Thorax (1969), **24**, 722.

Pulmonary monosporosis: An uncommon pulmonary mycotic infection

P. C. REDDY, C. S. CHRISTIANSON, D. F. GORELICK, AND H. W. LARSH

From Missouri State Sanatorium, Mt. Vernon, Missouri, and the Department of Botany and Microbiology, University of Oklahoma, Norman, Oklahoma

Pulmonary monosporosis is an uncommon form of fungal disease of the lung and broncho-respiratory passages. To date, only six isolated cases have been reported in the literature. It is the purpose of this communication to present the clinical findings, laboratory data, radiographic appearance, and description of the pathology findings in three additional cases identified at the Missouri State Sanatorium. The fungus *Monosporium apiospermum* is present in the soil and has a world-wide distribution. It has been shown to produce localized lesions in the foot called maduromycosis. Pulmonary infection due to this fungus has no characteristic clinical pattern, but the cultural characteristics of *M. apiospermum* permit specific identification. Histologically, the pulmonary involvement shows a variegated non-specific pattern. In the majority of cases, well-defined, predisposing factors are present. A review of the reported six cases and a study of our three cases strengthens our belief that the organism acts as a secondary invader. To date, no mode of therapy has appeared to exert a beneficial influence on the course of the disease. To our knowledge, no clinical trial using any of the antifungal agents has been attempted. Surgical treatment is indicated whenever the lesions are considered resectable. From our observations, we conclude that pulmonary infection with *M. apiospermum* could be recognized more frequently if physicians were more aware of this fungal infection and if the mycology laboratories would take additional care in specific identification.

Although it is well known that *Monosporium apiospermum* can produce pathological lesions in the foot, causing maduromycosis, its role in producing lung lesions is not quite clear. To our knowledge, there are only six such reported cases in the literature. We have identified three additional ones. It is the purpose of our communication to report these cases, discuss the pathological relationship of the fungus to pulmonary disease, review the literature to compare the pathology and symptomatology, and comment on treatment.

CASE REPORTS

CASE 1 A 62-year-old Caucasian male farmer was admitted to the Missouri State Sanatorium for the fifth time in October 1967 with complaints of cough and blood-streaking of the sputum for the preceding 18 months.

The patient's first admission was in December 1938. At that time he gave a history of pleuritic type chest pain, cough, and blood-streaked sputum. Physical examination revealed bilateral crepitations in the lungs, and his chest radiograph showed dense fibrotic infiltration over the entire right lung field with evidence of cavitation in the right upper lobe. On the left there were scattered, less dense infiltrations in the lower two-thirds. Sputum smears for acid-fast bacilli initially were reported as Gaffky VI. Subsequent sputa were negative. No cultures were made. A diagnosis of far advanced, pulmonary tuberculosis was made, and treatment consisted of repeated artificial pneumothoraces on the right. After one year he was discharged as improved.

The patient remained well for two years, but was readmitted in 1941 because of shortness of breath, cough, and one episode of haemoptysis: at that time he received several additional artificial pneumothorax treatments. Sputum smears were negative for acid-fast bacilli.

His third admission was in 1948 for 10 days, and once more he was given a pneumothorax on the right.

The patient then felt well enough to do light work as a carpenter and as a farmer. He was admitted for the fourth time in November 1965 because of blood-streaking in the sputum. His chest radiograph showed dense infiltration in the upper two-thirds of the right lung with cavity formation, while the left lung was

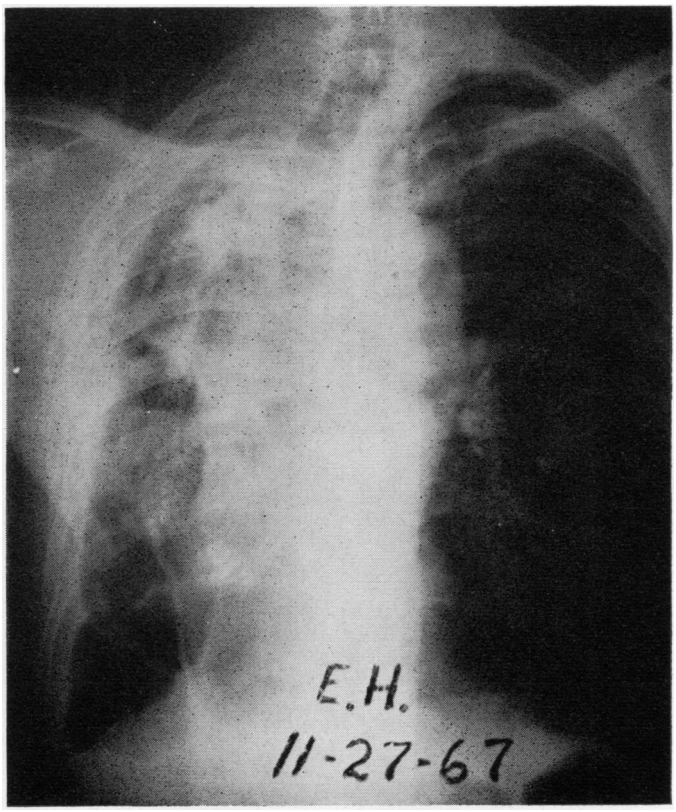

FIG. 1. *Case* 1. *Antero-posterior film of chest showing extensive involvement of the right lung with two fungus-balls in cavities.*

unchanged. A bronchogram revealed saccular bronchiectasis of the right upper lobe bronchi. Sputa were negative for acid-fast bacilli on culture. Fungus cultures were not obtained. Skin tests using PPD-S and histoplasmin were positive.

The final hospital admission was in October 1967 for increasing shortness of breath, easy fatigue, and cough productive of moderate amounts of yellowish-white sputum. On a few occasions he had blood-streaking and once coughed up a tablespoonful of bright red blood.

Physical examination revealed a shift of the trachea and mediastinum to the right, and several wheezes and coarse crackling sounds in the right upper lung with diminished breath sounds on the left. There was accentuation of the pulmonic component of the second sound with a grade 2/6 systolic murmur in the fourth interspace to the left of the sternum.

Sputum cultures were negative for acid-fast bacilli. Several successive fungal cultures yielded *M. apiospermum*.[1] His electrocardiogram showed right atrial and ventricular hypertrophy, and his chest film (Fig. 1) revealed tracheal and mediastinal shift to the right. There was a dense infiltrate in the upper two-thirds of the right lung with several cavities, the largest measuring 3 cm. in diameter. In addition, two well-formed fungus-balls were seen occupying the second and third interspaces medially. There was calcified infiltrate in the left lung.

A right pneumonectomy was carried out in January 1968, after which there was an uneventful post-operative course. Tissue cultures yielded *M. apiospermum* and sputum cultures continued to grow the fungus after the operation. Skin tests using 1 : 1,000 and 1 : 500 strength of *M. apiospermum* antigen[2] were negative.

The removed right lung weighed 600 grams. The pleural surfaces were partially covered by thickened fibrotic pleura. The anterolateral subapical portion of the upper lobe presented a number of discrete and intercommunicating cavities, some of which communi-

[1]Additional studies were done at the Microbiology Laboratory, University of Oklahoma

[2]Prepared for us by courtesy of the Microbiology Laboratory, University of Oklahoma

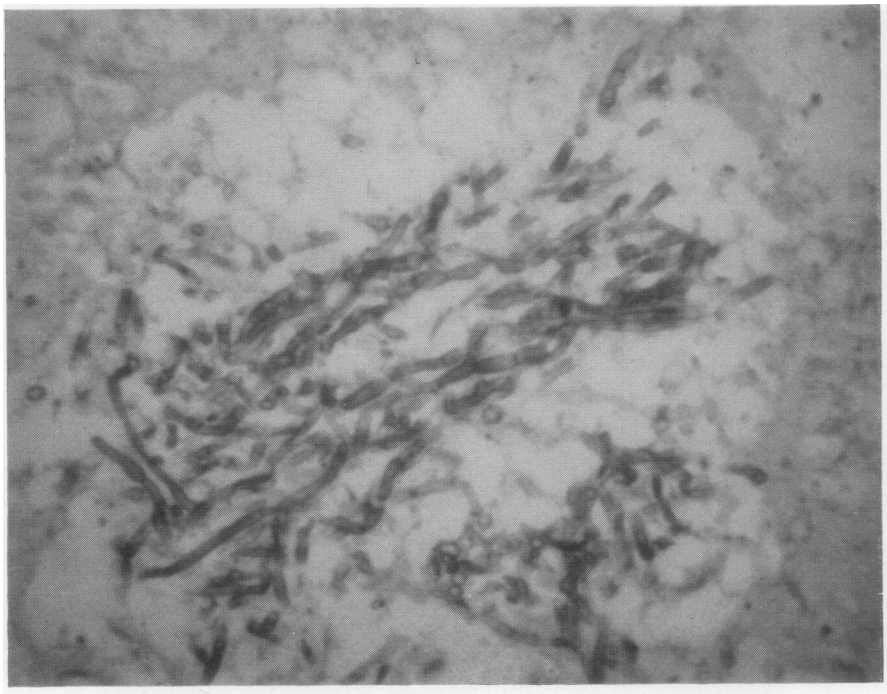

FIG. 2. *Shows mycelial fragments in area of necrosis. G.M.S. stain* × 430.

cated with bronchi. Their surfaces ranged from dull red and purulent to smooth, glistening, and grey and measured up to 3 cm. in greater dimension. Within some of the cavities there were smooth-surfaced, compressible, round to oval-shaped, light brown structures which on section had an 'onion-peel' appearance and looked like fungus-balls. In the posterior subapical areas were two irregular-shaped, calcified structures surrounded by compact, grey, fibrous tissue, which measured 18 and 11 mm. The bronchi in the basal segment of the upper lobe were moderately dilated, thick-walled, and typical of cylindrical bronchiectasis. Portions of decorticated fibrotic pleura contained flat, calcific plaques.

Sections from cavitary walls showed the inner surfaces to be lined by varying amounts of necrotic detritus, beneath which there was a granulomatous reaction made up of fibroblasts, epithelioid cells, lymphocytes, plasma cells, and small numbers of multinucleated foreign body giant cells. Within the granulomatous tissue there were bands of fibrinoid, as well as foci of necrosis with predominant neutrophilic reaction. In such areas remnants of bronchial cartilage plates were seen. Sections of the bronchiectatic bronchi showed chronic inflammation but no granulomata. The intracavitary structures were made up of irregularly arranged mycelial filaments. No acid-fast bacilli were demonstrated. The fungus-balls were made up of radially arranged mycelia and of segmented hyphae (Fig. 2). Identical mycotic structures were seen in the granulomatous walls of the cavities. Similar hyphal fragments were present in central amorphous material of the decalcified structures found in the subapex of the upper lobe.

COMMENT The appearances presented by the specimen removed at operation in this case suggest that the fungus had been present in the lung lesions for several years. The upper lobe lesions most probably followed an initial tuberculous involvement with a concomitant growth of Monosporium, remnants of which were incorporated in the calcified bodies. A residual saccular bronchiectasis and/or cavitation predisposed either to re-infection with or reactivation of Monosporium. Local tissue sensitization resulted in extension of the mycotic growth into the tissue itself. We think that tuberculosis was the initial offender but played a minor role in the patient's subsequent pulmonary disease. This is borne out by the negative acid-fast bacilli cultures after his first period in hospital in 1938. We believe that *M. apiospermum* was responsible for the patient's progressive lung disease.

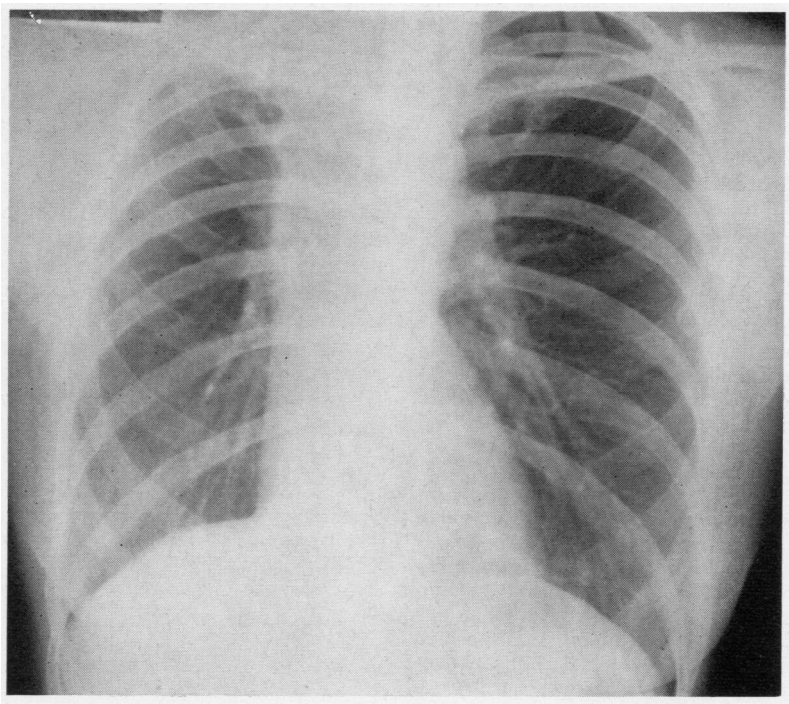

FIG. 3. *Case 2. Antero-posterior film of chest taken prior to surgery, showing infiltrative lesion of the right apex.*

CASE 2 A 52-year-old white woman was admitted to the Missouri State Sanatorium in December 1956 with a six-month history of intermittent fever, chills, cough productive of moderate amounts of expectoration, and blood-streaking of the sputum. Her appetite had been fair but she had a weight loss of 10 lb. (4·5 kg.). Her past history dated back to 1933, when she was in another hospital and thought to have pulmonary tuberculosis, but after one year she was discharged as improved.

She was readmitted in 1941, received several artificial pneumothoraces, and was discharged after 10 months. She was again admitted in 1942 and treated with pneumothoraces. In August 1956, because of weakness and blood-streaking of the sputum, she went for a brief period to Memorial Hospital, Lebanon, Missouri, but was admitted to our Sanatorium because of progression of her symptoms.

Physical examination revealed a well-developed, moderately nourished woman who was in no acute distress. Systemic examination was within normal limits except for crackling sounds over the right upper lung. Radiographs showed the trachea and mediastinum shifted slightly to the right (Fig. 3). The right lung exhibited dense infiltrates in the apex, with several less dense, nodular infiltrates in the upper third and evidence of radiolucency in the lower lung field. The left lung was normal.

Gastric and sputum cultures for acid-fast bacilli were negative on several occasions. The purified protein derivative (P.P.D.) was positive, whereas the histoplasmin skin test was negative. No fungus cultures were done prior to operation, which was advised because the lesion did not respond to antibiotics: a right upper lobectomy with decortication was carried out in February 1967.

The removed right upper lobe measured $10 \times 6 \times 2{\cdot}5$ cm. and presented a thickened fibrous pleura. On examination practically all the bronchi were found to be dilated, some measuring up to 2·5 cm. in diameter. The inner surfaces were smooth and glistening and some of the dilated bronchi contained thick mucoid material. The gross appearance was that of a mixed saccular and cylindrical bronchiectasis as well as chronic fibrous pleuritis.

Histological examination showed chronic nonspecific bronchiectasis and extensive secondary interstitial fibrous pneumonitis. The dilated bronchi were lined by intact epithelial mucosa. Sections stained with special stains were negative for acid-fast organisms or fungi. However, tissue cultures yielded *M. apiospermum*, which was probably recovered from the contents of the bronchiectatic bronchi.

COMMENT This 52-year-old woman with a history of pulmonary tuberculosis, quiescent for

several years, developed bronchiectasis. We believe that *M. apiospermum* cultured from the cavity contents was a secondary invader, since no tissue invasion by the fungus was seen in the microscopical examination.

CASE 3 A 77-year-old widow was admitted to the Missouri State Sanatorium in October 1963 because of pulmonary infiltration found on a survey chest radiograph. The patient had cough productive of small amounts of sputum. Her previous history had been entirely non-contributory. The patient had been a housewife and had lived on a farm with her husband for approximately 12 years.

Physical examination on admission was within normal limits. An initial radiograph in August 1963 was interpreted as showing dense, calcific infiltrate in both apices. Repeat radiographs in October and December 1963 showed very little change. On admission she was classified as having minimal pulmonary infiltration in both apices, which was considered suspicious of tuberculosis, although the P.P.D. test was negative. The histoplasmin skin test was positive, although histoplasmin and blastomycin complement fixation tests were negative. Several sputum cultures yielded no growth of acid-fast bacilli. Four successive fungal cultures were reported as positive for *M. apiospermum*.[3] In December 1963 the patient left hospital against medical advice. Subsequently readmission was advised but to date she has not complied with the hospital's request, although she is still alive in advanced cor pulmonale.

COMMENT In this case the fungus was isolated only from the sputum and no tissue cultures were available. It is significant that no other aetiological agent was isolated from the sputum on repeated examination, and that the patient also lived on a farm for 12 years.

DISCUSSION

There is little doubt that fungal infections of the lung are being recognized more frequently. The reason for the apparent increase in the diagnosis of mycotic pulmonary infections is the increasing awareness of the physician of these disease entities, the decline in pulmonary tuberculosis, and the improved techniques in mycology laboratories. Since a number of fungi are common laboratory contaminants, such possible contamination must be borne in mind, and care taken to avoid it. Repeated isolation of a fungus from clinical material is good but not conclusive evidence that the fungus may be a pathogen. In recent years, Histoplasma, Cryptococcus, Aspergillus, Blastomyces, and Coccidioidomyces are well recognized as pathogens, but few clinicians are aware of the role of *M. apiospermum* in producing pulmonary lesions.

Murray, Haegelin, Hewitt, Latta, McVickar, Rasmussen, and Rigler (1966) discussed the role played by predisposing factors (as listed in the Table) in altering the host–tissue response and the development of secondary fungal infections. These fungal infections have adapted themselves to those unique circumstances which favour their growth, and there is little doubt that the prevalence of opportunistic infections is increasing. Six of the eight cases discussed (*vide supra* and *infra*) in this paper have shown one or more predisposing factors which could have led to opportunistic infection with *M. apiospermum*.

TABLE

OPPORTUNISTIC PULMONARY INFECTIONS

Predisposing Diseases	Predisposing Conditions
Diabetes mellitus	Agammaglobulinaemia
Leukaemia	Neutropenia
Lymphoma	Splenectomy
Cancer	*X*-ray therapy
Aplastic anaemia	Corticosteroids
Cushing's disease	Antineoplastic drugs
Collagen diseases	Antibiotics
Alveolar proteinosis	Immune suppression

The specific terminology of the disease is dependent upon the cultural phase of the fungus at the time of observation. What later proved to be the imperfect stage of the causal fungus was described by Tarozzi (1909) from a Sardinian case of Madura foot. Later, Boyd and Crutchfield (1921) isolated an ascomycetous fungus from a human case of mycetoma. This isolate was considered by Shear (1922) to be a new species of the genus Allescheria and was named *Allescheria boydii*. Emmons (1944), however, subsequently proved the relationship of *M. apiospermum* to *A. boydii* as stages in the life cycle of one of the causal organisms of maduromycosis. In addition to producing cutaneous mycetomas, the fungus has been isolated from other lesions. Thus Belding and Umanzio (1935) described it as a rare cause of otomycosis, Benham and Georg (1948) as an aetiological agent in a case of meningitis, and Zaffiro (1938) has described a case of septicaemia caused by this organism.

Pulmonary infection is also uncommon, but we have been able to trace six reported cases. The first was reported by Drouhet (1955) in a patient with pulmonary mycetoma. Several consecutive sputum isolates grew *M. apiospermum*. In the same year, Creitz and Harris (1955) reported the

[3]All cultures were identified and further confirmed in the Communicable Disease Center at Kansas City, Missouri

case of a 56-year-old Spanish farmer from whose sputum *A. boydii* was repeatedly isolated. This patient was subsequently transferred to a Veterans Administration hospital in Denver, Colorado, and the case was published by Tong, Valentine, Durrance, Wilson, and Fischer (1958). The radiographs on admission revealed several abscesses and sputum cultures yielded *M. apiospermum*. Initially, he was treated with chloramphenicol, and 2-hydroxy stilbamidine was later added to this regimen. At first the patient showed improvement with this therapy, but later deteriorated. He underwent right upper and middle lobectomies, but his subsequent clinical course was progressively downhill and he died on the twenty-fourth postoperative day. The resected lung showed several cavities and tissue cultures grew *M. apiospermum*.

Scharyj, Levene, and Gordon (1960) reported a 26-year-old farmer's wife who was admitted with haemoptysis and whose radiographs revealed cavitary lesions in the right upper lobe. This was removed, and the cavity contents on culture grew *M. apiospermum*.

Travis, Ulrich, and Phillips (1961) recorded a 30-year-old farmer who presented with a history of several bouts of haemoptysis. Radiographs revealed bilateral infiltration with cavitation: sarcoidosis was suspected and the patient was started on steroids. Even though the P.P.D. test was negative, he was placed on isoniazid and PAS. The patient's disease progressed gradually and he was admitted four years later. In spite of vigorous therapy for the cor pulmonale which the patient had developed, he died seven weeks after admission. Sputum cultures reported later and tissue cultures from the autopsied lung yielded *M. apiospermum*. Louria, Lieberman, Collins, and Blevins (1966) reported a 43-year-old woman with a history of haemoptysis who had a solitary round lesion on her chest radiograph. At operation a bronchogenic cyst was found and cultures of the cyst contents grew *M. apiospermum*. Finally, Adelson and Malcolm (1968) described a 43-year-old Negro man with severe rheumatoid spondylitis. In 1955 the patient had an abnormal chest radiograph and was thought to have active pulmonary tuberculosis, although sputum smears and cultures were negative for acid-fast bacilli. Despite treatment with streptomycin and isoniazid, the patient's disease progressed. Radiographs in October 1964 showed cavitation with " fungus-ball " formation. *A. boydii* was repeatedly isolated from the sputum. In May 1965 the patient received endocavitary treatment with a 2% solution of sodium iodide introduced through a subcutaneous catheter into the cavities. His chest film showed almost complete disappearance of the mycetomas one year after treatment. In January 1968 the patient was readmitted because of an exacerbation of bronchitis, and he died suddenly on the eighth day in hospital.

DIAGNOSIS In all nine of these cases, the diagnosis was made by the isolation of *M. apiospermum* from the sputum and/or tissue cultures. The diagnosis was confirmed by repeated isolation of the same organism. In seven out of the nine, the organisms were obtained from sputum cultures while in six out of eight cases[4] it was isolated from tissue cultures. In five out of eight, both tissue and sputum cultures were positive for this fungus.

Clinically, there are no signs or symptoms which we can ascribe as characteristics of the disease. Complaints of cough and expectoration were consistently the only manifestations of pulmonary disease. Haemoptysis was noted in five out of eight cases. Fever, chills, night sweats, and chest pain were seldom seen in these patients. Radiological features revealed diverse patterns. Pulmonary infiltration without cavitation was seen in three; cavity formation was present in six. In three, the characteristic radiographic features of a 'fungus-ball' were identified. Radiographs of one of the cases presented as a solitary round lesion which proved to be a bronchogenic cyst on pathological examination. In four out of eight cases, the disease was bilateral and in the other four, lesions were seen only in the right lung. In three, the disease was localized to the right upper lobe.

EPIDEMIOLOGY Isolation of *M. apiospermum* from soil, by Ajello (1952), has given proof of its saprophytic existence in nature. Pulmonary allescheria might be caused by inhalation of spores, but it is not known whether in the majority of patients the infection is benign, self-limited, and inapparent, since there are no specific modalities to test this. It is of interest that in our cases, and those reported in the literature, five patients have been either farmers or lived on a farm for a number of years. The disease shows no predilection for either sex; in the reported cases there are five males and four females.

PATHOLOGICAL FEATURES Although infection with *M. apiospermum* in tissues other than lung, such as maduromycosis, has been described as primary, such has not been the case in the involvement of lung tissue. In the majority of the cases there is

[4]Information on the case published by Drouhet (1955) could not be obtained.

an apparent underlying condition which acts as a predisposing factor. This may be a cavity concomitant with tuberculous infection, a bronchogenic cyst, or chronic bronchiectasis, especially of the saccular type. The infection by the fungus appears to be an opportunistic growth within a cavity, a cyst, or a dilated bronchus. Its pathogenicity is usually limited to the portion of lung involved by the predisposing disease. Systemic involvement, such as is seen in histoplasmosis, coccidioidomycosis, and blastomycosis, is unusual with *M. apiospermum*. As a result, there is no apparent elaboration of specific antibody response such as occurs with some of the other fungal infections. Local invasion of the tissue by the fungus may be due to local sensitization or to a breakdown of the tissue barrier represented by the epithelial lining of the space in which the fungus is growing. Such histological features are well demonstrated in our case 1.

Histologically, the pulmonary involvement offers a variegated non-specific pattern. The gross appearance of the fungus-balls is not specific. The morphological appearance of the differentially stained sections of the contents of some of the involved cavities or spaces, or invaded tissue, affords a clue to the identity of the fungus. However, the specific identification of *M. apiospermum* is possible only through its cultural characteristics.

TREATMENT There is currently no satisfactory treatment for pulmonary infections due to *M. apiospermum*. *In vitro* studies show that in most cases the organism is sensitive to amphotericin B, but to our knowledge this drug has not been tried in any case. In our laboratory, one culture of *M. apiospermum* was shown to be highly sensitive *in vitro* to the new antifungal agent 5-fluorocytosine. This drug is at present undergoing a limited clinical trial, since it appears to be an effective and safe antifungal agent useful in certain mycotic infections.

Another therapeutic measure mentioned above (Adelson and Malcolm, 1968) was the instillation of 2% sodium iodide directly into the cavities by subcutaneous catheter. This immediately resulted in the patient's violent coughing and expectoration of the fungus-balls. Radiographs after therapy showed sustained improvement with almost complete disappearance of the mycetomas one year after treatment. We think this improvement might be due more to the stimulation of the cough reflex than to the direct effect of iodides on the fungus. In this patient, sputa continued to yield *M. apiospermum* after therapy.

Two of our patients who underwent operation are doing well 12 years (case 2) and one year (case 1) post-operatively. Resection may be indicated in focal pulmonary lesions, since other measures appear to exert no beneficial influence on the course of the disease.

REFERENCES

Adelson, H. T., and Malcolm, J. A. (1968). Endocavitary treatment of pulmonary mycetomas. *Amer. Rev. res. Dis.*, **98**, 87.

Ajello, L. (1952). The isolation of *Allescheria boydii* Shear, an etiological agent of mycetomas, from soil. *Amer. J. trop. Med. Hyg.*, **1**, 226.

Belding, D. L., and Umanzio, C. B. (1935). A new species of the genus Monosporium associated with chronic otomycosis. *Amer. J. Path.*, **11**, 856.

Benham, R. W., and Georg, L. K. (1948). *Allescheria boydii*, causative agent in a case of meningitis. *J. invest. Derm.*, **10**, 99.

Boyd, M. F., and Crutchfield, E. D. (1921). A contribution to the study of mycetoma in North America. *Amer. J. trop. Med.*, **1**, 215.

Creitz, J., and Harris, H. W. (1955). Isolation of *Allescheria boydii* from sputum. *Amer. Rev. Tuberc.*, **71**, 126.

Drouhet, E. (1955). The status of fungus diseases in France. In the *Therapy of Fungus Diseases: An International Symposium*, ed. Sternberg, T. H., and Newcomer, V. D., p. 43. Little, Brown and Co., Boston.

Emmons, C. W. (1944). *Allescheria Boydii* and *Monosporium apiospermum*. *Mycologia*, **36**, 188.

Louria, D. B., Lieberman, P. H., Collins, H. S., and Blevins, A. (1966). Pulmonary mycetoma due to *Allescheria boydii*. *Arch. intern. Med.*, **117**, 748.

Murray, J. F., Haegelin, H. F., Hewitt, W. L., Latta, H., McVickar, D., Rasmussen, A. F., and Rigler, L. G. (1966). The UCLA Interdepartmental Conference. 'Opportunistic Pulmonary Infections'. *Ann. intern. Med.*, **65**, 566.

Scharyj, M., Levene, N., and Gordon, H. (1960). Pulmonary infection with *Monosporium apiospermum*. *J. infect. Dis.*, **106**, 141.

Shear, C. L. (1922). Life history of an undescribed ascomycete from a granular mycetoma of Man. *Mycologia*, **14**, 239.

Tarozzi, G. (1909). Ricerche anatomo-patologiche, bacteriologiche e sperimentali sopra un caso di actinomicosi del piede. *Arch. Sci. med.*, **33**, 553.

Tong, J. L., Valentine, E. H., Durrance, J. R., Wilson, G. M., and Fischer, D. A. (1958). Pulmonary infection with *Allescheria boydii*. Report of a fatal case. *Amer. Rev. Tuberc.*, **78**, 604.

Travis, R. E., Ulrich, E. W., and Phillips, S. (1961). Pulmonary allescheriasis. *Ann. intern. Med.*, **54**, 141.

Zaffiro, A. (1938). Forma singolare di mycosi cutanea da Monosporium apiospermum a sviluppo clinicamente setticemico. Considerazioni diagnostiche e deduzioni medico-legali. *G. Med. milit.*, **86**, 636.