5-Fluorocytosine Treatment of Meningeal and Pulmonary Aspergillosis

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Aspergillosis is widely regarded as an opportunistic infection of concern chiefly to physicians treating patients with terminal disease. Pulmonary aspergillosis is being recognized with increasing frequency as a cause of suppuration and hemorrhage. Twelve such cases and one of Aspergillus meningitis have been treated with 5-fluorocytosine. This oral medication has proved highly effective in many patients, with eradication of infection in several. In patients with underlying chronic pulmonary damage, drug resistance has developed, and relapse or reinfection has been frequent.

Aspergillus species have long been familiar as ubiquitous saprophytes, but their importance as pathogens has only recently been recognized. Reports of aspergillosis in disseminated form as a complication of cytotoxic chemotherapy [1], as a cause of pulmonary hemorrhage [2], as an incitant of immunologic lung disease [3] and as a primary pathogen [4], are rapidly accumulating. The role of Aspergillus as a pyogen has not been adequately emphasized in the past; this study demonstrates its frequency as a cause of suppurative lung disease.

Antifungal chemotherapy has been limited by the fact that the two agents reported to have some efficacy in aspergillosis, amphotericin B [5] and clotrimazole [6], have considerable toxicity. Amphotericin has a low therapeutic index, and resistance develops rapidly. Clotrimazole, an investigational drug, has in our limited experience been poorly tolerated. A new drug, 5-fluorocytosine, has been recognized as a major advance in the therapy of cryptococcosis and candidiasis [7]. We have employed this agent in 13 patients with various forms of disease due to A. fumigatus; the results indicate that 5-fluorocytosine deserves a primary role in the treatment of this infection.

MATERIAL AND METHODS

Diagnostic methods included culture, wet mount smears of sputum specimens revealing characteristic hyphae, positive serum precipitating antibodies in agar gel to standard Aspergillus antigens and morphologic identification of the organisms in histologic preparations of biopsy material.

Aspergillus antigens were prepared from standard strains of A. fumigatus grown at 31°C for 5 weeks in Sabourand dextrose broth cultures. Antigen was harvested by cold acetone precipitation and standardized by the Anthrone test to 1,000 μg/ml carbohydrate. Immunodiffusion tests were performed in 1 per cent agar buffered to pH 8.6 by standard double diffusion [8].

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TABLE I 5-Fluorocytosine Treatment of 13 Patients with Aspergillosis

Case No.	Principal Manifestation of Aspergillosis	Other Manifestations of Aspergillosis	Underlying Disease	Outcome
1	Meningitis	None	Sarcoidosis	Recovery
2	Pulmonary suppuration	Aspergilloma, pleural infection	Lung cyst	Improvement, recurrence, and improvement on retreatment
3	Pulmonary suppuration	Aspergilloma	Sarcoidosis	Improvement, recurrence, and improvement on retreatment
4	Pulmonary suppuration	None	None	Recovery
5	Pulmonary suppuration	None	Pulmonary infarct, gram negative septicemia	Recovery
6	Pulmonary suppuration	Empyema, aspergilloma	Sarcoidosis	Improvement, recurrence and recovery after retreatment
7	Pulmonary suppuration	None	Atypical mycobacteriosis	Improvement, relapse, death
8	Pulmonary suppuration	None	Lung cyst	Recovery
9	Pulmonary suppuration	None	Ankylosing spondylitis	Improved
10	Empyema	Pneumonia	Anthracosilicosis	Improvement, recurrence
11	Fungus ball with hemorrhage	None	Sarcoidosis	Unimproved
12	Fungus ball with hemorrhage	Abscess	Sarcoidosis	Recovered
13	Fungus ball with hemorrhage	None	Sarcoidosis	Death

5-Fluorocytosine, 100 to 150 mg/kg, was administered orally in divided doses every 6 hours; the usual dose was 6 to 12 g/day. In three instances combined therapy consisting of daily 5-fluorocytosine and weekly amphotericin therapy were used. When amphotericin B was given concommitently, 50 mg was given intravenously over a 6-hour period. Most patients received treatment for 90 days.

Toxicity was monitored clinically and by weekly determinations of the hemoglobin, hematocrit, leukocyte and differential count, platelet count, urinalysis, blood glucose, blood urea nitrogen, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total bilirubin, uric acid, calcium and phosphorus.

RESULTS

Pertinent clinical, seriologic and cultural findings are summarized in Table I, with more complete data regarding the patients and response to treatment presented in the appendix. A. fumigatus was cultured and serum precipitins demonstrated in each case.

TABLE II Case 1—Spinal Fluid Findings

Date	White Blood Cell Count	Cultures	Therapy
10/19/70	17	A. fumigatus	Prednisone, 40 mg, started 10/22/72
10/28/70	46	A. fumigatus	
11/04/70	144 (90 per cent lymphocytes)	A. fumigatus	Discharged 11/7/70; 5-fluorocytosine, 6.0 g daily, started 11/18/70
11/28/70	11	No growth	...
2/10/70	3	No growth	5-Fluorocytosine stopped 2/17/71, prednisone continued

The principal indications for treatment were meningitis (one case), pulmonary suppuration (eight cases), empyema (one case) and hemoptysis due to aspergillomas (three cases). As Table I indicates, multiple problems were often present. Six patients recovered, five patients showed improvement, one showed no change and one died. In five instances relapse occurred during or after therapy; retreatment resulted in recovery or improvement in three.

The most impressive evidence of therapeutic effectiveness of 5-fluorocytosine is provided by a case of meningitis. In this patient with sarcoidosis and uveitis, unsteadiness and abnormal reflexes led to lumbar puncture and to the discovery of pleocytosis. Three cultures demonstrated A. fumigatus. Use of oral 5-fluorocytosine resulted in prompt reduction in cell count (Table II), and all subsequent cultures were negative. Chemotherapy together with prednisone required for the uveitis was given for 90 days, and prednisone was continued for an additional 6 months. The patient has been observed for 2 years following cessation of 5-fluorocytosine therapy. Hilar adenopathy has persisted, but there has been no recurrence of uveitis or meningitis.

In patients with pulmonary suppuration, improvement was consistently observed with prompt reduction in cough, purulent sputum and fever. Anatomic involvement varied from abscess (one case) to infected cysts or bullae (six cases) and pneumonia (three cases). In two patients presenting with pneumonia, evidence of a cyst with

aspergilloma was subsequently demonstrated by tomograms.

Although the initial response was uniformly good, intracavitary and pleural infection persisted in several patients. In vitro susceptibility studies demonstrated the development of resistance to 5-fluorocytosine in one case. Pleural infection complicated lobectomy in two patients despite administration of 5-fluorocytosine before and after surgery.

In patients with aspergillomas the results were inconstant. One with pulmonary hemorrhage recovered with disappearance of the fungus ball, one showed no improvement and one died.

The recognition of resistance to 5-fluorocytosine led to trials in three patients of combined chemotherapy, employing amphotericin B weekly in conjunction with 5-fluorocytosine. This proved effective in two patients as judged by cultures and precipitins, but in both instances recurrence (or reinfection) followed.

TOXICITY

Ninety day courses in dosages of 6 to 12 g daily were tolerated without interruption by 11 patients. In one (Case 8) 5-fluorocytosine therapy was interrupted because of staphylococcal enterocolitis which occurred during the 4th week of treatment. After a lapse of 2 weeks 5-fluorocytosine was resumed and well tolerated. Another (Case 12), a neurotic subject, claimed gastrointestinal intolerance to 5-fluorocytosine and took it irregularly.

One patient (Case 2) received 180 g of 5-fluorocytosine in 1970 for pneumonia, 180 g in 1971 before and after lobectomy, 180 g in the spring of 1972 together with amphotericin B for pleural infection, and a fourth course in the autumn of 1972 when infection recurred. The last course was interrupted when an allergic pneumonia of uncertain etiology developed. Another patient (Case 3) received a 90 day course in 1970, and when infection recurred in 1972, another 90 day course given together with weekly amphotericin B injections was well tolerated.

No hematologic, hepatic or renal toxicity was observed.

COMMENTS

5-Fluorocytosine, a new antifungal agent, has proved effective in systemic cryptococcosis and candidiasis. In vitro data indicate the minimum inhibitory concentrations of 5-fluorocytosine to be low for both organisms [9]. Minimum fungicidal concentrations are somewhat higher, particularly for Cryptococcus neoformans [10,11], but such levels are achievable when 5-fluorocytosine is given in the 150 mg/kg body weight dosage [12]. The frequent or rapid development of antibiotic resistance by these organisms has been reported [13].

Minimum inhibitory concentrations of 5-fluorocytosine for Aspergillus species are somewhat higher than for Cryptococcus or Candida but are within a range which is achievable [15]. On the other hand, in vitro testing has shown that only 28 per cent of Aspergillus strains tested are within clinically achievable minimum fungicidal levels, and this fact has discouraged trials of 5-fluorocytosine for the treatment of aspergillosis [9]. Shadomy [12] subsequently showed that the previously reported minimum inhibitory concentrations and minimum fungicidal concentrations values for 5-fluorocytosine may be erroneously high because early in vitro testing was carried out in synthetic media containing nuclei acid supplements, thought to be competitive inhibitors of 5-fluorocytosine.

Reports of clinical use of 5-fluorocytosine in the treatment of aspergillosis have not been encouraging. Vandevelde et al. [14] reported 5-fluorocytosine to be successful in a case of Aspergillus osteochondritis of the sternum. Steer et al. [15] described four patients with disseminated aspergillosis who, having failed to respond to amphotericin B, were given brief courses of 5-fluorocytosine. Two died before a meaningful amount of therapy could be given, and two treated for 2 weeks showed no improvement. Our experience with meningeal and pulmonary aspergillosis is far more encouraging. None of our patients had neoplasms, endocarditis, septicemia or immunologic disorder other than sarcoidosis. None were receiving immunosuppressive or cytotoxic therapy except for prednisone.

There appear to be many applications of 5-fluorocytosine in the treatment of aspergillosis. The prompt and permanent response exhibited by the patient with meningeal aspergillosis represents the most impressive evidence of the fungicidal capacities of 5-fluorocytosine. The immediate effects in some patients with pulmonary infection have also been excellent, but the presence of chronic pulmonary damage has resulted in frequent relapse or reinfection.

Pulmonary aspergillosis assumes many guises: pneumonia, abscess, infected cysts, aspergillomas and recurrent allergic bronchopulmonary aspergillosis. Corticosteroids, rather than antifungal therapy, are appropriate in the latter disorder, but 5-fluorocytosine treatment is indicated in the other types of pulmonary involvement.

When pulmonary cavities are colonized by Aspergillus species, a "fungus ball" may mature within the free space [16]. Severe and sometimes fatal hemorrhages [17] often result, presumably as the result of erosion of the mucosa and secretion of anticoagulant [18]. Aspergillosis may produce suppurative infection with fever and purulent sputum [19]. Marked thickening of the overlying pleura is a characteristic feature of cavitary aspergillosis [20]. Chronic cavitary aspergillosis may remain quiescent for long periods of time, and spontaneous cure has been observed [18], but once hemoptysis occurs, fatal hemorrhage is a constant threat.

Surgical excision is indicated in the event of recurrent hemoptysis [21], but frequently the underlying disease is bilateral and compromises respiratory function, making surgical therapy impossible. Medical treatment of such cases is unsatisfactory since there is little diffusion of systemic medication into the cysts. The role of 5-fluorocytosine is more important when surgery is attempted. Pleural infection is a common sequel of surgical excision of fungal pulmonary lesions, and 5-fluorocytosine may have been partially effective in the three patients in this series who received it during the operative period.

The initial response to 5-fluorocytosine was uniformly good in patients with suppurative Aspergillus infections of the lung, and it is probable that this drug alone is adequate for patients with primary infections. In most cases, however, the acute pulmonary invasions originate in intracavitary infections or occur in lungs damaged by sarcoidosis or ankylosing spondylitis; in these circumstances recurrence or reinfection is common. Surgical excision of the cavitary foci is often impossible or unsuccessful (Case 2). When medical therapy is employed, combined drug therapy may delay or avert the development of resistance to 5-fluorocytosine. Amphotericin B is well tolerated when given weekly on an ambulatory basis. In vitro development of organism resistance to 5-fluorocytosine using Sabourand dextrose agar tubes was demonstrated in only one case (Case 7), but clinical evidence suggested that drug resistance was a frequent problem in patients with extensive pulmonary damage. Combined amphotericin and 5-fluorocytosine therapy was accordingly employed in three patients with chronic or relapsing disease.

Pneumonic spreads have been observed by us in only one patient (not treated with 5-fluorocytosine and hence not included in this series) as the result of large doses of corticosteroids required after lobectomy. Steroids in small doses have been required for treatment of many of our patients with sarcoidosis, and spread or dissemination has not occurred. The prolonged use of wide spectrum antibiotics appears to us to be more likely to promote fungal disease (Case 5), and the combined use of antibiotics and anti-inflammatory drugs is especially hazardous.

APPENDIX

Case 1. A 27 year old black hospital attendant (H.T., TJUH No. 306150) was admitted in October 1970 with headache and blurred vision. A chest roentgenogram revealed hilar adenopathy. Acute uveitis was found and three successive spinal fluid specimens revealed a lymphocytic pleocytosis (Table II). Smears and cultures for Cryptococcus were negative, and prednisone therapy was instituted for the acute uveitis. Subsequently, all cultures grew A. fumigatus. A serologic test for precipitating antibodies against Aspergillus antigens was strongly positive. 5-Fluorocytosine, 6 g daily in divided doses, was given for 3 months. Clinical signs and symptoms of central nervous system disease cleared by the 3rd week of therapy, and three subsequent spinal fluid cultures were sterile (Table II). Prednisone therapy was continued for another 6 months. The patient has been well without recurrence of uveitis or meningitis, but had persistent hilar adenopathy in March 1973.

Comment: This patient with underlying sarcoidosis represents an impressive cure of meningeal aspergillosis, demonstrating the clinical effectiveness of 5-fluorocytosine alone in this form of the disease.

Case 2. A 47 year old white accountant (D.B., TJUH No. 302789) had left apical fibrosis which had shown no change on annual chest examination for 20 years. Tuberculin skin tests had been repeatedly negative. In July 1970 he became ill with chills, fever and purulent sputum. No bacterial diagnosis could be made, and fever persisted for 6 weeks despite the administration of mutliple antibiotics including antituberculosis therapy. In August he had rapid spread of pulmonary inflammatory disease and abscess formation (Figure 1). He was transferred to Thomas Jefferson University Hospital. Multiple sputum cultures were positive for A. fumigatus, and serologic tests for Aspergillus precipitins were strongly positive. He was treated with 5-fluorocytosine, 6 g daily divided doses, for 3 months. By October 1970 (Figure 2) the roentgenogram showed marked clearing of the inflammatory infiltrate, but a cavity and an intracavitary fungus ball were demonstrated by tomography. Because of an episode of pleuritis and persistently positive cultures for A. fumigatus, a left upper lobectomy was performed in March 1971 which confirmed the intracavitary fungus ball but revealed no underlying pulmonary disease. Another 90 day course of 5-fluorocytosine therapy was given before and after surgery.

After lobectomy the lower lobe failed to expand, and

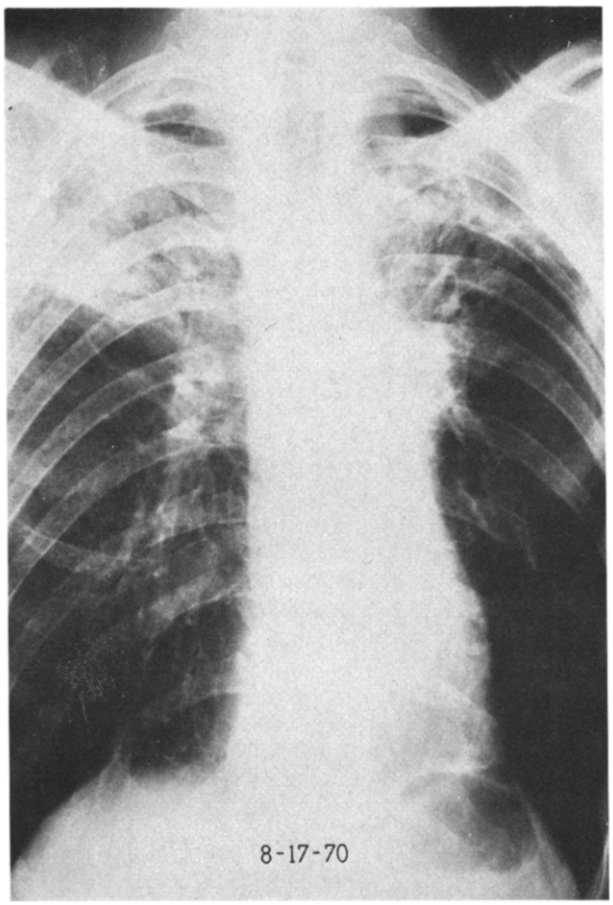

Figure 1. *Case 2. Chest roentgenograms of August 17, 1970, taken after 6 weeks of fever and purulent sputum, showing cavitary lesion of upper lobe of left lung and acute pneumonic spread to upper lobe of right lung. Treatment with 5-fluorocytosine was instituted on August 31, 1970.*

a large residual pleural space persisted. Cough and malaise recurred in January 1972. The patient was given another 3 month course of 5-fluorocytosine, 12 g in daily divided doses, and weekly amphotericin B (50 mg) injections. With this therapy, symptoms and pleural effusion cleared, sputum cultures became negative for A. fumigatus and serum precipitating antibodies against Aspergillus antigens could not be demonstrated. The patient resumed work and was asymptomatic for 6 months. In November 1972 he again had cough and fever, and roentgenograms revealed pleural effusion and an infiltrate in the apical segment of the lower lobe of the left lung. Precipitating antibodies against Aspergillus antigen reappeared in his serum. Another 3 month course of daily 5-fluorocytosine and weekly amphotericin B at previous dosage schedules was instituted, but in December there was spread of inflammatory changes throughout the lower lobe of the left lung. The patient had lost 30 pounds and appeared chronically ill.

When readmitted in December, immunogloic study revealed no type I hypersensitivity to Aspergillus extract. Delayed hypersensitivity was absent to tuberculin, streptokinase. mumps and fungal antigens, but there was a 15 mm reaction to Aspergillus antigen 1:100. A normal response to DNCB was demonstrated. Circulating precipitin antibodies to A. fumigatus persisted. However, no cultural evidence of A. fumigatus was obtained, and lung biopsy revealed only eosinophilic pneumonitis; no Aspergillus hyphae were seen on special histologic preparation and culture of the biopsy material was negative. Prednisone and clotrimazole therapy was begun, with improvement, but gastrointestinal distress necessitated discontinuation of the clotrimazole after 1 month. The patient improved symptomatically and resumed full-time work. Precipitating antibodies to A. fumigatus were less markedly positive.

Comment: This case represents an initial response to 5-fluorocytosine, postoperative relapse and a second response to combined 5-fluorocytosine and amphotericin therapy. The eventual outcome of this case remains in doubt.

Case 3. A 41 year old black nurse (I.V., TJUH No. 294561) had had sarcoidosis since 1960. She was well and required no treatment until June 1970, when fever and a productive cough developed. Roentgeno-

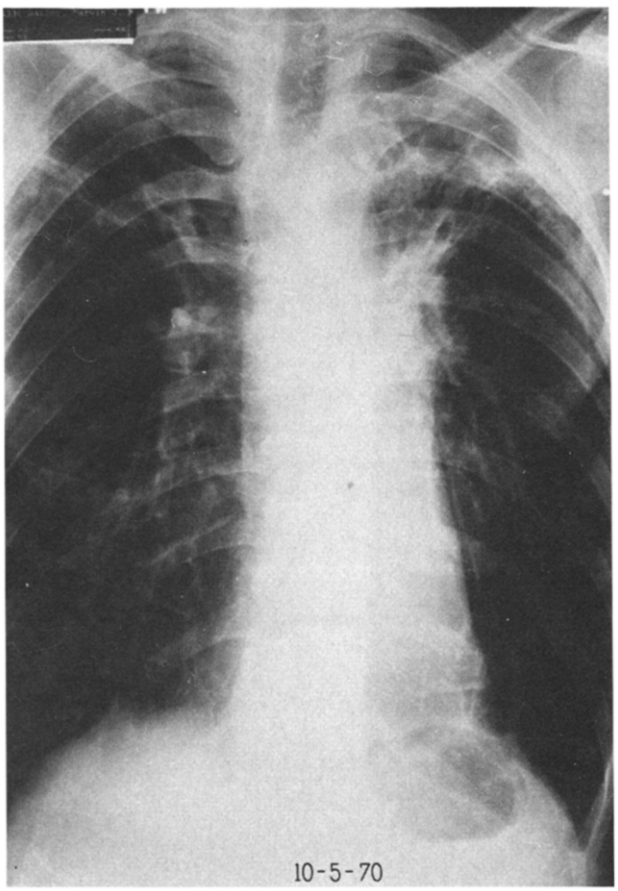

Figure 2. *Case 2. Chest roentgenogram of October 15, 1970, showing clearing of infiltration.*

grams showed diffuse pulmonary infiltration. Sputum cultures were repeatedly positive for A. fumigatus, and serum precipitating antibodies against antigens of A. fumigatus were demonstrable. 5-Fluorocytosine, 6 g daily in divided doses, was given for 3 months. The symptoms cleared in the first month, and by November 1970 partial resolution of the inflammation could be seen on roentgenograms. At that time, no cultural or serologic evidence of Aspergillus infection could be found. The patient remained well until July 1972, when she had hemoptysis and cultural evidence of A. fumigatus in her sputum. Serum precipitating antibodies were again strongly positive against Aspergillus antigens. Tomography failed to demonstrate a fungus ball.

Combined therapy consisting of daily 5-flourocytosine, 6 g in divided doses, and weekly intravenous amphotericin B, 50 mg, was begun; her symptoms cleared rapidly; A. fumigatus disappeared from her sputum. Serum precipitins reverted to negative in November 1972. The patient remains well, without evidence of recurrence, 6 months after cessation of treatment.

Comment: This case demonstrates the effectiveness of 5-fluorocytosine alone and in combination with amphotericin B against suppurative Aspergillus infection.

Case 4. A 62 year old white bartender (H.B.) entered a local hospital in October 1971 because of hemoptysis. He gave no history of antecedent chest disease and had previously been well. Chest roentgenogram showed an infiltrate in the upper lobe of the right lung thought to be carcinoma. Sputum cultures were negative for fungi, bacterial pathogens and M. tuberculosis. A tuberculin skin test was negative. Bronchoscopic washings revealed no pathogenic organism or cancer cells. Thoractomy revealed an abscess in the upper lobe of the right lung and inflammatory lung disease without evidence of carcinoma. Cultures revealed A. fumigatus and histologic sections showed Aspergillus hyphae. A serologic test for precipitating antibodies to Aspergillus antigens was strongly positive. The administration of 5-fluorocytosine, 10 g in daily divided doses, was begun in the immediate postoperative period and continued for 3 months. The pulmonary infiltrate cleared by the 4th week of therapy, and no evidence of pulmonary aspergillosis could be found at the completion of the drug therapy. Serum precipitating antibodies against A. fumigatus reverted to negative. The patient remains well 18 months later.

Comment: This case represents a de novo Aspergillus abscess arising in an otherwise normal lung. No evidence of immunologic deficiency could be demonstrated. Rapid clearing of the inflammatory process with 5-fluorocytosine therapy ensued after biopsy established the diagnosis.

Case 5. A 42 year old white alcoholic (J.H., PGH No. 369849) was admitted to the hospital on April 24, 1970, with a subcapsular hematoma of the liver. After laparotomy and drainage thrombophlebitis developed, and on May 22 he had a massive pulmonary embolism. There was a good response to heparin therapy, but on June 18 he was found to have spreading infection from the area of infarction. Sputum cultures were positive for Klebsiella, and the patient was given gentimycin, cephalothin and kanamycin serially and in combination for the next 2 months. Fever persisted and roentgenograms in July showed an abscess with surrounding pneumonia. On August 26 serologic tests revealed precipitins against A. fumigatus. Sputum cultures subsequently grew A. fumigatus, and precipitins were demonstrated on a second occasion. Treatment with 5-fluorocytosine was started on September 29, 1970, and this was continued for 90 days. Sputum cultures were subsequently negative for Aspergillus. Chest films on July 20, 1971, showed diffuse obstructive pulmonary disease with a chronic infiltrate in the lower lobe and bullous changes. In October 1971 the lower lobe of the left lung was resected. Bronchiectasis was found with no evidence of aspergillosis.

The last admission of this patient to Philadelphia General Hospital was on October 26, 1972, when chest films showed old inflammatory and postoperative changes. Cultures for fungi were negative.

Comment: Fungal infection in this case may be attributable to prolonged and intensive antibacterial therapy. When Aspergillus infection was recognized, treatment with 5-fluorocytosine resulted in cure.

Case 6. A 43 year old diabetic black housewife (D.J., TJUH No. 298271) had had pulmonary sarcoidosis since May 1970 for which she was treated with corticosteroids until January 1971. At that time, diabetes became difficult to control, and corticosteroid therapy was stopped with return of good diabetic control. In February 1971, she became febrile and a fresh infiltrate was found in the lower lobe of the right lung. In June she became febrile, and cavitation was found in the lower lobe of the right lung. An air fluid level was present in the cavity, surrounded by an increasing dense infiltrate; tomograms confirmed the presence of an intracavitary fungal ball. Precipitin tests for Aspergillus were strongly positive and, after repeated culture, A. fumigatus was demonstrated in the sputum. In July, 10 days after admission, the administration of 5-fluorocytosine, 6 g daily in divided doses, was begun, with decline in fever and partial resolution of the infiltrate by the 2nd week of therapy. However, diabetic ketoacidosis recurred and was refractory to large doses of insulin. Thoracotomy was performed with resection of the lower lobe of the right lung. Pathologic examination of the specimen confirmed the presence of an intracavitary fungus ball with parenchymal invasion by Aspergillus. Culture of the specimen revealed A. fumigatus. Postoperatively the diabetes came under good control with the same doses of insulin used formerly. In January 1972 dyspnea increased without fever or cough. At that time, extensive pleural thickening in the right hemithorax and multiple extrapulmo-

nary air fluid levels were found. Another course of 5-fluorocytosine therapy, 12 g daily in divided oral doses, was given for 6 weeks. No progression in parenchymal disease has been observed in the 9 months since therapy was stopped, and the pleural disease has resolved. Sputum cultures for Aspergillus remain negative, and precipitins against antigens of A. fumigatus can no longer be found in her serum.

Comment: This case represents a partial response to 5-fluorocytosine prior to resection of local disease necessitated by uncontrolled diabetes mellitus. Relapse took the form of a pleural infection with bronchopleural fistula which was cured by retreatment at a higher dosage. One must surmise that pleural contamination with A. fumigatus took place at the time of surgery.

Case 7. A 46 year old man (N.F., TJUH No. 326357) had left apical scarring and infiltrates in the lower lobe of the right lung with cavity formation in 1967. After prolonged study a diagnosis was made of pulmonary mycobacteriosis, due to type III nonchromogenic mycobacteria. Initial therapy consisted of isoniazid and ethionamide. In August evidence of spreading infiltrate was observed and rifampin was added. In October 1972 the patient entered the hospital with fever, productive cough, severe dyspnea and respiratory failure. Roentgenogram revealed an increase in the inflammatory infiltrate in the upper lobe of the left lung with cavity formation. Cultures of sputum were negative for mycobacteria but A. fumigatus was repeatedly recovered. Serum precipitating antibodies were strongly positive against antigens of A. fumigatus. The usual measures for treatment of ventilatory insufficiency were undertaken and the administration of 5-fluorocytosine, 12 g daily in divided doses, was begun. By the 3rd week of treatment there was clinical improvement, lysis of fever, and the patient was taken off the ventilator intermittently. A. fumigatus could no longer be recovered from his sputum, and the infiltrate in the upper lobe of the left lung had begun to clear leaving a fluid-filled cavity. The disease in the lower lobe of the right lung remained unchanged, but there was spread of inflammatory infiltrate to the lower lobe of the left lung. Subsequent cultures revealed Pseudomonas, and gentimycin was added to the therapeutic regimen. By the 8th week of 5-fluorocytosine therapy, the patient was taken off the ventilator, but Pseudomonas persisted in the sputum and A. fumigatus reappeared. A chest film revealed progression of the infiltrate in the lower lobe of the left lung. The subsequent course was downhill, with recurrence of ventilatory insufficiency and overwhelming pneumonia. The patient died in December 1972, 3 months after the onset of illness. Necropsy was refused. Tube dilution sensitivity studies demonstrated the development of resistance by A. fumigatus to 5-fluorocytosine. The initial isolate was inhibited by less than 10 μg/ml. 5-fluorocytosine, whereas the organism isolated terminally was inhibited only at a level greater than 150 μg/ml.

Comment: This case represents an initial response by A. fumigatus to 5-fluorocytosine therapy with the subsequent emergence of a resistant strain. The remission was complicated by a Pseudomonas pneumonia which, together with resistant A. fumigatus, resulted in the patient's death.

Case 8. A 54 year old asymptomatic white bartender (S.A., TJUH No. 324104) was found to have disease in the upper lobe of the right lung and pleural thickening in 1968 on a survey roentgenogram. Despite negative tuberculin tests and negative sputum cultures, he was treated for tuberculosis with isoniazid and streptomycin without change in his chest roentgenogram. Chest films showed slow progression of the pleural and cystic disease through 1971. In October 1971, the patient had fever, productive cough and a 40 pound weight loss accompanied by progressive destruction of the upper lobe of the right lung and pneumonic infiltrates in the middle and lower lobes of the right lung. A tuberculin test was again negative and sputum cultures were negative for pathogenic bacteria and M. tuberculosis. A. fumigatus was isolated from sputum specimens and bronchoscopic washings. Serum precipitins to standard Aspergillus antigens were strongly positive. 5-Fluorocytosine, 12 g daily in four divided doses, was given for a total of 6 weeks. Treatment was interrupted for 2 weeks in the 4th week of therapy because of severe diarrhea secondary to staphylococcal colitis. Reinstitution of 5-fluorocytosine therapy was not accompanied by a recurrence of the diarrhea. By the 2nd week cultures were free of Aspergillus species, and the patient was afebrile. Clearing of the infiltrates in the middle and lower lobes was evident on roentgenograms in the 3rd week. A serologic test was weakly positive 9 months after the onset of his illness.

Comment: Although this patient remains clinically well and culture-free of A. fumigatus 1 year after therapy, serologic precipitins are weakly positive and the roentgenogram still shows extensive cystic and fibrotic changes. 5-Fluorocytosine was clearly effective in the acute phase of this illness.

Case 9. In October 1972 profuse purulent sputum, dyspnea on exertion and 20 pound weight loss developed in a 59 year old white steel worker (L.H., TJUH No. 354419).

The past history was of interest since the patient was discharged from military service in 1944 because of ankylosing spondylitis. In 1962, when the patient had had hemoptysis, chest films revealed pulmonary disease and the patient was subsequently studied for tuberculosis. Although no bacteriologic confirma-

tion was obtained, he was given chemotherapy for 2 years.

The patient was seen in consultation in November 1972. He appeared chronically ill. X-ray examination revealed a cavity with overlying pleural thickening at the right apex and minimal scarring at the left apex. There was no reaction to intermediate strength purified protein derivative, but sputum was reported to contain acid-fast rods. A second strength tuberculin test was reported positive. Treatment with isoniazid and ethambutol was started, with no diminution in symptoms. When cultures proved negative, the patient was admitted to Thomas Jefferson University Hospital. The profuse purulent sputum showed few bacteria but after a long search, Aspergillus hyphae were found. Serum was strongly positive for precipitins against A. fumigatus.

Treatment with 5-fluorocytosine, 10 g daily, was given with amphotericin B, 50 mg intravenously weekly. Symptomatic improvement and reduction in sputum were observed in 2 weeks, but purulent sputum persisted after 3 months of treatment. Sputum cultures were negative for A. fumigatus.

Comment: This patient represents the syndrome of ankylosing spondylitis and pulmonary aspergillosis. Treatment has resulted in symptomatic improvement and clearing of Aspergillus from the sputum.

Case 10. A 57 year old white anthracite miner (P.P., TJUH No. 332490) with long-standing pneumoconiosis was admitted with complaints of recent fever, dyspnea and weight loss. His tuberculin test converted to positive in 1969 and he had been given isoniazid 300 mg daily for 2 years. In January 1972 pleural thickening developed over the upper lobe of the right lung, and subsequent cystic destruction and inflammatory infiltrate occurred in that area. Roentgenograms obtained on admission revealed a right pleural effusion with an air-fluid level. Cultures for bacterial pathogens and M. tuberculosis were negative, but sputum cultures grew A. fumigatus. Serologic tests for antibodies against Asperigillus were strongly positive. A biopsy specimen of the pleura contained Aspergillus hyphae histologically, and subsequent culture of the biopsy material and pleural fluid grew A. fumigatus.

5-Fluorocytosine therapy, 12 g in daily divided doses, was begun with clearing of the inflammatory infiltrate and pleural fluid. However, the fever persisted as did the bronchopleural fistula. Culture of purulent sputum during the 3rd week of therapy failed to show any Aspergillus species but was overgrown with Bacteroides species. Oral tetracycline, 250 mg four times a day, was given for a month with resolution of the fever and closure of the bronchopleural fistula. Therapy with 5-fluorocytosine was continued for 3 months resulting in further improvement, as noted on the chest roentgenogram, and return to normal weight. The patient's condition was greatly improved when he was readmitted in March 1972 for further evaluation. No evidence of aspergillosis was found at that time. In February 1973 a costochondral abscess developed; cultures were negative but serum precipitins were positive. Another course of 5-fluorocytosine therapy was instituted. There has been no progression of his disease in 2 months and the abscess has healed.

Comment: This case represents successful 5-fluorocytosine therapy of aspergillosis with Bacteroides species superinfection. It is interesting that in this man the disease presented initially as a bronchopleural fistula.

Case 11. A 54 year old white executive (J.I.) had had sarcoidosis with cystic changes in the upper lobes of both lungs since 1957. Corticosteroids were taken intermittently. In 1965 he had hemoptysis for the first time, attributed to bronchiectasis. By 1969 the hemoptysis had become severe. Roentgenograms showed an intracavitary fungus ball in the upper lobe of the left lung; nystatin aerosols were given without success. The patient continued to have hemoptysis and, in December 1970, expectorated fragments containing characteristic Aspergillus hyphae. Culture of this material confirmed the presence of A. fumigatus, and serum precipitins were strongly positive against Aspergillus antigens. 5-Fluorocytosine, 6 g daily, was given for 3 months with cessation of the hemoptysis and decreased sputum production by March 1971. Serum precipitins gave a weaker reaction. The patient subsequently had pulmonary hemorrhages in April, May and June. Serologic test for precipitating antibodies against A. fumigatus was still strongly positive, but cultures for A. fumigatus remained negative. Thoracotomy was performed in another hospital in November 1971, but complete excision of the upper lobe of the left lung proved impossible. Intermittent hemoptysis continued, and serum precipitins in November 1972 were still positive.

Comment: 5-Fluorocytosine therapy in this instance appeared for a time to reduce hemoptysis and resulted in a temporary decrease in the level of precipitating antibodies to A. fumigatus. The sputum remained free of Aspergillus for 2 years, but repeated hemorrhages led to an unsuccessful attempt at resection of the cavity and aspergilloma.

Case 12. A 40 year old black housewife (C.P., TJUH No. 221206) with respiratory insufficiency due to long-standing sarcoidosis was found to have fluid in a cyst in the upper lobe of the right lung. Sputum cultures grew A. fumigatus, and a serologic test for precipitating antibodies to Aspergillus antigens was strongly positive. 5-Fluorocytosine therapy, 6 g daily in divided oral doses, was begun. The drug was taken irregularly because of gastrointestinal symptoms. She subsequently had severe episodes of pulmonary hemorrhage, and in November 1970 tomograms confirmed

the presence of an intracavitary fungus ball in the area in which the fluid had previously been observed. Nevertheless, in March 1971, she was well and a roentgenogram revealed disappearance of the intracavitary fungus ball and no evidence of inflammatory lung disease or fluid. Although serologic tests for precipitating antibodies to Aspergillus antigen remained positive, no further cultural evidence of A. fumigatus was found. In the 2 years of follow-up there has been no recurrence of aspergillosis.

Comment: This patient recovered both from pulmonary hemorrhage and suppuration due to aspergillosis; the course of 5-fluorocytosine therapy was abbreviated and may have merely contributed to spontaneous improvement.

Case 13. A 51 year old black laborer (F.H., TJUH No. 127214) had chronic sarcoidosis with respiratory failure. He entered the hospital in August 1971 with severe pulmonary hemorrhage. Conventional films showed extensive bilateral fibrosis with no demonstrable cavities, but tomograms showed a fungus ball in the upper lobe of the left lung. Sputum smears revealed branched hyphae characteristic of Aspergillus species and subsequent cultures confirmed the presence of A. fumigatus. Serologic study revealed the presence of precipitating antibodies to antigens of Aspergillus fumigatus. 5-Fluorocytosine, 6 g, was given in divided daily doses, while measures were taken to support ventilation and control hemorrhage. During the 4th week of therapy the patient's condition was improved. He was discharged and was to continue treatment as an outpatient. He was readmitted 2 weeks later with profuse pulmonary hemorrhage. He died on the day of admission, 6 weeks after the initiation of therapy.

Comment: This represents a therapeutic failure of 5-fluorocytosine in a patient who died of hemorrhage from an intracavitary fungus ball.

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