

# Pulmonary aspergillosis: A review and a description of three new cases

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Aspergillosis, a comparatively rare disease in man though a common one in birds, is caused by the aspergillus, a genus of minute fungi which, in common with other fungi, lacks chlorophyll. It is either parasitic or saprophytic and has a particular affinity for decaying vegetable matter. Included among its species are *Aspergillus fumigatus*, *A. niger*, *A. clavatus*, *A. nidulans*, *A. flavus*, and *A. versicolor*, of which *A. fumigatus* is regarded as the most important, and only occasionally have other species been mentioned in connexion with human pulmonary infection (Montes, 1963).

Bennett (1844) was the first to describe a case of fungal invasion of the lungs. The patient suffered from phthisis, but doubt exists as to whether the fungus was an aspergillus. The first case of pulmonary aspergillosis was reported by Sluyter (1847) in a woman dying from a chest illness who had a fungal mass in a lung cavity. The fungus, originally reported as a mucor, was later recognized as an aspergillus.

A series of cases of pulmonary aspergillosis were recorded about this time (Friedreich, 1856; von Dusch and Pagenstecher, 1857; Cohnheim, 1865; Virchow, 1856). The latter described in detail four patients with dysentery, pneumonia, emphysema, and gastric carcinoma, in whom the role of the aspergillus was regarded as secondary.

The first description of an allergic type of aspergillosis was in 1887, by Popoff. A woman of 21 years had symptoms of bronchial asthma, and her sputum was negative for tuberculosis but contained many bronchial casts made up of the mycelium and spores of *A. fumigatus*.

The French contributions to the problem of aspergillosis have been many, especially in the late nineteenth century (Rénon, 1893, 1897; Dieulafoy, Chantemesse, and Vidal, 1890; Dévé, 1938; and Monod, Pesle, and Labeguerie, 1952). Additional significant progress in aetiology and classification has come from Hinson, Moon, and Plummer (1952) and Pepys, Riddell, Citron, Clayton, and

Short (1959), but many facets of the disease are still unexplained.

The following case histories concern three patients in whom aspergillosis was confirmed histologically.

## CASE REPORTS

**CASE 1 (W.W.)** A miner, aged 52 years at the time of admission in 1956, had been unfit for work since 1942. A chest radiograph in 1941 (Fig. 1) had suggested cystic bullae in the left upper lobe. After admission to hospital in 1943 because of a perforated gastric ulcer, pulmonary tuberculosis of the left apex was suspected, and, although the sputum was negative, he was transferred to a sanatorium for one month. Serial radiographs from 1945 (Figs. 2-7) revealed a slowly enlarging, solid mass, lying within a thick-walled cavity in the left upper lobe. Beginning in 1947, haemoptysis of varying degree persisted intermittently. The patient was admitted to hospital in 1956 with a diagnosis of aspergilloma and had additional gross bronchiectasis in the left lower lobe. At bronchoscopy a generally inflamed mucosa was seen but no stenosis of the left upper lobe bronchus. Bronchial washings were cultured for fungi and tubercle bacilli, but only *Candida albicans* was isolated. Sputum examinations were repeatedly negative for fungi. A blood count showed a haemoglobin of 80% (11.8 g./100 ml.); E.S.R. 49 mm. fall in one hour; W.B.C. 9,800/c.mm.; polymorphs 71%; lymphocytes 25%; monocytes 3%; and eosinophils 1%.

Because of inadequate respiratory reserve and bronchiectasis, surgery was considered inadvisable. After discharge the patient survived until 1958 when he developed cor pulmonale due to bronchiectasis and died. At necropsy two adjacent mycetomata were found in the left upper lobe (Fig. 8). The larger of the two consisted of a brownish, putty-like, mycelial mass, lying loose within a thick-walled cavity. Culture after 48 hours at 37°C. produced a pure growth of *A. fumigatus*.

**CASE 2 (B.M.C.)** A clerk aged 22 years was first seen at the chest clinic on 25 May 1955. Six days earlier he had had an haemoptysis which had persisted. The

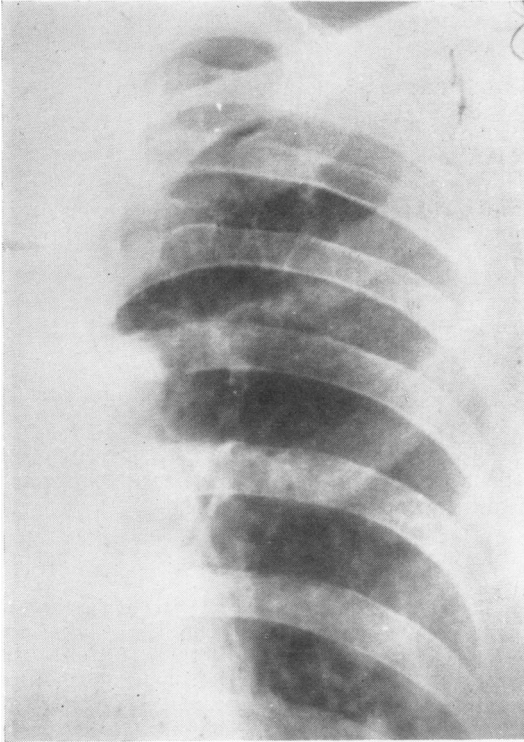


FIG. 1

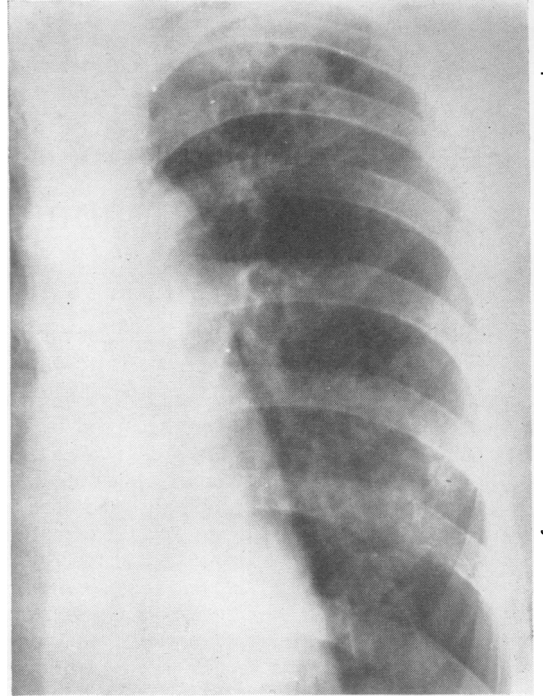


FIG. 2

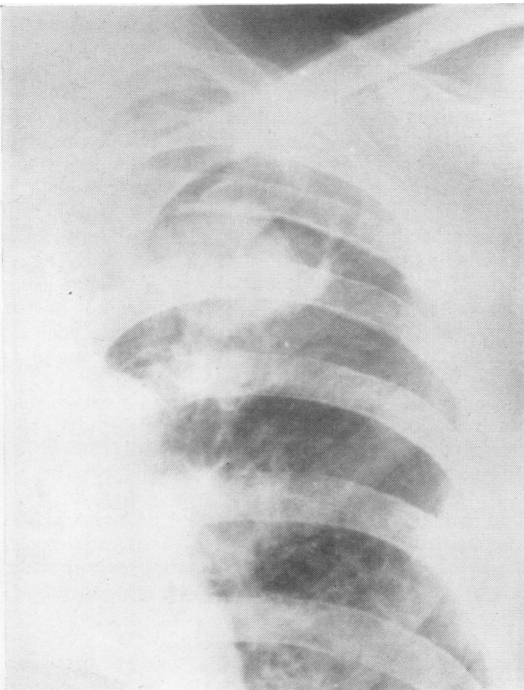


FIG. 3

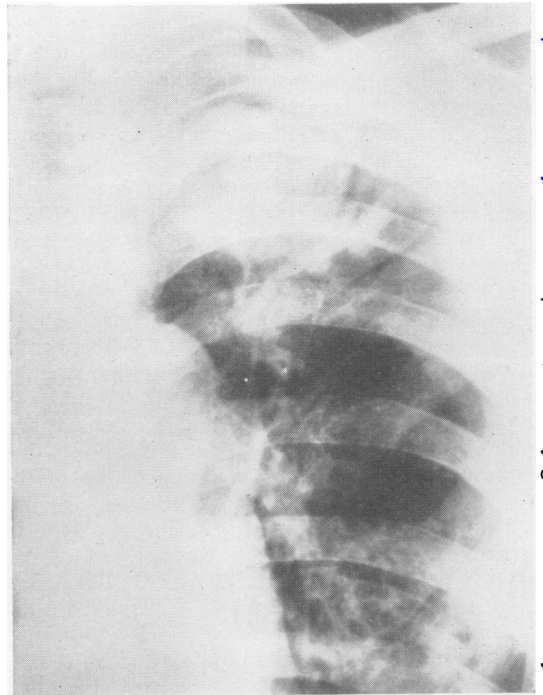


FIG. 4



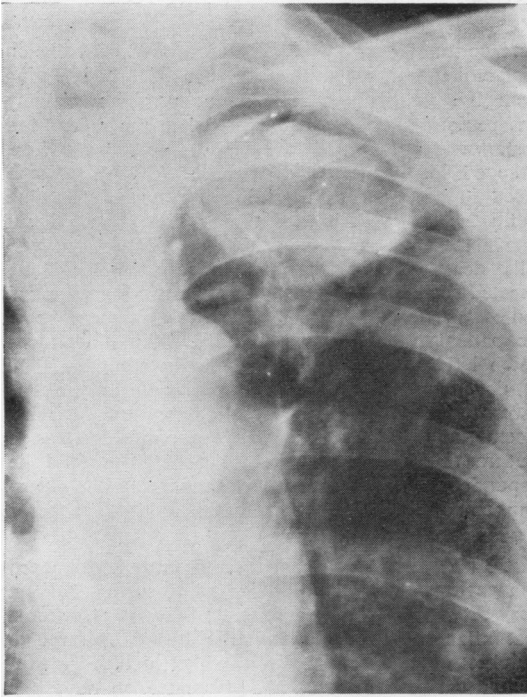


FIG. 5



FIG. 6

FIGS. 1-7. Radiographs covering the period 1941 to 1958 and showing the gradual formation of a mycetoma.

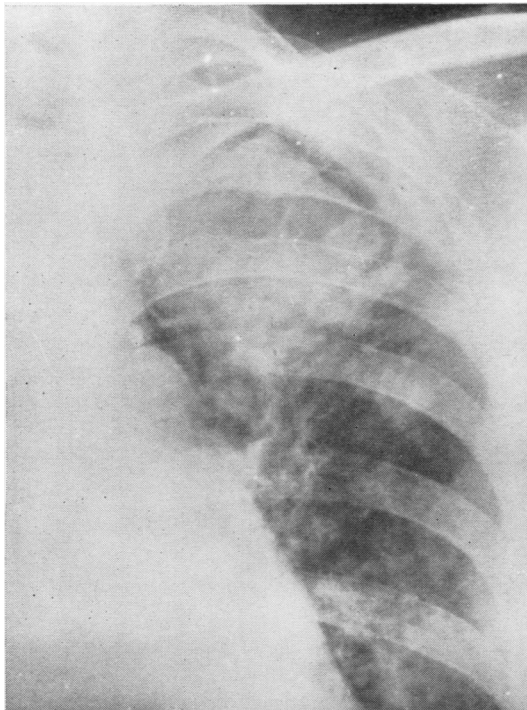


FIG. 7

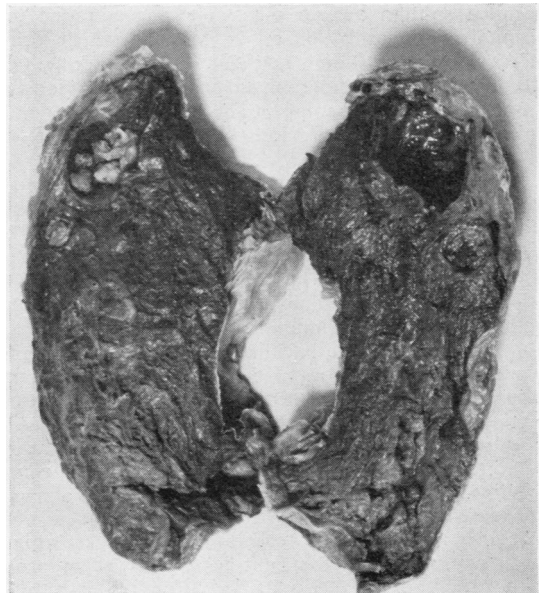


FIG. 8. Necropsy specimen showing two mycetomata. The smaller of the two is situated immediately below the large apical cavity.

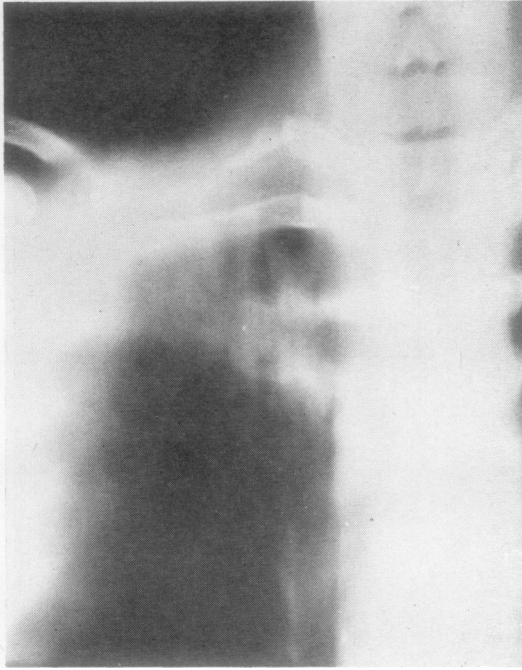


FIG. 9. Tomogram showing a mycetoma in the right upper lobe.

patient had been a known asthmatic since the age of 2 years and had a chronic, productive cough with purulent sputum but no plugs. He was admitted to hospital for investigation on 26 May, at which time physical examination revealed no abnormality, although a chest radiograph taken a week previously showed pleural thickening at the right apex. A mass radiograph taken the previous year had been reported as normal.

A blood count on 27 May was as follows: Haemoglobin 90% (13.4 g./100 ml.); E.S.R. 24 mm. fall in one hour; W.B.C. 4,600/c.mm.; polymorphs 59%; lymphocytes 38%; monocytes 2%; and eosinophils 1%.

The blood pressure and urine were normal, and on examination of the sputum numerous pus cells were found but no tubercle bacilli. Sputum culture showed a mixed growth of normal flora. Subsequent sputum examinations were repeatedly negative, with the exception of one occasion when gastric lavage produced an acid and alcohol-fast bacillus on direct smear examination. However, the eventual culture was negative. A tomogram taken on 31 August is shown in Figure 9.

**Treatment** Originally chloramphenicol, 250 mg. six-hourly, was given for eight days, followed by procaine penicillin, 300,000 units daily, for five days, but without any improvement symptomatically or radiologically. Streptomycin and isoniazid were begun, together with potassium iodide and stramonium, and

were continued until October 1955. Bronchoscopy on 25 October confirmed the presence of blood oozing from the right upper lobe bronchus. Thoracotomy was performed on 1 November, when the apical and posterior segments of the right upper lobe were removed. Post-operatively, some difficulty was experienced in getting the remaining portion of the lung to fill the space. A limited thoracoplasty carried out on 17 November, with a partial decortication, successfully dealt with this problem. Examination of the resected specimen showed the presence of a mycetoma, and *A. fumigatus* was isolated. In subsequent years the patient has continued to have asthmatic attacks which have interfered with his employment. In 1957 he developed a transient consolidation in the left lower lobe, accompanied by slight sputum staining, pyrexia, and wheezing but no eosinophilia. Successive sputum tests were negative for aspergillus, and he responded satisfactorily to treatment with chloramphenicol and potassium iodide.

**CASE 3 (W.F.)** This patient aged 58 years had worked at a variety of occupations, including spring making, lorry driving, and coal mining. In May 1959, after a post-influenzal bronchopneumonia, he was referred to the chest clinic. His symptoms, which included a productive cough, wheezing, and dyspnoea on moderate exertion, dated back to childhood but had recently

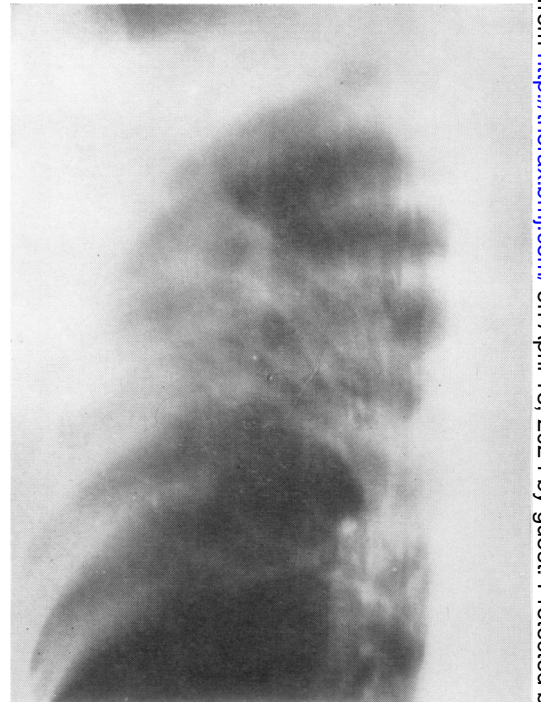


FIG. 10. Radiograph showing cavitation in the right upper lobe.



become more marked. The sputum was yellowish but never contained blood or plugs. He smoked 15 cigarettes daily. A localized opacity, present in the right upper lobe near the periphery in May, had cavitated by July (Fig. 10).

A blood count was as follows: Haemoglobin 65% (9.8 g./100 ml.); W.B.C. 6,200/c.mm.; film normal apart from hypochromic R.B.C.s with slight anisocytosis; E.S.R. 27 mm. fall in one hour.

Sputum examinations revealed no tubercle bacilli.

In September, despite the fact that the sputum was negative, P.A.S. and isoniazid were prescribed pending his admission for thoracotomy, and on 19 October 1959, apical and posterior segments of the right upper lobe were resected, numerous soft pleural adhesions being encountered at operation. The pathological report on the resected specimen was as follows: 'Collapsed lung, showing extensive infiltration and numerous mycotic foci, probably *A. fumigatus*. No yeasts or spores'.

Convalescence after surgery was uneventful, and for two months nystatin tablets were given. Follow-up has been satisfactory but he still suffers from asthma. Repeated sputum examinations have failed to reveal the presence of fungi or eosinophils.

#### COMMENT

The natural onset and evolution of an aspergilloma that has been left undisturbed by drugs or surgery has not so far been described. The nearest approach to such a description is Neilson's (1959) account of a fungal infection of a pre-existing lung cyst in a woman who had been irradiated because of a breast carcinoma. Surgical resection of the cyst was necessary, however, and evolution of the fungus was terminated. Case 1, therefore, is of particular interest, as radiographs ranging over a 17-year period clearly trace the fungal changes which ensued. Surgery was not considered advisable for this patient because of poor respiratory reserve caused by bronchiectasis.

The earliest chest film in December 1941 (Fig. 1), while strongly suggesting cystic changes in the left upper lobe, also revealed a small discrete opacity, 0.5 cm. in diameter, opposite the fourth left interspace posteriorly. The slight mediastinal shift to the left was caused by gross bronchiectasis of the left lower lobe, and this finding was subsequently confirmed by bronchography. Four years later in 1945 (Fig. 2) the nodule in the left upper lobe measured 1.5 cm. By 1950, however, a definite mycetoma had developed consisting of a dense central mass, 4×2.5 cm., within a thick-walled cavity, 5.5×5 cm., and capped by an air halo (Fig. 3). Four years later in 1954 (Fig. 4) the fungal mass had continued to enlarge, measuring 5.5×4 cm., and further slight

increases were noted in the following years (Figs. 5 and 6). Eight months before death a definite enlargement of the cavity (7×6.5 cm.) and of the central mass (6.5×6 cm.) was noted (Fig. 7). In addition, a new focus had appeared adjacent to the lower border of the cyst. From 1950 onwards the mycetoma increased, both in size and density, while over the same period the air halo was consistently present. The nodule, first seen in 1941, probably represents a fungal nidus which, establishing its hold on a pre-existing air cyst, took nine years to reach the maturity of a mycetoma.

Case 2 displays many of the usual features of a mycetoma, including repeated haemoptyses. The long history of asthma present in cases 2 and 3 is uncommon in association with a mycetoma but may have been a significant factor. In all three cases pulmonary tuberculosis was suspected, and although in case 1 a correct diagnosis was eventually established, in the others it was made only after histological examination of the resected specimens.

#### DISCUSSION

Only rarely have cases of primary aspergillosis been described, where the fungus has established itself definitely as the only disease (Schneider, 1930; Hunt, Broders, Stinson, and Carabasi, 1961; Montes, 1963). Orie, de Vries, and Kikstra (1960), finding pre-existent disease so frequently in a series of 51 cases, assumed that secondary fungal involvement is the most common, if not the only form of aspergillosis.

Saprophytism probably explains cases associated with bronchial cysts (Hemphill, 1946; Gerstl, Weidman, and Newmann, 1948; Corpe and Cope, 1956), bronchiectasis (Boyce, 1893; Barlow, 1954; Bruce, 1957), pneumoconiosis (Heppleston and Gloyne, 1949), tuberculosis (Barlow, 1954; Kelmenson, 1959; Peer, 1960), cardiac disease (Zimmerman, 1950), mastoiditis (Stuart and Blank, 1955), carcinoma (Sochocky, 1959), asbestosis (Hinson *et al.*, 1952), endocarditis (Welsh and Buchness, 1955), pneumonia (Hertzog, Smith, and Goblin, 1949; Ross, 1951; Abbott, Fernando, Gurling, and Meade, 1952; Darke, Warwick, and Whitehead, 1957; Toigo, 1960), histoplasmosis (Procknow and Loewen, 1960), the orbit (Wright, 1927), sarcoidosis (Pepys *et al.*, 1959), and lung abscess (Wheaton, 1890; Yesner and Hurwitz, 1950; Stevenson and Reid, 1957).

Hinson *et al.* (1952) classified aspergillosis as allergic, saprophytic, and septicaemic. The allergic form is associated with recurrent pyrexia, typical brown sputum plugs, the presence of *A. fumigatus*

in the sputum, blood eosinophilia, transient lung infiltrates, and asthma. Bronchoscopy often shows a polypoid mass causing bronchial obstruction of the affected segment. They explained these findings as allergic manifestations after sensitization to the fungus. In two of their three cases saccular bronchiectasis was present, but whether it preceded or followed the bronchial obstruction could not be determined. Discussion concerning the role of bronchiectasis in aspergillosis originated with Dévé (1938) and has never been solved. The mycetoma or solid fungal mass is usually regarded as a saprophytic manifestation of a fungus growing in a pre-formed cyst, but in France there has always been support for the theory of a fungal ball growing within the lumen of a bronchus and thereby forming its own cyst.

In the pyaemic or septicaemic variety of aspergillosis, multiple abscesses affect all parts of the body, constituting the most serious form and affecting mainly children.

**OCCUPATION** Between 1958 and 1961, of a total of 980 deaths among birds at the London Zoo, 4% were due to aspergillosis (Fiennes, 1962). This susceptibility of birds to fungal infection has been known for over a century (Virchow, 1856), and has frequently been reported. It is hardly surprising that a tendency exists to explain human aspergillosis almost as an occupational disease among persons in close contact with birds, grain, flour, and agriculture (Conant, Smith, Baker, Callaway, and Martin, 1954; Riddell and Clayton, 1958; Spencer, 1962). Legal support for this view was obtained in 1942 (Coe, 1945), when a middle-aged stockyard worker, whose occupation for 20 years had exposed him to hay, grain, corn, and straw, and whose sputum contained *A. fumigatus*, was awarded compensation for chronic chest symptoms. The fact that this case is solitary in the world literature suggests that aspergillosis and occupation are not closely linked.

Few papers or textbooks dealing with aspergillosis omit to mention its close association with agriculture, bird-feeding (especially of pigeons), milling, fur cleaning, and wig making. As this view stems almost entirely from research carried on between 1890 and 1897 in Paris and appears to be generally accepted without question to-day, it is worth while considering the evidence anew. The gaveurs de pigeons and the peigneurs de cheveux (pigeon crammers and wig-makers) are the two occupations on which the original findings were based. The wig-makers, using rye-flour to degrease hair, worked continually in an atmosphere of dust. The work of the pigeon crammers in Paris and its

environs declined towards the end of the nineteenth century, and by 1895 the number of persons so employed was small. A pigeon crammer, having mixed equal parts of water, millet, and vetch in a tub and then filled his mouth with the mixture, would take each pigeon in turn by the wings with one hand, open the beak with the other and forcibly feed his charge, taking on an average one to two seconds per pigeon. Some workers in a day would average 4,000 to 6,000 pigeons.

It was in August 1890 at the International Congress in Berlin that Dieulafoy *et al.* first described three pigeon crammers with chronic chest symptoms, which they attributed to aspergillosis. The progress of the disease resembled that of chronic phthisis, with dyspnoea, cough, purulent sputum, repeated small haemoptyses, and pleurisy. The sputum microscopically was negative for tubercle bacilli but contained *A. fumigatus*. The authors suggested that grain used for the pigeons and known to be heavily contaminated with the fungus caused the disease which they named *pseudo tuberculose mycosique*. Presumably, the three patients never came to necropsy, as no post-mortem findings were given. Rénon, however, examined one of these men six years later, and, finding him in reasonable health with sputum that contained neither fungi nor tubercle bacilli, concluded that he was cured. A somewhat similar case was described in 1894 by Gaucher and Sergent.

Rénon, pursuing his interest in pulmonary aspergillosis, devoted his thesis in January 1893 in Paris to this subject, describing two patients, both pigeon crammers, with symptoms similar to those described by Dieulafoy *et al.* The first man had an additional complication in the form of an anal fistula, but his sputum at that time, although containing *A. fumigatus*, was negative for tubercle bacilli. A few years later, in his book *Etude sur l'Aspergillose*, Rénon (1897), reporting on his follow-up of this patient, mentioned that numerous tubercle bacilli had appeared eventually in the sputum, while the following year he attributed the disappearance of *A. fumigatus* and tubercle bacilli from the sputum to healing and fibrosis.

His second patient, also a pigeon crammer with chronic chest symptoms, a skin tuberculide but no haemoptysis, had sputum containing tubercle bacilli and *A. fumigatus*. He died in hospital in 1895, and the post-mortem findings were reported by Rénon (1897). Although the lungs were considerably fibrosed, some caseous foci were present, but no aspergilli or tubercle bacilli could be discovered histologically. It is worth noting that this case is the only one in the series

in which a necropsy was performed. In Rénon's view, while the fungus was responsible for the secondary invasion by tuberculosis, it tended to ensure that the latter progressed slowly, with marked fibrosis.

Rénon's only other cases concern a family, father, mother, and 16-year-old son, who were engaged in wig-making. The son had a chronic tracheitis but no evidence of aspergilli or tubercle bacilli in the sputum. Both parents had chronic coughs with haemoptysis, and their sputum contained *A. fumigatus* but no tubercle bacilli. The father had clinical signs of a marked pulmonary fibrosis.

The only indisputable fact emerging from all these reports is that the patients were engaged in occupations which, by their nature, exposed them to a high concentration of fungal contamination. Riddell and Clayton (1958) and Pepys *et al.* (1959) have shown that approximately 7% of patients suffering from a wide variety of chest conditions harbour *A. fumigatus* in their sputum, and Rénon (1897), investigating sputum and nasal secretions in 56 persons, many of whom were healthy, had found the fungus in seven instances. Therefore the presence of *A. fumigatus* need not imply a pathogenic role.

If the incidence of pulmonary aspergillosis were linked to atmospheric fungal pollution, one would expect to find a high proportion of cases in industries where such conditions exist, but this theory is not supported by experience. For example, bagasse shredding by machines produces room dust containing 240 million fungal spores per gramme. Mentioning this fact, Hunter and Perry (1946) also reported that the sputum from four men who operated the shredder contained numerous species of fungi including aspergillus. They regarded these fungal elements as the result of recent dust inhalation and could find no evidence of survival of the fungi in the lungs after the men had been removed from exposure to the atmosphere of the shredding room. In one of the men who died, only chronic bronchiolitis and bronchiectasis was found, but no evidence of aspergillosis. Stallybrass' (1961) study of atmospheric pollution by aspergillus spores in a large animal-provender mill, in which various grains were unloaded, stored, and processed, tends to confirm this view. The catch rate of spores in the normal working atmosphere of the mill was 30 times higher than appeared in the urban atmosphere, and of all the grains handled, maize was the most highly contaminated. Compensation for disease or injury arising out of work was sought by a total of 31 employees between 1956 and

1959, but none was claiming for this disease, and between 1951 and 1959 not a single case of pulmonary aspergillosis was reported. Stallybrass concluded that workers in such industries suffer no additional risk of contracting aspergillosis. Dünner, Hardy, Nakielny, Robinson, and Smart (1958), reporting on necropsy findings in five men out of a total of 31 employed in handling grain and flour, found no evidence of pulmonary aspergillosis.

Taking these facts into consideration, the presence of *A. fumigatus* in the sputum of pigeon crammers and wig-makers is hardly surprising and not diagnostic of a pathological fungus infection in the lungs. Further, when one appreciates that the two patients on whom Rénon based his main argument were both suffering from pulmonary tuberculosis, additional doubts arise as to whether in fact there was any reliable evidence of pulmonary aspergillosis. Certainly chronic phthisis could explain the symptoms in all the cases, and in addition these patients were engaged in highly unhygienic occupations in an era when tuberculosis was rife. It is worth while noting that in the single instance where a necropsy was performed, the histology, although excluding aspergillosis, was extremely suggestive of tuberculosis. Whilst acknowledging the valuable and exacting studies in mycology conducted by Rénon and his co-workers, it cannot be accepted that there is any convincing evidence to date connecting pulmonary aspergillosis with certain occupations, notably those concerned with birds, grain, and their associated trades.

**MYCOLOGY** It is unwise to place too much importance on the presence or absence of the fungus. Isolation of *A. fumigatus* from the sputum does not carry the same significance as a single culture of a known, pathogenic fungus, such as *Histoplasma capsulatum* (Chick, 1962). Even when the fungus has been clearly demonstrated by frequent sputum cultures, it may still be impossible to see it microscopically in the sputum. Some aspergillomata have no permanent bronchial connexions, and therefore sputum cultures may be negative (Orie *et al.*, 1960). Probably case 1 was of this type, and even suction applied to the left upper lobe orifice produced a negative aspirate.

Saliba, Pacini, and Beatty (1961) successfully demonstrated that, by inserting a needle into an aspergilloma, using local anaesthetic, material can be aspirated for culture. It is advisable to collect sputum specimens in sterile glass containers, incubating at 37°C. on Sabouraud's medium or on

blood agar, spread with 1 in 1,000 streptomycin. *A. fumigatus*, if present, will usually appear within 48 hours, but it is advisable to keep plates up to seven days. Sporing cultures are typically smoky green in colour and show on microscopic examination flask-shaped vesicles with a single row of phialides over the upper two-thirds only. An adequate oxygen tension is essential to the development of sporing elements, but mycelium grows under relatively anaerobic conditions (Cawley, 1947). Patency of bronchial communications, therefore, can decide whether or not spores are present.

Aspergillosis may be confused with other conditions, notably actinomycosis. Weed and Dahlin (1950), in reviewing the literature on actinomycosis, were impressed by the number of reports in which photomicrographs showed wide filaments which, in fact, were probably aspergillus. This point is underlined by a description of a woman aged 48 years with a chronic empyema and multiple fistulae. At operation greyish sulphur bodies were obtained, which were reported by the laboratory as being actinomyces but on culture proved to be *A. fumigatus*. Hughes, Gourley, and Burwell (1956) mention a similar resemblance to the sulphur granules of actinomycosis, produced by *A. fumigatus* forming small clumps of actinomycetoid bodies.

**ANTIBIOTICS AND STEROIDS** Although the evidence to date is inconclusive, antibiotics and steroids came under early suspicion as agents promoting fungal invasion in man (Hiddlestone, Rosser, and Seal, 1954; Darke *et al.*, 1957; Torack, 1957). In a case of drug-induced agranulocytosis with secondary aspergillosis, such as that described by Rankin (1953), the responsibility of the drug cannot be questioned. Welsh and Buckness (1955), reporting a case of agranulocytosis treated with antibiotics and steroids, regarded the widespread fungal involvement as a terminal event. Similarly, when Greer and Gemoets (1943) in the pre-antibiotic and steroid era stated that there seemed to be a tendency for pulmonary tuberculosis to develop a more devastating course when associated with the invasion of a parasitic fungus, they may have been describing how fungal colonization tends to select individuals with the grossest pulmonary disease. Streptomycin, which has been used extensively over the past decade, has not been associated with an increase in fungal disease. Nor have surgical resection of tuberculous tissue after prolonged chemotherapy and the concomitant histological and bacteriological investigations revealed significant fungal intrusion.

Abbott *et al.* (1952) described a housewife admitted in 1951 with a post-influenzal bronchopneumonia and toxic purpura. She was treated unsuccessfully with penicillin and chloramphenicol and died in coma. At necropsy a thin-walled cavity, 5 cm. in diameter, was found to be lined with a densely felted layer of fungal mycelium and conidia. Material from the cavity, when cultured, produced *A. fumigatus*, *Candida albicans*, coagulase-negative staphylococci, and haemolytic streptococci. The cause of death was considered to be toxæmia, due to a post-influenzal bronchopneumonia, complicated by an aspergillus infection arising from the use of antibiotics. The known characteristics of the aspergillus—saprophytic, ubiquitous, with a preference for cavitated areas—would explain its appearance in this case without invoking the use of antibiotics as an important factor. A similar case was described a century ago by Virchow (1856) at a time when antibiotics could not be incriminated.

Although Sidransky and Pearl (1961) and Torack (1957) place considerable stress on past treatment with antibiotics and steroids, it is worth noting that all their cases were suffering from serious primary diseases, such as agranulocytosis, lymphocytic leukaemia, lupus erythematosus, and carcinoma of the cervix and oesophagus. In four of these the duration of steroid therapy was only 10 days or less, while in a fifth case none was given. Cases coming to necropsy, where evidence of aspergillosis is discovered, almost invariably have died from serious underlying disease (Orie *et al.*, 1960), and the evidence so far suggests that any previous treatment with steroids or antibiotics is coincidental so far as the fungus is concerned.

**SYMPTOMS** At bronchoscopy in case 2 described earlier, blood was seen issuing from the orifice of the right upper lobe where the fungal infection was situated. Endeavours to establish the source of bleeding in case 1 were unsuccessful, as he had ceased to bleed a few hours before bronchoscopy. The lower lobe was bronchiectatic and must share suspicion. In case 3 there was no history of sputum staining, despite the presence of a cavitated zone in the right upper lobe. Although asymptomatic cases have been described, chronic productive cough, accompanied by repeated intermittent haemoptyses, without obvious deterioration in the patient's general condition, is often associated with an aspergilloma. Levin (1956), for example, estimated that haemoptysis occurred in over half the patients, and in this respect cases 1 and 2 are characteristic. In general, although the pathogenicity of the asper-



gillus is low, haemoptysis in such cases is usually regarded as directly attributable to the fungus. An endotoxin that causes tissue necrosis has been isolated from the aspergillus and may be responsible for the bleeding.

**RADIOLOGICAL CHANGES** Frequently, but not invariably, the radiological changes in pulmonary aspergillosis can be non-specific, such as mottling and fibrotic infiltration, confluent nodular infiltrates, clouding, and multiple fleeting shadows. In secondary aspergillosis, the primary condition, such as tuberculosis or neoplasm, may impose its own particular pattern, masking the presence of the fungus. The classical picture of a mycetoma—described by Monod *et al.* (1952) as a 'rounded opacity, topped by a clear crescent—is, however, diagnostic. Irregular, calcified densities within the cavities have been described by Villar, Pimentel, and Costa (1962), who also attribute cavity shrinkage to a ball-valve mechanism produced by a mobile intracavitary mass. The central mass, for example, has occasionally been observed to move as the patient changes his position (Hemphill, 1946). A mycetoma is usually solitary but can be multiple, as shown in case 1, and even bilateral (Saliba *et al.*, 1961).

It is difficult, if not impossible, to distinguish radiologically between pulmonary fibrosis and increased vascularity of lung tissue (Simon, 1962). The unusual cirrus-like markings extending from the hilum to the mycetoma in case 3 (Fig. 10) probably represent a combination of both these processes. In the other two cases similar changes could not be detected, possibly because the mycetomata were localized adjacent to the mediastinum. None of these cases had periostitis of adjacent ribs, such as Bates and Cruickshank (1957) noted in respect of actinomycosis.

**ALLERGY** In two of the three cases described in this paper, asthmatic symptoms had been present since childhood, and both patients, while showing no 'late' reactions, have vigorous immediate skin reactions to mixed inhalants and fungal allergens (*Alternaria*, *Aspergillus*, *Gladosporum*, *Neurospora mucor*, and *Penicillium*). Case 3, when tested for aspergillus precipitins, reacted in a non-specific manner, but case 2 gave a positive reaction. Positive skin reactions to fungal allergens have been noted often but do not necessarily imply actual infection (Conant *et al.*, 1954). Case 1, representing an invasion of a pre-formed cyst, was without asthma, and, as might be expected, did not react to skin tests. In none of the three cases was eosino-

philia noted, but case 2 has had at least one infective chest episode since surgery.

It is possible that in the two patients who displayed symptoms of hypersensitivity, their allergy may have been a factor in promoting the formation of a mycetoma. For example, Dunnill (1960), describing areas of cystic bronchiectasis in patients dying of status asthmaticus, frequently found them to have a similar distribution as focal areas of collapse in the upper and lower lobes. Mucosal shedding of great magnitude due to subepithelial oedema occurs in asthma (Naylor, 1962). In addition, sputum and bronchial plugs expectorated by asthmatics are known to contain *A. fumigatus* more frequently than bronchial secretions from patients with other respiratory diseases. In such a complicated situation, an allergic response to inhaled aspergillus spores, as suggested by Hinson *et al.* (1952), might lead to fungal retention and eventually to the formation of a mycetoma.

Cases of asthma displaying the features associated with allergic pulmonary aspergillosis, namely, transient lung infiltrates, sputum plugs containing *A. fumigatus*, and eosinophilia, have not so far been recognized in the Walsall area, but they do undoubtedly exist. Pepys *et al.* (1959) consider that the infiltrates are related to an Arthus type of reaction and suggest that there are two types of antibody against aspergillus extracts. The first, a non-precipitating skin-sensitizing antibody, is associated with the skin and bronchial test reactions and is responsible for the rhinitis and asthma. The second, a precipitating antibody, mediates the 'late' Arthus skin reactions and pulmonary eosinophilia.

**DRUG THERAPY** None of the three cases described here was given antifungal drugs, apart from potassium iodide in case 2 and nystatin post-operatively in case 3. However, a wide variety of drugs have been used, especially in North America, among which are amphotericin B, nystatin, hydroxystilbamidine, and iodides. The most authoritative statement so far has been the report of the American Thoracic Society Committee on Therapy (1963), which places amphotericin B as the most valuable drug in aspergillosis, followed by nystatin, hydroxystilbamidine, X5079C, and iodides. Amphotericin B is usually given by intravenous infusion on alternate days, in a dosage rarely exceeding 1.5 mg./kg. body weight. The total duration of treatment varies from 16 to 36 weeks, but limiting factors are nausea, anorexia, vomiting, fever, chills, anxiety, headache, and thrombophlebitis. Antipyretic and antihistamine drugs, as well as hydrocortisone, are

useful in combating these side-effects. Renal toxicity is encountered, and, although usually reversible, may be serious. The Committee advised that amphotericin B, because of its disadvantages and despite its high rating as an antifungal agent, should only be used to combat severe or progressive fungal infections. It seems unnecessary to use amphotericin B as a routine measure in simple aspergillomata, even as surgical cover. Reports on its use in allergic aspergillosis are lacking. The original encouraging reports on X5079C (Emmons, 1961), a drug produced from a strain of streptomycetes, have unfortunately not been sustained.

**SURGERY** Once diagnosed, and often when misdiagnosed, the tendency is to resect the mycetoma, and there are few instances where it has been left undisturbed. The aspergillus, especially when it has successfully established itself in a bronchogenic cyst, appear to be invulnerable both to the host and to antifungal agents. The process is irreversible, and, even if the fungus dies, it remains entombed. It is hardly surprising, therefore, that since the first successful resection of a mycetoma was performed in 1943 (Gerstl, Weidman, and Newmann, 1948) the claims of surgery have been pressed as the only effective form of treatment (Pesle and Monod, 1954).

Satisfactory surgical results, as in cases 2 and 3, have been reported on many occasions (Hochberg, Griffin, and Bicunas, 1950; Yesner and Hurwitz, 1950; Friedman, Mishkin, and Lubliner, 1956; Corpe and Cope, 1956; Vellios, Crawford, Gatzimos, and Haynes, 1957), including a case of histoplasmosis with cavitation secondarily infected with *A. fumigatus* (Procknow and Loewen, 1960). Belcher and Plummer (1960), however, consider resection justifiable only if there is a marked increase in the size of the lesion or frequent troublesome haemoptyses, such as were experienced by case 2. Finding that no symptomatic improvement followed surgery in allergic aspergillosis and that the fungus persisted in the sputum, they advised against surgical intervention in this type of case. Like other authors, they noted a high incidence of complications accompanying surgery where the aspergillosis was superimposed on primary disease, such as tuberculosis or bronchiectasis. Hiddlestone *et al.* (1954) and Golebiowski (1958) reported pleural involvement by the aspergillus after resection for tuberculosis in two patients. Such a complication's response to treatment is no more tedious than an empyema due to other organisms. For example, in 1924 Cleland described an aspergillus-infected empyema caused by a gunshot wound, which was

successfully treated by partial rib resection, 'scraping' of the cavity, and excision.

#### SUMMARY

Three cases of aspergillus infection of the lungs are presented, and in one the gradual development of a mycetoma is traced over a 17-year period. The evolution of the original fungal nidus was shown to be progressive, terminating only with the patient's death.

A marked pulmonary reaction, producing an unusual cirriform radiological appearance, was noted in one of the cases, and in similar circumstances might be of diagnostic importance.

Sputum frequently contains aspergillus if the person concerned works in an atmosphere contaminated with the fungal spores, but such people show no increased incidence of aspergillosis.

The basis for the theory supporting a close association between pulmonary aspergillosis and birds, grain, flour, and allied products as well as occupations, has been re-examined. It is suggested that no such association exists and that the cases originally described by French workers towards the end of the nineteenth century were suffering from chronic tuberculosis and not aspergillosis. As bird fancier's disease, pigeon crammer's disease, and other similar descriptive terms are misnomers, it is proposed that they should cease to be used.

Aspergillosis of the lungs is essentially secondary in character. The underlying primary disease, especially if serious, plays a dominant role in establishing the fungus.

Evidence incriminating antibiotics and steroids is unconvincing.

Amphotericin B, despite its toxic side-effects remains the most valuable drug for the treatment of severe aspergillus infections.

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