ASPERGILLOSIS

THE SPECTRUM OF THE DISEASE IN 98 PATIENTS

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INTRODUCTION

Invasive fungal diseases are becoming increasingly important in patient populations whose host defenses have been altered by severe primary disease or immunosuppressive therapy. The increasing incidence of fungal complications in these susceptible populations has been chronicled by several authors and now seems well established (5, 9, 17, 37, 44, 48, 121).

The early experience with aspergillosis at our institution was summarized up to 1961 by Carbone et al who reported 22 cases from 1953 to 1961 (13). In the present series, which includes those original 22 patients, over three-fourths of the patients with aspergillosis have been seen since 1961. In our experience, as in the experience of others (37), aspergillosis is second only to candidiasis in frequency of mycoses among cancer patients.

Not only is aspergillosis assuming great importance in patients with malignant disease, but it is becoming increasingly important in patients receiving immunosuppressive therapy for a wide range of illnesses. In this series, and in others, collagen vascular disease (34, 76) has been complicated by aspergillosis, as have sarcoidosis (73) and renal homotransplantation (82). More recently, the first cardiac transplantation performed in the United States was complicated by disseminated aspergillosis (86). It is apparent that aspergillosis will continue to play an increasing role in the changing patterns of infectious disease brought about by increasing use of various kinds of chemotherapeutic agents.

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We have had the opportunity to review 98 cases of aspergillosis occurring at a single institution since 1953. This paper represents a summary of this experience. It is hoped that an analysis of the characteristics of aspergillosis in this large series will contribute to earlier and more frequent diagnoses, and more frequent and appropriate therapy.

HISTORY

Micheli in 1729 described a fungus which he named Aspergillus (rough head) because of the microscopic appearance of the spore-bearing structure (68). The first infection in man, recognized to be due to a fungus in this genus, according to Renon, was described by Sluyter in 1847 (80). Virchow (111) in 1856 reviewed the early literature and presented four autopsy proven cases of aspergillosis in which secondary invasion of pre-existing lung lesions had occurred. Around the turn of the 19th century a great deal of attention was drawn to the occupational hazards of pigeon keepers, bird watchers, fur cleaners, and other individuals who were exposed to large numbers of Aspergillus spores. It became accepted, largely from the work of Renon (80, 81), and others (31), that these occupational predispositions to aspergillosis were well established. Macartney (62), in a detailed review of the subject, has cast considerable doubt on the validity of these early cases and on the occupational predisposition. Only one of the cases in these early series came to autopsy and in this one no evidence of Aspergillus was found; several of these patients had cultural evidence of tuberculosis during life.

Since Aspergillus has been found in 7 per cent of sputum cultures in patients with a wide variety of chest diseases (75) cultural evidence, as in the above mentioned cases, is not sufficient for diagnosis. Furthermore, more recent studies with bagasse workers (43) and in grain mills (90), where occupational exposure to spores is of equal in-
tensity, have failed to substantiate an increased incidence of pulmonary aspergillosis. Macartney concludes that "it cannot be accepted that there is any convincing evidence to date connecting pulmonary aspergillosis with certain occupations, notably those concerned with birds, grain, and their associated trades."

Since these early descriptions, a wide variety of pulmonary and extrapulmonary manifestations of this illness have been described and several reviews (14, 28, 40, 50, 112) have dealt largely with the saprophytic and allergic forms of the disease. The invasive form of the disease has received less attention.

**MATERIALS AND METHODS**

All the autopsy records of the National Institutes of Health (NIH) were reviewed for the period from July, 1963, when the Clinical Center opened, to January, 1968. Over this period 3,374 autopsies were completed and 93 patients were found to have histological evidence of aspergillosis. Five additional cases have been added since January, 1968, from the personal experience of the authors.

The NIH Clinical Center is a referral center and, because of special research interests, has a large proportion of cardiac and oncology patients. It is from these two groups that the majority of our autopsied cases comes and, as such, our autopsy experience is not similar to the experience of a general medical center.

The diagnosis of aspergillosis was made when any of the following criteria were met: (a) histological evidence of Aspergillus hyphae in autopsy tissue with or without cultural confirmation (97 cases), (b) culture of Aspergillus from an autopsy specimen in the presence of a compatible clinical history but in the absence of histological evidence (1 case).

Morphologic identification of hyphae in tissue was sometimes possible on hematoxylin and eosin stain, but was more reliably accomplished when hyphae were stained with periodic-acid-Schiff or Gomori-methenamine-silver. Aspergillus hyphae were characterized uniformly, about 4 μ in diameter (range 2 to 7 μ), septate, and often branched dichotomously. Although the characteristic conidiophore of Aspergillus has been seen occasionally in lung or parasal sinus tissue, it was not observed in our cases. If adequate material is available, the vegetative hyphae of Aspergillus usually may be distinguished from other filamentous fungal pathogens by differences in histological appearance. Candida pseudohyphae are, on the average, of smaller diameter, and usually can be distinguished by the presence of yeast-like as well as filamentous forms, by the absence of true branching, and by constrictions at the septae.

With a little experience, cross sections of Aspergillus hyphae are rarely confused with yeast-like forms of Candida, nor is multiple budding of Candida pseudohyphae confused with branching of Aspergillus hyphae. Phycomyete hyphae are distinguished by the great breadth, irregular thickness and the usual absence of septae (6). *Cladosporium bantianum* can be distinguished from Aspergillus by the presence of brown hyphae on hematoxylin and eosin stain. Invasion of viscera by hyphae of *Paecilomyces variotii* (110) and *Alescheria boydii* (84) has been reported, but the few cases available have suggested that these hyphae can be distinguished morphologically from Aspergillus.

The most difficult distinction in histological appearance arises between Aspergillus and Penicillium, although hyphae of the latter described in the tissues of a single case in the literature were said to be broader and less septate than Aspergillus hyphae (27). To complicate the distinction, the hallmark of invasive aspergillosis and of mucormycosis, i.e. vascular invasion and thrombosis, was also present in the case of peniciliosis (42). In spite of this potential area of confusion, no cases of peniciliosis have been recognized at our institution in spite of a policy of identifying molds when they are the predominant growth in any clinical specimen. No patient in this series grew Penicillium from any organ culture at autopsy. On the other hand, among 61 patients in this series who had cultures for fungi made from autopsy tissue, 43 (70 per cent) had *Aspergillus* spp. isolated. *A. fumigatus* was isolated from 18 patients, *A. flavus* from five, *A. glaucus* from three, *A. niger* from two, and unidentified *Aspergillus* spp. from 14. One patient had *A. fumigatus* cultured from the lung and *A. glaucus* from the spleen. Identification of Aspergillus species on culture was based upon gross and microscopic morphology (104).

By the present criteria, the diagnosis of aspergillosis can be made histologically with some confidence. However, as immunosuppression receives broader clinical use, and *pari passu* more systemic infections with saprophytic molds are seen, it may be found that current morphologic criteria for identifying Aspergillus are not specific for that genus.

**GENERAL COMMENTS**

The pre-existent diseases associated with aspergillosis in these 98 cases are listed in Table 1. As in other series, there is a great predomi-
nance of hematologic and lymphoreticular malignancies and 90 per cent of the patients fell into this category. Two additional patients had other malignant diseases. Four per cent had nonmalignant disorders in which profound pancytopenia was similar to the group with hematological malignancy. Four per cent had collagen vascular diseases. Only three patients in the entire series had illnesses which were primarily cardiac or pulmonary and in each of these the aspergillosis was focal or noninvasive.

The organ involvement with aspergillosis in these 98 cases is listed in Table 2. It must be stressed that in this kind of patient population, the disease rarely is of the saprophytic or allergic form so commonly described in other series. Tissue invasion is the hallmark of most of these cases and in 35 per cent of our patients aspergillosis was the primary cause of death. An additional 10 per cent died of a complex of factors in which aspergillosis was felt to play a major, although not exclusive role in the patient’s demise.

The importance of fungal disease in this kind of patient population has been highlighted by the realization that 14 per cent of the deaths in a large series of leukemic patients studied at the National Institutes of Health were attributable to fungus infections (9). As a result of the danger of fungal complications in our patients, rather aggressive cultural efforts are made to implicate etiologic fungal agents. Eighty-two per cent of the patients in this series had fungal cultures at some point in their terminal illness. In spite of these vigorous attempts, Aspergillus was infrequently cultured antemortem. Only 34 per cent of the patients had one antemortem culture positive for Aspergillus and only 9 per cent had more than a single antemortem culture positive. It has been generally accepted that repeated isolations of Aspergillus are necessary to implicate this fungus in a disease state. As a consequence of adherence to this criteria, the diagnosis of aspergillosis was rarely suspected antemortem in our patients.

SITES OF INFECTION

Pulmonary Aspergillosis. Aspergillosis is most commonly found to involve the respiratory tract. In this series, 92 patients had pulmonary aspergillosis identifiable at autopsy and 60 of these had pulmonary aspergillosis as their only site of infection. Of those having pulmonary aspergillosis, 27 (30 per cent) died as a direct result of their respiratory infection. An additional nine patients (10 per cent) had mixed pulmonary infections which were primarily responsible for the patient’s death. In these nine, Aspergillus played an important but not exclusive role in the fatal outcome. Candida and Pseudomonas were the most common agents associated with mixed pulmonary infections but Klebsiella, Escherichia coli, and Serratia were also seen. The pulmonary lesions seen in this patient population tended to be severe

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**TABLE 1**

**Pre-Existing Diseases Associated with Aspergillosis**

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<thead>
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<th>Diagnosis</th>
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<tr>
<td>Chronic myelogenous leukemia with blastic transformation</td>
<td>9</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>5</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>5</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>3</td>
</tr>
<tr>
<td>Systemic lupus erythematosis</td>
<td>3</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Agnogenec myeloidmetaplasia</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma of the rectum</td>
<td>1</td>
</tr>
<tr>
<td>Periarteritis nodosa</td>
<td>1</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>1</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1</td>
</tr>
<tr>
<td>Prostatic carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Saccular bronchiectasis</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive cardiocascular disease</td>
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</tr>
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**TABLE 2**

**Organ Involvement in Aspergillosis**

<table>
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<tr>
<td>Gastrointestinal tract</td>
<td>21</td>
</tr>
<tr>
<td>Brain</td>
<td>13</td>
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<td>Liver</td>
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<td>Kidney</td>
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</tr>
<tr>
<td>Testis</td>
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</tr>
<tr>
<td>Adrenal</td>
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</table>
Table 3

Pulmonary Manifestations of Aspergillosis
92 Patients

<table>
<thead>
<tr>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Necrotizing bronchopneumonia</td>
</tr>
<tr>
<td>2) Hemorrhagic pulmonary infarction</td>
</tr>
<tr>
<td>3) Miliary micro-abscesses</td>
</tr>
<tr>
<td>4) Focal lung abscesses</td>
</tr>
<tr>
<td>5) Solitary lung abscess</td>
</tr>
<tr>
<td>6) Lobar pneumonia</td>
</tr>
<tr>
<td>7) Aspergillar bronchitis</td>
</tr>
<tr>
<td>8) Aspergilloma</td>
</tr>
<tr>
<td>9) Solitary granuloma</td>
</tr>
</tbody>
</table>

and in only 11 patients was pulmonary aspergillosis felt to be of minor significance when examined at autopsy.

The pattern of pulmonary aspergillosis is unusual in this patient population. The pulmonary manifestations of aspergillosis in our series are summarized in Table 3.

The two commonly reported pulmonary forms of aspergillosis, the intracavitary fungus ball, and allergic broncho-pulmonary aspergillosis, were either uncommonly seen or absent in this series. Only one patient had aspergilloma.

There are many reports of isolated cases of more invasive forms of aspergillosis such as bilateral bronchopneumonia (39, 19), solitary lung abscesses (102), and miliary microabscesses (107), but these are uncommon in most series. It must be stressed that in our kind of patient population these are much more frequently seen than the more commonly described Aspergillus syndromes. Of the 92 patients with pulmonary aspergillosis, 82 (89 per cent) had one of the more invasive forms of the disease.

Thirty patients in the series had a necrotizing patchy bronchopneumonia caused by Aspergillus. The pneumonia was felt to be of sufficient severity to be the primary cause of death in one-third of this group. This form of the illness is extremely protean in its manifestations. Pathological findings ranged from focal necrotic bronchopneumonia involving a few bronchopulmonary segments to dense hemorrhagic consolidation involving the entire lungs bilaterally. Four patients had micro-abscesses within areas of necrotic consolidation. Only nine (30 per cent) of the patients had vascular invasion associated with the patchy bronchopneumonia. All but three patients had some pulmonary symptoms at some point in their terminal illness. Dysnea, fever, and tachypnea were most frequently seen. Cough was commonly nonproductive and only two had copious sputum production; in neither was Aspergillus cultured from the sputum although 3 to 5 sputum cultures for fungus were obtained. Only three patients had hemoptysis, and six had pleuritic chest pain. Roentgenographic evidence was varied. Five patients (17 per cent) had no x-ray evidence of pneumonia although they were studied at a time when they had pulmonary symptoms shortly before death. In those patients with positive x-rays, patchy pneumonitis was often first noticed within the last week of life at a time when the patients were critically ill. Seven patients, however, had x-ray evidence of pneumonitis which persisted for 19 to 43 days. In six of these seven, autopsy proven Aspergillus pneumonia was present in the areas shown to be involved by x-ray. Cultural evidence of Aspergillus in this group was frequently obtained antemortem. Only four patients (13 per cent) had Aspergillus grown from the sputum and only two had more than two positive cultures, although 25 (83 per cent) had sputum cultured for fungus. The difficulty in obtaining cultural evidence of Aspergillus is well highlighted by two cases. Both had persistent, round, homogenous densities on x-ray consistent with "fungus ball." In the first patient, five serial sputums were negative for fungi as was culture of material from an involved bronchus obtained during bronchoscopy. Aspergillus was finally grown from the bone marrow. The second patient had three serial sputums which grew only Candida albicans. Bronchial brushing was performed under fluoroscopic visualization and pure growth of A. fumigatus was obtained. Subsequently, three sputums were positive as well.

Twenty-nine additional patients (32 per cent) of those with pulmonary aspergillosis had a distinctive pattern of hemorrhagic pulmonary infarction. One-third of this group died as direct result of the pulmonary lesions. These patients all had a characteristic pathology at autopsy. Grossly, dark, reddish, purple, nodular zones of consolidation were present within the pulmonary parenchyma and these areas were often surrounded by hemorrhage (Fig. 1). Seven patients had central abscesses within the areas of infarction. Two patients had peripheral wedge-shaped nodular lesions with the base of the wedge abutting on the visceral pleura. Microscopically,
each of these 29 patients had prominent vascular invasion by mycelial elements with occlusion and thrombosis of pulmonary vessels, pulmonary infarction and hemorrhage. Some of the thromboses were visible grossly (Fig. 2).

The clinical course of these patients was also characteristic. Fever, dyspnea, and nonproductive cough were common, as in the other cases of pulmonary Aspergillus, but there were several distinctive features. Pleuritic chest pain occurred in 61 per cent and was often accompanied by a pleural friction rub. Their symptoms were often episodic and characterized by the sudden onset of dyspnea, pleuritic chest pain, tachycardia, gallop rhythm, and cough. Three patients had hemoptysis. Many of these patients were felt to have sustained pulmonary emboli at the time they were examined; others were felt to have developed sudden congestive heart failure and pulmonary edema.

Roentgenographic studies were often unrevealing if performed only on the day of onset of the symptoms. Almost one-third of the patients had no roentgenographic pulmonary abnormality of any kind when studied acutely and in three patients who died within several days after the on-
Fig. 2. Gross appearance of Aspergillus pulmonary infarction containing thrombosed blood vessels.

set of pulmonary symptoms, no roentgenographic changes were seen at any time. In most of the other patients, findings compatible with pulmonary embolism or septic embolism gradually evolved, or patchy pneumonia appeared and became slowly progressive.

Vascular invasion with infarction was seen with species other than A. fumigatus so there appears to be no species predilection for this complication. Postmortem cultural evidence was obtained in 14 patients (50 per cent), six were identified as A. fumigatus, three were A. flavus, one was A. glaucus, one was A. niger, and three were unidentified as to species.

Fifteen patients had pulmonary lesions characterized primarily by abscess formation. Three patients had solitary lesions, three had focal abscesses and nine had miliary microabscesses. The three patients with solitary lung abscesses had a characteristic clinical history. In each, a bacterial pneumonitis associated with an episode of staphylococcal or pseudomonas sepsis had developed several weeks before death. This pneumonia had responded to antibiotic therapy and no residual changes were present on x-ray at the time of death. At autopsy, however, small cavitary lesions were present which contained Aspergillus. Apparently, secondary involvement by the fungus had occurred after initial bacterial damage.

The three patients with focal abscesses had no clinical symptoms and the lesions were merely isolated findings at autopsy.

Nine patients had miliary microabscesses and in two this was felt to be the primary cause of death. Four had these miliary abscesses in the setting of disseminated aspergillosis presumably from hematogenous spread. The abscesses were 0.5 to 2 cm in diameter, yellow tan in color and in five, vascular invasion was noted in the center of the abscess. Four of these patients had clinical
histories consistent with recurrent pulmonary embolism but at autopsy small septic infarcts with Aspergillus were noted. Three patients in this group had mixed infections with Pseudomonas or Serratia in which the abscess cavities seemed secondarily involved with Aspergillus.

In previous reports, aspergilloma is the most clearly defined pulmonary form of aspergillosis because of its characteristic roentgenographic appearance; something over 100 cases have been described (3, 33, 52, 54, 73, 83, 85, 89). The intracavitary fungus ball often develops at a site of previous pulmonary disease such as an area of cavernous bronchiectasis, tuberculous cavities, histoplasmosis cavities, lung cysts, or pulmonary neoplasms, but occasionally no previous pulmonary disease is present (29). The aspergilloma is a large, ball-like mass of Aspergillus mycelia lying within an ovoid cavity. These masses may be lying free within the cavity but more often are attached to the cavity wall (52). Roentgenographically, the aspergilloma appears as a round, homogeneous opacity occupying a variable portion of a cavitary lesion. It is usually surrounded by an air crescent connected by one or more bronchi to the bronchial tree (33). The lesions may be single or multiple and calcification within the fungus ball has been described (58). The lesions are most frequently seen in the apical segments of the upper lobes or less frequently, the superior segments of the lower lobes. In most instances the fungal infection is not invasive and spread outside the confines of the cavity does not occur. While the lesion is characteristic roentgenographically, it is by no means pathognomonic; similar lesions having been described in tuberculosis (73), in echinococcal cysts (25), and in hematomas occupying abscess cavities (83). Other fungi such as Candida (54), Nocardia (71), and Mucorales (89) have been reported to produce similar lesions, but documentation has not always been complete.

Allergic bronchopulmonary aspergillosis is another of the more frequently recognized syndromes associated with Aspergillus (8, 23, 40). In this illness, recurrent febrile episodes are associated with severe cough, wheezing, and the production of purulent sputum containing Aspergillus mycelial plugs, Charcot-Leyden crystals, Curschmann's spirals and eosinophils. It is associated with migratory pulmonary consolidation and peripheral blood eosinophilia. Bronchoscopy in these patients reveals plugs of mycelia obstructing bronchial lumen and aspiration of the inspissated plugs will often allow the collapsed pulmonary segment to re-expand. The illness usually follows a chronic recurrent course and Aspergillus can frequently be isolated from the sputum. The syndrome is felt to be related to the development of bronchial hypersensitivity to the fungus (75). Precipitating antibody to Aspergillus extracts is found in about two-thirds of the patients (69). In spite of the importance of this syndrome in the over-all spectrum of disease produced by Aspergillus, no patient in this series had allergic bronchopulmonary aspergillosis. It should be noted that the disease has occurred previously in a population of patients not receiving immunosuppressive therapy.

Aspergillar bronchitis (91) is a localized form of aspergillosis characterized by bronchial casts containing mucus and mycelia. The mycelia form small compact masses which are periodically expectorated. The fungus is not usually invasive in this form and the bronchial mucosa is usually preserved, however, superficial erosion may progress to extensive ulceration and black membrane formation (53). Eight patients in this series had aspergillosis primarily involving the superficial tracheobronchial tree, consistent with a diagnosis of mycotic bronchitis. As in many of the other pulmonary syndromes, however, the fungus tended to be more invasive in these patients than in the normal population. All eight patients had superficial erosions and ulcerations and three had focal parenchymal involvement with consolidation and abscess formation. In some of these eight patients, the tracheobronchial tree contained thick gelatinous reddish brown mucoid material containing Aspergillus mycelia. In one patient, this tenacious material filled large portions of the tracheobronchial tree and the patient died of respiratory insufficiency. With the exception of this one patient, the mycotic bronchitis was not felt to be a primary cause of death. All of the patients had respiratory symptoms during life. Dyspnea, wheezing, and cough were the most common and four had mild hemoptysis. Interestingly in the light of the pathology findings was the fact that sputum production was scanty in all but one. This particular patient was a 29 year old man without a malignancy with a 12 year history of pulmonary aspergillosis with cavities containing Aspergillus niger cultured at autopsy. Micro-
scopically no invasion of the lung parenchyma by the fungus was seen. This man had chronic sputum production and multiple sputum cultures had been positive for *A. fumigatus* and *A. niger*. Only one of the other seven patients had a positive sputum culture for Aspergillus during their illness, although six of the eight had multiple sputum samples cultured for fungus.

It is of note that these eight patients with fairly localized disease had less white blood count depression and less exposure to corticosteroids and anti-neoplastic agents. Four patients had absolute granulocyte counts over 1000 mm$^3$ throughout their illness and three others had only a brief period of white count depression. Only one patient had a long period of profound white count depression often characteristic of this patient population. Only half of the group received corticosteroids and anti-neoplastic agents although all received multiple antibiotics. Perhaps these factors contribute to the less invasive character of the fungus in this group of eight patients.

Eight patients in this series had lobar pneumonia caused by Aspergillus and have been previously reported (119). In these patients, the striking clinical and roentgenologic evidence of dense lobar consolidation suggested specific bacterial agents such as Klebsiella and Pneumococcus, and the possibility of a fungus infection was not seriously considered, in spite of the fact that *Aspergillus fumigatus* was cultured from five patients (four sputum and one nasal) antemortem. At autopsy, however, densely consolidated lobes were found to be involved with a necrotizing hemorrhagic pneumonia containing masses of fungal hyphae. Six (75 per cent) of these patients had vascular invasion and hemorrhage. Clinical symptoms were consistent with the pathologic findings and cough, pleuritic chest pain, dyspnea, and hemoptysis often mimicked pulmonary embolism. Postmortem cultures of *A. fumigatus* were obtained from the involved lobe in four patients and only two who were cultured at autopsy failed to grow the fungus. Histologic evidence of Aspergillus was obtained in all cases. In all eight patients the lobar pneumonia was severe, and aspergillosis was considered to be the major cause of death in five patients and a contributory cause in the three others.

**Disseminated Aspergillus.** Thirty-four patients had evidence of disseminated aspergillosis at autopsy. For purposes of this study disseminated aspergillosis was felt to be present when two or more noncontiguous visceral organs were involved. Eight patients had only two organs involved, while 26 of the 34 had widespread organ involvement. The patterns of organ involvement can be seen in Table 4. In 32 patients (94 per cent), the prominent lesion was in the lung. Only two patients had disseminated disease without pulmonary involvement; one having miliary abscesses in the liver and spleen and the other having intestinal ulcerations and brain abscesses. The high incidence of intestinal aspergillosis (47 per cent) is in contrast to other reviews (36, 103) in which this was an uncommon site of infection. This may be partly related to the intensive chemotherapy given most of these patients which often produces gastrointestinal toxicity enhancing the portal of entry for secondary invaders such as Aspergillus. The brain was the next most common site of involvement followed respectively by the kidneys, liver, and esophagus. The thyroid gland was involved in 26 per cent of the cases which reinforced the suggestion in several other studies (36, 103) that the thyroid is frequently involved in disseminated aspergillosis out of proportion to its size and vascular supply.

All of the patients who developed disseminated Aspergillus had severe underlying disease states. The primary diseases are listed in Table 5. All but

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**Table 4**

<table>
<thead>
<tr>
<th>Organ</th>
<th>No. patients</th>
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<tr>
<td>Lung</td>
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<tr>
<td>Intestines</td>
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<tr>
<td>Brain</td>
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<td>Spleen</td>
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TABLE 5
Primary Diseases in Patients with Disseminated Aspergillosis
34 Patients

<table>
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<tr>
<th>Diagnosis</th>
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<td>Acute lymphocytic leukemia</td>
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<td>Aplastic anemia</td>
<td>1</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>1</td>
</tr>
<tr>
<td>Agnogenic myeloid metaplasia</td>
<td>1</td>
</tr>
</tbody>
</table>

four had hemopoietic malignancies and only three had nonmalignant diseases and two of these were characterized by severe alteration in hemopoiesis. Acute leukemias head the list probably as a reflection of their increased number in our patient population.

Corticosteroid therapy in high doses was given to all but one of these patients. Most received continuous therapy for the last two to four weeks prior to death and many received corticosteroids throughout the duration of their illness. Multiple antibiotics were administered to all of these patients during the course of their terminal illness. Only five of these 34 patients did not receive any anti-neoplastic or cytotoxic agent at any time during the course of their illness. Six of the patients who developed disseminated disease were not leukopenic during the course of their illness and had persistent absolute granulocyte counts above 2,000 mm$^3$. Two additional patients had granulocyte counts above 1,000 mm$^3$ during the course of their terminal illness. The remaining 26 patients (76 per cent) had severe depressions of their white blood counts, 22 of these having absolute granulocyte counts of less than 200 mm$^3$ throughout the duration of their terminal illness.

Of the 34 patients with disseminated disease, aspergillosis was the primary cause of death in 21 (61.8 per cent). Six patients died of bacterial sepsis and two died from massive hemorrhage. Five patients had a mixed fungal dissemination (four with Candida and one with a Phycomycete species). Among the 34 patients, 15 had no other significant infection present at autopsy. The immediate cause of death in those patients dying with aspergillosis as the primary cause was usually related to their pulmonary or intracerebral lesions. A summary of the immediate causes of death in disseminated aspergillosis is listed in Table 6. Only those patients in whom aspergillosis was the primary cause of death are included. It can be seen from this table that thrombosis, infarction, and hemorrhage produced by vascular invasion and plugging of the vessels by masses of fungal hyphae is a major etiologic factor in over half of these cases.

It was not possible to determine the species of Aspergillus involved in all cases of disseminated aspergillosis because histological evidence only was used in 12 cases and species identification requires detailed examination of the fruiting head (104). The fruiting head is not usually seen in tissue sections, and therefore species identification rests on cultural evidence. Twenty-two of the 34 patients (65 per cent) had evidence of Aspergillus from autopsy cultures but only 15 of these were identified as to species. Only five patients in this group who were cultured for fungus at autopsy failed to grow Aspergillus; the other seven were not cultured. In this series, patients who had disseminated aspergillosis at autopsy, and who had cultural evidence of a particular Aspergillus species grown from an infected organ were used to establish the frequency of various Aspergillus species in disseminated aspergillosis. Using this criteria, ten patients had disseminated A. fumigatus, three had disseminated A. flavus, and one had disseminated A. glaucus. One patient had

TABLE 6
Immediate Cause of Death in 31 Patients with Disseminated Aspergillosis

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage with aspergillus invasion thrombosis and infarction</td>
<td>5</td>
</tr>
<tr>
<td>Diffuse bilateral pneumonitis</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral massive pulmonary infarction with aspergillus vascular invasion</td>
<td>2</td>
</tr>
<tr>
<td>Brain abscess with tonsillar herniation</td>
<td>2</td>
</tr>
<tr>
<td>Brain abscess with rupture into 4th ventricle</td>
<td>1</td>
</tr>
<tr>
<td>Erosion of stomach wall with perforation</td>
<td>1</td>
</tr>
<tr>
<td>Asphyxia from occlusion of bronchi by masses of aspergillus</td>
<td>1</td>
</tr>
<tr>
<td>Undetermined immediate cause</td>
<td>6</td>
</tr>
</tbody>
</table>
TABLE 7

Location of Aspergillosis in the Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Location</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>10</td>
</tr>
<tr>
<td>Large intestine</td>
<td>9</td>
</tr>
<tr>
<td>Small intestine</td>
<td>7</td>
</tr>
<tr>
<td>Duodenum</td>
<td>0</td>
</tr>
<tr>
<td>Jejunum</td>
<td>5</td>
</tr>
<tr>
<td>Ileum</td>
<td>2</td>
</tr>
<tr>
<td>Stomach</td>
<td>5</td>
</tr>
<tr>
<td>Tongue</td>
<td>3</td>
</tr>
<tr>
<td>Soft palate</td>
<td>2</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>2</td>
</tr>
<tr>
<td>Epiglottis</td>
<td>2</td>
</tr>
</tbody>
</table>

Disseminated aspergillosis and at autopsy A. fumigatus was cultured from the lung and A. glaucus was cultured from the spleen. Isolation of multiple species of Aspergillus from a single patient has been described previously. Welsh and Buchanan (114) cultured A. fumigatus, A. flavus, and A. nidulans from different lesions in the lungs and heart of a single patient.

One patient may have had disseminated disease due to A. niger, but the stipulated criteria were not completely fulfilled. This patient had disseminated aspergillosis histologically and grew Aspergillus from the heart, blood, and lung at autopsy but the species was not identified. An autemortem urine culture had grown A. niger and at autopsy hemorrhagic infarcts of the kidney containing Aspergillus hyphae were noted.

A. fumigatus is the most commonly implicated species in disseminated disease (1, 14, 28, 30, 35), but A. flavus (103, 114), A. nidulans (114), A. sydowii (121), and A. niger (63) have been reported. No previous case of disseminated aspergillosis due to A. glaucus has been described.

Only 12 of the 34 patients with disseminated disease had any cultural evidence of aspergillosis autemortem, and only three had more than a single positive culture. Only two patients had Aspergillus isolated consistently from the same site. Therefore, persistent cultural evidence of Aspergillus, even in disseminated aspergillosis, is rare.

Gastrointestinal Tract. Twenty-one of the patients had aspergillosis of the gastrointestinal tract and 11 had multiple sites of involvement. The distribution of the lesions are shown in Table 7. Eighteen of the patients had disseminated aspergillosis with prominent pulmonary lesions. The esophagus was the most frequently involved site and ulcerative esophagitis with areas of confluent necrosis was the usual lesion although several patients had esophageal abscesses. Three patients had pseudomembrane formation with sheets of greyish-green friable vegetative material. Microscopically, necrotic debris, fibrin, and masses of branching septate hyphae were seen in these pseudomembranes. The ulcerative lesions differed from Candida esophagitis in that the fungi tended to be more invasive and extended from the mucosa into the muscularis. In one patient this through and through spread resulted in perforation of the esophagus into the mediastinum, and in another the esophagus became densely adherent to the posterior portion of the pericardium and heart.

Large bowel ulcers were seen in nine patients and were most frequently seen in the cecum. These varied from 1 to 6 cm in size and were usually well demarcated and circumscribed, but occasionally were serpiginous. The edges were slightly raised and whitish and the central portions of the ulcer contained black necrotic material surrounded by hemorrhagic tissue (Figs. 3 and 4). In five of the patients, large bowel infarcts around the areas of ulceration were produced by fungal invasion of intestinal arteries and veins with masses of fungal hyphae initiating thrombosis.

Seven patients had small intestinal lesions. The majority (5) had lesions in the jejenum and no lesions were found in the duodenum of any patient in this series. The lesions were characteristically multiple, 2 mm–2 cm sharply circumscribed ulcers with necrotic bases, and microscopically, the fungal hyphae were seen at the base of the ulcer. Three patients had prominent vascular invasion with thrombosis and infarction, and in these the lesions tended to be more invasive and extend from mucosa to serosa. In one patient perforation of the small intestine occurred in an area of ulceration, necrosis, and infarction. Microscopically, necrotic debris, fibrin, and branching septate hyphae were noted in the area of perforation. Scattered about this area as well were pseudohyphae and spores of Candida, but they were superficially located and were not felt to be primarily responsible for the invasive char-
acter of the lesion. Two patients with small bowel ulcerations had pseudomembrane formation which was pathologically similar to that found in the esophagus.

Five patients had Aspergillus lesions of the stomach. In two, this seemed to be a continuum from the esophageal ulcerations, but in others the lesions were separate and distinct. These lesions were histologically similar to those seen in the esophagus and intestines. One unique patient presumably had stomach involvement by direct extension from a lung lesion. In this individual, pulmonary aspergillosis involving the left lower lobe had spread through the diaphragm and invaded the stomach wall, finally producing actual perforation of the stomach.

Three patients had oropharyngeal aspergillosis of a distinctive type not previously described in reviews of aspergillosis. Two of these patients had yellowish necrotic ulceration of the posterior portion of the tongue extending down the hypo-

pharynx to involve the epiglottis. One of these two had necrotic ulcerations of the soft palate as well. A third patient in this group had a large black necrotic ulcerative lesion of the soft palate as the only oropharyngeal lesion. All three patients with oropharyngeal aspergillosis were symptomatic. All had intense local pain and oral bleeding. All had extreme difficulty swallowing and two progressed to the point that intravenous feedings were required because of inanition. Two of the patients with the most severe hypopharyngeal involvement became aphonic for the last few days of life.

All three patients who perforated a hollow viscus were on steroid therapy. Only one of the three had sudden catastrophic symptoms of abdominal pain, fever, and shock. Abdominal roentgenogram in this patient showed ileus with air fluid levels, but no free air was noted in the abdomen. At autopsy the patient had a perforation of the small intestine. The other two patients who
perforated, one with perforation of the esophagus into the mediastinum, and the other with the erosive lesion from hung into the stomach, had no sudden catastrophic symptoms suggesting perforation and the diagnosis was not established until autopsy.

Gastrointestinal perforation has not been described previously although invasion of the duodenal artery leading to massive gastrointestinal hemorrhage has been reported (115).

Gastrointestinal bleeding, as evidenced by positive stool guaiac examinations, was present in 80 per cent of these patients at some point in their hospital course although concomitant thrombocytopenia, steroid therapy, and cytotoxic antineoplastic therapy made it difficult to ascribe this to gastrointestinal aspergillosis. Nevertheless, six patients had massive gastrointestinal hemorrhage which was felt, at autopsy, to be related to Aspergillus ulceration.

Cultural efforts to establish the diagnosis were generally unsatisfactory. Sixteen of the 21 patients with involvement below the esophagus had stool cultures for fungi and each patient had from one to ten separate cultures over the duration of their illness. Only three patients grew *Aspergillus spp.* on at least one occasion. In contrast, ten patients grew *Candida spp.* in the stool cultures at least once, and two patients grew *Torulopsis glabrata*. Three patients had gastric aspirates—one grew *Candida albicans* and two had no growth on fungal culture. Two patients had rectal swab cultures for fungi and both grew *Candida albicans*. One individual had a piece of necrotic tissue from the soft palate cultured and this yielded *Aspergillus sp.* and Candida. Ulcerations of the gastrointestinal tract were not routinely cultured for fungus at autopsy, but one patient who had a large mycotic ulceration of the large bowel cultured *Aspergillus sp.* from the bowel lesion. Mouth and throat cultures for fungi were frequently obtained but consistently either grew *Candida albicans* or were sterile, even in the patients who had oropharyngeal aspergillosis.

Only 7 of the 21 patients with involvement below the esophagus had Aspergillus alone in their gastrointestinal lesions. Seven had mixed infections with Candida, but in all instances the more invasive lesions seemed to be predominantly Aspergillus. Often separate lesions contained fungi of only one type. One patient, for example, had Candida gastritis while having Aspergillus alone in a jejunal ulceration; another had Candida esophagitis while having small and large bowel ulcerations with Aspergillus and Candida. Candida was the usual associated infection. Half
of those lesions with pseudomembrane formation had bacterial overgrowth within them along with Aspergillus hyphae; Pseudomonas, Staphylococcus aureus, and Clostridium were cultured. It is difficult to define the precise role that each of the various infective agents played in the over-all disease state, but the progressive invasion of blood vessels with thrombosis, infarction, and necrosis was most clearly related to Aspergillus. In the three patients who perforated, Aspergillus seemed to be the agent responsible for the through and through infarction and necrosis.

Involvement of the gastrointestinal tract with Aspergillus is uncommonly described in reviews of this disease, even as a part of a generalized disseminated process (5, 35, 36, 79, 103). In our series, it was the most common site of involvement other than the lungs. The reason for this discrepancy between our findings and those of others is not clear, as the patient populations are comparable in most instances; most patients having severe underlying hemopoietic or lymphoreticular malignancies. However, it is probable that the frequency of involvement and degree of invasion of Aspergillus in the gastrointestinal tract increases with the intensity of chemotherapy and the duration of life in a debilitated state.

Central Nervous System. Thirteen patients had central nervous system (CNS) aspergillosis. In all cases this was associated with disseminated disease, and in all patients except one, the primary lesion appeared to be in the lung. The single exception was a patient with intestinal ulcerations and brain abscesses.

At autopsy, multiple Aspergillus lesions were found in the CNS of seven patients and solitary lesions were found in six. In no instance was there spinal cord involvement, although this has been reported by others (118). All patients manifested some degree of central nervous system depression, lethargy, and obtundation; localizing neurological signs were varied depending on the anatomic lesion (Table 8). In some cases the Aspergillus CNS lesions could explain some of the patient's signs and symptoms while intracerebral leukostasis, mucormycosis, or intracerebral hemorrhage, unassociated with Aspergillus infection, were responsible for other symptomatology. Involvement of the base of the brain, cerebellum, and areas supplied by the posterior circulation was present in ten patients (77 per cent), although in five of these patients, additional lesions were found in areas supplied by the anterior circulation. Lesions in areas of the brain supplied by the anterior circulation were present in eight patients (62 per cent). It has been stated in other reviews that Aspergillus lesions in the CNS are most often solitary and most often in the frontal lobes (50). However, most of those previously reported patients have had CNS involvement by direct extension from the paranasal sinuses and orbit (4, 46) and have not had hematogenously disseminated aspergillosis. Involvement of the cerebellum in patients with disseminated aspergillosis has been noted before (14, 106). Based on the experience presented here, Aspergillus does seem to involve the brain commonly via the posterior circulation in patients who have hematogenous dissemination. Likewise, with hematogenous dissemination, multiple lesions are almost as common as solitary ones.

Sinusitis has been felt to be a portal of entry for Aspergillus, and invasion from the sinus cavities into the orbit and cranial vault has been described (4, 46, 105). In this series, this portal of entry was not seen in any of the 13 patients. Only four patients of the group had persistent sinusitis during their terminal illness and in none of these four was invasion into the cranial vault observed at autopsy.

The most striking histologic characteristic in CNS aspergillosis was the degree of vascular invasion with secondary thrombosis of cerebral vessels (Fig. 5). Ten patients (77 per cent) had prominent vascular invasion and infarction. Abscess formation in the center of infarcted areas was also very common. The amount of inflammatory change varied from patient to patient. In some of the more acute lesions, polymorphonuclear leukocytes predominated while chronic inflammatory cells were found in older lesions. In some patients, the lack of inflammatory cells was striking and could have been related to depression of circulating leukocytes by chemotherapy.

Laboratory evaluation of CNS function in some of these patients included skull roentgenograms, electroencephalogram, lumbar puncture, radioisotopic scanning, and cerebral angiography. Skull roentgenograms were performed on four patients and were within normal limits in all four. Electroencephalography was performed on seven patients and was abnormal in six. Three of these patients had diffuse abnormalities and three had focal dysrhythmias. Of the three with focal
### Table 8

**Aspergillosis of the Central Nervous System**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration CNS symptoms</th>
<th>Laboratory studies*</th>
<th>Neurological examination</th>
<th>Major anatomic lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Electroencephalogram</td>
<td>Cerebrospinal fluid†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 months</td>
<td>ND</td>
<td>Protein 118</td>
<td>Nominal aphasia</td>
</tr>
<tr>
<td>2</td>
<td>3 months</td>
<td>+</td>
<td>Protein 148</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>1.5 months</td>
<td>+</td>
<td>Protein 145</td>
<td>Rt. facial twitch,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glucose 28</td>
<td>ataxia, nystagmus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 PMN</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 week</td>
<td>ND</td>
<td>ND</td>
<td>Rt. Horner's</td>
</tr>
<tr>
<td>5</td>
<td>2 weeks</td>
<td>+</td>
<td>0</td>
<td>Rt. cerebellum, mid-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>brain</td>
</tr>
<tr>
<td>6</td>
<td>2 days</td>
<td>ND</td>
<td>0</td>
<td>Lt. cerebrum, lt. cere-</td>
</tr>
<tr>
<td>7</td>
<td>1 day</td>
<td>ND</td>
<td>0</td>
<td>bellum</td>
</tr>
<tr>
<td>8</td>
<td>2 weeks</td>
<td>+</td>
<td>Nd</td>
<td>Pons, cerebellum, cere-</td>
</tr>
<tr>
<td>9</td>
<td>2 weeks</td>
<td>+</td>
<td>Nystagmus, ataxia</td>
<td>cebulum (multiple)</td>
</tr>
<tr>
<td>10</td>
<td>1 month</td>
<td>0</td>
<td>Pto sis of right eyelid</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>11</td>
<td>1 month</td>
<td>+</td>
<td>4-8 PMN</td>
<td>Lt. piriform cere-</td>
</tr>
<tr>
<td>12</td>
<td>2 weeks</td>
<td>ND</td>
<td>0</td>
<td>Thalamus, cerebellum,</td>
</tr>
<tr>
<td>13</td>
<td>2 weeks</td>
<td>ND</td>
<td>0</td>
<td>basal ganglia</td>
</tr>
</tbody>
</table>

* + = abnormal, 0 = normal, ND = not done.  † Normal values omitted. Protein and sugar values in mg/100 ml. PMN = neutrophiles/mm³.

dysrhythmias, two had anatomic lesions found at autopsy which could account for the electroencephalographic changes, but there was no correlation in the third.

The spinal fluid findings in our cases are in substantial agreement with previous reports. In many previous cases the spinal fluid was normal (36, 45) but leukocytosis, monocytes, and increased protein have been described (45, 46, 60, 66). Examination of the spinal fluid was performed in 11 of the 13 patients and was completely normal in 7 of these. The spinal fluid abnormalities of the other four patients are listed in Table 8. Three patients had elevated spinal fluid protein and three had small numbers of leukocytes present. Two of the three patients who had leukocytes present in the cerebrospinal fluid had evidence of extension of the aspergillosis from the brain to a focal area of the meninges. Eight of the patients had meningeal involvement with aspergillosis, but in each case it was associated with brain lesions and was focal. No patient had diffuse meningeal involvement with Aspergillus. Every patient who had meningeal involvement at autopsy, had a spinal fluid examination ante-mortem and none had fungal hyphae identified on smear. Furthermore, ten of the 13 patients (77 per cent) with CNS aspergillosis had spinal fluid cultured for bacteria and fungus and all cultures were negative. Aspergillus has been isolated from a spinal fluid culture previously, however (60).

A single patient with striking neurological signs had an extensive neurological workup which highlights the difficulty in making the diagnosis of CNS aspergillosis ante-mortem. This patient, a 52 year old female with Hodgkin's Disease, developed confusion, lethargy, and obtundation followed by the onset of right hemiparesis. Electro-
encephalography and brain scan suggested a left-sided cerebral focus. Spinal fluid examination on two separate occasions contained 4 to 8 polymorphonuclear leukocytes with normal protein and sugar determinations. Spinal fluid cultures were negative for fungus. A right carotid arteriogram was performed which was interpreted as consistent with left frontal lobe edema. Cranietomy was performed and diffuse cerebritis was noted in the area of the left frontal lobe. Aspiration of this area yielded no fluid, and a definitive diagnosis was not made. The patient died shortly after the operative procedure and a left frontoparietal abscess containing Aspergillus was discovered at postmortem. Culture from the brain abscess grew *A. fumigatus*.

The duration of symptoms in our patients with CNS aspergillosis was 5.3 weeks (range 0.1 to 28). In other reports, a similar range has been observed. The disease has been rapidly fatal in a matter of days in some patients (57, 121), while persisting for months in others. Several patients have survived for years (14, 46, 106). Rarely, recovery has occurred after surgical drainage and amphotericin B (16).

**Kidney.** Twelve patients had renal aspergillosis. All of the patients with kidney involvement had disseminated aspergillosis with multiple organ involvement. For the most part, the lesions were characteristic of hematogenous miliary spread. Multiple focal renal abscesses occurred in seven of the patients. These were 1 to 3 mm in diameter, firm and nodular, and had yellow necrotic centers surrounded by a rim of greyish-red hyperemic congestion. None of these patients had renal symptoms attributable to these scattered miliary abscesses. Four patients had more extensive involvement and, in each of these, vascular invasion led to multiple areas of renal infarction, ischemic necrosis, and irregular
abcess formation. Vascular invasion with infarction was more common in the medulla than in the cortex.

A single patient had an interesting and unusual complication of vascular invasion which led to renal papillary necrosis. This lesion was not recognized clinically antemortem, but at autopsy, numerous abscesses were visible on the cut surface of the kidney and some involved the papillary tips. Necrosis of the renal papillae had occurred secondary to the abscesses. Microscopic examination of the renal medulla revealed vascular invasion with Aspergillus and several papillary vessels were completely occluded with fungal hyphae. It is intriguing to postulate that the vascular invasion and thrombosis by Aspergillus produced the papillary ischemia and vascular insufficiency necessary for this unusual complication.

None of the 12 patients had symptoms suggesting localized renal involvement with Aspergillus. None had flank pain or dysuria, and although chills, fever, and hematuria were often present, they were not felt to be exclusively related to renal disease. Six patients had intravenous pyelography during the course of their illness, but in no instance was this diagnostic. Pyelograms in three were negative and in the other three showed diffusely enlarged kidneys felt to be related to leukemic infiltration.

Seventy per cent of the patients had hematuria at some time within the last three weeks of their illness. Five patients had intermittent gross hematuria and four had microscopic. All, however, had concomitant thrombocytopenia, which made interpretation of hematuria difficult. Eight of the patients had proteinuria and ten had pyuria. Four patients had small numbers of granular and hyaline casts.

Only three of the patients had other infections demonstrable in the kidneys at autopsy and all three were candidiasis. Three patients had cultures of the renal lesions taken at autopsy and only one failed to grow Aspergillus, and microscopic identification was made in that patient.

Antemortem urine cultures did not prove to be rewarding in the diagnosis of renal aspergillosis. Of the 12 patients with proven renal aspergillosis at autopsy, 8 had antemortem urine cultures for fungus at least once. Only two grew Aspergillus and each one on only one occasion. Six patients grew Candida, two grew Trichosporon sp., and one grew Torulopias glabrata on two occasions. All three patients who had concomitant renal candidiasis at autopsy grew Candida on antemortem fungal urine cultures.

Liver. Twelve patients had liver involvement with Aspergillus. In all instances this was associated with disseminated disease although in a single instance the spleen was the only other organ involved. Hematogenous spread from a primary pulmonary focus appears to be the most likely source as all of the patients except the aforementioned one had extensive pulmonary disease. Local spread via the portal system from primary lesions in the G.I. tract appears less likely as only five of the 12 patients had intestinal lesions in areas draining into the portal system. Liver pathology was consistent with hematogenous spread and the most common lesions were discrete, periporal, 0.5 to 1 cm milliary abscesses scattered throughout the liver. These were usually areas of yellow-tan coagulative necrosis surrounded by an area of hyperemic congestion. Microscopically, necrotic zones were filled with Aspergillus and the abscesses were surrounded by atrophic cords and congested sinusoids (Fig. 6).

Fifty per cent of the patients with liver involvement had invasion of hepatic vessels within the areas of abscess, and thrombosis of vessels with infarction of tissue surrounding abscess areas was common. In two of the patients this vascular invasion and thrombosis of the hepatic veins was extensive enough to produce a Budd-Chiari syndrome. These two patients were the subject of a previous report (120).

With the exception of the two cases of the Budd-Chiari syndrome, the clinical picture of aspergillosis of the liver has not been striking. Localized small abscesses were asymptomatic except for fever and even the fever was difficult to ascribe to the hepatic abscesses. Multiple abscesses clinically presented with tender hepatosplenomegaly, but hepatosplenomegaly when present was not usually massive and may well have been related to the primary disease or to chemotherapy. Only three patients had widespread hepatocellular damage from large Aspergillus abscesses and infarcts. These patients had crampy abdominal pain, fever, marked liver tenderness, and striking jaundice.

Liver function abnormalities may be a reflection of a complex of factors in severely ill patients of this type. However, liver function studies in these patients with hepatic aspergillosis were never strikingly abnormal enough to suggest widespread hepatocellular disease such as hep-
titis or drug toxicity. The six patients with scattered small abscesses had modest abnormalities of liver function, with slight elevations of the serum transaminases, alkaline phosphatase, and bilirubin. The three patients with large Aspergillus abscesses and infarcts had more marked liver function abnormalities. All three were jaundiced with a mean bilirubin of 6.7 mg/100 ml. The two patients with Budd-Chiari had liver function tests indicating mild to moderate impairment of hepatic function. Jaundice was never striking and the highest bilirubin observed was 2.6 mg/100 ml.

Seven of the patients with aspergillosis of the liver had no other organism present in the liver at autopsy. Of the remaining five, one had Pseudomonas and Proteus morganii abscesses; four had
Candida abscesses appearing grossly similar to the Aspergillus lesions. Occasionally these fungi were both present in the same abscess, but more often they were separate and distinct, only one fungus being present in a given abscess. It is of interest that, of the four patients with combined fungal infection, all grew Candida from postmortem cultures although only one grew Aspergillus. In spite of these cultural differences, Aspergillus was the predominant fungus in each case by microscopic examination. Apparently one can be misled by depending upon cultural evidence when these two fungi are present.

Heart. Seven patients had aspergillosis of the heart or pericardium. All seven had cardiac involvement as a manifestation of disseminated aspergillosis and all had prominent pulmonary infections.

Two of the patients had two to three focal myocardial abscesses which were 1 to 3 mm in size, sharply circumscribed and filled with yellow necrotic material. Microscopically, Aspergillus hyphae were seen in the necrotic debris and invading the surrounding myocardium (Fig. 7). These lesions were clearly hematogenous in origin and they were not considered clinically significant.

Three patients had extensive myocarditis. Large and small abscesses were present throughout the myocardium, and microscopically, the heart was extensively infiltrated with Aspergillus. In these patients, vascular invasion was prominent and coronary vessels were occluded with fungal masses producing small vessel thrombosis and infarction. In each of these patients the lesions often extended from epicardium, through the myocardium to produce smooth nonvegetative endocardial plaques of the type described by others (36, 61, 114). In no instance was a vegetative endocarditis (12, 72) seen, although a single patient in this group had numerous mural thrombi invaded by Aspergillus. Whether mural thrombosis took place on an area of endocardium disrupted and infamed by aspergillosis, or whether the fungus invaded pre-existing thrombi, is conjectural.

Four patients had Aspergillus pericarditis. Two of these had pericarditis in conjunction with the through and through myocarditis described above, and two had pericarditis as the only cardiac manifestation of aspergillosis, one having the pericardium involved by direct extension from the lung and the other having hematogenous spread. In all four patients, the pericardial cavity was involved with shaggy fibrinous adhesions on both the parietal and visceral pericardium. In two
patients 20 to 50 ml of yellow-green cloudy fluid was present, and the pericardial surfaces were studded with green friable granules, while in the other two, the pericardial fluid was straw colored and clear. Microscopically, however, Aspergillus mycelia were seen in all four cases. A single case of purulent pericarditis has been described previously (30) and their description closely parallels our first two cases. Zimmerman, however, reported a patient in which Aspergillus was cultured from the pericardial effusion although the fluid was straw colored and clear (121). Apparently Aspergillus pericarditis can be either purulent or serofibrinous and the appearance of the pericardial fluid may be deceptive.

Other unusual features of cardiac aspergillosis not found in our patients, but reported previously have been, septic embolization from vegetative endocarditis (12, 49, 114, 122); herniation of an abscess into the left ventricular chamber (14); perforation of the membranous portion of the interventricular septum (121); and rupture of the aorta caused by Aspergillus infection following operation for aortic stenosis (38). Aspergillus endocarditis complicating open heart surgery has been reported (47, 63, 72), and disseminated aspergillosis complicating cardiac transplantation has recently been described (86).

In five of our seven patients, dissemination of the fungus to the heart appeared to be hematogenous. In the other two patients, the infection involved the pericardium and heart by direct extension. In one instance, a left lower lobe lung lesion was continuous with the pericardial sac and in the other, a fungal lesion in the esophagus was firmly adherent to the posterior portion of the pericardium over the left atrium.

Symptoms related exclusively to cardiac aspergillosis were difficult to isolate. All of the seven patients had severe pulmonary aspergillosis which made interpretation of most of the clinical cardiac signs difficult. Nevertheless, five of the patients had congestive heart failure and peripheral edema out of proportion to their pulmonary disease and four died with intractable failure in recurrent pulmonary edema. Of these four patients, three had severe Aspergillus myocarditis and the other had focal myocardial abscesses. None of the four patients with pericarditis had clinical signs suggesting this disease and pericardial friction rubs were not heard.

Electrocardiographic changes were generally nonspecific, showing sinus tachycardia and mild ST and T wave abnormalities. Of the four patients with pericarditis, three had EKG’s and only two showed the ST segment changes characteristic of pericarditis. Two patients developed EKG changes compatible with myocardial ischemia or infarction within the last week of their illness, but only one had severe myocarditis with vascular invasion and thrombosis at autopsy; the other had focal 1 to 2 mm myocardial abscesses. Of the three patients who had severe Aspergillus myocarditis with coronary vessel invasion, thrombosis, and infarction, only one had EKG changes reflecting myocardial injury. The second had only sinus tachycardia with ST and T wave changes consistent with the rapid rate; the third patient was a seven year old child who never had an EKG during hospitalization.

Roentgenographic evidence of cardiac disease was uncommon although it may have been partially obscured by the extensive pneumonias present in each of the patients. One patient, a five year old boy with Aspergillus pericarditis, developed sudden changes in the cardiac silhouette which were consistent with pericardial effusion. Otherwise the small variations in cardiac size seen in the remaining six patients were nonspecific.

Cultural attempts at diagnosis were disappointing. All seven patients with cardiac aspergillosis had blood cultures for fungus drawn antemortem, and from two to 24 separate cultures were drawn on each patient over the course of their illness. In spite of this cultural effort, not a single blood culture grew Aspergillus. A single patient grew Candida tropicalis out of three blood cultures and at autopsy had disseminated candidiasis as well as aspergillosis, although his aspergillosis was qualitatively more severe. Heart blood for culture was obtained from all seven patients at autopsy and none grew Aspergillus. The myocardial abscesses were not cultured directly although pulmonary lesions in those patients cultured did grow Aspergillus. The single patient with positive Candida blood cultures grew Candida tropicalis in the heart blood at autopsy. Interestingly, this was the only patient of the seven who had a mixed fungal infection in the myocardium. At autopsy only scattered small foci of Candida were seen while extensive Aspergillus myocarditis with vascular invasion, thrombosis, and infarction was noted.

Thyroid. Nine patients had aspergillosis of the thyroid gland, a rather large number when one considers the size of the gland. This unusually
high incidence of thyroid involvement has been noted by others (103) and approximately nine other cases have been reported previously (1, 14, 30, 35, 36, 61, 103). All nine of our patients had disseminated aspergillosis and all had pulmonary involvement.

Three patterns of pathological involvement were noted. Six patients had focal 2 mm–1.5 cm firm yellowish nodules which on microscopic examination proved to be abscesses containing necrotic debris, hemorrhage, and Aspergillus hyphae. Two patients had patchy hemorrhagic areas of necrosis which contained Aspergillus hyphae, and in these patients vascular invasion with thrombosis and infarction was prominent. A single patient had a diffuse necrotizing thyroiditis with widespread thrombotic angiitis secondary to fungal invasion of blood vessels. It is not uncommon for acute suppurative thyroiditis to involve adenomatous glands (116) and two patients had pre-existing thyroid adenomas; in both instances this was the area involved with aspergillosis. One patient had involvement of a parathyroid gland as well as the thyroid lesion.

Typical symptoms of suppurative thyroiditis were not seen in any of these patients and in no instance was thyroiditis thought to be present clinically. The two patients with adenomas had palpable thyroid masses, but at no time were they tender or fluctuant.

Unlike other organ involvement where mixed infections were not uncommon, none of these patients had any other infective agent present in the thyroid at autopsy.

The factors which predispose the thyroid to aspergillosis infection are unclear, but it does not appear to be simply related to the relatively high blood flow directed to endocrine glands, because only one patient in this entire series had aspergillosis of the adrenal gland, and pituitary involvement was not noted in a single case.

**Paranasal and Mastoid Sinuses.** Autopsy examination of the paranasal and mastoid sinuses is not routinely performed at the National Institutes of Health unless some unusual clinical condition warrants this investigation. Because of this, an accurate estimate of the frequency of Aspergillus sinusitis in these 98 patients was not possible. Nevertheless, 12 patients did have persistent sinusitis, otitis media, or mastoiditis for two weeks to six months, unresponsive to multiple courses of antibiotic therapy. Three had severe pansinusitis and seven had chronic maxillary sinusitis. A single patient had persistent otitis media and another had sphenoid sinusitis.

Three patients of this group had examination of the sinuses at autopsy and all three had Aspergillus demonstrated pathologically. One patient, a 47 year old female with Hodgkin’s Disease involving the base of the brain, had multiple cranial nerve palsies and the sphenoid bone was examined in block. There was extensive necrosis and fibrosis within the sphenoid air sinuses and colonies of branching septate hyphae were seen. Aspergillus was found to be invading vascular walls producing thrombosis of small vessels within the sphenoid sinus; however, cranial nerve palsies were felt to be related to Hodgkin’s Disease rather than Aspergillus. No other site of Aspergillus was present in this patient. Aspergillus niger was cultured from the sputum antemortem.

The second patient, a 24 year old man with Hodgkin’s Disease had persistent symptomatic right otitis media. Aspiration was initially required for relief of pain, and yellow purulent fluid was obtained and grew Pneumococcus on routine culture. The fluid was not cultured for fungus. The otitis was not completely responsive to multiple antibiotics during the remainder of the patient’s course. At autopsy, on opening the temporal pyramid, the right middle ear cavity was filled with yellow purulent exudate and erosion into the mastoid air cells had occurred. Culture of the exudate grew E. coli, anaerobic Streptococcus and Aspergillus sp. Microscopic examination of the temporal bone revealed Aspergillus hyphae. The cranial cavity and brain were not involved and no other site of Aspergillus infection was present.

The third patient, a four year old boy with acute lymphocytic leukemia, presented with clinical and roentgenologic evidence of pansinusitis. After one month of persistent x-ray evidence of sinusitis he developed right orbital cellulitis and persistent yellow-green blood tinged nasal discharge from the right naris. Fungal culture of this discharge grew Aspergillus fumigatus. Over the seven days prior to death the periorbital edema and cellulitis progressed and a gradually enlarging brownish-black necrotic patch developed below the right orbit as well as on the soft palate. At autopsy, Aspergillus hyphae were demonstrated in the necrotic palatal lesion. The sinus cavities were not opened. There was no invasion into the cranial cavity.

Aspergillosis is said to be a common primary
fungal infection of the paranasal sinuses (87), but only approximately 25 cases of the disease involving the facial sinus cavities have been reported (7, 70, 90). The infection can spread from a focus in the sinuses to involve the periorbital tissues and invasion of the orbit with unilateral proptosis, visual impairment and extra-ocular muscle palsies have been described (4, 113, 117). Further extension of the infection into the cranial vault and brain has been reported (46, 106). None of the three patients in this series, who had demonstrable sinus disease, had erosion into the cranial vault and none had aspergillosis of the brain. Of the 13 cases in which the brain was involved with aspergillosis, only four had evidence of sinusitis and none of these had invasive lesions in the cranial vault at autopsy. It would seem that this portal of entry into the brain is much less common than hematogenous spread in this patient population.

The orbital and facial disease seen in the third patient described here resembles that seen in Phycomycete infections where diabetic ketoacidosis is felt to play a role (51). Unlike mucormycosis, predisposing factors are not frequently reported in sinus infections due to Aspergillus and none of our patients nor those described in the literature had diabetes mellitus.

Diaphragm. Five patients had diaphragmatic involvement and in all instances this was associated with prominent lesions in the lungs. Usually, thick plaques of fibrous adhesions involving the visceral and parietal pleura were present and microscopically, Aspergillus hyphae were seen within the fibrous meshwork. The diaphragm was involved by direct extension across the pleural adhesions. One patient had evidence of local Aspergillus peritonitis and pleuritis associated with the diaphragmatic involvement, and a single patient had direct extension through the diaphragm into the stomach wall producing perforation of the stomach.

Skin. Two patients had histologically proven aspergillosis of the skin. In one it appeared to be the portal of entry and in the other, a manifestation of cutaneous dissemination. Nine days prior to death, a five year old boy with acute lymphocytic leukemia developed an erythematous, indurated cellulitis of the dorsum of the right hand at the site of a previous intravenous infusion. This lesion progressed to 2 cm ulcerated area with a central hard black crust. Culture of the lesion yielded A. flavus. Six days after appearance of this lesion, the patient developed left basilar pneumonia for the first time. The pneumonia became progressively more severe and the patient died three days later. At autopsy, disseminated aspergillosis was present with lesions in the lungs, liver, kidneys, and heart. Culture of the lung grew A. flavus.

The second patient was a ten year old girl with acute lymphocytic leukemia. During the course of an undiagnosed febrile illness she developed 1.5 cm tender maculo-papular erythematous eruptions in the left anterior axillary fold and over the posterior margin of the right superior iliac spine. These progressed to become indurated lesions with a raised, purple border and a flat, dry central crust. Four days later a right lower lobe infiltrate appeared for the first time and was felt to be consistent with an early pneumonitis. Her pneumonia progressed and she expired eight days after the first appearance of the skin lesions. At autopsy, disseminated aspergillosis was found involving the lungs, esophagus, liver, kidneys, spleen, and brain. Biopsy of both skin lesions revealed subcutaneous and intradermal spread of Aspergillus hyphae (Fig. 8).

![Fig. 8. Photomicrograph of Aspergillus hyphae in the dermis. Gomori-Methenamine Silver × 40.](image-url)
Culture from the lung lesions grew *A. fumigatus* and the spleen grew *A. glaucus*.

Aspergillus skin lesions have been described in disseminated disease (55) and Aspergillus has been cultured from subcutaneous and cutaneous abscesses (14, 109). A child with disseminated aspergillosis developed skin lesions which were initially maculo-papular, but progressed to pustules containing greenish-yellow purulent material. One lesion on the thigh became a multiloculated vesicle containing serosanguinous fluid. Aspergillus hyphae were seen on histological examination of the pustular lesions (1). Another report (32) described lesions strikingly similar to those seen in our patients. The eruptions were maculo-papular, 2 to 15 mm in diameter and reddish purple in color.

Intravenous infusions have been implicated in the portal of entry of Aspergillus organisms previously (67) and the sequence of events in the first case suggests that this was the likely route of infection.

**Testis.** One patient had testicular involvement associated with disseminated aspergillosis. Vascular invasion with thrombosis, infarction, and hemorrhage were prominent in his lung, small and large bowel lesions, and diffuse hemorrhage into the right testis was noted at autopsy. Microscopically, in the center of the hemorrhagic area in the testis, venous thrombosis was associated with intraluminal growth of Aspergillus hyphae. The testicular lesion was not symptomatic clinically and there was no testicular enlargement.

Testicular infection with this fungus appears to be extremely uncommon even in widely disseminated disease. No mention of this complication was made in previous reviews of disseminated aspergillosis (28, 36, 103).

**PREDISPOSING FACTORS**

Perhaps as much has been written about the factors predisposing to fungal infections as has been written about the fungal infections themselves. Few discussions of mycoses, especially those complicating malignant diseases, fail to mention the influences of leukenemia, corticosteroid therapy, cytotoxic agents and antibiotics on the resistance of an already debilitated host. Several detailed reviews of the subject have been published (5, 37, 92, 108). It is difficult to get information which isolates each of these factors from one another so it is difficult to assess the relative role of each in the increased susceptibility. Nevertheless, there seem to be several observations worth reiteration.

Patients with leukemia and lymphoma seem unusually prone to mycoses and this susceptibility cannot altogether be explained by chemotherapy. Hutter and Collins (44) observed that leukemias and lymphomas comprised 60 per cent of the cancers associated with mycoses while only comprising 6 per cent of their cancer admissions. Experimentally, it has been demonstrated that mice with transplantable lymphoid leukemias have increased susceptibility to *A. fumis* infections even before chemotherapy (93). Avian myeloblastosis has also been shown to predispose to severe aspergillosis (15).

Granulocytopenia has been thought to contribute to diminished host resistance (5, 37, 44) and, indeed, 70 per cent of the patients in this series had absolute granulocyte counts below 500 mm$^3$. Fifty-three per cent had absolute granulocyte counts below 200 mm$^3$. Twenty per cent of the patients, however, had normal granulocyte counts throughout hospitalization. It has also been suggested that abnormal phagocytosis contributes to the lowered resistance even where the absolute count may be normal (10, 41), although this has not been substantiated by others (96).

The loss of normal immune mechanisms, either because of disease or therapy, has been suggested as a predisposing factor. Delayed hypersensitivity to antigens extracted from *Candida albicans* has been found to be impaired in some patients with hematopoietic and lymphoreticular malignancies (97), but this has not always correlated with frequency, severity, and duration of disease. Humoral antibody production reflected in serum gamma globulin levels has been commonly depressed in chronic lymphocytic leukemia (89), but no consistent abnormality has been found in other leukemias and lymphomas. In the present series, 81 of the 98 patients had serum globulin determinations and 79 (81 per cent), had normal globulins; nine patients (10 per cent) had slightly reduced globulin levels, and only three patients (3) had markedly low globulins. Serum paper electrophoresis was performed on 30 of the 98 patients and was normal in 26 (87 per cent) and abnormal, showing reduced gamma globulin in four (13 per cent). Two of the four patients with abnormal levels of gamma globulin had chronic
lymphocytic leukemia. Evidence presented here as well as from other studies suggests that hypogammaglobulinemia does not play a major role in predisposing these patients to mycoses.

There is considerable experimental (31, 92, 94) evidence that corticosteroid therapy enhances tissue invasion and dissemination of fungi. Mice exposed to aerosol sprays of A. fumigatus develop fatal pulmonary aspergillosis if pretreated with corticosteroids (94) and corneal ulceration from Aspergillus may be induced by inoculating spores after topical or systemic pretreatment with corticosteroids (11). Several clinical series (55, 92) have emphasized this relationship between corticosteroid therapy and fungal infections. In the present series 87 per cent of the patients received corticosteroids during the course of their terminal illness. Thirteen patients, however, received no corticosteroids during their illness and two of these had disseminated aspergillosis. Corticosteroids probably alter immunologic response (98, 101) and gastrointestinal flora (64, 65), and may produce direct tissue toxicity (2, 20, 22).

The role of antibiotics in the development of mycoses is difficult to define precisely. While many reports have noted the appearance of mycoses in patients being treated with multiple antibiotics there are several suggestions that they may not be related. Gruhn and Samson (37) noted that antibiotic therapy had been available for almost 10 years before a significant increase in secondary mycoses occurred. Bodey (9) found that antibiotics were no more frequently administered to those patients developing candidiasis than to a control group with similar primary diseases, but without candidiasis. In the present series, as in most with this type of patient population, 97 per cent of the patients received antibiotics within 30 days of their demise.

Anti-neoplastic agents were administered to 85 per cent of the patients in this series. Considerable clinical and experimental evidence suggests that anti-neoplastic agents probably predispose to fungus infections by inducing leukopenia (5, 37, 108) by immunosuppression (48), and by enhancing gastrointestinal portals of entry by direct tissue toxicity (17, 121).

TREATMENT

Fourteen patients received intravenous amphotericin B. All had serious diseases in addition to aspergillosis and this tended to obscure the results of antifungal therapy. The infrequency of Aspergillus in cultures from these patients interfered with any interpretation of culture conversion. In 11 patients, duration of therapy did not exceed 6 days, usually the last days of life. In other systemic mycoses it is rarely possible to see improvement in less than a week of amphotericin B. All things considered, it was no surprise that none of the eleven showed a definite response to therapy. Of the three patients who received treatment for more than six days, all showed on chest x-ray either stabilization or slight decrease in extent of pneumonia. One patient, who received 486 mg over the last 14 days of life, died of progressive cerebral aspergillosis despite slight improvement in her pulmonary aspergillosis. A second patient received 1,939 mg over 42 days and had no subsequent progression during the four months following therapy, at which time he died of E. coli septicemia. At autopsy, Aspergillus hyphae were readily demonstrated in the areas of unchanging pneumonia, but not elsewhere in the body. The third patient had a progressive pneumonia and had A. fumigatus in five of nine sputum cultures. She then received 1,346 mg amphotericin B intravenously over 32 days, over which interval no further extension of the pneumonia occurred. She died of Pseudomonas sepsis four days later. At autopsy, extensive Pseudomonas bronchopneumonia was present. A. fumigatus was cultured from the lung, but not demonstrated histologically.

Surgery was employed only in a case of endobronchial aspergillosis. Although removal of a bronchiectatic lobe resulted in temporary improvement, residual endobronchial disease was eventually fatal. This patient also received without success the experimental antibiotic X-5079C, supplied by Hoffmann-La Roche, Nutley, New Jersey, and later designated Saramycin.

The clinical experience reported here and in the literature is not sufficient to establish the place of any mode of therapy for widely invasive aspergillosis. Evaluations of antifungal antibiotics in experimental aspergillosis of mouse or rabbit have given conflicting results (26, 88, 95), perhaps in part because of deficiencies in the experimental model (24). Intravenous amphotericin B was used in our patients largely through lack of a reasonable alternative.

In less susceptible patients, certain therapeutic
maneuvers have occasionally appeared useful. These maneuvers, which have been reviewed well elsewhere (50, 77), have included the following: surgical excision of fungus ball of the lung, particularly when hemoptysis was marked (74); surgical excision of an abscess or granuloma, such as in the brain (16, 18); local instillation of antifungal antibiotic into an infected focus, such as the pleural space; and in endobronchial aspergillosis, inhalation or endobronchial lavage with antifungal antibiotics (78, 100). Iodides were once a popular remedy for aspergillosis, but the evidence of their beneficial effect, even in massive doses, remains very unconvincing (50).

CONCLUSION

Ninety-eight cases of aspergillosis have been seen at the NIH since 1953 when the Clinical Center opened. Eighty-six percent of these cases occurred in patients with lymphoreticular or hematopoietic malignancies and in this kind of population, the manifestations of the disease are often unusual. The hallmark of most of these cases is tissue and vascular invasion with thrombosis, infarction, and hemorrhage. In patients at high risk from fungal infections, the appearance of clinical manifestations of multiple thromboses should alert the physician to the possibility of aspergillosis. Clinical syndromes mimicking pulmonary embolism have been seen frequently in this series and strategic vascular invasion has produced the Budd-Chiari syndrome and renal papillary necrosis.

One of the most perplexing features of aspergillosis is the difficulty in culturing the fungus from antemortem specimens although it is easily grown from environmental sources. Only 34 per cent of the patients had Aspergillus cultured antemortem and only 9 per cent had multiple cultures positive. There was not a single patient in the series in whom Aspergillus was grown from a blood culture at any time although multiple blood cultures for fungus were obtained on most of the patients. In a single patient Aspergillus was grown from a bone marrow culture. It is frequently stated in discussions of Aspergillus that multiple cultures are necessary to implicate the fungus in a particular instance. While we have no disagreement with this in principle, it is obvious from the data presented here that the fungus will frequently not be suspected if this criteria is strictly applied. Certainly, the diagnosis can not be made from a single culture alone but, in a patient population predisposed to fungus infections, the presence of Aspergillus on a culture should alert the physician to the possibility of aspergillosis. Bodey (9) in reviewing fungal complications in 454 patients with acute leukemia, noted that Aspergillus was not found in the antemortem cultures of any patient in his series who did not have aspergillosis at autopsy. This suggests that, while in many circumstances a sputum culture growing Aspergillus may be treated more casually, it should be very critically evaluated in patients predisposed to invasive fungal infections.

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