Case of Aspergillosis Treated with Amphotericin ‘B’

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The problem of pulmonary aspergillosis is not new. The genus of moulds “Aspergillus” was described and named by Micheli in 1729. The name was probably given because of the similarity of the spore-bearing heads, and the brush used for sprinkling holy water (aspergillum).

This fungus was first found to be invasive in 1815 by Mayer, who discovered it in the lungs of a jay, later by others in different birds, and still later, in 1887, in a laryngeal swelling in a horse.

Fungus infection in man was probably first described by Hughes Bennett in 1842 in the Transactions of the Royal Society of Edinburgh. The fungus in this case was thought at that time to be a penicillium, but may have been a species of aspergillus. The same year a more or less similar case was described in Germany, and in 1855 a fungus infection was found in a patient who also had cancer of the lung.

The first unquestioned case of human pulmonary aspergillosis was described by Sluyter in 1847 in Berlin, and in 1856 Virchow collected four cases of pulmonary aspergillosis in patients dying of other diseases. Virchow’s account (the only one in the history of the disease mentioned in Garrison-Morton) begins, as we still must begin, with the problems of definite diagnosis, and a rather vexed statement of the special problems of mycology.

One might note in passing the preponderance of cases from the European mainland. The best readily available history of the disease is given by Hinson et al in Thorax, December 1952.

This fungus can be grown on simple media. Sabouraud’s media is often used, but ordinary blood agar is reported to be adequate for primary isolation. Clayton has pointed out recently that fungi may be separated more readily by incubating cultures at both 22 degrees room temperature, and 37 degrees centigrade simultaneously. Penicililum, for example, grows more commonly at 22 degrees, but aspergillus fumigatus at 37 degrees. Aspergillus may be incubated at temperatures up to 45 degrees centigrade which may be of further help in differentiating it. If sub-cultures are made on medium containing penicillin and streptomycin, to which aspergillus is resistant, bacterial contamination should be eliminated.

A colony of aspergillus is a white mass of interweaving mycelial threads, from which occasional cells enlarge known as “foot cells.” These give off a shoot which elongates upward, and bears a swollen vesicle at its free uppermost extremity. From this vesicle shorter stalks arise like the bristles of a brush (phialides), and on these, in turn, are born the spores (conidia). These may be coloured, giving the different tints to the mature colonies, and assisting in separating the genus into at least four groups, pathogenic to man, of which aspergillus fumigatus is much the most common (Figure 1).

The fungus is common in soil and decaying matter (compost piles,}

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spoiled grain, hay, straw and rotting wood). It is also a common pathogen of birds. These two factors explain the occurrence of the disease among agricultural workers, and those dealing with birds (bird crammers). However, the ubiquity of the spores assures the occurrence of the disease among all groups.

It is improbable that the fungus is always a secondary invader of already diseased tissue such as has been suggested occasionally. A primary form does occur, but it is not as common as the secondary variety. Riddell grew *aspergillus fumigatus* from 55 patients of 1,060 consecutive admissions to Brompton Hospital, twelve of whom were treated for bronchitis, eleven for asthma, seven for pneumonia, two for tuberculosis, four for carcinoma of the lung, two for lung abscess, one for sarcoidosis, three for heart disease, and five for diseases other than pulmonary. The remaining eight cases were treated for aspergillosis, but in at least two of the others listed, mycetomas were present along with the presenting disease.

In order to assess the frequency of fungal infections (whether pathogenic or not) in this area, we cultured sputum for fungi from a more

or less random group of older admissions to this sanatorium between March and July, 1959. Seventy cases were examined. In 26, no fungi were found; in 11, candida albicans was found; in 33, aspergilli were found. This indicates either an unexpectedly high incidence of infection with aspergilli, or a peculiar enthusiasm for the fungus in our laboratory. The diagnoses in the 33 patients growing aspergilli were later proven to be tuberculosis (10), asthma, bronchitis and emphysema (9), heart disease (5), bronchogenic carcinoma (3), lung abscess (2), empyema (1), and one whom we strongly suspect was another case of aspergillosis. Two cases were undiagnosed. There did seem to be a slight rise in incidence during the middle period when our weather is quite damp, with perhaps a little less in the colder and warmer periods, though much more work would be needed to prove this. Of those whose sputum grew aspergilli, 14 were skin tested with the antigen, and of these, 8 showed positive reactions. In 2 of these at least, the finding may have been of importance clinically.

The disease may be classified:

1. Acute — resembling bronchopneumonia.
2. Chronic — including mycetomas, resembling fibroid tuberculosis.
3. Allergic — producing bronchospasm and dyspnea ("Farmer's lung").

The case for discussion now came to our attention in the spring of 1950. The patient, at that time a 32-year-old white housewife, was found to have light infiltration in the first and second anterior interspaces on the right, with somewhat heavier infiltration in the same area on the left. No definite cavity was found on tomographs. She was admitted to the Niagara Peninsula Sanatorium on April 3, 1950. At that time, she was asymptomatic, family and occupational history were non-contributory, and physical examination revealed a normally developed fair-haired, blue-eyed, white woman, of approximately stated age, with no abnormality. All her laboratory examinations were within normal limits, although her differential white count showed only 23 per cent lymphocytes (total white count 9,300). One specimen of gastric washing was reported to be positive for tubercle bacilli on culture. She questioned this, but it was impossible to check the finding when her objection was known. All other sputum and gastric specimens were negative on smear and culture for tubercle bacilli.

She was given approximately 36 grams of streptomycin (1.0 gram per day) along with PAS. Right pneumothorax was established followed by pneumonolysis in May and June, 1950, and left pneumothorax was established in July, followed by pneumonolysis on that side in September, 1950. PAS was continued until her discharge on May 3, 1951.

She returned to her home and resumed light housekeeping for her husband and one son. Fluid formed in the right pleural space in early 1952, and the pneumothorax on that side was abandoned in June, 1952. Fluid obtained on aspiration of the space in May 1952 was negative for tubercle bacilli on smear, but positive on culture. Smear at that time showed abundant white blood cells, polymorphonuclears predominating. No non tubercle bacilli were grown. The left pneumothorax was discontinued uneventfully in July, 1956.
In the fall of 1955, she developed what was thought to be a cold abscess on her right anterior chest wall, above and medial to the breast. This was aspirated on several occasions, but no bacteria were found on smear or culture. She was begun on isoniazid (100 mgms. t.i.d.) and PAS (12.0 grams daily) toward the end of 1955, and these were continued until her second admission in the fall of 1957. During a large part of this time, she was in bed at home.

In June, 1956, the abscess disappeared. She was seen by our consultant surgeon at that time. It was agreed that the condition was probably tuberculous and that nothing other than periodic aspiration, along with her antituberculous drugs was indicated.

Nothing further happened until June, 1957 when she developed pain in the region of the old abscess and the mass re-appeared. She was re-

FIGURE 2: Temperature charts October 11 to December 29, 1957.
admitted on September 21, 1957, and shortly after this admission, in spite of repeated aspiration, the abscess discharged spontaneously, close to the lateral border of the sternum, leaving a chronic sinus about 0.5 cms. in diameter, with slightly overhanging edges. All material cultured from the abscess and sinus was negative on smear and culture for all bacteria.

Chest films on this admission showed an appreciable amount of disease in both lungs, with some suggestion of excavation on the left side.

Following this admission, many (70) specimens of sputum were all negative on smear and culture for tubercle bacilli. Other laboratory data were within normal limits, except that out of a total white count of 10,100, only 7 per cent were lymphocytes. Sedimentation rate was 11 mms. per hour (Westergren).

She had no symptom referable to her respiratory or other systems on admission, and there was no abnormality on physical examination, except diminution of breath sounds (which we associated with the former pleural reaction) on the right side.

She was begun on antituberculosis drugs on September 24, 1957, using streptomycin and PAS alternating month with isoniazid and pyrazinamide.

There was nothing further remarkable, and she continued to feel well (even if somewhat restless and apprehensive) until the day following her first injection of 0.5 c.c. of Asian influenza vaccine on October 26, 1957. At that time, this vaccine was offered to all the patients, and a great many accepted it (in two doses of 0.5 c.c. each) without any symptoms whatever. On October 27, she had malaise and headache, and the following day her temperature rose to 104° degrees F. in the evening. Fever continued each day thereafter for several months (Figure 2). It was usually between 99 and 100° in the morning, rising to 101 or 102 in the afternoon. In spite of this fever, she had remarkably few other symptoms at first, apart from fatigue. Her appetite and weight remained about the same. She had no cough or chest symptoms until the beginning of her fever, when an unproductive cough appeared. After about a week this became productive of dark greenish sputum, about two to three ounces in volume early in December, increasing further to three to four sputum boxes of foul greenish brown sputum by the first of February. This sputum was sufficiently thin to run out of the patient's mouth, when she was turned on her side.

In spite of her illness, the discharge from the sinus in the anterior chest wall decreased, and finally stopped, with healing of the sinus. Roentgenograms failed to show involvement of ribs or sternum. Chest roentgenograms at the beginning of her fever showed no significant change. However, by the end of January, 1958, chest films (including tomographs) showed extensive cavitation in the right upper lung field (Figure 3).

Sputum continued to be negative for tubercle bacilli. Only the common inhabitants of the respiratory tract, including non-haemolytic streptococci and staphylococci and pyocyanes could be cultured. These were reported at various times to be sensitive to tetracycline, streptomycin, erythromycin, chlorotetracycline, and all these were used in the usual doses without any benefit whatever.
A biopsy of the sinus tract was taken. This showed caseous granulomatous inflammation compatible with a diagnosis of tuberculosis, but no acid-fast bacilli or fungi could be identified.

There was a small collection of fluid lying over the apex of the left lung. In an attempt to obtain further material for culture, this was aspirated, but only a few c.c.'s of brownish fluid could be obtained, and this was sterile on culture. Unfortunately, following this aspiration she developed a small tension pneumothorax, which persisted for some months gradually decreasing in size.

Spinal tap was done, and cerebrospinal fluid obtained showed only a few white cells. It too was sterile on culture.

Early in January, 1958, we obtained a culture of aspergillus fumigatus. This was confirmed by the laboratory of the Mountain Sanatorium, and the Laboratory of the Provincial Department of Health in Toronto. We continued to obtain copious growth of this fungus on each occasion when her sputum was cultured until after specific therapy had been begun in February. When this fungus was first reported, we were not convinced it was the cause of her illness.

Examination of her blood showed a falling haemoglobin, which fell even further on treatment (down to 42 per cent by the middle of February, 1958), with a corresponding fall in red blood cells to 2,760,000 at the same time. Her white blood count rose to 15,400 by the end of December, 1957, and then fell somewhat for the next month to about 12,500. During treatment in February, it fell to 5,600 by the middle of the month, and then remained at about seven to eight thousand. She continued to show a low lymphocytic count ranging from 4 per cent to 12 per cent (usually about 6 or 7 per cent) of the total count. At no time did she have remarkable eosinophilia. In November, 1957, her eosinophile count was recorded once early in the month as 7 per cent, and late in the month as 9 per cent, but it varied principally between 1 and 3 per cent. Monocytes did not rise above 6 per cent. Her sedimentation rate rose to 84 mms. per hour (Westergren) by the end of January, 1958, but then

![FIGURE 3: Chest roentgenogram (and tomograph films at 4, 5, 6 and 7 cm levels from the posterior chest wall) January 28, 1958.](image-url)
FIGURE 4: Temperature chart and record of Amphobacterin administration February 1 to April 12, 1968.
gradually fell on specific therapy, and was recorded at 10 mm/hr. in June, 1958.

Electrophoretic fractionation of her serum in January, 1958 showed very low albumin with high alpha, increased beta and high gamma fractions.

When specific therapy was begun in February, she was gravely ill and weighed 94 lbs.

On February 3, 1958, amphotericin-B (Fungizone-Squibb) was begun. It was suggested that the dose be gradually increased to the maximum tolerated, but not to exceed 1.5 mgm. per kilogram of body weight. On the first day, 12.5 mgms. were given intravenously over a period of six hours. She developed some rigor and nausea, but on the following day 25 mgms. were given; the next day 37.5 mgms., and by the fourth day a full dose of 50 mgms. was used. The severity of the rigor and nausea on that day induced us to decrease the dose to 25 mgms. on the fifth day, but on the sixth we resumed the 50 mgm. dose, and this was continued daily (except Sundays), in spite of fevers, nausea and headaches till the middle of March (Figure 4).

During this time, cultures of her sputum for 

aspergillus fumigatus

produced the following record:

January 29: 3 plus growth
February 4: 4 plus
February 6: slight
February 8: 3 plus
February 10: slight
February 11: 3 plus
February 12: 1 plus
February 14: 3 plus
February 17: slight
February 18: slight

All subsequent cultures have shown no fungi up to the present.

The amount of cough and sputum decreased steadily, and the sputum became clear.

The most difficult problem, other than the toxic reaction during this period of amphotericin administration was the preservation of adequate venous channels for the introducing of the drug. A small amount of heparin was added to each bottle of solution in an attempt to solve this problem.

Because of the low haemoglobin in the middle of March, two transfusions of blood were given and the frequency of administration of amphotericin was decreased. On March 22, a small amount of the solution went interstitially. Following this, she had a little increase in expiratory effort, but she did not complain of dyspnea. On March 24, a larger amount of amphotericin escaped into the tissues. After this, she became severely dyspnoeic for several days. This was treated with aminophylline, steroids, and isuprel aerosol, and she gradually improved. The tissue at the site sloughed, and healed slowly. No further amphotericin was given.

After the discontinuance of therapy her fever gradually disappeared, and her general condition improved tremendously. She was allowed
outside walking exercise in June, and was discharged on July 12, 1958. Although her activity is still limited, her condition has remained satisfactory. Chest x-ray films show less excavation on the right.

In spite of the extensive pulmonary involvement, she has no dyspnoea on ordinary activity. However, ventilation studies in May, 1958 showed a total vital capacity of 1.25 litres (44 per cent of predicted normal), and a 3-second vital capacity of 39 per cent of predicted normal.

We feel that this is a case of aspergillosis complicating pulmonary tuberculosis. The relation of the influenza vaccine to the onset of clinical aspergillosis is a mystery. She states that she could never eat chicken without a gastro-intestinal upset and we understand that the vaccine is produced in eggs. Whether some allergic phenomenon lowered her resistance sufficiently to permit invasion by the fungus is a matter of conjecture.

There can be no reasonable doubt that, however severe the reactions to the amphotericin may have been, the drug was life-saving to this patient.

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BIBLIOGRAPHY


