Fungal endocarditis is rare, although its reported incidence has been rising coincident with the widespread use of steroids, antibiotics, cytotoxic agents, the advent of cardiac surgery, and increased intravenous heroin addiction. The genus *Aspergillus* rarely causes endocarditis. In two recent reviews, one of 98 patients and another of 98 patients with aspergillosis, none had endocarditis. Only four cases of *Aspergillus* endocarditis have been reported in patients who did not have previous cardiac surgery. Only one case was diagnosed antemortem and the patient treated with a short course of amphotericin B before death.

We wish to discuss the clinical course of a patient with *Aspergillus fumigatus* endocarditis who received full therapeutic exposure to amphotericin B. Despite treatment, he succumbed to the embolic complications of the disease. The discussion will concern the management of this rare entity and of fungal endocarditis in general.

**Patient Summary**

A 61-year-old white man was admitted to Bellevue Hospital for the second and final time on March 5, 1969 because of an arterial occlusion in his left lower extremity. In April 1968, a diagnosis of pulmonary and miliary tuberculosis was made in another hospital, and the patient was treated with isoniazid, aminosalicylic acid, streptomycin sulfate, and 40 to 80 mg of prednisone/day of eight weeks. A culture of the liver biopsy, which was taken before therapy, grew *Mycobacterium* tuberculosis. After transfer to Bellevue Hospital, ethambutal was substituted for aminosalicylic acid, the steroid treatment was discontinued, and during the next four months there was gradual clearing of the tuberculous pulmonary infiltrates. An intercurrent bacteria pneumonia was treated with antibiotics and a spontaneous pneumothorax with repeated needle aspiration with good result.

The patient continued to improve at a sanatorium from August 1968 until February 1969 when confusion and left hemiparesis developed suddenly; these manifestations cleared spontaneously in several days. Three weeks later, he was transferred to Bellevue Hospital after the acute onset of pain and pallor in the left leg.

Physical examination showed a thin wasted man in acute distress. His temperature was 38.3°C (101°F), pulse, 120 beats per minute; respirations, 30 breaths per minute; and blood pressure, 114/60 mm Hg. The lungs were clear; the heart was not enlarged, but there was a grade 2/6 holosystolic apical murmur that radiated to the axilla and was not changed with respiration. A non-tender liver edge was palpated two fingerbreadths below the right costal margin; the spleen was not felt. The left leg was pale, and all peripheral pulses in the left leg were absent below the femoral pulse.

The hematocrit reading was 32% with normal red blood cell morphology. The white blood cell count was 8,900 with polymorphonuclear leukocytosis. The urine contained more than 100 red blood cells per high power field. Results of blood glucose, urea nitrogen, and liver function tests were normal. The electrocardiogram showed sinus rhythm with ventricular premature systoles and runs of atrial tachycardia. Chest x-ray films showed a heart of normal size and contour with no calcification and lung fields with apical fibrosis and scarring.

**Hospital Course.**—A left femoral arterialogram performed on admission demonstrated obliteration of the left femoral artery. An embolectomy was performed with the patient under epidural anesthesia. Three grayish-black masses, measuring 4 to 15 mm in diameter, were removed. Microscopic examination showed a layered blood clot with masses of septated hyphae consistent with aspergillosis. The specimens were not cultured. The postoperative course was uneventful except for the presence of low-grade fever, and the patient was transferred to the medical service section.

Acute right anterior uveitis was noted and treated with topical preparations. Skin testing showed negative delayed reaction to second strength tuberculin, Candida, streptokinase, streptodornase, and Trichophyton. Eight blood cultures failed to grow bacteria or fungi.

The cerebrospinal fluid protein was 147 mg/100 ml with a glucose level of 84 mg/100 ml. Smears and cultures of the cerebrospinal fluid were negative for bacteria and fungi. An intravenous pyelogram showed normal tracts with no calculi. A presumptive diagnosis of *Aspergillus* endocarditis was made, and treatment...
with amphotericin B was begun on March 16, 1969. The dose was quickly increased to 1.2 mg/kg given on alternate days as a 60-mg intravenously administered dose. It was decided to defer valvular surgery until the patient had been observed on medical therapy for approximately four weeks.

Over the next three weeks, numerous blood and urine cultures were negative despite special attention to fungi. The patient lost 4.5 kg (10 lb); the hematocrit reading fell to 23%, and blood transfusions were given. The anemia was attributed to chronic infection or amphotericin B since there was no evidence of blood loss or hemolysis, and bone marrow showed only slight normoblastic erythroid hyperplasia. Urinary output and blood urea nitrogen and creatinine concentrations remained normal during therapy. Right heart catheterization and cineangiograms showed mitral regurgitation; the mean wedge pressure was 20 mm Hg, and the v wave was 27 mm Hg. Right heart pressures, cardiac output, and arterial-venous oxygen difference at rest were all normal. The levophase following right heart angiograms showed a thickened mitral valve.

On March 31, Roth's spots were noted in the fundus of the left eye. On April 15, the patient had sudden onset of pain in the right leg with loss of the right femoral pulse. A gray-brown mass was removed surgically from the bifurcation of the aorta in three segments, each of which was 3 × 2 cm. The embolus was composed of thick, septate branching hyphae, and Aspergillus fumigatus grew on culture. The patient weakened briefly from anesthesia but was confused and soon developed right upper-extremity and left lower-extremity paresis. Findings from examination of the spinal fluid were unchanged. The patient lapsed into coma on the second postoperative day, developed left papillary dilatation, and died on April 22, 1969 after receiving 1,260 mg of amphotericin B over a 38-day period.

Pathological Findings.—Heart.—The heart weighed 300 gm. The pericardial sac contained 70 ml of clear, serous fluid but was otherwise normal. The left atrium showed moderate dilatation. There was marked stenosis of the mitral valve caused by large, white, friable vegetations near the interventricular septum (Fig 1). The largest was 2 cm in diameter. Smaller vegetations were seen over the closing margins of the valve and the chordae tendineae. A vegetation 0.5-cm in diameter was present on the endocardium of the left ventricular wall. The remaining valves were normal. Sections from the mitral valve and papillary muscle vegetations showed large masses of broad-branching and septate hyphae, encompassed in fibrin with associated polymorphonuclear leukocytes, lymphocytes, and mononuclear cells (Fig 2). The mitral valve, papillary muscles, and chordae tendineae were destroyed focally by fungal colonies with associated inflammatory reaction. Several small and large myocardial abscesses were present. These consisted of central zones of suppuration with peripheral granulomatous and giant cell reaction (Fig 3). Fungal hyphae were present in both zones.

Lung.—There were 200 ml of serous fluid present in each pleural cavity. Moderate bronchial dilatation was present in the upper portions of the left upper, left lower, and right middle lobes. Focal areas of acute pneumonia and other areas of fibrosis and scarring were noted. Special stains for acid-fast bacilli and fungi were negative.

Brain.—The trunk of the left middle cerebral artery was occluded by grayish-brown material. Peripheral branches from the left middle cerebral artery were thrombosed, and a large, fresh, pale infarct was noted. Fresh infarcts were also present in the frontal lobes. Numerous petechial hemorrhages were present in the gray matter. An old infarct was noted over the right, middle, cerebral artery distribution. Fresh infarcts were also present in the caudate nucleus, the internal capsule, thalamus, and putamen. Microscopic sections showed large fungal colonies dis- tending the lumen of the left middle cere-
antibiotics and steroids. The route of exposure is assumed to have been the respiratory tract. Of note, however, is the eight-month period of relative well-being with only antituberculous therapy before the first embolic manifestations appeared. The anergy to skin test antigens probably occurred late and reflected the overwhelming fungal infection. The postmortem examination did not reveal active tuberculosis in the lungs or lymph nodes or any evidence of a lymphoproliferative disease. No underlying valvular lesion was seen at autopsy; it is likely that the infection had occurred on a normal valve as in three of four previously reported instances of Aspergillus endocarditis that did not follow cardiac surgery. The aggregate of reported cases share certain general characteristics (Table): (1) The fungus could not be cultured from the blood or the urine in the absence of prior cardiac surgery. (2) The fungus could not be cultured from the spinal fluid despite clinical and biochemical neurologic abnormalities. (3) Large emboli occurred frequently and often as the presenting sign of the disease.

The problem posed by this patient was not one of diagnosis but rather of management. In evaluating the indications for medical vs the surgical approaches, we were confronted with the following questions: (1) How successful is amphotericin B therapy in curing fungal endocarditis? (2) Is there a difference in prognosis or efficacy of the drug related to whether the patient presented with large or small emboli or positive blood cultures? (3) How does the cure rate with cardiac surgery compare with medical treatment alone? (4) If surgery is anticipated, is one justified in first maintaining the patient on amphotericin B therapy for several weeks in an attempt to sterilize the blood, peripheral embolic sites, and possibly the cardiac lesions before operation?

Prior to the present report, there had been no adequate experience regarding the use of amphotericin B in Aspergillus endocarditis. Only four other instances not associated with antecedent cardiac surgery have been reported (Table), and only one of these 

and are also summarized in the Table. In none of these was the organism identified from positive blood cultures during life, and in only two cases was amphotericin B therapy started after diagnosis was made from a large embolus. Cases of aspergillosis without endocarditis following cardiac transplantation have also been reported.

In another instance, Aspergillus glaucus was cultured only once from blood in a patient with a prosthetic valve who subsequently did well without therapy. The significance and question of infection in that case are not clear.

Good results have been reported in localized pulmonary infection with amphotericin B and with a combination of systemic therapy and local instillation into a pulmonary cavity. In vitro studies have shown minimal inhibitory concentrations of amphotericin B against Aspergillus species to be higher than reported serum concentrations.

For evaluation of amphotericin B in the treatment of fungal endocarditis, one must turn to the reported cases involving Candida, the fungus most frequently encountered in cardiac infections. Candida endocarditis is seen especially in narcotics addicts, as a complication of therapy of subacute bacterial endocarditis, or following cardiac surgery. There have been 22 reported instances of Candida endocarditis, ten nonsurgical, and 12 patients who received adequate amounts of amphotericin B after surgery, with only four survivors. Probability of survival with amphotericin B treatment alone was slight even when the presenting emboli were small. Death, in 12 of the 15 patients who had presented with either positive blood cultures alone or with small emboli, was due to subsequent large emboli; this was also the cause of death in the two patients who had presented with large emboli. All exhibited massive endocardial vegetations at postmortem examination.

A recent review by Utz also indicates that amphotericin B is not the critical factor in determining survival.
### Summary of Cases of Aspergillus Endocarditis

<table>
<thead>
<tr>
<th>Source</th>
<th>Organism</th>
<th>Premor-tem Diagnosis</th>
<th>Positive Cultures at Autopsy</th>
<th>Positive Cultures After Amphotericin B</th>
<th>Cultures From</th>
<th>Emboli</th>
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* Positive culture reported after death.
† Patient alive after replacement of prosthetic valve and administration of amphotericin B and fluocytosine.

with *Candida* endocarditis, but that the size of the vegetations and the frequency of embolization are important.

Kay et al have undertaken a surgical approach and reported three cures of *Candida* endocarditis. Their one reported fatality occurred in a case in which amphotericin B was not given postoperatively. Sudden death from large emboli even while preparing for cardiac surgery is also a danger.

These observations suggest that large fungal emboli mandate considering the immediate surgical approach with removal of the infected valve or valves, as well as preoperative and subsequent amphotericin B therapy. Since *Aspergillus* endocarditis seems to manifest itself most often by large emboli, immediate surgery may be considered even in the absence of congestive heart failure or the documentation of an uncontrolled infection after medical therapy.

Even when fungal endocarditis presents with only positive blood cultures or small embolic manifestations, medical treatment alone may not be curative; this is true when the infection occurs as a postoperative complication. Since large, proliferating endocardial vegetations are also frequent in the group without prior surgery, the surgical approach may be best in the absence of an antifungal agent more potent than amphotericin B.

**Summary**

Proliferative *Aspergillus* endocarditis, presenting as sudden femoral arterial occlusion, occurred in a 61-year-old white man in his tenth month of convalescence from pulmonary and miliary tuberculosis. To the authors knowledge, he was the first...
References


Nonproprietary Names and Trademarks of Drugs

Amphotericin B—Fungizone.
Flucytosine—Ancobon.