isoniazid and *p*-aminosalicylic acid. In carrying out the sensitivity tests there was no evidence that the growth of the mould was stimulated *in vitro* by low concentrations of the antibiotics.

Active research is at present being carried on in many centres to develop fungistatic agents, and certain information is now available on the new antifungal antibiotic nystatin, which has been used in certain fungus infections, particularly intestinal moniliasis (Newcomer *et al.*, 1954-5). With the possibility of similar agents becoming available for the treatment of fungal infections, it is clear that an aspergillus infection should be considered in every case where a respiratory infection fails to respond to antibiotics, particularly if lung destruction is present. In such cases special attention should be paid to examination of the sputum for moulds both by direct means and especially by culture. In direct wet preparations the mature conidiophores of *A. fumigatus* have a pale-brown colour, and their resistance to 4% caustic soda permits the use of this substance to digest the sputum and so facilitate their recognition. Mycelial fragments may also be detected by the periodic-acid-Schiff reaction, which is invaluable for the detection of fungi in paraffin-wax sections of sputum or tissue, although we have had no experience of its use in direct wet preparations.

The strain isolated from this case produced an abundant growth on blood agar after 48 hours' incubation at 37° C. When there is heavy bacterial contamination of the sputum, penicillin and streptomycin may be added to the medium to inhibit other organisms (Conant *et al.*, 1954). The fungus is identified by its colonial appearance and its microscopical morphology. For the latter purpose a portion of the growth may be mounted in a drop of lactophenol cotton blue, or, to obtain better preparations, agar block culture should be used.

Although there is no evidence that the antibiotics caused the patient's death, it seems likely that they favoured the saprophytic development of a fungus which led finally to direct invasion of the tissues and death.

Summary

A case of pulmonary aspergillosis complicating a diffuse bacterial pneumonia is described. Although there is no evidence that antibiotic treatment caused the patient's death, it seems likely that the antibiotics favoured the saprophytic development of a fungus which finally directly invaded the tissues and led to a fatal outcome.

Methods of investigating and treating similar cases are put forward.

We would like to thank Mr. C. A. Lambourne for technical assistance and photography.

REFERENCES

- Abbott, J. D., Fernando, H. V. J., Gurling, K., and Meade, B. W. (1952). *British Medical Journal*, 1, 523.
 Conant, N. F., Smith, D. T., Baker, R. D., Callaway, J. L., and Martin, D. S. (1954). *Manual of Clinical Mycology*, 2nd ed. Saunders, Philadelphia.
 Hinson, K. F. W., Moon, A. J., and Plummer, N. S. (1952). *Thorax*, 7, 317.
 Newcomer, V. D., Wright, E. T., and Sternberg, T. H. (1954-5). *Antibiotics Annual*, p. 686. New York.
 Rankin, N. E. (1953). *British Medical Journal*, 1, 918.
 Virchow, R. (1856). *Virchows Arch. path. Anat.*, 9, 557.

Minerva Nucleare, a new addition to the group of medical journals published by Edizione Minerva Medica, Turin, is a bi-monthly devoted to nuclear biology and medicine. It is the official organ of the Società di Biologia e Medicina Nucleare. Annual subscription is 4,000 lire, and the journal is obtainable from 83, Corso Bramante, Turin.

BRONCHO-PULMONARY ASPERGILLOSIS

REPORT OF A CASE

BY

J. G. STEVENSON, M.D., F.R.F.P.S.

AND

J. M. REID, M.B., M.R.C.P.Ed.

*From the Thoracic Unit, Mearns Kirk Hospital,
Renfrewshire*

Fungal infections of the lungs were first described in a variety of animals early in the nineteenth century, birds and horses being the commonest victims. The credit for the first account of this infection in human beings is given to Hughes Bennett (1842), but some doubt exists as to the validity of his description of the infecting fungus. The earliest definite identification of the aspergillus came from Sluyter (1847). Since that date the world literature on this subject has grown progressively, but contributions from this country have been sparse.

In 1952, however, broncho-pulmonary aspergillosis was admirably reviewed in this country by Hinson *et al.* In their paper eight new cases were reported, the mycology and literature considered exhaustively, and reference was made to both medical and surgical treatments for the condition. Resection measures were applied where the infection was confined to a lobe or a lung. In the medical management of more general disease "M. and B. 938" (4 : 4'-diamidinodiphenylamine dihydrochloride) was used both as an inhalant and an intravenous medication.

The case now described is of interest in that (1) it arose in a man working in close proximity to a cotton-mill; (2) the initial diagnosis was that of possible lung cancer; and (3) the correct diagnosis became obvious when *Aspergillus fumigatus* was grown on pure culture from aspiration material obtained at bronchoscopy. This led to the intravenous use of hydroxystilbamidine with considerable and sustained improvement in the clinical and radiological pictures.

Case History

The patient, a man of 62 years, had worked from the age of 26 onwards as a brass-dresser in a foundry. For many years before this present illness developed the premises adjacent to his place of employment had been used as a cotton-mill. His position while working exposed him to heavy clouds of cotton dust which emanated from the mill. Bronchitic afflictions, according to him, were common amongst his co-workers.

In August, 1955, he sustained a back injury when a heavy beam fell on him from a moderate height. No skeletal damage resulted, but he dates his symptoms of cough and sputum production from this event. In the next few weeks the cough became increasingly troublesome and was accompanied by progressive exertional dyspnoea. The coughing was so severe that vomiting occurred on several occasions. The sputum was copious and mucopurulent, but never blood-stained. Lassitude was marked, but there was neither chest pain nor undue weight loss. These symptoms led to radiological examination of the chest with the discovery of an excavated lesion in the left lung, and his admission to the Thoracic Unit, Mearns Kirk Hospital, on November 29, 1955.

Clinical examination showed a pale, thin, lethargic man, with slight finger clubbing, but no cyanosis or dyspnoea at

rest. A chest radiograph revealed a large abscess cavity with a fluid level occupying the greater part of the left lower lobe, and scattered infiltrative changes throughout the remainder of both lungs. The two possibilities of neoplasm with abscess formation and of tuberculosis were considered, and bronchoscopy under local analgesia was performed. There were copious purulent secretions, and the mucosa of the left main bronchus was severely congested. A random mucosal biopsy from the origin of the apex of the left lower lobe bronchus showed only severe non-specific inflammatory change.

A diagnosis of pyogenic lung abscess was made, and tetracycline therapy was instituted without improvement. Serial cultural examinations of the sputum failed to reveal tubercle bacilli; instead *A. fumigatus* was grown in almost pure culture. This finding being insufficient to establish a diagnosis of aspergillosis, bronchoscopy was repeated on January 3, 1956, with aspiration of bronchial secretions. The specimen was reported on as follows: "One fungus only was present, and on microscopic examination it was identified as an *Aspergillus* species. Careful examination of the microscopic characteristics and of the colonies on Czapek's solution of agar were carried out. The form and measurements of the smooth conidiophores and flask-shaped vesicles with the single series of crowded sterigmata conformed to those given by Thom and Raper (1945) for *A. fumigatus* Fresenius. The colonies were of the velvety strain described by the authors, at first white, becoming dark green to almost black with age, and with the reverse, which was at first colourless, becoming pale brown in two to three weeks."

Intravenous hydroxystilbamidine therapy was thereupon instituted, and two ten-day courses of 0.15 g. daily were administered, with a seven-day rest between courses. Progressive clinical and radiological improvement resulted. Oral nystatin therapy in a dosage of 500,000 units thrice daily followed the second course of hydroxystilbamidine and was continued for eight weeks. During this time albuminuria was noted, and a mid-stream specimen contained numerous pus cells and red blood cells, with only a very light growth of neisseriae on culture. No yeast-like structures were discovered, and no further renal investigations were undertaken.

The patient was discharged from hospital on March 3, 1956, much improved. He continued to report at intervals for out-patient supervision. At his last attendance on August 30 x-ray examination showed further clearing and the abscess cavity had almost totally disappeared. There was corresponding reduction of the infiltrative changes. His general condition, however, had deteriorated in the previous two months, and he complained of lassitude, some weight loss, and frequency of micturition. One month later he died at home after a rapid terminal illness in which urinary symptoms with incontinence and lower limb oedema were prominent. No post-mortem examination was carried out.

Discussion

Isolation of *A. fumigatus* from the sputum is of quite frequent occurrence. In the past such a finding has been the basis of a diagnosis of broncho-pulmonary aspergillosis in some cases, but, as Hinson *et al.* (1952) pointed out, such diagnoses are tenuous. These authors indicated more rigorous diagnostic criteria, the corner-stone of which was histological examination of the diseased tissue, which they were able to carry out in all three of their cases. In our case such examination was impossible, as necropsy was not performed, and resection treatment was not feasible in the earlier part of the illness. Instead the sputum findings were confirmed by cultural isolation from bronchial secretions of a solitary fungus identified as *A. fumigatus* Fresenius. In addition the response to hydroxystilbamidine therapy, although temporary, was gratifying, and seemed to support the diagnosis. The patient showed progressive radiological improvement over the space of nine months. Riddell (1956) mentions the efficacy of inhalations of nystatin, brilliant

green, or hydroxystilbamidine in *A. fumigatus* infections, but his paper was not published until after the death of our patient.

Aspergillosis may be a primary infection, or, probably more frequently, it may involve tissues already damaged by disease—for example, bronchiectasis, bronchial carcinoma, or tuberculosis. In the present case the initial diagnosis rested between a tuberculous excavation, and a lung abscess either of primary type or secondary to lung neoplasm. Serial bacteriological culture ruled out the former, while bronchoscopy coupled with the progressive nine-month period of radiological improvement excluded the latter. This infection was therefore felt to be primary in origin. Marshall and Perry (1952) described three types of primary involvement: (1) acute tracheo-bronchitis or (2) bronchopneumonia, both of which are rare; and (3) a chronic process simulating either tuberculosis or neoplasm. The third category would appear to cover our case.

An interesting feature of the case, and one which must remain a matter of conjecture, is the possibility of a secondary renal involvement by the fungus, presumably due to haematogenous spread, which has been reported in the literature. Death resulted in circumstances which suggested renal failure, although previous examination of the urine while the patient was in hospital failed to reveal the fungus. Presumably, too, if renal involvement had been present it would appear that the stilbamidine therapy had been ineffective.

A final point concerns the occupational history and requires little stressing. The disease occurs predominantly in those handling infected grain, flour, etc. (Norris and Landis, 1920; Davidson, 1948). Heppleston and Gloyne (1949) mentioned its occurrence in coal-miners.

Summary

A case of primary broncho-pulmonary aspergillosis which ended fatally despite a temporary favourable response to hydroxystilbamidine and nystatin therapy is described. Death occurred in circumstances suggesting renal failure, though *Aspergillus fumigatus* had not been isolated from the urine.

We acknowledge with pleasure the assistance afforded us by Mr. R. S. Barclay, thoracic surgeon, in whose ward the patient was treated. We are indebted for the careful bacteriological investigations to Dr. L. G. Bruce, consultant bacteriologist, and also Mr. J. C. Gentles, medical mycologist, at the Western Infirmary, Glasgow.

REFERENCES

- Bennett, J. H. (1942). *Trans. roy. Soc. Edinb.*, 15, 277.
 Davidson, M. (1948). *A Practical Manual of Diseases of the Chest*, p. 478. Oxford Univ. Press, London.
 Heppleston, A. G., and Gloyne, S. R. (1949). *Thorax*, 4, 168.
 Hinson, K. F. W., Moon, A. J., and Plummer, N. S. (1952). *Ibid.*, 7, 317.
 Marshall, G., and Perry, K. M. A. (1952). *Diseases of the Chest*, 1, 175. Butterworth, London.
 Norris, G. W., and Landis, H. R. M. (1920). *Diseases of the Chest*, p. 400. Saunders, Philadelphia.
 Rénon, L. (1897). *Etude sur l'Aspergilliose chez les Animaux et chez l'Homme*. Masson, Paris.
 Riddell, R. W. (1956). *British Medical Journal*, 2, 783.
 Sluyter, F. T. (1847). *Inaug. Diss.*, Berlin, p. 14. Cit. Rénon (1897).
 Thom, C., and Raper, K. B. (1945). *A Manual of the Aspergilli*. Williams and Wilkins, Baltimore.

Milk can now be frozen and stored for at least a year without deterioration, it is claimed. A method of doing this has been developed by the National Institute for Research in Dairying, with financial support from the National Research Development Corporation, and is discussed in the corporation's annual report published last month (H.M.S.O., price 1s. net). Pasteurized milk is treated with ultrasonic waves, poured into polythene bags, and quickly frozen in a brine bath. The report mentions the commercial possibilities of frozen milk, which include "the provision of fresh milk for passengers throughout long sea-voyages, storage of milk during times of over-production, and shipment to countries where good-quality fresh milk is unobtainable." The corporation, to whom the patent rights have been transferred, has licensed two British firms, who expect to go into production shortly.