STUDIES IN PRIMARY PLEURISY WITH EFFUSION*

BY

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This paper is on the subject of primary pleurisy with effusion and is not concerned with effusions arising in patients with established pulmonary tuberculosis. The pathogenesis of such cases is not difficult to imagine, though it is a curious fact that so many occur in patients with old-standing, often calcified, and apparently inactive pulmonary lesions, and that the prognosis is remarkably good (Thompson, 1947a). These can properly be called "secondary" tuberculous pleural effusions. The fluid which may form in the course of artificial-pneumothorax treatment is perhaps a special case in this group.

The "primary" effusion of my definition formed the subject of a previous investigation in which 190 cases were studied over a period of years, with follow-up results which were virtually complete, including regular routine radiography of the chest (Thompson, 1946, 1947b). Although by definition coexisting or preceding pulmonary tuberculosis was not present in this earlier series of cases, radiographs sometimes revealed lesions within the thorax that were typical of the tuberculous primary complex of Ghon. These lesions were characterized by enlargement of the hilar lymph glands, or by parenchymal infiltration, or by both together, sometimes including evidence of bronchial stenosis or atelectasis of a broncho-pulmonary segment. Where a parenchymal lesion was apparently alone, this was of the primary-infection type in which the glandular component could reasonably be regarded as radiologically invisible. These intrathoracic lesions were known sometimes to have preceded the pleural effusion; in no case did the effusion come first. In some cases the effusion occurred on the same side as the pulmo-glandular complex; in others it occurred on the opposite side.

Follow-up showed that 25% of all cases developed tuberculosis within five years. The earliest evidence of this subsequent disease often occurred within a few months, soon enough to indicate that it was directly associated with the preceding pleural effusion, and that it was not, for example, a further tuberculous infection from an outside source. In nearly one-half of the cases of subsequent tuberculosis, this became evident within the first year of observation. Two-thirds of the remainder occurred within the second year. None occurred later than the fifth year. The incidence, course, and prognosis of the subsequent tuberculosis was not apparently related to the age of the patient or his social state, or to such clinical conditions as the magnitude of the effusion, the degree of toxæmia, or the presence of demonstrable intrathoracic primary lesions. Nor, contrary to the opinion of Trudeau (1939), was there evidence that any treatment, or absence of treatment, of the original condition influenced the ultimate course of the disease.

Since the publication of the above studies, opportunity has arisen for observing the development of pleurisy with effusion from its earliest beginnings in persons already under observation, especially among nurses and medical

students at Dunedin Hospital, who undergo regular tuberculin testing and x-ray examination as part of their routine medical care. The following selected case histories are presented as clinical illustrations of some of the factors involved.

Case Reports

Case 1.—A student nurse aged 28 was negative to intradermal injection of tuberculin P.P.D. first and second strength on entry in March, 1946, and again in June. At her next routine examination in January, 1947, she gave a 4-plus reaction to P.P.D. first strength, and a radiograph showed involvement of the left lung and tracheo-bronchial glands typical of primary tuberculosis. Though well and without symptoms, she had evidently incurred a recent primary infection, probably a few weeks previously, when she had complained of a transient malaise and sore throat, but without reporting sick. After a month's leave at home she returned to duty. In July an acute left pleurisy with effusion supervened.

Comment.—This is a case of typical primary tuberculous infection in a previously uninfected adult with an intrathoracic primary complex, followed by pleural effusion on the same side six months later. Such an interval is regarded as about the average duration between the entry of tubercle bacilli and the development of pleurisy, but there are wide variations. Delay for a longer period is easily explained by the traditional latency of tuberculosis. The shortest period I have seen was in Case 2.

Case 2.—A student nurse aged 19 was negative to both strengths of P.P.D. on entry in September, 1945, and again in June, 1946. Sixteen weeks later she developed an acute left-sided pleurisy with lymphocytic effusion. Three weeks after that an effusion also occurred on the right side.

Comment.—A pleural effusion occurred four months after a negative tuberculin test and therefore not more than 10 weeks from the latest possible date of conversion to tuberculin-positivity, according to the accepted incubation period of about six weeks following primary infection (Wallgren, 1945). The subsequent contralateral pleurisy also occurred with unusual rapidity, and with no indication of its causation. The patient made an uneventful recovery and eventually returned to duty.

Case 3.—A nurse aged 18 on entry in 1942 was Mantoux-negative at that time and was repeatedly negative up to January, 1946, when she was found to be negative to the first strength of P.P.D. but positive to the second strength. The chest radiograph was clear. In September, 1946, she developed cough and pain in the left side. A pleural friction-rub was heard in the left axilla, corresponding to x-ray evidence of a pulmonary lesion of primary type, and the E.S.R. was 18 mm. Four months later a pleural effusion occurred on the opposite side.

Comment.—Pleural effusion developed contralateral to a primary tuberculous pulmonary lesion, over which dry pleurisy had been noted but which had not led to the formation of fluid. As in Case 3 there was nothing to suggest a haematogenous spread of disease. The passage of infection from the left to the right hemithorax could, however, have been by way of the mediastinal lymph glands.

Case 4.—A student nurse aged 23 was Mantoux-negative on entry in 1944. In January, 1946, she was still negative to both strengths of P.P.D., but 12 weeks later the sites of both these intradermal injections became acutely inflamed. A radiograph showed enlargement of glands in the left hilum (Fig. 1). She developed an irritative cough towards the end of the year, and in March, 1947, was found to have an accumulation of fluid between the upper and lower lobes of the left lung (Fig. 2), which was aspirated and replaced by air. Though no pulmonary lesion could be seen, she had a productive cough with tubercle bacilli in the sputum, and in view of a localized wheezing

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FIG. 1.—Case 4. April 30, 1946. Delayed positive reaction to Mantoux tests done 12 weeks previously. Left pleural effusion occurred 10 months later.

respiration it was suspected that the caseous gland mass had broken through into the bronchial tract. This was confirmed by bronchoscopy, which revealed an ulcerated area on the anterior aspect of the left main bronchus, just proximal to its upper division. After prolonged sanatorium treatment, during which she became entirely free from symptoms and from recoverable tubercle bacilli, she developed an acute pleural effusion on the right side, just 24 months from first becoming tuberculin-sensitive.

Comment.—The phenomenon of delayed reaction to tuberculin retained in the skin through the period of primary infection (Daniels, 1943) enables the date of that infection to be fixed very exactly. This nurse must have received her first dose of tubercle bacilli in the second

FIG. 2.—Case 4. March 8, 1947. Lateral view showing fluid lying in the interlobar fissure.

fortnight of February, 1946, her left-sided effusion appearing 12 months later, with persistence of the glandular component of the primary complex throughout that period. It may be significant that the fluid spread from the hilum in the interlobar fissure without extending widely over the costal surface, which it was quite free to do, as the subsequent artificial pneumothorax showed (Fig. 3). The mass of caseous glands radiologically seen at the hilum were found to press on and to erode the adjacent bronchus. It is reasonable to suppose that these same glands could similarly involve the pleural sac, lying as they do against its hilar reflection, and that extension to other lymph glands in the mediastinum could reach the opposite pleura, producing there the later effusion.

Case 5.—A medical student aged 22 was Mantoux-negative up to his final year, when he incurred a brief febrile illness with cough and chest pain. A radiograph showed a left-sided primary tuberculous complex. Ten months later an effu-

FIG. 3.—Case 4. July 3, 1947, after aspiration of fluid and replacement by air. A free pneumothorax is present, with some displacement of the heart to the right.

sion developed on the same side, associated with very severe toxic disturbance. Despite repeated aspiration the fluid always re-formed rapidly. His temperature remained high and he gradually declined into an almost typhoid state. Impaired percussion and bronchial breathing were found to the right of the sternum, and a small effusion eventually formed in the right pleural cavity. The clinical picture and x-ray appearances suggested the presence of so large a caseous gland mass as to constitute a tuberculous mediastinitis, with pressure atelectasis of the right lung base. After air-replacement of the left-sided effusion, a thoracoscope was introduced. There were no tubercles to be seen, but the pleura was intensely pink, and fine filamentous adhesions, easily separable, were forming between the upper lobe of the lung and the parietal pleura. Parenteral streptomycin was begun, 0.5 g. twice daily, with immediate and dramatic results. Within two days his temperature fell to normal, his appetite returned, apathy abated, and recovery steadily advanced to convalescence.

Comment.—The pleural effusion followed a primary tuberculous complex on the same side, and spread to the other side apparently by way of the mediastinum. Miliary

disease was excluded by thoracoscopy. Striking features were the unusual degree of toxæmia, so great that a fatal issue looked likely, and the prompt response to streptomycin.

Case 6.—A woman doctor aged 24 was Mantoux-negative throughout her training, and up to December, 1947, when for some weeks she experienced vague malaise, culminating in an outbreak of erythema nodosum. A radiograph showed a lesion in the right upper lung field typical of primary tuberculosis. On strict rest in bed her temperature fell from 100° F. (37.8° C.) to normal and her E.S.R. from 25 to 6 mm., and her general condition rapidly improved. Her only symptom occurred 16 weeks from the onset of the skin eruption—a transient pain beneath the right scapula aggravated by deep inspiration. There were no physical signs, but a radiograph showed a slight peripheral spread of the earlier lung lesion, with definite pleural reaction.

Comment.—The primary infection was marked by the occurrence of erythema nodosum. Pleurisy ensued on the same side as the primary lesion, clearly as a result of local spread from its pulmonary component. There was no constitutional upset and no rise of temperature, while the E.S.R. remained well within normal limits during this latter episode.

Case 7.—A schoolgirl aged 15 was examined as a contact of her father, who had recently died from acute pulmonary tuberculosis. She was found to have an active primary complex on the right, with contiguous bronchopneumonic spread from the focus in the lower lobe. This localized extension increased under conditions of strict rest in bed, and eight weeks later a right pleural effusion supervened. Thereafter she showed steady clinical improvement and was discharged from sanatorium 12 months later, in excellent condition, to live quietly on the family farm. Within a month there appeared below the left clavicle a new infiltration which spread slowly, to become arrested and show signs of regression only after 18 months of observation. Throughout this period, from the initial resolution of her effusion, she was entirely without symptoms, gained weight, and had a normal unchanging sedimentation rate. There was, however, radiological evidence of the glandular component of the primary complex persisting right up to the development of the subclavicular infiltration and resolving only when the latter reached apparent stability.

Comment.—This case is a further example of pleural effusion following a recent primary complex, which remained incompletely resolved during medical treatment and gave only radiological evidence of its existence, and subsequently led to pulmonary tuberculosis on the opposite side.

Discussion

These cases have been chosen for the light they throw on the pathogenesis of pleural effusion. All had undergone a recent primary tuberculous infection and were under close observation before and after that event. In six of the seven cases a primary complex within the thorax was seen to develop which was radiologically visible throughout the pleurisy in five. Case 7 is an example of the development of subsequent pulmonary tuberculosis, and the primary complex continued to be visible by radiograph.

One way in which the pleura may be invaded from the primary complex is illustrated by Cases 6 and 7, in which direct spread from the pulmonary focus was observed. Another way is shown in Cases 3, 4, and 5, in which there was strong evidence that the lymphatic gland component eroded the pleura near its mediastinal reflection. The opposite pleura was subsequently affected in three cases (Nos. 2, 4, and 5), indicating that so-called bilateral effusions are due probably to spread from adjacent lymph glands.

The latent period between primary infection and exudative pleurisy may be as short as 16 weeks (Case 2) but is

usually between 6 and 12 months. Persistence of evidence of an active primary complex should lead one to expect pleurisy in any case of recent tuberculous infection. The term "primary" pleurisy with effusion is therefore used definitively, to make clear this association, though in a strict pathological sense it doubtless belongs to the indeterminate post-primary phase. More distinctly post-primary is the relatively uncommon pleural effusion, usually bilateral, which may accompany generalized haematogenous dissemination from the primary complex, with miliary tuberculosis throughout the lungs, extrapulmonary lesions, and even polyserositis.

It seems that caseous lymph glands behave in the mediastinum in a manner similar to that often observed in the neck, as Erwin (1944) has suggested, by breaking through the boundary of least resistance. This may be the wall of a bronchus, clinically not uncommon, as in Case 4. It is reasonable to suppose that the contiguous pleura may be invaded in the same way, though Burke (1940) has advanced the possibility of retrograde spread by way of the subpleural lymphatics. Tubercle bacilli can nearly always be grown from the exudate by careful technique (Close, 1946), and one cannot doubt that they are directly concerned.

All these cases were in young adults. Pleurisy with effusion does of course occur in children, but very infrequently compared with the large number of primary tuberculous infections that occur during childhood (Hardy and Kendig, 1945). As children also do not tend to develop progressive pulmonary tuberculosis, it may be supposed that they are better able to resist such infections before puberty than after puberty, and to arrest the primary lesion usually at a stage short of pleural involvement.

This study offers no further evidence on the pathogenesis of subsequent tuberculosis. Case 7 illustrates the close succession of events—from primary lesion, through exudative pleurisy, to pulmonary infiltration—and the likelihood that the whole process is largely beyond the influence of our present therapeutic means.

Conclusions

Primary pleurisy with effusion is an incident in the natural history of tuberculosis. It arises by direct pleural involvement from either the pulmonary or the glandular component of an active intrathoracic primary complex, incurred as a rule a few months previously. Specially susceptible to this condition are adolescents and young adults who, having escaped the tubercle bacillus earlier in life, meet it for the first time by casual contact, usually outside the home.

The subsequent course is probably not different from that seen in other forms of late primary infection, with a marked tendency to pass into a stage of chronic pulmonary or extrapulmonary tuberculosis. Such progression may be entirely subclinical and may take place irrespective of or even during medical treatment.

The pleural effusion is to be regarded less as a disease in itself than as significant of persistent and dangerous primary tuberculosis.

REFERENCES

- Burke, H. E. (1940). *J. thorac. Surg.*, **9**, 506.
- Close, H. G. (1946). *Lancet*, **1**, 193.
- Daniels, M. (1943). *Ibid.*, **2**, 600.
- Erwin, G. S. (1944). *Tubercle*, **25**, 44.
- Hardy, J. B., and Kendig, E. L. (1945). *J. Pediat.*, **26**, 138.
- Thompson, B. C. (1946). *Amer. Rev. Tuberc.*, **54**, 349.
- (1947a). *Tubercle*, **28**, 229.
- (1947b). *British Medical Journal*, **1**, 487.
- Trudeau, F. B. (1939). *Amer. Rev. Tuberc.*, **39**, 57.
- Wallgren, A. (1945). *Amer. J. Dis. Child.*, **70**, 263.