

A GUIDE TO THE RECENT LITERATURE ON ASPERGILLOSIS AS CAUSED BY *ASPERGILLUS FUMIGATUS*, A FUNGUS FREQUENTLY FOUND IN SELF-HEATING ORGANIC MATTER

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Abstract

Spores of *Aspergillus fumigatus* have been found to be abundantly present in the outdoor air at a site where large scale experimental composting of sewage sludge is in progress at Beltsville, Maryland. The health significance of this finding, for that site and for others in the future, is still only incompletely understood. Further studies are in progress to characterize absolute concentrations of the spores of the fungus in air at the site, spore dispersal by air from composting operations, and background environmental spore levels in air.

The present paper contains a list of references to papers on health effects of *A. fumigatus*, many published in the past ten years, along with a review of the same designed to assist the reader in finding information on particular aspects of the subject in the literature. It is intended primarily as an aid to individuals interested in sludge composting and wishing to attain an insight into the *A. fumigatus*-composting situation, but it may also interest others concerned with other substrates which become moldy at 40–50 C. *A. fumigatus* has been found in great numbers in naturally and artificially heated environments such as decaying leaves, compost heaps, solar heated sloughs, cooling canals for nuclear power generators, silos, grain storage bins, boiler rooms, detritus around steam turbines and sauna baths.

The evident practical merits of sludge composting have been described elsewhere; the information presented here has its main significance in respect to requirements for choice of locations for composting sites and to process and design criteria.

Introduction

During an investigation at Beltsville into methods for com-

posting sewage sludge, a question arose concerning the possibility that the fungal opportunist *Aspergillus fumigatus* Fres. might present a health hazard at and around composting operations. A preliminary and semi-quantitative examination of the air at a composting site had revealed that the organism occurred there at levels far above those found in the air at distant locations (92). Wood chips used in the process appeared to be a major source. Thus, although sludge composting is a basically useful process (33, 104), the possibility of a need for accommodations in site selection and details of the composting process in response to *A. fumigatus* has recently come into consideration.

The occurrence of *A. fumigatus* at the Beltsville composting site was not surprising, because the fungus has a history of growing and sporulating profusely on damp hay, wood chips, and other self-heating organic matter (92, 114). The magnitude of any possible consequent health problem in connection with sludge composting, however, is still incompletely known. Uncertainty on this subject derives in part from a lack of information. Data are needed on the numbers of *A. fumigatus* spores emitted into the air during composting, the extent of their aerial dispersal into adjacent regions, and the number already in the air of the environmental background. Air samplings on these questions are in progress. Additional uncertainty may be related to an insufficient understanding on the part of compost scientists and of responsible officials of the health implications of *A. fumigatus*, i.e. what adverse effects it can cause, to whom, and under what circumstances.

The writers have considered that a record of recent literature concerned with the health effects of *A. fumigatus* might be helpful to individuals concerned with evaluations of plans for specific compost operations. The aim of the present paper is thus to assemble references useful in aiding any interested persons in arriving at their own

independent and informed judgments on this matter and to provide a brief informational background helpful in such an endeavor. In the information provided, medical judgments generally follow closely after those of original authors.

Background to facilitate use of reference list

General comments on sources of information

The total number of published papers containing information on health effects of *A. fumigatus* in humans is not known by the writers but is obviously large, probably well in excess of 500. Papers are scattered over a wide array of journals. Attention is focussed here mainly on papers published since 1968.

An excellent overview can be found in the chapters on aspergillosis in texts on medical mycology by Rippon (118) and Emmons et al. (31). Individuals needing to make a more detailed examination of one or more aspects of the subject can find in the present paper a means of selective entry into a voluminous and rapidly increasing body of additional published information, much of it relatively recent.

The literature on aspergillosis may be located in several ways. One convenient method, in addition to the present document, is through the Review of Medical and Veterinary Mycology (6), which presents current abstracts in English from a wide range of sources in several different original languages; relevant references are segregated under the heading 'aspergillosis.' Some papers cited in the present document contain lengthy lists of additional references; computer services for reference search may be helpful. Papers were selected for citation here mainly on the basis of recency and on availability of the article in its original published form but without reference to author viewpoint.

Only brief mention is made here of direct effects of inhaled spores of *A. fumigatus* acting as an extrinsic allergen in the lung, i.e. without major growth in the body. Such allergies, while fairly common and occasionally associated with serious health effects, are also caused by spores of many other fungi and actinomycetes (8). Spasmodic bronchial response to such spores, as well as to dust, chemical vapors, and many other allergens is common among asthmatics. Among non-asthmatics, sensitization to fungal spores can occur with repeated exposure to high spore concentrations; the typical response involves a

temporary episode of difficulty in breathing, nausea, and fever, beginning four to six hours after exposure (52, 168). The latter phenomenon is described in the literature under the terms 'farmer's lung' and 'extrinsic allergic alveolitis.' Fungal infections within the ear are not considered at all here, even though *A. niger* or *A. fumigatus* may be involved; for introduction to this subject, the reader is referred to Rippon (118) and Emmons et al. (31).

Information on factors influencing distance of movement of fungus spores in air is relevant in some situations in which buffer zones between composting sites and hospitals or other health care facilities are contemplated; information on fungus spores in air has been summarized by Gregory (47).

As general background, the writers recommend a review by Lowrance (82) which contains a penetrating analysis of the subject of health risk assessment as it relates to evolving public policy. The present paper hopefully represents a useful contribution to the careful fact-finding process regarded by Lowrance as a prerequisite to risk assessment.

Early history of the study of A. fumigatus and aspergillosis

Aspergillus fumigatus was well described as a species in 1863 (114) and has been recognized for many years as a biological entity differing in its morphology and behavior from other aspergilli. Much of the early literature about the fungus deals with natural lung infections by it in wild and domestic birds and as a cause of mycotic abortion in cattle and sheep (114, pp 82–98). Study and publication on the animal disease aspect of the subject continues to the present (48, pp 88–93) but, with a few exceptions specifically noted, all further reference here is to the disease in man. The disease was first reported in man in the middle of the 19th century (31, 118) and has been the subject of a great many accounts since that time. The role of primary disease as a cause of predisposition to attack by the fungus was known in 1900, while the role of cortisone and other drugs in causing impairment of immunity to it and other opportunists has been recognized for about 30 years.

A. fumigatus has been observed repeatedly to occur in abundance in composts and other self-heating organic matter and other natural situations where temperatures are in the range of 40 to 50 C (7, 92, 114). It obviously enjoys a competitive advantage over other organisms in natural situations at such temperatures. Beyond this, however, detailed information on its occurrence in nature, particularly quantitative information, is very limited (114). The interested reader will find several reports on its physio-

logy in appropriate sources. The fungus can utilize inorganic nitrogen, requires no amino acids or vitamins for growth and can use many sugars as well as native cellulose (86) as a source of carbon. Under some conditions it can form soluble by-products toxic to animals, i.e. mycotoxins, but the role of these in disease production is not understood (62).

Orienting facts on the nature of the disease

Numerous reports attest to the pathogenicity of *Aspergillus fumigatus* in individuals predisposed to it by certain prior health problems. It grows and produces aspergillosis only rarely if ever in individuals not already suffering from some other health difficulty. Because of its propensity for attacking persons whose immunological defenses have been weakened by other health problems or situations, it is termed an 'opportunistic.'

Among the aspergilli, *A. fumigatus* is by far the most frequently reported species involved in growth and disease in the human body, although *Aspergillus niger*, *Aspergillus flavus*, and other species have also been reported (3, 4, 19, 171). Most citations in this paper refer to disease attributed by original authors to *A. fumigatus*. Natural inoculation with *A. fumigatus* occurs usually, although not invariably, through the inhalation of the spores, which are 2-3 microns in diameter and thus of a size to enter the respiratory tract and penetrate readily to the alveoli (8). Growth may be confined to a non-invasive colonization of the air passages of the lungs and of pre-existing cavities resulting from tuberculosis, sarcoidosis, or other causes. Occasionally, however, the fungus invades lung tissue; rarely it becomes disseminated from the lungs through the blood stream to heart, kidneys, and/or central nervous system. Invasion and dissemination are invariably serious (4, 45, 73).

The colonization of cavities is often chronic and may be accompanied by the formation of 'fungus balls' and/or by a cough productive of mucus and blood (67). Great variation in the severity of such disease, from mild to life-threatening, occurs from one individual case to another. *A. fumigatus* is the organism usually found in fungus balls, but other fungi have been reported (161).

Allergic bronchopulmonary aspergillosis ('ABPA') as defined by Rippon (118) involves colonization of air passages and is frequently found to have been preceded by asthma (10, 51, 57, 67, 74, 80, 99, 125, 139, 157). A period of several years often intervenes between the onset of the asthma and the appearance of the aspergillosis (48, p 112).

Asthma without *A. fumigatus* colonization has been reported, however, to be common in the vicinity of Baltimore, Md., where sputum from only 2 of 54 asthma patients grew *A. fumigatus* on more than one occasion (2). All 54 patients in the study had given significant reactions to one or more common antigens; of 35 tested with additional skin tests with one or more aspergillus antigens, 17 were considered positive and 18 negative, but the positive reactions were not judged to warrant a diagnosis of allergic bronchopulmonary aspergillosis. The authors state (2): 'The association of bronchial aspergillosis and asthma may be more frequent in England, as most recognized cases have come from that country. The infrequency of aspergillosis in our series of asthmatic patients suggests that it is a rare cause of asthma in our area.' Pepys (48, p 111) states 'Allergic bronchopulmonary aspergillosis is the major cause of pulmonary eosinophilia with asthma in the UK.' Some uncertainty about constancy in the etiology of 'bronchopulmonary aspergillosis' as defined by Pepys seems evident; he states in respect to *Candida albicans* 'The possible participation of this fungus in patients with allergic bronchopulmonary aspergillosis has yet to be assessed, but I think that this is probable' (152). Colleagues appear to question whether any *Aspergillus* is necessarily involved in every case considered by Pepys to exhibit allergic bronchopulmonary aspergillosis (152). Contrary to the definition by Rippon (118, p 409), some authors apply the term 'allergic bronchopulmonary aspergillosis' to cases in which, in spite of other positive indications, no cultural or other proof has been provided of growth of any *Aspergillus* in the lungs (57, 74, 124). Others stress the importance of positive sputum cultures; Khan et al. (70), for example, report that over 80 % of the individuals considered in their study to have allergic bronchopulmonary aspergillosis exhibited *A. fumigatus* repeatedly in sputum cultures. Llamas et al. (80), to cite another example, report a case in which the fungus was clearly detectable in the bronchi by fiberoptic methods, also in bronchial washings.

Individuals of all races and both sexes are included among the reported cases of aspergillosis. Children and teen-agers may be affected (19, 23, 57, 139, 155) but incidence appears to be greatest among older people (49), who are most likely to suffer from predisposing conditions.

Opportunism by A. fumigatus following immunity impairment

A. fumigatus has long been known as an opportunist which

follows other health problems, especially diseases and disorders of the lungs but also certain other health problems as well. Physicians reporting lung infections by it have recorded tuberculosis, sarcoidosis, histoplasmosis, chronic bronchitis, asthma, and emphysema as elements believed or suspected to have been predisposing to aspergillosis in their patients. They have also mentioned cancer and leukemia as predisposing (37, 56, 108, 132). Aisner et al. (3) state, for example: 'Infection is the major cause of mortality in patients with acute leukemia and lymphoma. - Fungal infections caused by *Aspergillus* spp. are second in frequency only to candidiasis in these patient populations. When present, *Aspergillus* infections are the major contributory factor to their demise.' Bacterial and viral organisms of many kinds are also well known to represent a more serious hazard to compromised (i.e. immunity-impaired) than to non-compromised hosts (35). Diabetes has also been considered a predisposing element in some cases (31).

Infection with any of a wide variety of opportunists (35), including *A. fumigatus* (5, 23, 46) is typical of the chronic granulomatous disease of childhood, a problem associated with an inherited immunity defect. A case involving *A. fumigatus* infection in the lungs and in lesions in the skin of a 3-year-old girl without apparent prior debilitating condition was reported in 1969 (155), seemingly a case of primary aspergillosis; more recent evidence on the same patient, however, has disclosed that chronic granulomatous disease was present as an underlying disease.*

Underlying disease, however, is not the only factor favoring the development of aspergillosis. Treatment for disease may also predispose. Thus, many physicians believe, as a result of numerous case records over the past 30 years, that aspergillosis and other opportunistic infections have increased in the population as a result of the use of antibiotics, immunosuppressants, cytotoxic drugs, and corticosteroids (e.g. cortisone, prednisone) (31, 118). The effect has been demonstrated experimentally in mice. Treatments of mice with cortisone prior to inhalation of spores of *A. fumigatus* increased mortality to 25-100 % as compared with 0 % mortality for non-cortisone-treated controls (162). Sidransky has performed and reviewed (135) many experiments in which he and others have, by administration of immunity-impairing drugs or conditions, stimulated pulmonary and disseminated aspergillosis in mice subsequently allowed to inhale spores of *Aspergillus*

flavus. Rabbits treated with doses of cyclophosphamide equivalent to those used in leukemia or with methyl prednisolone at a therapeutic dose exhibited greatly increased infection and mortality with a standardized dose of spores of *A. fumigatus* (119).

Although apparently not clearly proven, it seems possible that inhalation of massive doses of *A. fumigatus* spores might overwhelm the immunity system and cause infection in a previously healthy individual (118). In any event, no data on dose-response relationships seem to be available in the literature for either predisposed or non-predisposed persons. Austwick (7, 8) indicates that incitement of respiratory allergy probably requires a very low minimum level of inhaled spores, with higher levels being needed to produce chronic infection, and still higher ones for acute infection; differences in the resistance of the host are obviously also of major importance. He states elsewhere (114, pp 109-110): 'Many factors enter into the establishment of infection in man and animals by *Aspergilli*, but the number of conidia taken into the body is the main external one.'

In some cases, invasive aspergillosis represents an end-stage complication in a person already seriously ill from an underlying disease and susceptible to attack by any of several commonly present opportunists (91), but in other cases it is a major and decisive element in an overall health problem. Among its serious consequences is that it may severely affect a person who is coping moderately or even very well with his underlying disease or health difficulty. Blank and Castellino (13), for example, state: 'The problem of pulmonary infection in patients with altered immunity is formidable. If infection in these patients only occurred concomitant with end-stage disease, there would be less sense of urgency in its management. In fact, however, infection often supervenes when the patient has achieved a *modus vivendi* with his underlying disease, or in the case of a transplant recipient, when he has successfully emerged from a rejection episode, or even when rejection has not been an immediate threat. Therefore, the prompt recognition of infectious complications, identification of the organisms responsible, and institution of appropriate treatment are critical.'

Clinical observations

Many papers assert the great difficulty of diagnosing aspergillosis (4, 65, 95, 96, 117, 151, 152, 163, 164) and also the inadequacy of known therapeutic measures (153, 164). Details may be found in papers on allergic broncho-

* Personal communication. Dr. H.J. Nickerson, Marshfield, WI, Nov. 1978.

pulmonary aspergillosis (1, 17, 21, 29, 43, 51, 57, 59, 67, 70, 71, 74, 77, 85, 99, 100, 103, 109, 112, 128, 130, 133, 152, 157, 159), aspergilloma (12, 24, 31, 53, 88, 100, 116, 118, 131), problems with growth around prosthetic heart valves and elsewhere in the circulatory system (20, 40, 65, 111, 121, 148), myocardial infections (163), and infections in the central nervous system (45, 60, 68, 73, 94, 95, 102, 134, 156), also in papers on the related subject of extrinsic allergic alveolitis (8, 48, 66, 97, 159, 168).

Aspergilloma, involving fungus balls growing in pre-formed cavities resulting from tuberculosis, sarcoidosis, or other causes, is characterized by repeated episodes of coughing up of blood (hemoptysis), sometimes in small amounts but also sometimes to the point of fatal hemorrhage (118, p 411). In a different but also non-invasive situation, the fungus may grow and stimulate mucus production in the bronchi; related histology has been described in detail by Katzenstein et al. (67).

As many of the above-cited papers indicate, prognosis in the invasive and disseminated forms of aspergillosis is poor and few patients in such circumstances survive. The organism usually spreads through the blood stream and often grows luxuriantly in blood vessels. In disseminated disease, post mortem examinations have often revealed *A. fumigatus* as the cause of death when cultures from the patient's blood and other ante-mortem diagnostic methods have failed to point to its presence (65, 111, 127, 163). 'Vegetations' of *A. fumigatus*, i.e. hyphal masses of the fungus, growing around prosthetic heart valves may cause failure of these valves to function and plugging of vessels by the fungus may also occur (65, 111). Papers cited above record that infections in the brain and spinal cord are usually fatal. Numerous accounts deal with serious and often fatal infections in immuno-suppressed kidney transplant recipients (16, 60, 76, 96, 117), and in individuals already affected with leukemia (37, 120, 132, 133, 164) or cancer (3, 4, 13, 37, 56, 91, 120, 151, 153). Pleural infection by *A. fumigatus* has been reported, but infrequently, is sometimes fatal (90).

Growth of *A. fumigatus* may occur in the paranasal sinuses; recent reports of individual cases (88, 147) describe treatment by surgical removal of the hyphal mass and include references to the literature relating to further cases. This type of infection is usually associated with *A. flavus*. A case involving the paranasal sinuses and periorbital tissues with extension to the bone and repeated recovery of *A. fumigatus*, is described by Emmons et al. (31, p 294).

The opening of new portals of entry for the fungus into

the body during surgery and testing in hospitals, particularly in heart surgery (65, 111), represents an increased risk. In one reported case, a rapidly fatal outcome followed peritoneal dialysis and a resulting major infection with *A. fumigatus* (127). Rippon (118, p 417) makes special mention of hospital-acquired or 'iatrogenic' aspergillosis and notes a personally observed case following disc fusion. The fungus was *A. terreus*.

A case of massive aspergillus growth in the kidney following obstruction in the flow of urine has been reported (28). None of the predisposing factors so commonly found to precede such infection, e.g. malignant disease, insulin-dependent diabetes, corticosteroid therapy, was present.

Surgical removal of *A. fumigatus*-colonized lung tissue has been practiced for many years, apparently with a moderate frequency of success (72, 116, 118). Varkey and Rose (154), however, concluded that 'Contrary to the conclusions of previous reports, the experience in our series of patients suggests that routine surgical excision of aspergilloma is not indicated.' Reservations about the efficacy of routine surgical removal in cases of aspergilloma are also expressed by others (48, pp 148-151). Still others (145) have concluded that '-excision of a solitary 'fungus ball' is recommended-' (italics added).

No regularly effective anti-microbial treatment against *A. fumigatus* infection seems to have been reported (153). Amphotericin B has been tried many times but with only occasional success (50, 103, 116, 153, 165). Aisner et al. (4) have found early and aggressive diagnosis, followed by prompt use of amphotericin to improve chances of survival in cancer patients. The material has a high potential for causing kidney damage. Rippon (118, pp 534-8) provides a general summary of experience with the drug in the control of several fungus diseases.

Numerous reports have appeared on serological phenomena and test procedures in relation to *A. fumigatus*, only a few of which are listed here (9, 24, 25, 44, 75, 76, 85, 89, 106, 107, 109, 125, 126, 129, 132, 141, 150, 158, 167); basic knowledge and techniques in this field are changing rapidly so that even relatively recent conclusions may quickly become outdated. As is indicated in papers cited just below, many authorities currently place only limited reliance upon serological results as an independent criterion in the diagnosis of aspergillosis.

Patients with widespread invasive aspergillosis, mostly confirmed later at autopsy by cultures of *A. fumigatus*, showed no detectable antibodies to the fungus in their serum (169); according to Emmons et al. (31) 'Immune mechanism of these patients has been altered by severe

underlying diseases and/or immunosuppressive therapy.' Patients with non-invasive forms of the disease are more likely to exhibit positive results in precipitin tests and to aspergillus antigen in skin tests (31, p 298). Rippon (118, p 424) states: 'Precipitins are always present in aspergilloma patients. This is especially useful for diagnosis when sputum is culturally negative due to lack of connection of the cavity with a patent bronchiole.'

In respect to asthmatics, Emmons et al. remark (31, p 66): 'Precipitin antibody can be demonstrated in approximately two thirds of asthmatic patients with pulmonary infiltrations. The relationship of these antibodies to whatever fungal infection is or had been present is not clear, however.' Tosh (150) writes: 'The lack of specificity of serological tests is not limited to the fungal diseases, but it may be more common in fungal serology because many of the fungi appear to share common antigens. Experienced investigators in the field accept cross-reactions as a fact of life and rely upon other diagnostic procedures to establish the correct diagnosis.'

Bardana (9) concludes that 'nearly everyone has some circulating antibody to aspergilli' and that 'with the possible exception of untreated aspergillomas, immunological testing cannot be exclusively relied upon to discriminate aspergillus-induced syndromes consistently.' He also notes that 'commercial preparations of house dust contain antigens which share antigenicity with *A. fumigatus*.' Jameson (63) also reports antibodies to certain components of some extracts of *A. fumigatus* in a high proportion of normal serum and Reed (115) states similarly that 'Approximately 2 % of the group of healthy Madison dwellers had precipitins to *A. fumigatus*.' Malo et al. (85) remark that the presence of precipitins against *A. fumigatus* has been reported in asthmatics without evidence of aspergillosis, and the 'the results of precipitin tests have to be interpreted in the light of clinical findings.'

Katzenstein et al. (67) caution that 'the significance of serum precipitins to aspergillus must be interpreted with some caution,' and in respect to allergic bronchopulmonary aspergillosis state that 'Similarly, skin tests with aspergillus antigens, while usually required for diagnosis, also are not highly specific for this condition.' Gordon et al. (44) claim high specificity for a modified indirect fluorescent antibody test which employs germinated spores or 'germlings' of *A. fumigatus* rather than hyphae; accumulation of further experience with this recent test seems desirable.

Rippon and Anderson (119) state '... personal experience and that of others... indicate that these tests

(immunodiffusion, complement fixation and indirect fluorescent antibody) are usually lacking in definition in sera from patients with systemic invasive aspergillosis.'

Only a very low degree of specificity was attributed by Louridas (81) to intradermal testing with *A. fumigatus* as used in his work. A much higher proportion of asthmatic than non-asthmatic subjects yielded positive skin test results in his observations. From a group of 534 asthmatics, 130 exhibited positive skin test results but of these 130 there were 109 who responded to other antigens also. The author states (81) '109 of the patients who exhibited multiple cutaneous allergies were probably atopic subjects in whom the specific significance of a positive Aspergillus skin test is doubtful.' Eleven positive skin test results were observed in supposedly healthy control subjects showing no other sign of disease; the author states 'The absence of other positive tests supports the innocuousness of the positive skin reactivity.' In agreement with these findings, Reed (115) states: 'Another problem with the skin test as a diagnostic procedure is that it is not specific for allergic aspergillosis. For example, in a group of asthmatic patients without aspergillosis and a group of 'normal' subjects, skin test results were positive in 12 % and 4 %, respectively.'

The work of Chen and Chuang (22) demonstrated clearly the high frequency of occurrence of positive dermal and inhalation challenge responses to many fungi among asthmatics. The results of 2960 intradermal tests and as many scratch tests on 488 asthmatic patients and 112 healthy persons with antigenic extracts of 10 fungi showed that positive reactions were much more common in asthmatics than in healthy persons. Of 618 bronchial sensitivity tests with fungus extracts on asthmatics, 50 % showed positive responses. Bronchial tests were positive in the majority of patients who had shown positive skin tests to the same antigens, negative in most patients with negative skin tests. Many of the asthmatics exhibited response to house dust as well as to spores.

A rising level of total serum immunoglobulin E (IgE) is reported to have occurred among a group of 12 patients with allergic bronchopulmonary aspergillosis (ABPA) during periods of flare in disease activity manifested by new roentgenographic infiltration or more than 3 days of fever, chest pain, and cough with purulent sputum, or hemoptysis (58); a stable or declining IgE level was associated with disease remission. No very clear relation of the changes in IgE level to activity of the fungus was shown, nor indeed is it evident that the proven presence of any aspergillus in the patient was required for the diagnosis of ABPA in this

study (58). Precipitins and IgE antibodies to *A. fumigatus* and other aspergilli were of much more frequent occurrence in individuals with cystic fibrosis than in control subjects (41, 89).

Comments on the interpretation of radiographs in regard to growth of *A. fumigatus* in the bronchi have been provided by Simon (136, pp 69–74). He states: 'A bronchogram is rarely needed for diagnosis, but if one is done, evidence of bronchial damage is usually obvious.' In accord with this, three patients with clinically evident allergic bronchopulmonary aspergillosis had normal chest x-rays but showed evidence of bronchiectasis in bronchograms (124).

Lung scans with radiostrontium have also recently been suggested to be applicable (1). Scans were positive in all of the 12 individuals already known to have allergic pulmonary aspergillosis or aspergilloma, negative in 13 control subjects, but positive in 4 other controls (1); a negative scan appears to exclude the diagnosis of allergic pulmonary aspergillosis or aspergilloma, while a positive scan may be much less specifically informative.

Surgery may be used to establish diagnosis. McElvein (87) states: 'A patient with pulmonary fungal disease may have nonspecific respiratory symptoms, and the x-rays of the chest may be non-diagnostic. Skin tests and complement-fixation tests, because of cross-reactions and low specific antigenicity, are not always sufficiently precise to enable diagnosis with certainty. The surgeon can obtain material which should be handled properly and submitted to a good laboratory to establish diagnosis and to institute proper therapy.'

The characteristic microscopic appearance of aspergilli in pathologic material is illustrated by Emmons et al. (31), who also provide descriptions of suitable culture methods and microscopic criteria for species identification in culture. The fungal hyphae display septation and typical bifurcate branching in tissue specimens and are easily distinguished from the wider and mostly non-septate hyphae of *Phycomycetes*. Distinction between the hyphal forms of *Petriellidium* and of *Aspergillus* in pathologic sections may be difficult or impossible unless the conidiophores of *Aspergillus* are present (83). The necessity of cultures in diagnosis is emphasized (48, p 80), along with the comment that 'So often the question of a fungal infection is first raised only after the only available specimen has been fixed in formalin or exposed to airborne contamination.'

Emmons et al. (31) indicate that the spore-bearing apparatus in *A. fumigatus* is highly typical of the species.

They state: 'The gradual widening of the tip of the conidiophore into a vesicle, production of phialides on only the upper half or two-thirds of the vesicle, production of primary phialides only, the bending of the lower phialides so that they approach a parallel orientation with those above, resulting in production of a columnar mass of conidia and the grey-green color of the colony are characteristics which easily identify this species.' Photos illustrating the typical conidiophore structure in *A. fumigatus* have been published (31, 114, 118). Raper and Fennell (114) present a comprehensive and detailed discussion of morphology and taxonomy of the *A. fumigatus* group. Temperatures of 37 to 50 C tend to eliminate competing organisms in cultures with mixed inoculum and to facilitate detection of *A. fumigatus* (15). The use of oxgall in the medium decreases radial growth of colonies of fungi, thus limiting confluence and facilitating counting (92).

Identification of the grey-green colonies of *A. fumigatus* in cultures from sputum samples is regarded as having uncertain diagnostic significance unless the fungus is cultured rather consistently from a series of samples, and even then the results might indicate only repeated exposure to inhalation of spores of the fungus rather than internal growth (130). If positive cultures are obtained, then the presence of hyphal fragments and/or the typical conidiophores in the original sputum increases the diagnostic significance (32). Background information on the fungal flora of the sputum of healthy men has been provided by Comstock et al. (26). These authors offer the following interesting comment: 'The role of fungi in bronchopulmonary disease is puzzling. Even when they are not dismissed out of hand as contaminants of the respiratory secretions, careful study may still fail to tell whether fungi caused the disease process as primary pathogens, aggravated it as secondary invaders, or as saprophytes merely found it to their liking.' Isolation from sputum samples of Aspergilli of many species present as 'transient residents in the human respiratory tract following their inhalation from the environment' has been reported by Sandhu and Sandhu (130). Sputum samples may in some cases contain mucus plugs with the fungus microscopically visible in them; in some patients they may also be visible in situ in the bronchoscopic examination (80).

Epidemiology

This subject is poorly understood (137), probably in large part because of inadequate reporting of cases. An obvious reason for such poor reporting is the unavailability of good

diagnostic techniques and the diversity of the different aspects of the disease. Rippon (118, p 408) makes the relevant remark that 'The pathogenic spectrum of aspergillosis is complicated, confusing, . . . and represents a group of diseases.'

The bronchopulmonary phase of aspergillosis appears to have been reported more frequently from Britain than elsewhere (48, 57, 74, 109, 137), a situation which Solomon and Burge (143) tentatively attribute to 'an atmospheric burden of *A. fumigatus* substantially lower, in our locality, than in Britain.' While the disease may actually occur more frequently in Britain, Parker et al. (103), however, state 'Mainly because of the lack of diagnostic criteria and methods, there are no reliable data concerning the incidence of pulmonary aspergillosis in chest disease hospitals.' In reference to the relatively low levels of allergic bronchopulmonary aspergillosis recorded for the United States in comparison with records on the same in England, Pepys (110) offers the comment that 'Apparently, differences in recognition of the disease appeared to be related to the inadequacy of the antigens used for skin test diagnostic purposes. In a comparison of the incidence of allergy to *Aspergillus fumigatus* in centers in the United States and in London, the commercially supplied Aspergillus antigen mixture did not in fact contain the antigen being studied, namely *Aspergillus fumigatus*.' On the basis of recent experience, Patterson (105) states 'Allergic bronchopulmonary aspergillosis is not a rare disease in the United States despite the lag in recognition as compared with case discovery for many years in England.' Without questioning the usefulness in a clinical setting of intradermal and serological testing with Aspergillus preparations, it may merit noting that some cases described as 'allergic bronchopulmonary aspergillosis' do not involve a proven connection with any fungus; two of three cases reported by Imbeau et al. (57), for example, seem to fall into this category. Critical proof of any particular fungus growing in the body seems also to be lacking in the studies of Rosenberg et al. (126) and Mintzer et al. (93). Cases of pulmonary aspergillosis in large numbers, often treated surgically, have been reported from Poland; for reports on these, the reader is referred to numerous abstracts, not here individually cited, in the Review of Medical and Veterinary Mycology (6).

Records of incidence of hospitalized cases of systemic mycotic infections for the United States in 1970, including aspergillosis, have been collected by Hammerman, Powell, and Tosh (49); the data show very low levels of aspergillosis but the authors state that they provide 'undoubtedly a low

estimate of the incidence of all infections discussed.' Systemic mycoses were observed in 2 % (109/5142) of autopsies at University Hospital in Oklahoma City over the period 1955-1975, with 8 of these 109 cases being attributed to systemic aspergillosis (113).

In cane-sugar processing in India, two of 131 workers occupationally exposed repeatedly to high concentrations of *A. fumigatus* in air exhibited allergic bronchopulmonary aspergillosis (171); the authors conclude that 'constitutional predisposition of the host may be a more important factor than the extent of exposure to the fungus in the development of allergic bronchopulmonary aspergillosis.' Many other workers displayed chronic lung difficulties of uncertain etiology.

Although unusual among the fungi in its ability to grow within the human body, *A. fumigatus* is only one of many fungi and actinomycetes whose spores may act as extrinsic allergens in provoking asthmatic and other allergic responses within the respiratory system (8, 22, 118, pp 502-507). The farmer's lung phenomenon occurring among mushroom compost workers and others (14, 77), is believed to result from massive allergic assault on the alveoli by exceedingly large numbers of inhaled spores (77, 78). Unlike exclusively extrinsic allergens, which can often be avoided by restricting individuals from situations in which they occur, *A. fumigatus* can also grow internally in the air passages of the lungs and thus can not be avoided by such simple means (107, 138).

Risk assessment and control

The obvious practical merits of sludge composting leave little doubt that some one or several versions of the practice will be employed at some locations in the United States; the remaining uncertainty relates mainly to the question of where this will occur and to particulars of the composting process. Assessment of health risk from point sources of *A. fumigatus* is a complex matter which should include inputs from physicians familiar with aspergillosis working together with mycologists knowledgeable about *A. fumigatus* and others with relevant information. Professional personnel informed about aspergillosis could be located in many cases through medical schools or large hospitals, alternatively in many large cities through authorship of the papers here cited.

A wide range of verbal opinion has been heard already in respect to probable degree of risk from *A. fumigatus* at and around sludge composting sites, with some estimating

risk to be minor or non-existent and others considering it significant and possibly even major in some situations. The need for more thorough exposition of the facts, the assumptions, and the logic underlying such opinions seems evident. Risk assessment is made difficult by (a) a shortage of data on background environmental levels for *A. fumigatus* in air, (b) lack of quantitative information on emission rates and dispersal patterns of spores of the same at composting sites, and (c) lack of a dosage response curve relating inoculum levels of the fungus to disease incidence in humans.

In respect to risk assessment in the situations under consideration the present writers find such statements as 'Aspergilli and other moulds are ubiquitous to be of uncertain usefulness. 'Ubiquitous' is non-quantitative and *A. fumigatus* is frequently named as a species in individual medical reports rather than the less specific 'Aspergillus sp.' While the literature cited in the present paper makes it clear that aspergilli other than *A. fumigatus* can infect highly compromised individuals, the same literature also makes it equally clear that *A. fumigatus* is the most frequently recorded species among the aspergilli reported in the literature as a cause of infection in humans. Emmons et al. (31) state '*Aspergillus fumigatus* is the usual etiologic agent of the pulmonary aspergillosis of the typical, severe, invasive form with eventual hematogenous dissemination to other organs,' also 'In its clinical manifestations, *Aspergillus fumigatus* is the most virulent and most versatile of the Aspergilli.'

Many of the writers here cited appear to think of *A. fumigatus* as omnipresent at infective levels in all situations and to attribute overwhelming importance to the pre-disposed condition of the host in comparison with any possible importance of differences in level of inoculum. Rippon (118, p 3) states, for example: 'opportunistic infections are caused by universally present organisms of low virulence. Establishment of disease depends entirely on lowered resistance of the host.' Recent interest and action relating to control of sources, situations, and procedures in hospitals which may lead to presence of the fungus is reflected in numerous publications (3, 40, 60, 65, 76, 111, 120, 127, 148); air sterility in operating rooms and intensive care units in respect to *A. fumigatus* has been a point of particular concern. Kammer and Utz (65), for example, state 'Careful surveillance and control of fungal contamination of the surgical environment is urged.' Corrective action to date has related mainly to hospitals' ventilation and air filtration facilities (16, 40, 65, 11, 120, 122, 123). A few details recounted just below may further reinforce

for the benefit of planners and operators of composting ventures the fact that doctors are currently looking with increasing concern into the sources of inoculum of *A. fumigatus* in hospitals.

Gage et al. (40) reported aspergillus endocarditis in three patients after heart surgery and ascribed the infection to growth of *A. fumigatus* on pigeon excreta near the intake of the ventilating system in the operating room, while Burton et al. (16) isolated *A. fumigatus* from external air inlets to an isolation room following four cases of aspergillosis in kidney transplant recipients, removed the suspected source of infection and stated that in a year since the corrective action no aspergillosis was observed in 20 subsequent kidney transplant recipients.

Petheram and Seal (111), after reporting seven cases of *A. fumigatus* prosthetic valve endocarditis, also reported what they considered to be the probable source of infection: 'After identifying the first three patients in this outbreak, a careful search was made of the operating theatre environment for a possible source of entry of the spores. Green dust containing small natural and man-made fibres from theatre swabs and surgeons' gowns was collected from the ventilation system in quantities sufficient to fill a large sweet jar. Culture of this dust revealed a profuse growth of *A. fumigatus*.' A cluster of four cases of aspergillosis appearing within a few weeks in an intensive care unit remained unexplained when a search failed to reveal an intramural source of the fungus (64). Staib et al. (146) suggest that conidia in the air exhaled by a hospital patient infected with *A. fumigatus* may serve as inoculum to infect another patient. They state that their studies have 'revealed that aspergillosis patients, clinical material sampled from them, decaying plant material (agriculture, horticulture), and used clothes and linen may form foci for the spread of *A. fumigatus* conidia.'

Rose (120) reported that 'Terminal Aspergillus pneumonia developed in 11 patients on the wards of an old naturally ventilated hospital during the last five years of its occupancy. All patients were moved to a new, mechanically ventilated hospital and this infection was not seen during the next five years.' Concerning their work, they (120) write: 'This study suggests that hospital-acquired infections of the lung might be eliminated if all incoming hospital air is filtered, properly vented, and not recirculated.' In a basically similar situation, Rosen and Sternberg (123) have reported a decrease in numbers of cases of aspergillosis and mucormycosis coincident with a move from an old into a new hospital; they tentatively attribute the improvement to 'the elimination of some sources of contamination

as a result of an improved ventilation system.'

Aisner et al. (3) reported a cluster of eight *Aspergillus* infections in cancer patients within a period of seven months soon after transfer of patients to a new hospital facility; they developed strong circumstantial evidence that this striking increase in aspergillosis was traceable to fungal contamination from growth on fire-proofing material used in the false ceiling of the new facility.

Solomon et al. (144) made fairly extensive volumetric air samplings for fungi able to grow at 37 C in a hospital in Michigan and reported mean levels for *A. fumigatus* of less than 10 colony forming units per m³; the mean at an outdoor collection point was 6.3/m³. Their samples were 1.7–3.4 m³ in volume; more than half of all indoor and outdoor samples contained the fungus in low but readily detectable amounts. The authors contrast their data with the generally higher in-hospital levels of *A. fumigatus* recorded by Noble and Clayton (98) and comment that 'The possibility that *A. fumigatus* levels encountered by these workers were derived from discrete intramural sources is not easily dismissed.'

The measured levels of *A. fumigatus* in air found by Solomon et al. (144) were of the same order of magnitude as reported earlier for outside air by Austwick (7) and Hudson (54). In summarizing his data, Hudson (54) states: 'Some 550 colonies of thermophilous and thermotolerant fungi were isolated during the year. Total counts ranged from 0 to 14 spores/m³ with a mean of 3.2 spores/m³. This is extremely low, as might be expected when compared with the total counts of the mesophiles. At the same site, the mean concentration of mesophilous fungi in 1967 ranged from 330 to 12243 spores/m³ (Hudson, 1969). Twelve fungi listed in Table 1, were encountered. Of these, *Aspergillus fumigatus* was by far the most common and made up 69.0 % of the total count.' Hudson's mean levels for *A. fumigatus* thus were 2.21 spores/m³. For comparison, it may be noted that total counts for all fungal spores in outdoor air in summer often exceed 10⁴/m³ (47) and that counts of the same type in a barn containing moldy hay often exceed 10⁷/m³ (77). Further information on levels of spores of *A. fumigatus* in air is provided by the data of Burge et al. (15), whose aerometric spore counts for this organism in 11 libraries of the University of Michigan averaged 6 spores/m³ in summer and 0 spores/m³ in winter, as compared with readings of 0 and 1 spores/m³ outdoors in the same seasons.

When adequately investigated, the occurrence of *A. fumigatus* in nature may turn out to be governed to a significant degree by its ability – or lack of it – to grow

at relatively low moisture levels. Such very limited information as seems presently available does not suggest such adaptation to any high degree. In one report, growth of the fungus was stated to have occurred on naturally infected hay at 42 % moisture and was accompanied by heating to a maximum of 64 C, whereas at 28 % moisture the growth consisted mainly of the low moisture-adapted *A. glaucus* group species and heating reached only 44 C (7). Another report (48, p 17) states that molding of hay is absent below 13 % moisture, consists of *A. glaucus* group species up to 25 % moisture, of *A. versicolor*, *A. nidulans*, and *Absidia* spp. at about 30 % moisture, and is dominated by *A. fumigatus*, *Mucor pusillus*, *Humicola lanuginosa*, and certain actinomycetes above 40 %. Water potential may turn out to be more informative than water content.

In assessing any *A. fumigatus*-associated health risk which might exist at and around a composting site, the probable degree of predisposition of any individuals likely to be exposed and the number of such individuals must be considered. Proximity of the site to hospitals, nursing homes, medical clinics, doctors' – office buildings, major blood collection centers, and other health care facilities may need to be examined closely. The possibilities for serious consequences from *A. fumigatus* in a large hospital of diversified function have been emphasized in references cited in this text and it seems reasonable to conclude that any activity resulting in heavy air contamination with the fungus in the vicinity of such hospitals would merit special attention. Not only open windows but also every individual entering the hospital from an outdoor parking lot may offer an avenue of entry for the fungus into the building by mechanical transfer on hair, hands, and outer clothes. Intramural monitoring for point sources of air contamination within the hospital facility is also emphasized.

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