

Infection of the pleura by *Aspergillus fumigatus*

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Pleural aspergillosis occurs mostly in established cases of pleural empyema with a broncho-pleural fistula. Ten such patients are reported here: in all, *Aspergillus fumigatus* infection was related to tuberculosis. In three cases with an active, sputum-positive tuberculous process the pleural empyema was a complication of spontaneous pneumothorax in two, and of lung resection in one. In two cases the empyema occurred as a complication of tuberculous pleuritis, but *A. fumigatus* infection was noted only after the sputum had become negative for tubercle bacilli. In five patients with inactive tuberculosis, the empyema was a late complication of pneumothorax therapy. The diagnosis of pleural aspergillosis is made on the basis of microscopical examination and culture of *A. fumigatus* in the pleural pus. The cultures were positive in seven of the 10 cases presented. In two cases in which the culture was negative microscopical examination of the pus revealed the presence of numerous fungal hyphae which was evidence of fungal necrosis. In one case the diagnosis was not made until necropsy. Serum precipitin tests with filtrates of *A. fumigatus* are further valuable evidence of aspergillous infection. Of 10 presented patients, this test was positive in all seven cases in which it was done. The treatment of pleural aspergillosis by local instillation of nystatin or amphotericin B was effective in six out of seven cases in which it was used.

From 1960 to 1968 10 patients with mycosis of the pleura were observed in the First Department of Tuberculosis and Chest Diseases of the Institute of Tuberculosis. All the patients had active or healed pulmonary tuberculosis and developed pleural empyema in the course of this disease.

CASE REPORTS

We have divided these patients into three groups:

GROUP 1 These three patients had active tuberculous lesions at the time of aspergillous infection of the pleura.

Case 1 A journalist aged 74 was admitted to the Institute of Tuberculosis on 13 July 1960 because of a spontaneous pneumothorax in the course of pulmonary tuberculosis complicated by diabetes mellitus. His general condition was poor, he was orthopnoeic, and his chest radiograph showed a pneumothorax space on the right side with adhesions of the apex and the peripheral region of the right lung. Within the right upper lobe many cavities were seen, while the middle and lower left lung fields were covered by confluent shadows. Acid-fast bacilli were found in the sputum. A catheter was inserted into the pleural cavity, and Gram-negative bacilli sensitive to chloramphenicol were recovered from the pleural fluid. The patient was given a course of streptomycin, isoniazid, penicillin, and chlor-

amphenicol therapy. In spite of this he deteriorated and after two months died of circulatory and respiratory failure. At necropsy both the adhesions and the pleura were covered by greenish fibrous masses which showed *Aspergillus fumigatus* on microscopical examination. In the apical posterior part of the visceral pleura an opening communication with the parenchymal lung cavity was found. Multiple tuberculous cavities were seen in both lungs.

In this case the empyema resulted from perforation of the tuberculous cavity into the pleura. Secondary aspergillous infection of the empyema was not recognized during lifetime.

Case 2 A radio broadcaster aged 37 was admitted to the Institute of Tuberculosis on 4 January 1963 because of bilateral cavitory tuberculosis complicated by a left-sided empyema. He had suffered from pulmonary tuberculosis since 1944 and his tubercle bacilli were resistant to streptomycin, isoniazid, and para-aminosalicylic acid. At the time of admission his general condition was poor, he had dyspnoea at rest with a respiratory rate of 36 per minute and signs of circulatory failure. Radiological examination revealed bilateral cavitory lesions with marked retraction of the left lung and a pleural space with fluid level on the left side. Tubercle bacilli, *Streptococcus faecalis*, coliform bacilli, and *A. fumigatus* were cultured from the pleural pus. Therapy with antituberculosis drugs, ouabain, lanatoside C, penicillin, and locally nystatin into the pleural space was given. Despite treatment the patient deteriorated

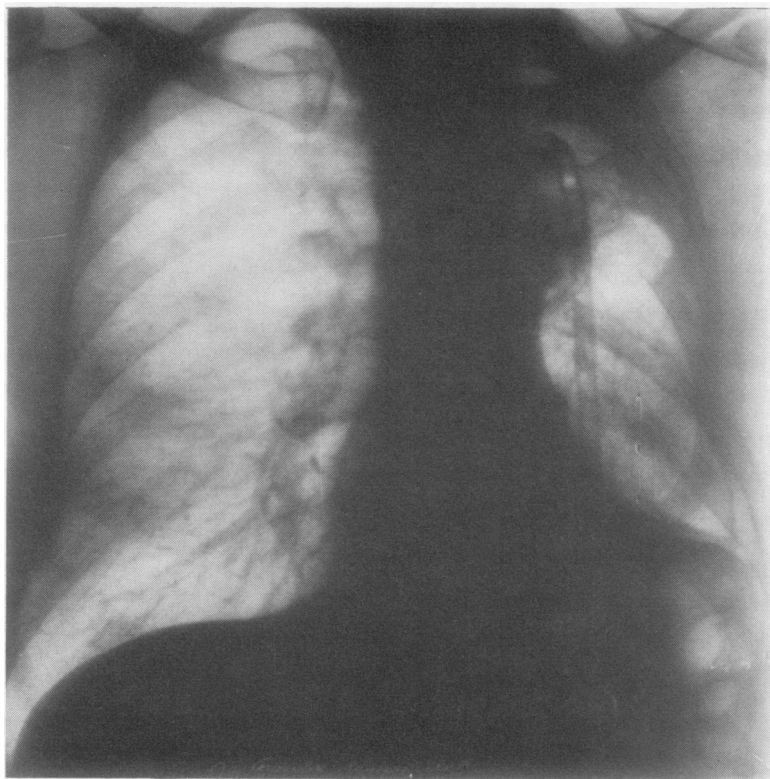


FIG. 1. Case 3. Empyema of left pleural space after pulmonary resection. Drainage.

steadily and died on 2 February 1963. At necropsy numerous bilateral tuberculous cavities and a left pleural empyema with a bronchopleural fistula were found. Pleural pus cultures made at necropsy did not yield a growth of *A. fumigatus*.

In this case the secondary infection occurred in the course of the tuberculous pleural empyema of two years' duration. A progressive tuberculous process with a secondary circulatory failure was the cause of death. After treatment with local nystatin the empyema space became sterile for fungi.

Case 3 A lawyer aged 51 was admitted to the Institute of Tuberculosis on 24 October 1962. The patient had developed pulmonary tuberculosis in 1946. In 1955 resection of the left upper lobe was performed because of a tuberculous cavity. He had remained well until 1962, when the manifestations of a left pleural empyema with a bronchopleural fistula and dissemination of tuberculosis occurred. Tubercle bacilli resistant to streptomycin and isoniazid were isolated from the sputum. Empyema drainage and therapy with antituberculosis drugs—viomycin, cycloserine, ethionamide, and para-aminosalicylic

acid—were begun (Fig. 1). *A. fumigatus* was recovered on smear and culture from pus aspirated from the pleural cavity. In the blood serum precipitins against *A. fumigatus* filtrates were found. The patient was subsequently given a course of nystatin administered locally into the pleural space. The combined antimicrobial and antimycotic treatment resulted in conversion of the sputum and sterilization of the pleura for fungi. In order to obtain closure of the empyema space, thoracoplasty was subsequently performed. A violent haemorrhage from the digestive tract followed the operation and caused the patient's death.

In this case infection of the pleura by *A. fumigatus* occurred in the course of the tuberculous empyema, which developed as a late post-operative complication following resection of lung tissue. Therapy was effective in sterilizing the sputum for bacilli and fungi. The patient's death was not related to tuberculosis or mycosis.

GROUP 2 These two patients had a fungous infection of the pleura as a complication of active tuberculosis, but only after conversion of the sputum for tubercle

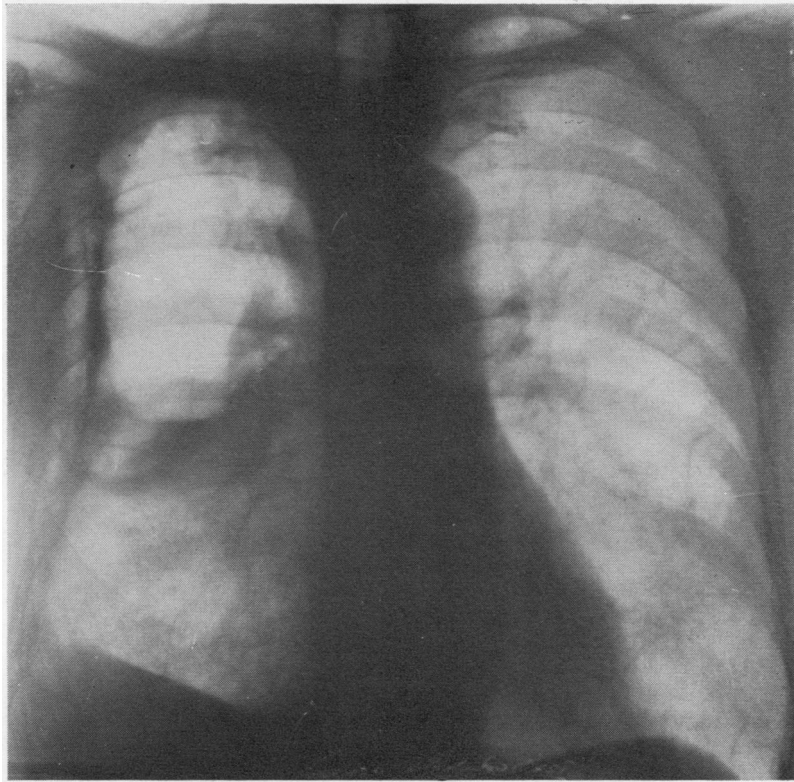


FIG. 2. Case 4. Empyema of right pleural space with intensive calcification. In the right lung a huge abscess with fluid level is seen.

bacilli during antituberculosis treatment had been obtained.

Case 4 A pensioner aged 75 was admitted to the Institute of Tuberculosis on 5 September 1964. In 1909 he had suffered from right pleuritis; since then a radiograph had shown a persistent intensive pleural calcification. In February 1964 the diagnosis of tuberculosis and diabetes mellitus was established, and tubercle bacilli were recovered from the sputum. He was given streptomycin, isoniazid, and para-aminosalicylic acid, and conversion of the sputum was obtained. In July 1964 the patient showed some deterioration, elevation of body temperature, and cough with purulent sputum which was negative for acid-fast bacilli. A chest radiograph showed a pleural space with fluid levels at the site of the previous pleural shadow (Fig. 2). A drainage tube was inserted into the pleural space. Examination of the pus revealed *Staphylococcus aureus* and *A. fumigatus*. Precipitin reaction of the patient's sera with filtrates of *A. fumigatus* was positive. The patient was given local therapy with nystatin and antibiotics. Despite treatment he deteriorated steadily and died on 29

November 1967. At necropsy a right pleural empyema with brown masses in it and with a broncho-pleural fistula was found. There were numerous cavities in both lungs. A direct smear of pus revealed hyphal fragments, but cultures yielded no growth of *A. fumigatus*.

Case 5 A fitter aged 36 was admitted to the Institute of Tuberculosis on 30 March 1966. In 1957 right-sided exudative pleuritis and right lung lesions were observed. In 1964 a right pleural empyema with symptoms of broncho-pleural fistula were recognized. The sputum was positive for acid-fast bacilli. Treatment with viomycin, ethionamide, and pyrazinamide was given. Conversion of the sputum with improvement of the patient's general condition was obtained. After six months' antituberculosis treatment the patient began to cough and expectorate a large amount of sputum negative for tubercle bacilli but positive for *A. fumigatus*. The serum precipitin test with *A. fumigatus* filtrates was positive. His chest radiograph showed in the upper part of the pleural empyema a shadow surrounded by a halo of air and a thickening of the pleura (Fig. 3). On admission to

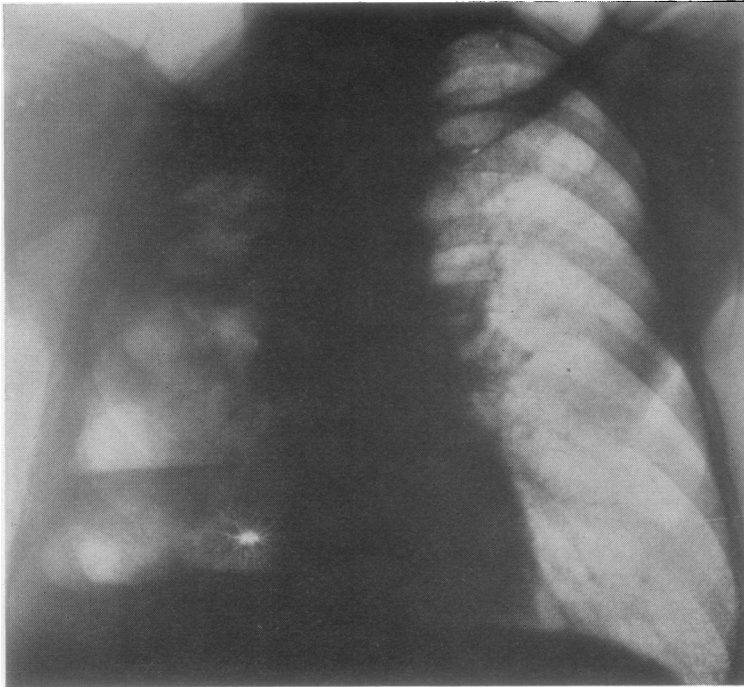


FIG. 3. Case 5. Right pleural empyema with thickening of the pleura. In the upper part of the empyema an aspergilloma is seen.

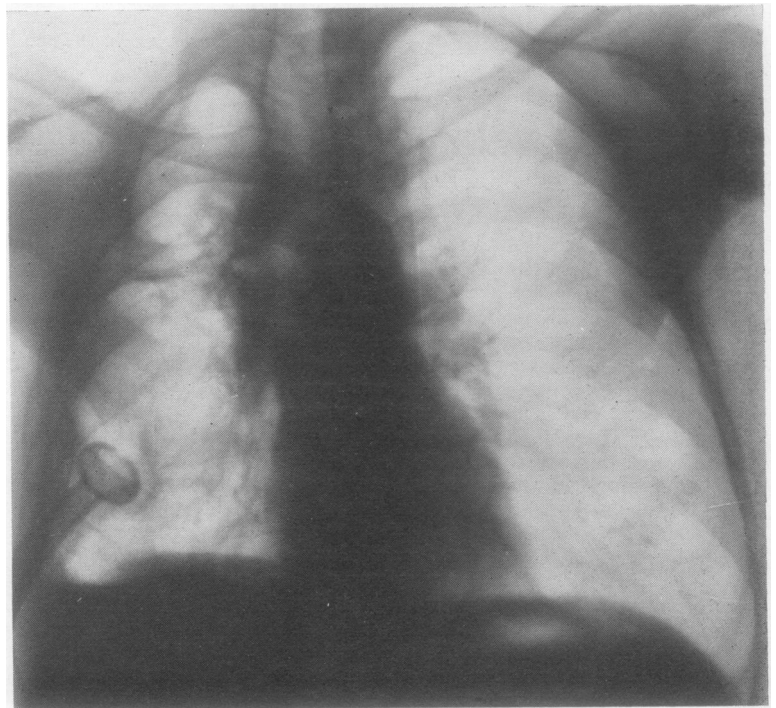


FIG. 4. Case 5. Regression of aspergilloma and pleural changes after local treatment by drainage.

the Institute the patient's condition was poor. He had a heavy paroxysmal cough with daily expectoration of 300 ml. of purulent sputum, fever, and anaemia. After draining the pleural cavity, multiple clumps composed of *A. fumigatus* mycelium flowed with pus out of the drainage tube for a long time. Cultures of pus were positive for *A. fumigatus* but negative for other micro-organisms. *A. fumigatus* infection of the pleural empyema with broncho-pleural fistula was diagnosed. A course of local nystatin in concentrations of 80–240 mg. in 500 ml. water daily was given. The treatment was effective in sterilizing the pleura for fungi; there was a marked improvement in the patient's general condition and clearing of symptoms such as fever, anaemia, cough, and expectoration (Fig. 4).

In the two cases mentioned above tuberculosis was an underlying disease, giving rise to the pleural empyema. Infection with *A. fumigatus* developed only after conversion of the sputum had been noted. Deterioration of the patients' general condition with pyrexia, cough, and purulent sputum was attributable to a mixed infection due to *Staph. aureus* and *A. fumigatus* in the first case and to *A. fumigatus* only in the second.

GROUP 3 Five patients with inactive pulmonary tuberculosis had been treated previously with artificial pneumothorax which had led to the formation of an empyema.

Case 6 An agricultural engineer aged 39 had suffered from tuberculosis since 1940. She was treated for four years with right pneumothorax complicated by an effusion. On 12 January 1959 she was admitted to the Institute of Tuberculosis because of mild fever, pain in the right thorax, and anaemia. Sputum examination was negative for acid-fast bacilli. A right-sided pleural empyema with broncho-pleural fistula was diagnosed. Beta-haemolytic streptococci, coliform bacilli, and *A. fumigatus* were cultured from the pleural fluid. In spite of empyema drainage and antibiotic therapy her general condition was grave and the fever did not subside. Nystatin was administered into the pleural space. Within two weeks sterilization of the pleural space for fungi and a return of the temperature to normal was noted. However, after three weeks the patient died of excessive bleeding from the pleural cavity. At necropsy rupture of an aneurysm of the innominate artery into the pleura was diagnosed as the cause of her haemorrhage. Post-mortem cultures were negative for fungi,

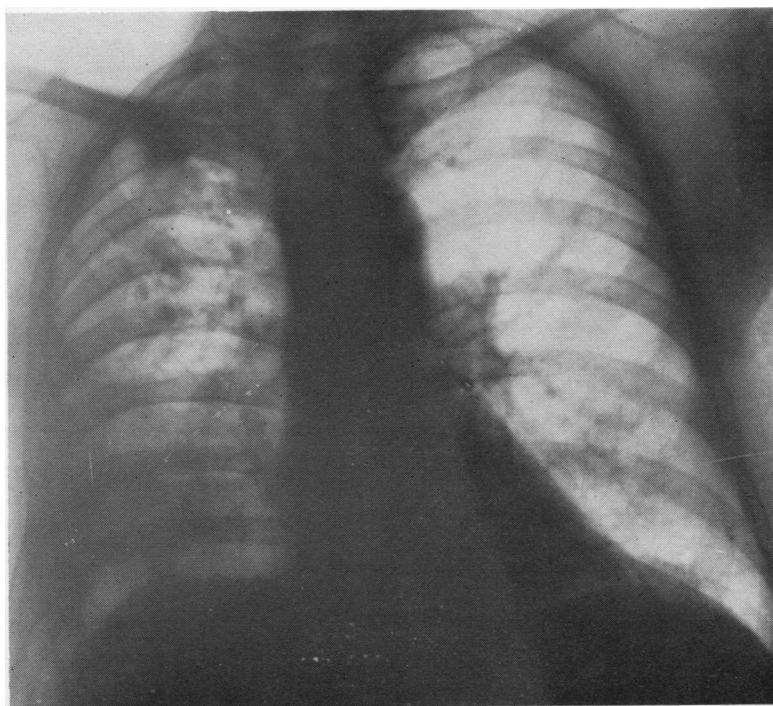


FIG. 5. Case 7. Right pleural empyema with fluid level after pneumothorax treatment.

which showed the effectiveness of the local administration of nystatin.

Case 7 A priest aged 53 was admitted to the Institute of Tuberculosis on 6 August 1966 because of persistent cough, dyspnoea, weakness, haemoptysis, and intensive expectoration of purulent sputum negative for acid-fast bacilli of one year's duration. He had suffered from tuberculosis since 1942. For two and a half years he had been treated with right pneumothorax. In 1960, after the episode of fever, pneumonia and right pleurisy were diagnosed. The chest radiograph taken on admission to the Institute of Tuberculosis showed a pleural empyema with extensive pleural thickening and adhesions on the right side of the chest (Fig. 5). The patient was started on repeat punctures and pus aspirations. Expectoration of methylene blue instilled into the pleural space indicated the presence of a broncho-pleural fistula. Examination of pus obtained from the pleural space was negative for tubercle bacilli and other pathogenic bacteria but revealed the presence of hyphae of *A. fumigatus*. Pus culture did not yield a growth of fungi which was evidence of their necrosis. The serum precipitin test with *A. fumigatus* filtrates was positive. On 28 April 1967 decortication with a partial right lung resection and closure of the bronchial

fistula was performed. Examination of the operation specimen revealed a pleural empyema with bronchial fistula. On macroscopic and microscopic examination of the empyema mycelium of *A. fumigatus* was found, but the fungus was not grown on culture.

Case 8 A housewife aged 49 was admitted to the Institute of Tuberculosis on 27 March 1967. In 1937 pulmonary tuberculosis had been diagnosed. From 1937 till 1944 she had been treated with a left artificial pneumothorax, which was complicated by an empyema in 1945. She was then treated by punctures and lavages of the pleural empyema with physiological saline solution and was well until 1960, when she developed pain in the left chest, cough, and purulent sputum. Since 1965 she had suffered from recurrent haemoptyses. On admission her general condition was good, and acid-fast bacilli were not recovered from the sputum. The chest radiograph showed extensive thickening of the left pleura with a fluid level (Fig. 6). *Pseudomonas aeruginosa* and numerous hyphae of *A. fumigatus* were recovered from the pleural pus. Cultures yielded no growth of *A. fumigatus*. The serum precipitin test with *A. fumigatus* filtrates was positive. In view of the persistence of the broncho-pleural fistula and infection with *Ps. aeruginosa* surgical intervention was considered, but the patient refused treatment.

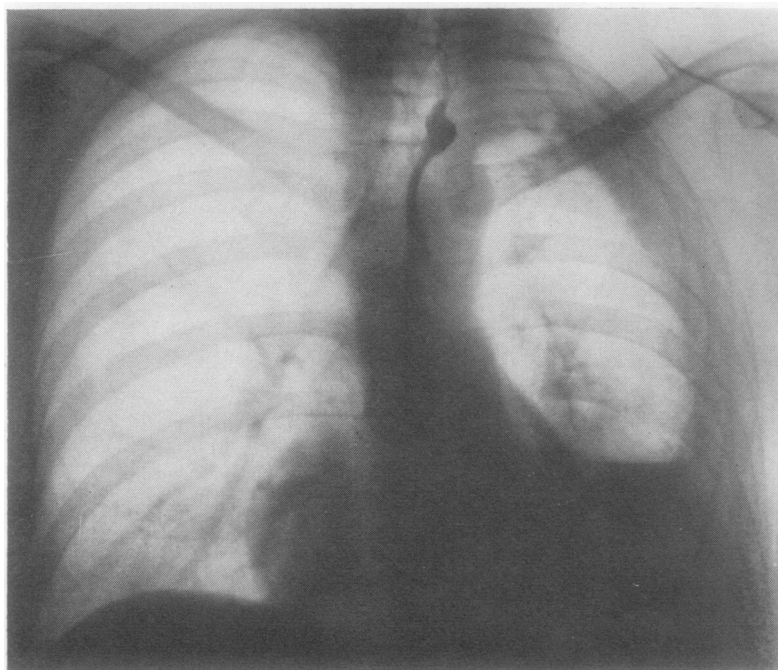


FIG. 6. Case 8. Left pleural empyema with fluid level after pneumothorax treatment.

Case 9 An engineer aged 41 was admitted to the Institute of Tuberculosis on 27 July 1967. In 1948 pulmonary tuberculosis, sputum positive, had been diagnosed. He was treated with bilateral artificial pneumothoraces for six years. After that he was well until 1967, when he developed fever, cough, and purulent sputum. On admission his general condition was poor. His sputum was negative for acid-fast bacilli but positive for *A. fumigatus*. The chest radiograph showed extensive pleural thickening on both sides. On the right side pleural fluid was seen. Both upper lobes were diminished in size with evidence of cavities. In the upper part of the right lung an abnormal shadow was seen possibly corresponding to an aspergilloma inside the parenchymal cavity or pleural space (Fig. 7). Culture of pus obtained from the pleural space was negative for tubercle bacilli and other pathogenic bacteria but positive for *A. fumigatus*. In addition microscopical examination of the pus revealed the presence of hyphae of *A. fumigatus*. Examination of the pleural space with lipiodol revealed the presence of a broncho-pleural fistula. The serum precipitin test with *A. fumigatus* filtrates was positive. The patient refused insertion of a drain into the pleural cavity, and so was started on repeat punctures and pus aspirations. Ampho-

tericin B, 25 mg. in water solution, was put three times weekly into the pleural space. After six months' treatment the pleural pus was sterile for fungi. At the same time the abnormal shadow in the upper part of the right lung disappeared and the sputum became negative for *A. fumigatus*. This indicated the pleural origin of the shadow. The general condition of the patient has greatly improved. Surgical intervention in this case is impossible because of the bilateral lesions.

Case 10 A writer aged 66 was admitted to the Institute of Tuberculosis on 13 August 1967. In 1929 he was treated with right pneumothorax because of a tuberculous cavity in the right lung. In 1930 his pneumothorax space was filled with oil. He was well until 1955, when a right pyopneumothorax with broncho-pleural fistula developed.

His sputum was negative for tubercle bacilli at that time. He was treated with puncture and local instillations of antibiotics with some improvement. The broncho-pleural fistula was closed. After that he was well and sputum negative until 1967, when he developed fever and cough and expectorated large quantities of pus (Fig. 8). Sputum and pleural pus were negative for tubercle bacilli but positive for

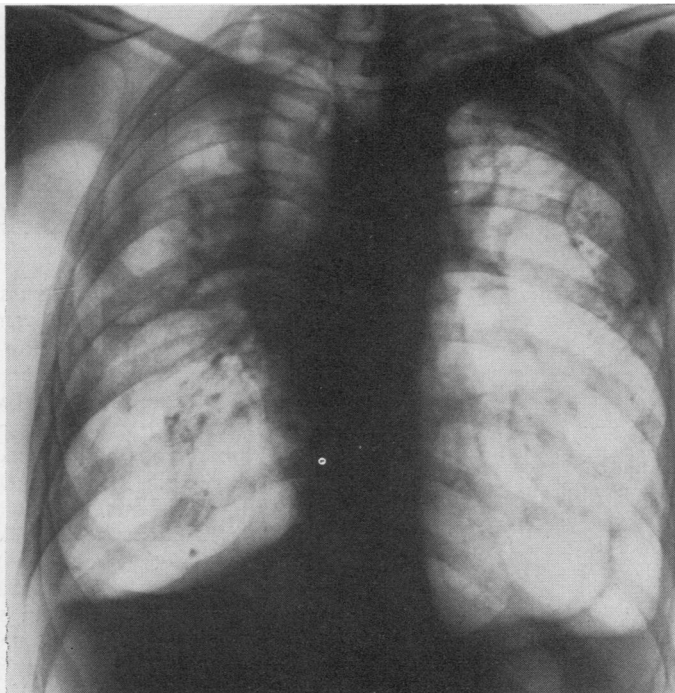


FIG. 7. Case 9. Right pleural empyema with masses corresponding to aspergilloma in the upper part.

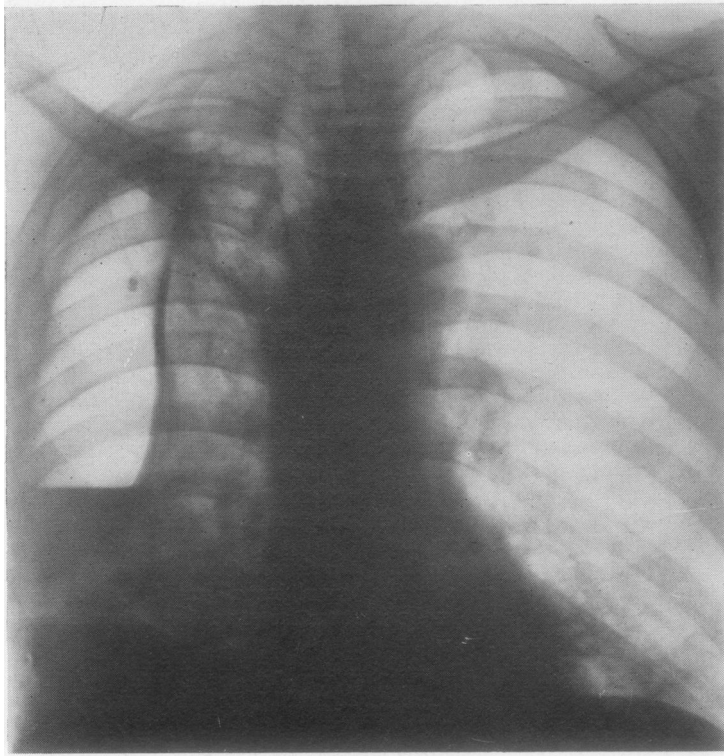


FIG. 8. Case 10. Right pleural empyema with collapse of the right lung and fluid level after pneumo- and oleothorax treatment.

Klebsiella pneumoniae and *Staph. aureus*. A serum precipitin test with *A. fumigatus* antigens was negative at that time. He was treated with antibiotics locally into the pleural space, but after a transient improvement of seven months' duration a second deterioration occurred. At that time *A. fumigatus* was cultured from the sputum and pus. Microscopical examination of the sputum and pleural pus revealed numerous fungal hyphae. Serum precipitin tests with *A. fumigatus* filtrates became positive. The pleural space was drained and nystatin was instilled locally; after that amphotericin B and rifamycin were started. At present, cultures of the pleural pus are still positive for *A. fumigatus*. The general condition of the patient is, however, improved.

DISCUSSION

Among the many diseases of the chest caused by *A. fumigatus* infection of the pleura has relatively seldom been reported. It probably occurs, however, much more frequently than is generally recognized, as is shown by the study of Luizy, Mathey, Le Brigand, and Galey (1966).

In 31 patients with a pleural empyema these authors observed three cases of pleural aspergillosis.

Pleural aspergillosis occurs mostly in established cases of pleural empyema with a broncho-pleural fistula. It may develop as a post-operative complication following resection of lung tissue (Monod, Dieudonné, and Tardieu, 1964). Five cases of pleural aspergillosis after surgical resection of tuberculous lung tissue have been reported by Belcher and Plummer (1960), Golebiowski (1958), and Sitkowski, Piotrowski, and Kryszkiewicz (1959). Sochocky (1959) has described aspergillosis of the pleura in two cases after resection of lung cancer, and Barlow (1954) in one patient after resection of an aspergilloma of the lung. Infection of tuberculous empyema by *A. fumigatus* has been reported by Krakówka, Chodkowska, Klott, and Kochanowicz (1962), Fréour, Laumonier, Carré, Potaux, and Morvan (1963), Fourchon and Lancestre (1964), and Tardieu, Dieudonné, Monod, and Atchoarena

(1964). These latter authors have also described a case of post-pneumonic empyema secondarily infected by *Aspergillus*. Morel, Maret, Peltier, Delgrove, and Routier (1961) and Salfelder, Capretti, Hartung, and Moncada Reyes (1961) have described cases of infection of the pleura in the course of pulmonary aspergillosis.

In the cases of established empyema of other origin additional aspergillous infection may cause new clinical manifestations. Undiagnosed mycosis of the pleura may lead even to death, as has been reported by Sitkowski *et al.* (1959), whose patient developed infection of the pleura after resection of lung tissue.

The diagnosis of fungal infection of the pleura can be established easily. The presence of brown clumps containing fungal hyphae in the pleural pus or abundant growth of *A. fumigatus* on Sabouraud's medium are to be noted. Antibodies against aspergillus antigens can be found in the blood serum by means of precipitation tests in agar-gel. Determination of the correct diagnosis permits local administration of a suspension of antimycotic drugs which are effective in sterilizing the pleura for fungi.

In five of our patients, fungal infection followed the occurrence of a pleural empyema which has been a complication of pneumothorax therapy. In Cases 7 and 9, *A. fumigatus* was the only micro-organism recovered from the pus and all of the patients' symptoms might have been attributed to this infection. In Cases 6 and 10 infection of the pleura was of mixed origin. The return of the body temperature to normal in Case 6 after local treatment with nystatin is evidence of the significance of fungal infection in causing clinical symptoms. In Case 8 *Ps. aeruginosa* was recovered from the pus and infection by *A. fumigatus* was only an additional finding. In two cases, 7 and 8, spontaneous necrosis of fungi unrelated to nystatin therapy was observed.

The diagnosis was made in one case only after necropsy. In seven cases the diagnosis was made on the basis of culture of *A. fumigatus* from the pleural pus. In six of these cases *A. fumigatus* hyphae were also found. In two cases numerous clumps composed of fungal hyphae were recovered from pus but cultures did not yield a growth of fungi which was evidence of spontaneous necrosis. In both cases a small broncho-pleural fistula was recognized and the spontaneous necrosis of the fungi could possibly have been due to insufficient passage of air into the empyema space. Precipitins against filtrates of *A. fumigatus* were found in all seven cases investigated.

In seven cases a mixed infection of the empyema was found, fungi, tubercle bacilli, and other bacteria being isolated. In view of the presence of lung lesions and the mixed character of the infection in the majority of cases, it is difficult to estimate the pathogenic role of *A. fumigatus* in causing the clinical symptoms. Only three cases with healed tuberculosis, fever, cough, and a serious general condition could be related to fungal infection. The symptoms disappeared following sterilization of the pleura for fungi, thus confirming the link.

Aspergillosis of the pleura only seldom gives rise to radiographic appearances. A thickening of the pleura due to a fungal infection and the development of an aspergilloma within the empyema space has been seen radiographically in only two cases. In the remaining cases thickening of the pleura related to the pleural empyema was observed.

The local instillation of nystatin is an effective therapeutic method and within a few weeks the pleura is sterile for fungi. This treatment was effective in six of our seven patients in whom it was performed. The seventh patient is still having treatment.

Five patients died, but in no case was death related to the fungal infection.

REFERENCES

- Barlow, D. (1954). Aspergillosis complicating pulmonary tuberculosis. *Proc. roy. Soc. Med.*, **47**, 877.
- Belcher, J. R., and Plummer, N. S. (1960). Surgery in bronchopulmonary aspergillosis. *Brit. J. Dis. Chest*, **54**, 335.
- Fourchon, J., and Lancestre, G. (1964). Aspergillome pleural. *J. franç. Méd. Chir. thor.*, **18**, 679.
- Fréour, P., Laumonier, P., Carré, J. C., Potaux, L., and Morvan, A. (1963). Sur un volumineux aspergillome intra-pleural. *J. franç. Méd. Chir. thor.*, **17**, 419.
- Golebiowski, A. K. (1958). Pleural aspergillosis following resection for pulmonary tuberculosis. *Tubercle*, **39**, 111.
- Krakówka, P., Chodkowska, S., Klott, M., and Kochanowicz, J. (1962). Dwa przypadki zakażenia ropniaka opłucnej grzybem *Aspergillus fumigatus* u chorych na gruźlicę płuc. (Two cases of *Aspergillus fumigatus* infection of empyema in patients with pulmonary tuberculosis.) *Gruźlica*, **30**, 259.
- Luizy, J., Mathey, J., Le Brigand, H., and Galey, J. J. (1966). Technique d'irrigation pleurale sous dépression continue dans le traitement des pyothorax (premiers résultats cliniques). *Rev. Tuberc. (Paris)*, **30**, 393.
- Monod, O., Dieudonné, P., and Tardieu, P. (1964). Les aspergilloses pulmonaires post-opératoires. *J. franç. Méd. Chir. thor.*, **18**, 579.
- Morel, Maret, Peltier, Delgrove, and Routier (1961). Aspergillome pleuro-pulmonaire secondaire et récédive contro-latérale après exérèse. *J. franç. Méd. Chir. thor.*, **15**, 577.
- Salfelder, K., Capretti, C., Hartung, M., and Moncada Reyes, F. (1961). 2 casos poco comunes de aspergilosis pulmonar y pleural. *Mycopathologia (Den Haag)*, **14**, 78.
- Sitkowski, W., Piotrowski, A., and Kryszkiewicz, T. (1959). *Aspergillus fumigatus* jako przyczyna powikłania pooperacyjnego. (*Aspergillus fumigatus* as the cause of post-operative complications.) *Gruźlica*, **27**, 1069.
- Sochocky, S. (1959). Infection of pneumonectomy space with *Aspergillus fumigatus* treated by "Nystatin". *Dis Chest*, **36**, 554.
- Tardieu, P., Dieudonné, P., Monod, O., and Atchoarena, J. B. (1964). Aspergillomes pleuraux. *J. franç. Méd. Chir. thor.*, **18**, 591.