also contribute to a continued incidence. The mechanism is apparently different from that in childhood tuberculosis, where pleural effusion as a manifestation of primary infection is infrequent.

Edwards' observed a group of nurses on whom monthly tuberculin skin tests were applied and found that there was an average interval of six months between the development of skin allergy to tuberculin and the onset of pleurisy with effusion. Arborelius' found that one-third of a group of Swedish army conscripts with initially negative Mantoux reactions developed pleurisy with effusion within a six-month period of the Mantoux reaction becoming positive. Similarly, Israel and Long' reported that primary tuberculous infection in adults, as evidenced by a change in tuberculin sensitivity from negative to positive, may be followed after a short interval by an attack of pleurisy, without other manifest intrathoracic tuberculosis. Malmros and Hedvall' in a careful investigation of nearly 3000 students and student nurses found that parenchymal tuberculosis appeared at an average of 10 months after the first positive Mantoux, with frequent interpolation of a pleural effusion. These findings have been confirmed by many other investigators and indicate that pleurisy with effusion in the majority of instances is a manifestation of a post-primary tuberculous infection.

The pathogenesis and mechanism for the production of idiopathic or post-primary effusion is perhaps best explained on the basis of the work of both Patterson' and Rich,' who found that the injection of viable tubercle bacilli into the pleural space or other serous cavities of a normal test animal produced little or
no local reaction and no fluid. The similar introduction of tubercle bacilli into an animal previously infected with tubercle bacilli and consequently in a hyperallergic or hypersensitive state would result in considerable pleural reaction with the exudation of serum, leukocytes, red cells and fibrin to produce a characteristic effusion. A similar reaction might also occur from the introduction of dead tubercle bacilli or the protein portions of destroyed bacilli, as might result from the evacuation of a caseous focus, but only in a previously sensitized animal.

The production of tuberculous pleural effusion in man is believed to follow a somewhat similar train of events. The generally accepted mechanism is that of an extension to the pleura of tubercle bacilli from a primary subpleural focus in an individual who has become sensitized as a result of the primary infection. Erwin\textsuperscript{11} has also postulated that a caseous primary tracheobronchial node may penetrate into the sensitized pleura with production of an inflammatory exudate. This may be a more likely mechanism in children in whom tuberculous hilar adenopathy is frequent, but is probably an infrequent occurrence in the older age groups. Pinner\textsuperscript{12} states that even if no parenchymal lesions are demonstrable, the presence of a pleural or subpleural tuberculous focus as the source of pleural infection should be postulated. Hematogenous dissemination is probably a rare source for the production of tuberculous effusion, particularly when unilateral, but may be implicated in the infrequent, simultaneous bilateral pleural effusion. Pleural effusion may be the first evidence of hematogenous or parenchymal miliary tuberculosis, may occur subsequent to the extension of re-infection parenchymal tuberculosis or at any stage of pulmonary tuberculosis, but such effusions differ materially in mechanism, course and prognosis from those of the post-primary infection or "idiopathic" variety.

The signs and symptoms of post-primary pleural effusion are variable in their onset, severity, findings and duration. Physical signs vary with the amount of fluid in the pleural space or fibrin deposition on the pleural surfaces. Rigler\textsuperscript{13} has noted that as much as 400 cc. of fluid may be present in the pleural space and not demonstrable by the usual posterior-anterior chest film, but lateral decubitus films may be quite helpful in revealing small amounts of fluid.

Laboratory studies in pleural effusion have been extensive, but with the exception of positive bacteriologic results do not contribute reliable criteria for diagnosis. Pinner and Moerke\textsuperscript{14} after an extensive study concluded that neither chemical nor cytological nor serologic data per se offered dependable diagnostic or prognostic criteria. The various clinical tests and studies will not be
detailed here, except for some comment upon their clinical significance.

The tuberculin skin test is almost invariably positive in primary pleural effusion, usually to a fresh preparation of first strength PPD or 1:1000 Old Tuberculin. A small number of cases may require second strength doses to produce a significant reaction in the absence of an adequate response to the lower dilutions. The absence of a positive skin test should cast considerable doubt upon the tuberculous etiology of the effusion. The possibility of an effusion following so rapidly after the primary infection that tuberculin allergy has not developed and the skin test is negative cannot be excluded, but is unlikely. Should the skin test remain negative for a period of six to eight weeks following the appearance of the effusion, the possible tuberculous etiology of the effusion can nearly always be discarded. The tuberculin skin test, particularly if the previous reaction of the patient is known to have been recently negative, may contribute considerably toward the etiologic evaluation of the effusion in the absence of definitive bacteriologic studies.

The erythrocyte sedimentation rate is usually increased and falls to normal values with the subsidence of the clinical signs and the effusion. Not uncommonly the sedimentation rate remains moderately elevated for a considerable period after the effusion has subsided due to the residual fibrinous process or the activity of some other tuberculous focus which is not evident. It is most important that the early return of the sedimentation rate to normal values should not be considered an evidence of complete subsidence of the tuberculous process and an indication to allow the patient to resume activity. It is a not uncommon experience in the treatment of active pulmonary tuberculosis to find that the sedimentation rate falls to a normal range while the patient is on bed rest, even though the lesions remain unchanged and other evidences of an active process are apparent. The active tuberculous process which precipitated the effusion must be overcome by the normal defense mechanisms of the body and this requires a much longer period of convalescence than may be reflected by the fall in sedimentation rate. The sedimentation rate may serve as a guide to the duration of the acute phase or of continuing activity, but clinical reliance upon it directed toward adequate treatment of the patient must be limited.

Every effort should be made to obtain pleural fluid, particularly for bacteriologic study. Culture and guinea pig inoculation of the fluid for the demonstration of tubercle bacilli should be done in every instance. Direct smears of the fluid are of little value, since tubercle bacilli are rarely numerous in such effusions. Positive
bacteriologic results by both culture and animal inoculation are reported in only 20 to 35 per cent in various series, but guinea pig inoculation has given positive results more frequently than culture. Success in obtaining positive bacteriologic results from pleural fluid will depend on the frequency with which fluid is aspirated and bacteriologically studied. The highest percentage of positive results has been obtained by those investigators who secure at least 500 cc. of fluid for concentration prior to culture and are able to secure consecutive specimens for such study.

Although only about 35 per cent positive bacteriologic results on pleural fluid are reported by the most careful investigators, a negative report should not be considered as evidence that the fluid is not the result of a tuberculous process. Reports of filterable or atypical tubercle bacilli which do not grow with the usual laboratory techniques, the possibility in some cases that the pleural process is based on an antigen-antibody reaction without viable bacilli or the paucity of bacilli in the fluid at the time the specimen is taken may offer some explanation for the failure to demonstrate the organism bacteriologically in all cases. Kraft's data indicates that 14 of 21 cases who developed pulmonary tuberculosis within one year from the onset of primary pleural effusion had bacteriologically negative pleural fluids, even though very adequate studies were made. The results in other well studied series reinforce the value of positive bacteriologic findings, but decry the fallacy of accepting negative findings as critical evidence of non-tuberculous etiology.

The pleural fluid sugar content has recently been suggested as a diagnostic aid in the determination of the tuberculous etiology of pleural effusion by Gelenger and Wiggers. Values below 30 mgs. per 100 cc. were considered diagnostic of a tuberculous etiology, based on cases with fluid later proved to be tuberculous. Values between 30 and 60 mgs. per 100 cc. were considered presumptive evidence and those above 60 mgs. per 100 cc. as non-tuberculous in origin. These findings are interesting, but the small size of their series makes further evaluation necessary.

The treatment of patients with pleural effusion may be divided into two categories, that of the acute period with the problem of the effusion and that following the acute period directed toward control of the underlying process. Any course of treatment must have as its basis the recognition of these effusions as a manifestation of frank, active and early tuberculosis. Kraft stresses that the responsibility upon the physician to regard these effusions as "probably tuberculous" and to initiate recognized treatment is tremendous. Landau neatly summarizes her viewpoint by stating, "It is more logical to speak of investigations in
the prognosis of a recent primary infection, indicated by the appearance of an idiopathic pleural effusion than place pleural effusion and its prognosis into a special category."

The acute phase of the illness with its fever, chest pain and development of fluid is best treated symptomatically. The pain usually subsides rapidly as fluid forms. The problem of the removal of accumulated fluid in the pleural space has been the basis for several approaches depending chiefly upon the frequency of aspiration and quantity withdrawn. The removal of only a small amount of fluid for diagnostic purposes in the early phase of the process, delaying the removal of the larger portion until the acute phase has subsided or the fluid has spontaneously absorbed, unless pressure symptoms supervene to make aspiration mandatory, has been the usually suggested method. However, the fibrin content in the pleural fluid is known to be usually high and even a slight delay in the adequate removal of a considerable effusion may result in extensive deposition of fibrin, with formation of fibrinothorax and often severe and permanent compression of the lung. Feldman and Lewis adopted an eight-week period of observation in their series, during which the effusion was given an opportunity to absorb, with aspiration following if fluid persisted. They noted that even with this relatively short delay in the evacuation of fluid, chronic thickening of the pleural membranes and spontaneous coagulation of the whole exudate had taken place in many instances with marked impairment of pulmonary function.

Anticoagulants such as sodium citrate and heparin have been injected into the pleural space to prevent coagulation of the fluid and deposition of fibrin, but without notable effect. Recent studies suggest that a fibrinolytic agent, such as streptokinase, may prove to be of benefit in preventing fibrin deposition in the pleural space or removing deposits recently formed. The injection of air into the pleural space to prevent adherence of the pleural layers has also been recommended, but it is extremely doubtful that this measure has ever preserved the integrity of the pleural space. A small pneumothorax of 200 cc. of air may be very helpful in visualizing the underlying lung for evidence of parenchymal involvement, but according to Amberson should otherwise be avoided, as it interferes with healing and prolongs the exudation of fluid.

The approach to the control of the effusion itself at this hospital has been primarily to secure fluid for diagnostic purposes, even when the effusion is very small. With larger effusions every effort is made to keep the pleural space as dry as possible, although strenuous efforts are not made to secure fluid accumula-
tions remaining below the level of the dome of the diaphragm. It is felt that 500 to 1000 cc. of fluid can usually be safely removed at one sitting and aspirations repeated at daily intervals if necessary, until the desired result is obtained. Removal of fluid allows the underlying lung to be adequately visualized roentgenographically, retards the deposition of fibrin upon the pleura and adds considerably to the comfort of the patient. "Pocketing" of fluid may occur, sometimes very early in the process, but careful fluoroscopic observation or the use of roentgenograms taken in lateral and oblique views frequently localizes the area sufficiently to allow adequate aspiration.

We have been considerably impressed with the residual damage to lung ventilatory function that may occur secondarily to the deposition of fibrin from pleural effusion, usually from failure to aspirate the pleural space frequently and adequately when fibrin formation is rapid. Although considerable resolution of such deposits may take place over a period of years, the finding of obliteration of the costophrenic angle, impaired motion of the diaphragm, mediastinal fixation or a "bound" lung with narrowing of the rib interspaces and pulmonary crippling after pleural effusion are not infrequent residuals. Such impairment may be of considerable importance to the patient's future welfare and physical ability, as well as the possible control of tuberculosis or other pulmonary disease that may subsequently develop in either lung. Two cases illustrating this problem are cited below.

J. O., a 25 year old white male student, was admitted on March 9, 1949. He had been a patient at a private hospital from November 1947 to early January 1948 for treatment of left pleurisy with effusion initially diagnosed as pneumonia (Fig. 2). One thousand cc. of fluid was removed on each of two aspirations, but bacteriologic studies were not done. Tuberculin skin test was reported positive at that time. At discharge he was told that his chest "was not entirely clear," but was advised to rest at home for three months and then return to school, which he did. The patient admits that though he remained indoors most of the time, he was in bed very little. He did not again consult his physician until after a chest survey film taken in November 1948 was reported suspicious of parenchymal disease, but had remained entirely asymptomatic during the intervening period.

Admission chest film revealed extensive pleural reaction on the left, with a cavity in the right mid-lung field (Fig. 2). Sputum concentrates and cultures were positive for acid-fast bacilli. Bronchoscopy on April 12, 1949 revealed a normal tracheo-bronchial tree. It was realized that any need for collapse therapy on the right would depend on function of the left lung. Bronchospirometric studies revealed pulmonary function on the left to be approximately one-third that on the right, with vital capacity determinations of 500 cc. and 2000 cc. respectively. Excellent patient cooperation was secured on a strict bed rest program with fortunate gradual clearing of the cavity and conversion of sputum and gastric
cultures to negative. Planigrams taken in December 1949 failed to reveal any evidence of residual cavitation in the right lung.

Comment: This patient had about six weeks of hospitalization and was discharged to his home with an active pleural process. The patient was not told of the implications of his illness, nor was any planned period of observation indicated. Subsequent organization of the fibrinophorax re-

**FIGURE 2a**

*Figure 2a, Case J.O.:* Film taken November 21, 1947 at onset of pleural effusion, which later involved entire left pleural space.—**FIGURE 2b:** Film taken March 10, 1949 demonstrating marked residual pleural reaction on left 16 months later, with tuberculous cavity in hilar area of the right lung.

**FIGURE 3a**

*Figure 3a, Case N.H.:* Admission film taken June 12, 1948 showing extensive left pleural effusion with heart displaced to the right, and normal right lung. **Figure 3b:** Film taken March 29, 1949 reveals parenchymal disease in left lower lobe and large tuberculous cavity in left midlung field. The pleural reaction on the left has entirely subsided.
sulted in marked impairment of pulmonary ventilatory function, which might have seriously impeded treatment of the lesion in the contralateral lung had it not responded to bed rest alone. Active pulmonary tuberculosis was demonstrable within one year from the onset of the pleurisy with effusion. The problem of the severely impaired left lung function remains and decortication of the pleura may be considered in the future to improve ventilatory function.

D. H., a 19 year old white male soldier, was admitted on July 14, 1949. On June 28, 1949 while home on furlough he had noted right chest aching, fever, malaise and several drenching night sweats. Treatment with sulfadiazine and penicillin at home did not ameliorate his symptoms and he was transferred to this hospital. In May 1949 he had had an illness lasting several days, with fever, nausea and vomiting and vague chest tightness and aching but this subsided rapidly and no studies were made. Upon admission he was acutely ill, and chest films revealed fluid or pleural reaction at both lung bases, most marked on the left (Fig. 5). Fluid was obtained on several aspirations from the left pleural space, but aspiration attempts were repeatedly unsuccessful on the right. The aspirated fluid was positive for tubercle bacilli on culture. Bone marrow aspiration revealed no tubercles or granulomata suggesting hematogenous tuberculous dissemination. Tuberculin skin test was positive. Fever gradually subsided to normal over a period of four months, but sedimentation rate remained moderately elevated. Repeated sputa and gastric aspirations were bacteriologically negative.

Chest films revealed no evidence of parenchymal disease, but extensive pleural thickening was present bilaterally, most marked on the right. Bronchiospirometric studies revealed pulmonary function on the right to be approximately 50 per cent of that on the left.

Comment: It is likely that the process on the right antedated that on the left, rather than this being a simultaneous bilateral effusion. Considerable impairment of pulmonary function already exists and pleural decortication may be indicated in the future to improve function.

The use of antibiotics such as penicillin and aureomycin during the acute phase of a primary pleural effusion appears to have little or no effect, as might be expected from the etiology of such effusions. Such agents are not infrequently used during the acute period before the diagnosis becomes obvious, but their continued use is not beneficial or warranted unless specific indications exist. The intrapleural instillation of penicillin is similarly of no value and by some observers has been implicated in the production of increased effusion and increased fibrin deposition, particularly when dosage above 25,000 units is employed. The use of such dosage intrapleurally may be indicated when very frequent aspirations are necessary and a break in sterile technique is feared.

The advent of streptomycin in the treatment of tuberculosis has suggested its use in the treatment of pleural effusion, of either suspected or proved tuberculous bacteriologic identity. The danger of the emergence of streptomycin-resistant tubercle bacilli which might well preclude retreatment in a future critical need
Figure 4a, Case I.S.: Army film taken February 28, 1945 reveals bilateral pleural effusion four months after onset.—Figure 4b: Film taken May 11, 1949 reveals destruction of superior pole, major calyx, of right kidney due to tuberculosis.

Figure 5, Case D.H.: Admission film taken July 14, 1949 reveals bilateral pleural effusion, most marked on the right. Little change on the right had occurred to February 1950, and pulmonary function is markedly impaired on that side (see text).
has been a valid argument against the treatment of primary pleural effusion as well as minimal pulmonary tuberculosis, both of which usually respond well to conservative therapy. The introduction of PAS (para-amino salicylic acid), which appears to have a delaying effect on the emergence of resistance to streptomycin when given in combined dosage, as well as a primary therapeutic effect when used alone, may offer an agent of value in the treatment of patients with extensive bilateral effusions, a maintained acute phase with recurrent effusion, continued fever and toxicity, or other evidences of an unfavorable course. Moyer\textsuperscript{20} has recently reported a small series showing very favorable response to such therapy, when the usual therapeutic regimen had not been effective. Other anti-tuberculosis drugs are now in experimental use or on the horizon which may offer effective therapy in all forms of tuberculosis, without fear of toxicity or the emergence of resistant strains of tubercle bacilli. The use of streptomycin intrapleurally in primary pleural effusion is without value, and its use in the treatment of post-primary pleural effusion should be strictly reserved for those few instances cited where there is unfavorable response to the usual regimen. Those who have had extensive experience with this antibiotic and realize its limitations and dangers advise strongly against its indiscriminate use in the treatment of tuberculous disease.

Other than the treatment of the acute phase and the effusion itself, the primary concern of the physician should be with the therapeutic implications of the underlying process. The primary or idiopathic pleural effusion is not infrequently followed by tuberculosis of the reinfection type, pulmonary or extrapulmonary in location. It is estimated that about 15 per cent of cases of pulmonary tuberculosis have had a previous pleurisy with effusion. Pulmonary lesions may be present concomitantly with the effusion but hidden by it or the pleural reaction, or may appear soon after the effusion and clinical signs subside. If the patient is prematurely discharged or lost to observation at this point, the implications are obvious. It is against these frequently insidious manifestations of tuberculosis following the effusion, that the most careful vigilance should be employed. The pleural effusion may be small or subside rapidly, but the very fact of its presence affords the physician a clinical signal of invaluable significance. Landau\textsuperscript{16} states that the effusion is at any age only a symptom without prognostic importance, but the presence of an active underlying focus is axiomatic and this focus is likely to follow its course steadily, consistently and sometimes inexorably. The problem of pleural effusion was recognized early in the war and resulted in the issuance of a War Department Technical Bulletin...
(TB Med. 71) in July 1944 emphasizing the probable tuberculous origin of any "idiopathic" effusion in young adults and the need for adequate diagnosis and treatment.

Numerous reports in the literature have indicated that the incidence of pulmonary tuberculosis following idiopathic pleural effusion varies from 17 to 50 per cent, but is considered to be 25 to 35 per cent in the United States. The results of some of the larger surveys are shown in Table I. Although based on a five-year observation period, an analysis of the reports indicates that the greatest incidence usually occurred within the first year following the pleural effusion. Kraft in a carefully followed series of 100 cases of primary pleural effusion in Army personnel found that 21 per cent developed pulmonary tuberculosis within one year, averaging 6.2 months, and all while on a sanatorium regimen. Thompson reports a "breakdown" rate in the first year following the primary effusion of more than 50 per cent of the five year total. The incidence of subsequent extrapulmonary tuberculosis is about 15 per cent, is not infrequently found in association with pulmonary involvement and usually affects the genito-urinary tract, bone, peritoneum or lymph nodes. The mortality rate from subsequent tuberculosis during the five year observation period is estimated at about 10 per cent, although this varies considerably with nationality, race, extent of disease and treatment. Table I indicates the variance in mortality statistics from reported series. The extremely high rate of 71 per cent in Farber's series reflects a group which had no sanatorium care following the acute phase of the effusion. Jones and Dooley reported a mortality

### Table I

Incidence of Pulmonary Tuberculosis Following Idiopathic Pleural Effusion

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Cases</th>
<th>Pulm. Tuberc.</th>
<th>Observation Years</th>
<th>Deaths Per Cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaarde</td>
<td>1930</td>
<td>126</td>
<td>50</td>
<td>1-26</td>
<td></td>
</tr>
<tr>
<td>Schuman</td>
<td>1941</td>
<td>94</td>
<td>38</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bonilla</td>
<td>1942</td>
<td>40</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Farber</td>
<td>1943</td>
<td>111</td>
<td>38</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>Jones and Dooley</td>
<td>1946</td>
<td>99</td>
<td>16</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Thompson</td>
<td>1946</td>
<td>190</td>
<td>47</td>
<td>5</td>
<td>3.5</td>
</tr>
<tr>
<td>Kraft</td>
<td>1949</td>
<td>100</td>
<td>21</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*None had sanatorium care following the acute phase.*
rate of 20 per cent in their series, mainly Negroes with extensive extrapulmonary dissemination. Thompson's\textsuperscript{21} series, reflecting better initial care, had a five year mortality rate of only 3.5 per cent. Bonilla\textsuperscript{23} found a 9 per cent mortality in a five year follow-up of patients who had four months of bed rest after onset of pleurisy with effusion, but a 24 per cent mortality in the group refusing such care. The influence of adequate care and treatment upon subsequent tuberculous dissemination and mortality rate cannot be underestimated.

All authors agree upon the necessity for adequate sanatorium care or very carefully supervised bed rest at home, if favorable conditions for such home treatment exist, for patients convalescing from pleurisy with effusion. Lowry\textsuperscript{22} states that 7 to 13 per cent of those cases of pleural effusion who receive at least four to six months of sanatorium care at the time of their effusion will later develop pulmonary tuberculosis, compared to a morbidity of 30 to 50 per cent in those not receiving adequate care. Amber-son\textsuperscript{19} similarly recommends convalescence under sanatorium conditions of four to six months, while Kraft\textsuperscript{3} recommends at least one year of good sanatorium care. One cannot overestimate the importance of the first year following the effusion when sanatorium care may not only prevent complications but allow detection of subsequent lesions when effective therapeutic measures can be applied and further dissemination controlled. Bonilla\textsuperscript{23} found that patients whose lesions became known during rest had a better prognosis than those whose lesions, after the effusion, were first detected during periods of physical activity. Several cases noting these aspects of treatment and complications are cited below.

J. G., a 23 year old white male student, was admitted on January 27, 1949, with history of cough, fever, left chest pain and weight loss of one month's duration. He had been previously hospitalized here from August 1946 to February 1947 for treatment of left pleurisy with effusion, from which aspirated fluid was bacteriologically negative. Tuberculin skin test was positive. He was rehospitalized within three weeks for treatment of right pleurisy with effusion, also bacteriologically negative, and was again discharged in October 1947. He was seen once subsequently for a follow-up examination, but apparently ignored further invitations to return. He began attending radio school in the Spring of 1948, and in September 1948 began working an additional six to eight hours daily in a radio repair shop. Symptoms began in December 1948 leading to his readmission.

Findings on admission revealed fibro-cavernous disease in the left upper lung field, residuals of the previous pleural effusions and positive direct smears of the sputum for tubercle bacilli. Previous chest films had shown no parenchymal disease. Despite bed rest and streptomycin the lesions did not respond, positive sputum continued and left thoracoplasty
was done in October 1949. There has been no evidence of extra-pulmonary involvement. Bronchospirometry studies prior to thoracoplasty revealed a ventilatory equivalent of 2.6 on the right, compared to 1.2 on the left, indicating impairment of pulmonary function from pleural residuals on the right.

Comment: This patient had two episodes of pleurisy with effusion with six and eight months of hospitalization respectively for each episode. Lack of cooperation on the part of the patient and failure of adequate observation resulted in the appearance of extensive parenchymal disease within 26 months of the initial effusion.

N. H., a 23 year old white male carpenter was admitted on June 12, 1948. In February 1948 while employed on Guam he noted pleuritic pain in the left chest, malaise and fever. His chest was strapped by a physician, and he returned to work, with subsidence of all symptoms in a few days. In late May 1948, while in San Francisco, he again had pain in the left chest, malaise, fever and a 10 pound weight loss and was found to have pleural effusion. Tuberculin skin test was positive at that time. Immediate hospitalization was recommended, but he returned to Minnesota. Upon admission he was found to have considerable fluid in the left chest and about 2500 cc. was removed on several aspirations, but was negative on culture. Several sputum smears were positive shortly after admission. Chest films (Fig. 3) indicated a parenchymal cavitary lesion in the left lower lung field and a left phrenemphraxis was done in July 1948 with almost immediate sputum conversion. The patient remained on bed rest and did very well until March 1949 when positive sputa were again reported and chest films revealed a cavity in the left lower lobe. He was given a course of streptomycin and pneumoperitoneum instituted but without favorable effect upon the cavity or sputum findings. A left lower lobectomy was done in July 1949 with a subsequent uneventful course and negative sputum and gastric bacteriologic findings.

Comment: Parenchymal disease with positive sputum evidently existed at the time of the second episode of pleurisy with effusion, yet the aspirated fluid was bacteriologically negative. This again demonstrates the false sense of security that may come from placing definitive reliance upon negative findings in this entity.

I. S., a 29 year old white male student was admitted on February 17, 1949. A right pleurisy with effusion was noted in October 1944, while in the Army, with subsequent involvement on the left. A positive guinea pig was reported from right pleural fluid. He was kept at "bed rest" in various Army hospitals and in March 1945 a small infiltration was noted in the apex of the right lung which stabilized rapidly and without the finding of positive sputum or gastric studies. He was discharged in the Fall of 1948.

He was seen from time to time at another Veterans Administration hospital and remained well until January 1947, when a left apical lesion was noted as well as some reaccumulation of fluid at the right base. He received bed rest and sanatorium care until July 1948, when he left against medical advice. Bacteriologic studies of the sputum were negative, as were those of small amounts of fluid aspirated from a pleural "pocket" on the right. The apical lesion did not increase and stabilized satisfactorily. He was again followed at another Veterans Administration
hospital and remained apparently well, although small amounts of fluid were aspirated from time to time from the right pleural pocket which were positive on culture for tubercle bacilli. He was transferred to this hospital for possible surgical treatment of the pleural pocket. Frequent aspirations secured small amounts of serous fluid, which remained positive for tubercle bacilli, and eventually resulted in apparent cessation of fluid formation and obliteration of the pocket.

Shortly after admission the patient was found to have an increase in white blood cells, a few red blood cells and a trace of albumin in the urine on repeated specimens. Cultures of bladder urine were positive for tubercle bacilli. Intravenous pyelography (Fig. 4), retrograde studies and bacteriologic studies of ureteral urine specimens revealed destruction of the superior pole of the major calyx of the right kidney, with urine specimens from that kidney alone positive for tubercle bacilli. Right nephrectomy was done on August 9, 1949 with an adjunct course of streptomycin. Histologic study revealed an active tuberculous cavity in the upper pole of the kidney. Repeated urine cultures since nephrectomy have been negative. Sputum and gastric cultures are negative, as is a bone survey of the entire spine.

Comment: Despite a year of presumed inactivity following the initial right pleural effusion, the patient developed an apical infiltrate within six months and subsequently a similar infiltrate on the contralateral side, reactivation of the pleural effusion and eventually renal tuberculosis. This man is a very intelligent individual to whom the significance of his initial pleural effusion was never adequately explained, with consequent tendency to circumvent adequate bed rest while in the Army. This case illustrates the need for careful indoctrination of the patient, adequate primary care and for continued observation of these cases for a considerable period following their first illness.

G. M., a 26 year old white male farmer was admitted on July 21, 1949. He had had left chest pain in March 1948, diagnosed as "pleurisy" on the basis of an x-ray film taken by his physician at that time. He remained at home for a few days and then resumed his usual activities. In May 1948 a small mass was noted on the anterior chest, overlying the sixth costo-sternal junction. This was curetted and reported as "ill defined granuloma" histologically. A draining sinus persisted at the site subsequently. In November 1948 stiffness and swelling of the left knee was noted, gradually increasing to involve the leg almost to the ankle. Aspiration of the knee joint at another Veterans Administration hospital in April 1949 secured purulent material which was positive for tubercle bacilli on culture and guinea pig inoculation. Tuberculin skin test was positive. Sputa and gastric cultures were negative for acid-fast bacilli. He left the hospital against advice in June 1949 due to certain domestic difficulties.

Marked fluctuant swelling of the left knee and leg were noted upon admission here and aspiration secured purulent material which was consistently positive bacteriologically for tubercle bacilli. Roentgenograms of the knee revealed a destructive process of the joint cartilage and bony margins of the tibia. Arthrodesis of the knee joint was done on September 23, 1949 with an adjunct course of streptomycin given during and after the surgical period. Spine survey and bacteriologic studies of the urine have been negative. The chest wall sinus has closed under strepto-
mycin therapy, but future surgery may be necessary to excise this tuberculous focus. There has been no evidence of parenchymal pulmonary disease, although the area of pleural involvement remains essentially unchanged at the left base.

Comment: This patient received no treatment for his initial pleurisy with effusion. Within six months there was evidence of tuberculous involvement of the bony thorax and of the left knee joint. Surgery of the left knee was necessary due to the destructive involvement, which will leave this still young man with considerable disability.

Our approach at this hospital to the treatment of these effusions after the acute phase provides at least six months of bed rest, under sanatorium conditions, limiting activity to one bathroom privilege per day. Those with extensive effusions or evidence of activity which does not rapidly subside are treated with the same period of rest, but dated from the time the process began to show definite evidence of inactivity. Chest roentgenograms and blood sedimentation rate values are secured at six week intervals during this period, as well as bacteriologic study of sputum and gastric expressions at monthly intervals. The patients are also carefully observed for any evidences of extrapulmonary tuberculosis. At the end of the six month period the patient is reevaluated and may be allowed a program of gradual reambulation over a period of three to four months, or may be required to take additional bed rest if his progress has not been entirely satisfactory. Gradual return to full activity is recommended over a period of six months following discharge from the hospital, and the patient is recalled at intervals of two to three months for reexamination for the first year following discharge and at gradually lengthening intervals for at least five years. This is essentially the usual sanatorium program and its long term implications for the patient make it most difficult for the physician effectively to treat these patients at home, unless exceptional circumstances exist. Although this program has been in effect at this hospital for only about three years and complete follow-up data are not available, it is estimated that less than 5 per cent of those patients treated and effectively cooperating on this regimen have subsequently developed any evidence of pulmonary or extrapulmonary tuberculosis.

It is not an easy task for the physician to recommend a long period of inactivity to a patient with "idiopathic" pleural effusion, especially when the diagnosis must be based on the clinical picture and a positive tuberculin skin test, without bacteriologic evidence with which the patient can be confronted and persuaded. The temptation to "take a chance" is sometimes difficult to resist in such an instance, although few physicians would recommend such a course were the patient found to have active minimal pulmonary
tuberculosis instead of pleural effusion. The prognosis and clinical significance of post-primary pleural effusion is essentially that of such a pulmonary lesion, and the treatment in each instance should be little different to achieve optimum results. Thorough and repeated explanation to the patient and his family of the nature and possible consequences of the effusion must be made to aid them in reaching the proper decision. The social, domestic and financial implications for a patient who must spend six or more months in a sanatorium for the treatment of "idiopathic" pleural effusion requires firmness and conviction on the part of the physician who makes that recommendation. When there is question or choice of diagnosis, often prompted by the physician's own lack of conviction, the patient will usually apply the diagnosis of lesser consequence to his case.

The fact that pleurisy with effusion occurs most frequently in the late adolescent and early adult age groups makes adequate treatment vital, although patient resistance to treatment is also high in this group. The benefits resulting from adequate care in this group are obvious. Sanatorium physicians have an acute awareness of the problem of pleural effusion, and little difficulty should be encountered in securing treatment for these patients. Should the patient fail to be convinced of the necessity for continued inactivity after subsidence of the acute phase of the effusion, every effort should be made to have him return at two month intervals for reexamination, including careful fluoroscopy or chest roentgenogram, for a period of at least six months following the effusion and at gradually lengthening intervals for the next five years. Local or county health units are also available for the continued follow-up of these patients upon referral, and such observations may be invaluable in detecting early pulmonary or extrapulmonary activity from the standpoint of both the patient and the public.

This paper has attempted to present some aspects of the problem of post-primary or idiopathic pleural effusion and its significance as a manifestation of an active tuberculous process. The conclusion is inescapable that the practicing physician stands in a most important position with relation to the recognition and adequate treatment of the patient with pleural effusion. Physicians active in tuberculous work who have seen patients admitted for the treatment of sometimes far advanced pulmonary or extrapulmonary disease and whose history included a previous episode of inadequately treated pleural effusion cannot but feel that an important aspect of preventive medicine has been neglected and a valuable clinical sign overlooked.
SUMMARY

1) Idiopathic pleurisy with effusion in the tuberculin positive individual should be considered a manifestation of tuberculosis in every instance, despite negative cultures of the aspirated fluid, and offers a sign of valuable clinical significance to the physician.

2) The age group involved makes recognition of the tuberculous etiology an important tuberculosis control factor, with obvious social and economic implications for the group.

3) A high incidence of pulmonary and extrapulmonary tuberculosis follows inadequately treated pleurisy with effusion, chiefly within the first two years following the effusion.

4) Sanatorium treatment, similar to that employed for minimal active tuberculosis, is strongly recommended in every case, with an observation period of at least five years following the effusion.

5) Control of the effusion by adequate aspiration is indicated to avoid pleural changes and subsequent impairment of pulmonary ventilatory function as an added complication.

RESUMEN

1) La pleurésia con derrame idiopática en individuos tuberculin-positivos debe considerarse indicación de tuberculosis en todo caso, no importa si los cultivos del líquido aspirado sean negativos, y es, para el médico, un signo de valioso significado clínico.

2) Debido principalmente a la edad del grupo afectado, el reconocimiento de la etiología tuberculosa de ese estado es un factor importante en el control de la tuberculosis, con claras implicaciones sociales y económicas para ese grupo.

3) La pleurésia con derrame tratada inadecuadamente conduce a una elevada incidencia de tuberculosis pulmonar y extrapulmonar, especialmente en los dos años que siguen al derrame.

4) Se recomienda vehemente que todo caso reciba tratamiento sanatorial semejante al que se emplea en casos de tuberculosis mínima activa, con un periodo de observación de, por lo menos, cinco años después del derrame.

5) Se indica el control del derrame mediante la aspiración adecuada para evitar la complicación de alteraciones pleurales que causen daño subsiguiente a la función ventilatoria del pulmón.

REFERENCES