PULMONARY ASPERGILLOSIS

REPORT OF A CASE

BY

C. S. DARKE, M.D., M.R.C.P.

Consultant Physician, City General Hospital, Sheffield

A. J. N. WARRACK, M.B.E., M.D., D.T.M.&H.

Consultant Pathologist, City General Hospital, Sheffield

AND

J. E. M. WHITEHEAD, M.A., M.B., B.Chir.

Dip. Bact.

Deputy Director, Public Health Laboratory (M.R.C.),
Sheffield

[WITH SPECIAL PLATE]

A century has elapsed since Virchow (1856) first reported the post-mortem findings of pulmonary aspergillosis, and many cases of this disease have subsequently been described. While pulmonary aspergillosis as a primary infection remains a rare and mainly occupational disease, its occurrence as a fatal complication of bacterial infections of the lung treated with antibiotics has become important with the increasing use of these agents for the treatment of pulmonary diseases. Fatal cases have recently been described by Abbott *et al.* (1952) and by Rankin (1953), although in the latter instance agranulocytosis and a monilial infection were also present. The object of this report is to describe another case of aspergillosis which proved fatal, and to suggest that it is an example of secondary rather than primary infection.

Case History

A male road worker aged 63 was admitted to hospital on the 18th day of a respiratory infection. The illness began acutely with fever, cough, and left pleuritic pain, and initial treatment was with sulphonamides. There was some response, but later a relapse set in with increasing breathlessness and right-sided pleurisy. A routine chest radiograph taken two years previously during investigation for schizophrenia showed calcified tuberculous lesions, moderate emphysema, and pleural thickening at the base of the right lung.

Clinical examination now indicated bronchopneumonia with a severe bilateral pleurisy, and a radiograph showed mottled opacities in the right lower lobe and base of the right upper lobe. Culture of the sputum, which was mucoid, yielded a heavy growth of *Streptococcus viridans* and a scanty growth of *Neisseria catarrhalis*. Pneumococcus Type XXVII was isolated by mouse inoculation. Blood culture was sterile.

Tetracycline, 0.5 g. six-hourly for 4 days and then 0.25 g. six-hourly for 8 days, was given. Despite this therapy the temperature ranged from 97.6 to 102° F. (36.4 to 38.9° C.) for the next 14 days. The general response was poor and quite unlike that expected in the ordinary case of pneumococcal infection. A chest radiograph taken eight days after admission showed the appearance of bronchopneumonia throughout the whole of the right lung with excavation in the upper lobe. Weakness, delirium, and a flushed facies developed, and 14 days after admission the sputum, which had remained essentially mucoid, became russet-brown and later black in colour. A further radiograph at this time showed progressive bronchopneumonic consolidation in the right lung with spread to the left upper lobe. Chloramphenicol, 2 g. followed by 0.5 g. six-hourly, was given by mouth for the next three days, and finally one intramuscular injection of 200 mg. of pentamidine as

well as potassium iodide by mouth. Mental confusion and early heart failure developed shortly before the patient's death 19 days after admission and on the 37th day of the disease.

A leucocyte count showed a polymorphonuclear leucocytosis rising in 20 days from 12,000 to 29,000 per c.mm. A radiograph taken on the day before death showed extension of the disease to the whole of both lungs with multiple abscess formation, particularly in the upper lobes. Culture of the sputum at intervals showed little change in the bacteriological flora, which throughout remained sensitive to tetracycline and chloramphenicol. No acid-alcohol-fast bacilli were found on several examinations. Complement-fixing antibodies to influenza virus A and B, to the psittacosis-LGV group of viruses, and to *Rickettsia burneti* were not detected. Cold agglutinins and agglutinins against *Streptococcus M.G.* were not found.

In view of the lack of clinical response, and unusual radiological course, and the colour of the sputum, a secondary fungus infection of the lung was suspected. Direct examination of the sputum for yeast or mycelial fragments was consistently negative, but a specimen taken two days before death yielded, after 48 hours, a growth of a fungus which was identified as *Aspergillus fumigatus*.

Post-mortem Examination.—Positive findings were confined to the respiratory system. The larynx, trachea, and main bronchi showed congestion only. There were old pleural adhesions on the anterior surface of both upper lobes. Both lungs showed extensive pneumonic consolidation with a scattered cystic appearance. This was particularly marked in the left lower lobe, where there were small, ragged abscess cavities. Thrombosis of the small pulmonary arteries was evident in the left lung. Wet preparations of scrapings from the abscesses revealed the fruiting heads of an *Aspergillus*. Cultures taken under sterile precautions from the main bronchi and from two separate lung lesions yielded a heavy growth of a mould of the genus *Aspergillus*, which was kindly identified for us as *A. fumigatus* by Dr. Jacqueline Walker, of the Mycological Reference Laboratory. A scanty growth of this mould was also obtained from the spleen.

In the lungs the general histological picture was that of a resolving pneumonia with abscess formation. In the left upper lobe there was an acute inflammatory exudate, mainly cellular, but fibrinous in some places. Other areas showed similar pneumonic changes with abscesses but with evidence of some resolution. Most of the abscesses were lined by a layer of fungal mycelia about 10 μ thick, and in one cavity the characteristic fruiting bodies of *A. fumigatus* were found (see Special Plate). The bronchial mucosa was mainly intact, and the bronchioles contained pus but no fungal mycelium.

Discussion

Although death was due to a diffuse bacterial pneumonia and pulmonary arterial thrombosis, there was histological evidence that resolution of the pneumonia had begun. Antibiotic therapy had, however, failed to limit the spread of pneumonia, and was complicated by the growth of a fungus which had invaded necrotic areas in both lungs. The eradication of a fungus infection in these circumstances is difficult, although in this instance specific therapy was employed only terminally.

In cases of pulmonary aspergillosis, iodides in full doses and neoarsphenamine have been used (Conant *et al.*, 1954), although they were found by Hinson *et al.* (1952) to be of no value in two of their cases. The latter authors state that *A. fumigatus* was inhibited *in vitro* by "M. and B. 938" (4:4'-diamidinodiphenylamine dihydrochloride) in a concentration of 1 in 100,000. This substance was used by them in one case with equivocal results, and unpleasant hypotensive symptoms followed intravenous injection.

In the present case the strain of *A. fumigatus* was found to be resistant to the commonly used antibiotics and also to

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.

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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.

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

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J. SHARP: ANKYLOSING SPONDYLITIS

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FIG. 1.—Antero-posterior views of left sacro-iliac joints. *a.* Male aged 24 with typical ankylosing spondylitis, showing large erosions of joint surfaces and fluffy juxta-articular bone sclerosis. *b.* Female aged 42 with severe rheumatoid arthritis, showing erosions of lower parts of joints with slight sclerosis of adjacent ilium. *c.* Male aged 35, following recurrent rheumatic fever since age of 9, showing erosions of joint surfaces, slight juxta-articular bone sclerosis, and partial fusion. *d.* Male aged 34 with Reiter's disease, showing erosions of joint surfaces and juxta-articular bone sclerosis. Appearances in *c* and *d* are indistinguishable from those in ankylosing spondylitis.

Aspergillus fumigatus, showing characteristic fruiting body. (×525.)

FIG. 2.—Lateral radiographs of cervical spine. *a.* Male aged 45 with advanced typical ankylosing spondylitis, showing ossification of margins of disks with retention of normal central disk spaces, "squaring" of vertebral bodies, and bony ankylosis of some apophyseal joints. *b.* Female aged 63 with severe rheumatoid arthritis, showing narrowing of multiple disk spaces with irregularity of adjacent vertebral plates and erosions and ankylosis of apophyseal joints. *c.* Female aged 24 whose rheumatoid arthritis started at age of 2, showing hypoplasia of vertebrae, gross narrowing of disk spaces, fusion of margins of adjacent vertebral bodies, and bony ankylosis of apophyseal joints. *d.* Same patient as Fig. 1c, showing hypoplasia of lower vertebrae, narrowing and ossification of disks, and bony ankylosis of apophyseal joints. *e.* Male aged 44 with Reiter's disease, showing ossification of both anterior longitudinal ligament and disk margins.

FIG. 3.—Lateral radiographs of lumbar spine. *a.* Male aged 52 with typical ankylosing spondylitis, showing osteoporosis, ossification of disk margins, "squaring" of vertebral bodies, and bony ankylosis of apophyseal joints. *b.* Patient illustrated in text. Appearances normal. Radiographs of cervical spine revealed bambooing of multiple disk spaces. *c.* Same patient as Figs. 1c and 2d, showing slight antero-posterior narrowing of vertebral bodies, narrowing of multiple disk spaces without osteophytosis, and small infarctions in opposed vertebral plates of upper two vertebrae surrounded by sclerosed bone. *d.* Same patient as Fig. 2e, showing ossification of anterior longitudinal ligament. *e.* Male aged 66 with "senile ankylosing hyperostosis," showing massive new bone formation on anterior aspects of vertebral bodies and posterior articular processes.