Seminar on Mycotic Infections

Aspergillosis*

A Review and Report of Twelve Cases

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ASPERGILLOSIS is caused by several different species of aspergillus; it is characterized by granulomatous, inflammatory or necrotizing lesions which may involve any tissue of the body. The lung is the most common site of significant infection. Aspergillosis varies in severity from an incidental, saprophytic relationship to a fulminating, fatal infection. The disease is found in all races throughout the world. It is more common in adults than children and in males than females [*1*]. Excellent reviews of aspergillosis were presented in 1928 by Wahl and Erickson [*2*] and in 1952 by Hinson, Moon and Plummer [*3*]. In recent years there have been a number of case reports indicating a relationship between the use of antimicrobials and steroid hormones and aspergillus infection.

This report presents clinical and pathological data from twelve cases of aspergillosis seen at the authors' institutions in the past six years, eleven within the past four years. Eleven of these twelve cases were associated with the use of antibiotics or sulfonamides; other possible predisposing factors were debilitating illness, use of adrenocortical steroids and corticotropin, leukopenia, radiation, use of anti-neoplastic drugs and recent surgery. Cases of aspergillosis in the literature in which antibacterial chemotherapy or steroid therapy may have played a role are summarized in tabular form. A new classification of aspergillosis is proposed.

CASE REPORTS

CASE I. M. C., a seventy-four year old white man, was admitted to the Wadsworth Veterans Hospital in 1953 complaining of rectal pain. Two years previously he had had x-ray therapy for squamous cell carcinoma of the anus. Following preparation of the bowel with sulfasuxidine and oxytetracycline, a combined abdominoperineal resection was performed. The urethra was inadvertently entered during the difficult dissection, requiring an indwelling catheter. After one week of postoperative penicillin and streptomycin therapy chills and fever developed. An infiltration was present in the right lung. With sulfisoxazole therapy the temperature promptly became normal. A urethrocutaneous fistula developed shortly thereafter, with high daily fever. The patient's condition gradually deteriorated, and on the sixtieth postoperative day nausea, vomiting and diarrhea developed; he went into shock and died.

Autopsy showed necrotizing pseudomembranous colitis, acute fibrinous pericarditis, chronic prostatitis and seminal vesiculitis, and extensive bilateral bronchopneumonia with abscess cavities in the upper lobes. Microscopically, in addition to the acute bronchopneumonia and organized and organizing pneumonitis, the cavities were lined by fibrin and patchy granulation tissue with some Langhans-type giant cells. In the amorphous granular debris in the cavities there were stellate masses of large, irregular septate hyphae consistent with aspergillus, with focal invasion of the cavity wall. A small vessel showed invasion of the vascular wall. Cultures were not taken.

Comment: This example of invasive secondary aspergillosis was manifested as multiple small pulmonary abscesses in an acute bronchopneumonia. Predisposing factors included recent surgery for carcinoma of the anus and extensive antibacterial therapy with both antibiotics and sulfonamides.

CASE II. J. G., a sixty-two year old white man, entered the Wadsworth Veterans Hospital in 1954 for evaluation of an anemia intermittently present for ten years. There was a history of exposure to benzene, ethyl acetate and butyl acetate. The patient was pale,

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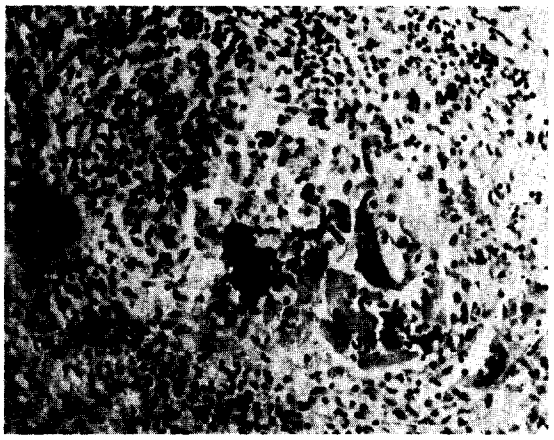

FIG. 1. Case III. Photomicrograph showing a small granuloma surrounding a group of fungi. Some hyphae can be seen in giant cells.

with many petechiae, retinal hemorrhages and inspiratory wheezes in both lungs. Laboratory studies showed a hemoglobin of 9.5 gm. per 100 ml., a leukocyte count of 1,800 per cu. mm. with 87 per cent lymphocytes and 119,000 platelets per cu. mm. The bone marrow was hypoplastic and erythrocyte survival time was one-third of normal. There was a right hilar mass. Following treatment on an outpatient basis with multiple transfusions, he was readmitted for a trial of cortisone therapy (300 mg. administered daily). After one week, fever and productive cough appeared which did not respond to penicillin or tetracycline. He died two days later. Staphylococcus aureus was cultured from the sputum.

Autopsy showed extensive patchy bronchopneumonia with consolidation and a pleomorphic epidermoid carcinoma of the right lung involving mediastinal nodes. In an area of acute necrotizing bronchitis there was a superimposed infection by organisms consistent with aspergillus. Elsewhere a chronic esophagitis and bronchitis due to candida was noted. The bone marrow showed erythroid hypoplasia, leukocytic maturation arrest and diminished megakaryocytes.

Comment: This case of localized secondary aspergillosis occurred in a patient with refractory anemia and profound leukopenia complicated by bronchogenic carcinoma. A fatal staphylococcal pneumonia developed during cortisone therapy, and antibiotics were used briefly.

CASE III. G. L., a thirty year old white man, was admitted to the Wadsworth Veterans Hospital in 1954 complaining of back and chest pains of one week's duration, and numbness and weakness of the lower extremities dating from a lumbar puncture two weeks prior to admission. Physical examination showed slight hepatosplenomegaly, hyperactive deep tendon reflexes in the lower extremities, bilateral ankle clonus and positive Babinski signs. Hematologic studies revealed the presence of acute myeloblastic leukemia. After a sudden increase in pain with flaccid hemiplegia at the level of T-6, surgical decompression revealed a hemorrhagic extradural mass infiltrated by leukemic cells. Paraplegia remained and an indwelling catheter was required. Recurrent infections of the urinary tract necessitated sulfonamide and antibiotic therapy. Cortisone and amethopterin treatment resulted in a transient leukemic remission. Terminally, bleeding developed and the patient died with evidence of bilateral bronchopneumonia three and a half months after admission.

Autopsy showed acute myelogenous leukemia, extensive hemorrhagic and gangrenous cystitis, prostatitis and epididymitis, chronic pyelonephritis and acute hemorrhagic bronchopneumonia. Organisms consistent with aspergillus were present in small granulomas in the lungs within multinucleated giant cells. (Fig. 1.)

Comment: This is an example of localized secondary aspergillosis in the form of pulmonary granulomas. Predisposing factors included acute leukemia and bronchopneumonia, with prolonged treatment incorporating cortisone, sulfonamides, antibiotics, amethopterin and surgery.

CASE IV. J. H., a seventy-eight year old white man, was admitted to the Wadsworth Veterans Hospital in 1955 with an intertrochanteric fracture of the right hip. An open reduction with internal fixation was followed by an unexplained fever which responded gradually to the administration of tetracycline, penicillin and streptomycin. (Fig. 2.) One month later a volvulus required resection of a large segment of gangrenous bowel. A bilateral staphylococcal parotitis occurred postoperatively which was treated with x-ray, antibiotics and surgical drainage. However, a staphylococcic bacteremia followed. This responded initially to the administration of tetracycline, ACTH and hydrocortisone; a relapse was treated with other antibiotics. Four days before the patient's death dehiscence of the abdominal wound with evisceration occurred, which was repaired under local anesthesia. His condition deteriorated rapidly and he died suddenly on the sixtieth hospital day. Three blood cultures on the last day contained coagulase-positive staphylococci.

The chief autopsy findings were bilateral necrotizing parotitis, bilateral acute bronchopneumonia, cystitis and arteriosclerotic heart disease. An abscess in the right lung, 1.5 cm. in size, was lined with fibrin and acute inflammatory cells, and contained a mass of branching hyphae consistent with aspergillus. Some

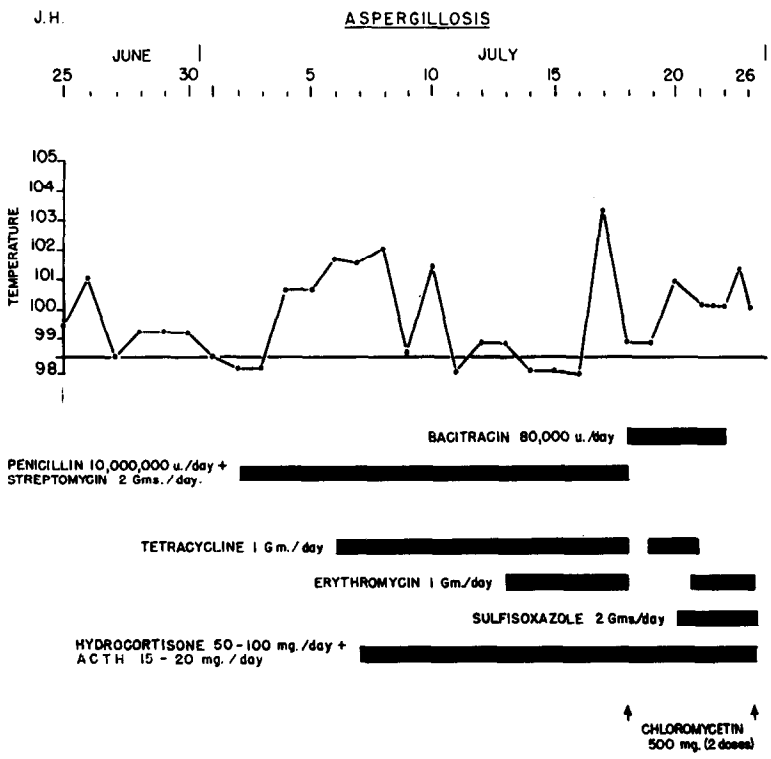

FIG. 2. The clinical course and therapy in Case IV.

filaments were noted to invade the wall of a blood vessel.

Comment: This patient had invasive secondary aspergillosis in the form of a small mycetoma with involvement of the blood vessels. Predisposing factors included debility from multiple causes, surgery and prolonged treatment with ACTH, hydrocortisone, a sulfonamide and several antibiotics.

CASE V. J. K., a thirty-five year old man with a brief history of fever and weight loss, was admitted to the Wadsworth Veterans Hospital in 1953 with a diagnosis of chronic myelogenous leukemia. He had generalized lymphadenopathy and hepatosplenomegaly. The hemoglobin was 9.5 gm. per cent, the leukocyte count was 270,000 per cu. mm., predominantly neutrophils. Radiation of the spleen produced improvement. During the following two years, relapses were treated with additional radiation and the administration of Myleran.® On his last admission in 1955 he was anemic and febrile. Radiation therapy resulted in a leukopenia of 500 cells per cu. mm. with 65 per cent basophils; this lasted four weeks, gradually changing to a leucocytosis prior to death. Febrile episodes did not respond to long courses of tetracycline and erythromycin. Further therapy with Myleran and cortisone failed and the patient died of bronchopneumonia.

Diffuse myelofibrosis was present at autopsy, in addition to granulocytic leukemia. There was an organizing pneumonitis and a focal necrotizing pneumonia which contained aspergilli. An esophageal ulceration was not sectioned and may have represented either candida or aspergillus infection.

Comment: This case illustrates the occurrence of invasive secondary pulmonary aspergillosis in a patient predisposed by chronic leukemia, pneumonitis, agranulocytosis and therapy with antibiotics and cortisone. Radiation and Myleran therapy also may have played a role.

CASE VI. A. R., a fifty-eight year old white man, was admitted to the Wadsworth Veterans Hospital in 1955 with severe headaches and vomiting. He previously had had bilateral iliac vein thrombosis with multiple pulmonary emboli. Evidence of a left frontotemporal lesion was present and, at craniotomy, a metastatic adenocarcinoma of the dura was found; decompression was carried out. Further studies were indicative of a primary bronchogenic carcinoma of the left lung. The patient's condition gradually de-

FIG. 3. Case VII. Photomicrograph showing aspergillus with recognizable conidiophores within an abscess cavity. Note the invasion of the abscess wall.

teriorated and he became confused and semicomatose; he died seven months after his last admission. Several courses of penicillin, alone or combined with streptomycin, were given during the course of his illness.

A left bronchiolar carcinoma with widespread metastases was found at autopsy. There were multiple old pulmonary emboli with infarctions, emphysema, bronchiectasis and organizing pneumonitis. A loculated, thin walled, pulmonary abscess cavity, 7.0 cm. in size, located at the margin of the carcinoma, contained a large clump of matted septate hyphae, consistent morphologically with aspergillus, and also many small masses of cocci.

Comment: This man with chronic pulmonary disease and bronchiolar carcinoma had received penicillin and streptomycin before death. Autopsy revealed localized secondary pulmonary aspergillosis in the form of an abscess cavity in close proximity to the carcinoma.

CASE VII. H. M., a fifty-eight year old white man, was initially admitted to the UCLA Medical Center in 1957 with fever and malaise. Five years previously he had had a left pneumonectomy for adenocarcinoma. A diagnosis of Hodgkin's disease had been made three years previously on the basis of a cervical lymph node biopsy. He had generalized lymphadenopathy, hepatomegaly, a hemoglobin of 8.7 gm. per cent and moderate neutropenia. He responded initially to the administration of nitrogen mustard, but subsequently fever, anemia, maxillary sinusitis, diarrhea and periods of severe neutropenia developed. On his second admission prednisolone therapy was begun and this was continued until his death. Intensive tetracycline treatment was given; erythromycin and nystatin also were used during the last two weeks of life. He also received Leukeran® for three weeks.

At autopsy the left lung was absent. The right lung contained many small gray-white nodules in the upper lobe and numerous cyst-like cavities lined by a gray-green powdery substance resembling, in all respects, the subsequent growth of fungi on laboratory media. Microscopically, the nodules and cavity walls contained abundant hyphae; many conidiophores recognizable as aspergillus lined the cavities. (Fig. 3.) The organism was identified on culture as A. fumigatus.

Comment: This man showed invasive secondary aspergillosis (bronchopneumonia) with many small cavities containing A. fumigatus. The recognition of typical conidiophores in tissue sections is uncommon. Predisposing factors were Hodgkin's disease and leukopenia, with prednisolone, Leukeran and antibiotic therapy.

CASE VIII. W. E., a sixty-eight year old man, was admitted to the UCLA Medical Center in 1957 with a two-week history of pain in the left side of the chest, cough and fever which progressed despite penicillin therapy. A past history of hypertensive cardiovascular disease, chronic congestive failure and emphysema was elicited. On admission, there was evidence of consolidation of the upper lobe of the left lung, and a leukocytosis with a shift to the left. Sputum cultures yielded coagulase-positive Staph. aureus, a klebsiella-aerobacter species and Escherichia coli. His hospital course is illustrated in Figure 4. Selected chest roentgenograms are illustrated in Figure 5. Despite intensive antibiotic therapy, a large cavity appeared in the upper lobe of the left lung. During several months of antibiotic and sulfonamide treatment, the cavity became smaller and was gradually filled with an enlarging mass. Bronchoscopy following a sudden hemoptysis disclosed no bleeding point, but washings yielded A. fumigatus on culture. A left upper lobectomy was performed; this was complicated by severe blood loss and contamination of the pleural space by the friable unattached intracavitary mass. The patient's postoperative course was marked by episodes of hypotension and anoxia. He was improving gradually when he died suddenly two weeks later.

The resected specimen consisted of necrotic lung with a large abscess cavity which contained a free mass of dense filamentous septate hyphae. Cultures of this material yielded A. fumigatus. At autopsy no further evidence of aspergillosis was noted. There was an extensive old posterior myocardial infarction mild pulmonary edema and emphysema.

Comment: This patient had acute necrotizing bacterial pneumonia with abscess formation.

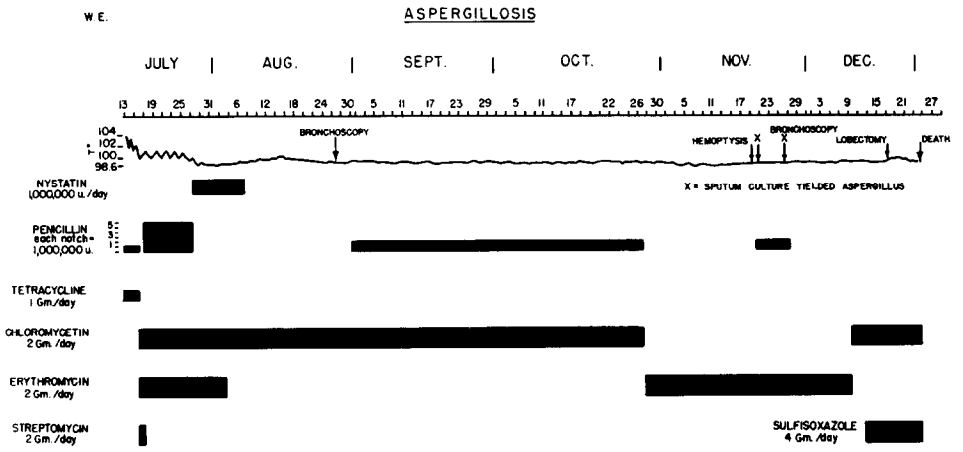

FIG. 4. The clinical course and therapy in Case VIII.

Long-term antibiotic and sulfonamide therapy was associated with secondary infection by A. fumigatus in the form of an intracavitary mycetoma.

CASE IX. H. V., a thirty-three year old woman, entered another hospital in 1958 following the acute onset of chills and fever. Twenty-four hours after expelling a macerated fetus she was found to be in shock and was treated with norepinephrine and dilatation and curettage. A blood transfusion, which had been started at the same time, was stopped after 200 ml. had been infused because of an apparent reaction. Following these procedures she became markedly oliguric and was transferred to the UCLA Medical Center. On examination, she was acutely ill and had slight icterus, bilateral flank tenderness and a slightly enlarged, tender uterus with a bloody discharge. She had a hemoglobin of 11.4 gm. per 100 ml., a leukocyte count of 45,250 per cu. mm. and a blood urea nitrogen of 36 mg. per 100 ml. She remained oliguric, with increasing azotemia and acidosis. The

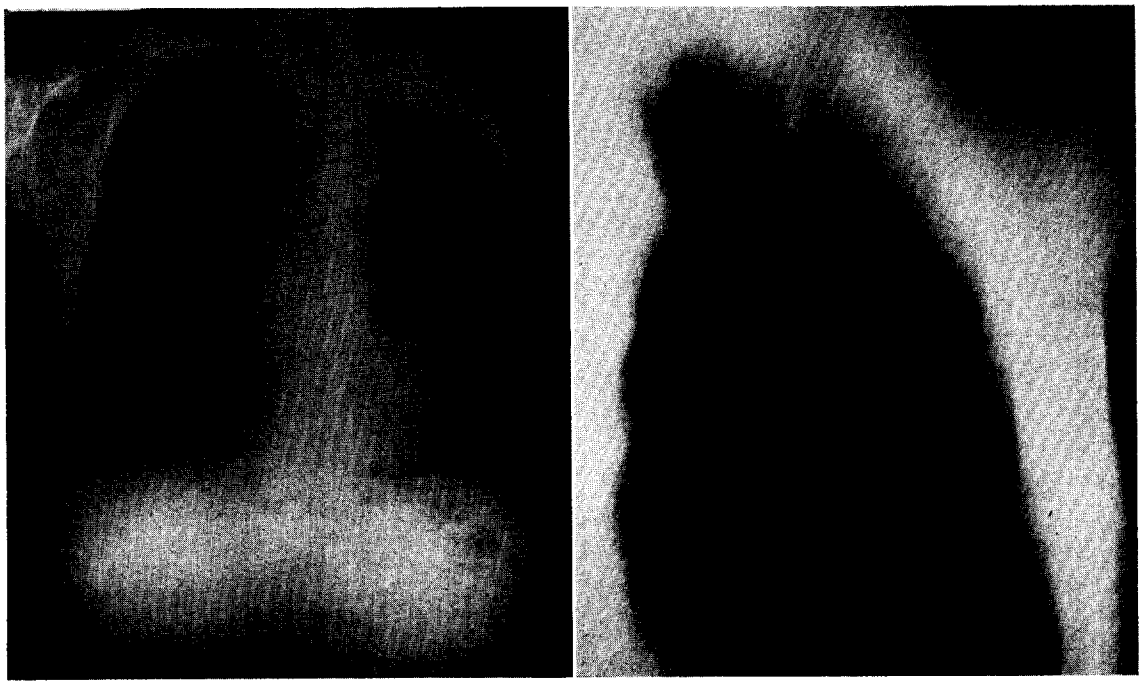

FIG. 5. Case VIII. Two roentgenograms show a mycetoma in the upper lobe of the left lung; a detailed view of this is shown in the planigram which reveals the crescentic radiolucency surrounding the fungus ball.

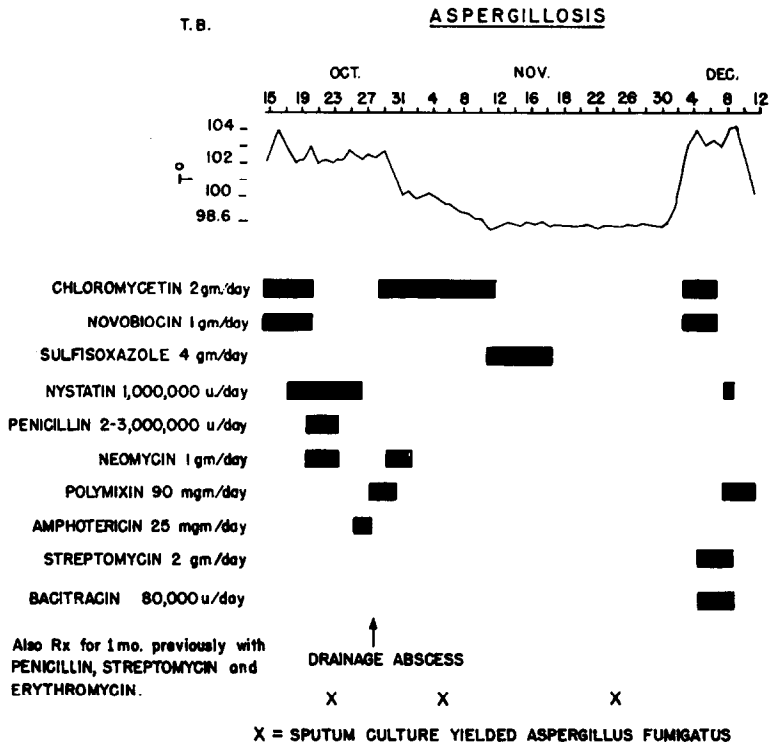

FIG. 6. The clinical course and therapy in Case x.

course was transiently improved by treatment with the artificial kidney and two peritoneal dialyses. She was intermittently febrile throughout her hospital course and was treated with intravenous chloramphenicol, erythromycin and penicillin. She died on the fifty-first hospital day.

Necropsy revealed a well developed, well nourished woman. There were many cutaneous petechiae. The lungs contained numerous grayish white nodules up to 4 cm. in diameter. Small similar gray areas were found in the myocardium. There were many small hemorrhagic and necrotic foci in the brain. The endometrial surface of the uterus was necrotic. Sections of the heart, lungs, spleen, brain and uterus showed large numbers of filamentous septate hyphae in areas of acute inflammation, necrosis and hemorrhage. Numerous vessels in these foci showed intraluminal hyphae invading the vascular walls and surrounding tissue. A. fumigatus was isolated from the uterus, brain and lung tissue.

Comment: This young woman had a septic abortion and a transfusion reaction followed by renal failure, which was unsuccessfully treated by dialysis. Death occurred from sepsis, and necropsy revealed A. fumigatus in the lung, uterus and brain. Hyphae were also seen in the heart and spleen. It is probable that the fungus infection occurred after the initial abortion, as slides of the initial curettings were reviewed and no fungus elements were seen. This is an example of disseminated, secondary aspergillosis.

CASE X. T. B., a forty-seven year old physician with chronic lymphatic leukemia was admitted to the UCLA Medical Center following an upper respiratory infection of one month's duration which had proved refractory to the administration of a variety of antibiotics. On examination he was febrile, with moderate dyspnea and cough. There were rales at both bases and hepatosplenomegaly. He had a hemoglobin of 12.9 gm. per 100 ml. and a leukocyte count of 220,000 per cu. mm. with 99 per cent lymphocytes. Proteus mirabilis and Streptococcus zymogenes were cultured from the sputum. The patient had a fluctuating course, as shown in Figure 6. An area of infiltration in the left lung did not respond to antibiotic treatment. A. fumigatus was cultured from the sputum on three separate occasions. His blood picture improved on Leukeran therapy but he suddenly went into shock and died on the fifty-seventh hospital day.

Necropsy revealed chronic lymphatic leukemia involving the spleen, liver, lymph nodes and bone marrow, with marked hepatosplenomegaly. In an area of organizing pneumonitis in the upper lobe

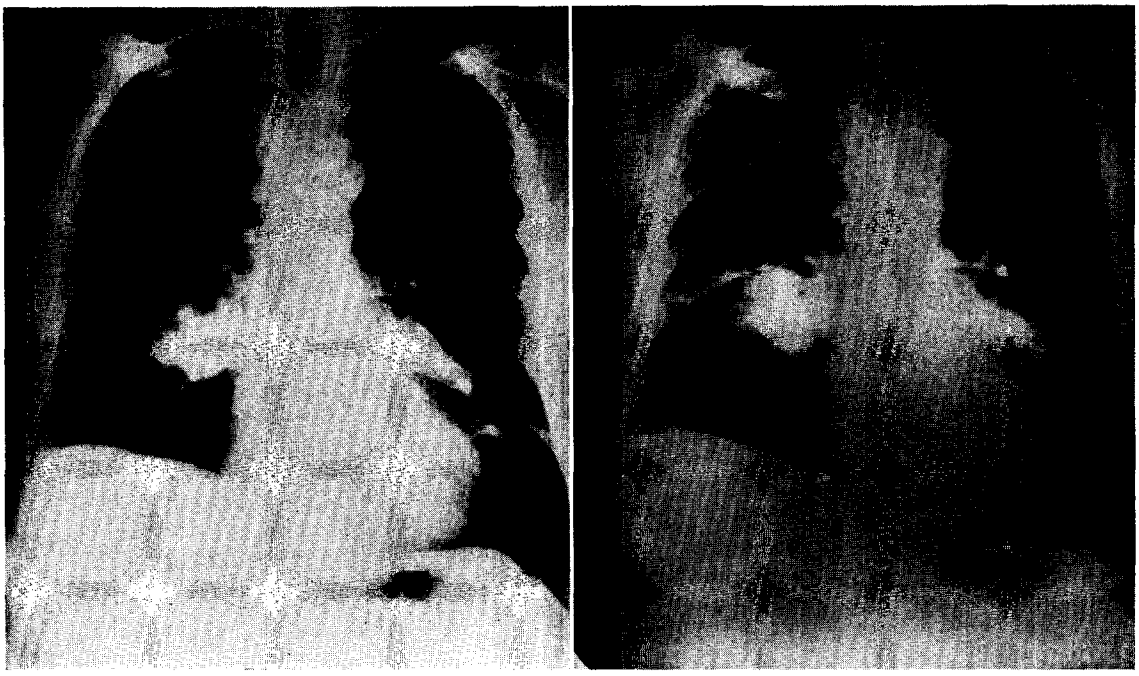

FIG. 7. Case XII. Posteroanterior views of the chest show parahilar infiltrate bilaterally and a small infiltrate in the right first anterior interspace. Progression is shown between the films of November 13, 1958 and January 15, 1959.

of the left lung there was a small cystic space lined by necrotic tissue and small granulomatous areas with giant cells. Septate hyphal fragments were present in several giant cells. Cultures of several lung fragments failed to grow fungi.

Comment: In this patient with chronic lymphatic leukemia an area of superimposed pulmonary infection contained organisms histologically consistent with aspergillus. Although autopsy cultures were negative, A. fumigatus had been cultivated on several occasions from sputum. He had received intensive antibacterial therapy over long periods and had been treated with Leukeran. This is an example of localized secondary aspergillosis.

In the original pathological study of this patient the aspergilli were not seen. We had originally intended using this patient to illustrate the difficulties in establishing a diagnosis with only positive cultures as evidence. When the lung sections were reviewed with this in mind the organisms were seen. This case also demonstrates how positive histological evidence may be overlooked.

CASE XI. F. K., a thirty-nine year old man, had had severe pneumonia in 1953 followed by a persistent productive cough and progressive dyspnea. Since his original illness he had been hospitalized ten times for pneumonia and chronic lung disease. He was admitted to the UCLA Medical Center in 1958. Physical examination revealed a dyspneic and orthopneic man with a cough productive of yellowish green sputum. There was cyanosis of the lips and mucous membranes, venous distention, edema of the ankles and marked clubbing. Breath sounds were prolonged, with scattered rales throughout the lung fields. Laboratory examination revealed a hemoglobin of 19.1 gm. per 100 ml., leukocytes 6,100 per cu. mm. and a heavy growth of Pseudomonas aeruginosa in the sputum. Pulmonary function data showed a combined restrictive and obstructive ventilatory insufficiency, with an arterial oxygen saturation of 74 per cent. A chest roentgenogram showed far advanced pulmonary fibrosis. The electrocardiogram was compatible with chronic cor pulmonale.

The patient was treated with antibiotics, drainage, digitalis and diuretics. Prednisolone was added after one week. Two weeks later, after initial improvement in his cough and sputum production, his symptoms again became pronounced, and A. fumigatus was cultured from his sputum on two occasions. A six-day course of amphotericin B was given, without change in his clinical status. Three additional cultures, one before and two after amphotericin therapy, were overgrown by pseudomonas. The patient was discharged to be followed up in the Outpatient Department. Five months later the patient entered another hospital in cardiopulmonary failure and died.

TABLE I
CLASSIFICATION OF ASPERGILLOSIS

I. Primary aspergillosis—in the absence of underlying disease or other predisposing factors
  A. Localized
    1. Abscesses or granulomas (including mycetoma)
    2. Allergic—bronchitis with asthma and/or eosinophilia
  B. Invasive
    1. Acute—usually bronchopneumonic
    2. Chronic granulomatous disease—usually pulmonary
  C. Disseminated—widespread abscesses or granulomas
II. Secondary aspergillosis—associated with a local process, debilitating illness, impaired host defenses, or complicating antibacterial and/or steroid hormone therapy
  A. Localized—usually pulmonary
    1. Saprophytic relationship
      a. Abscess (or mycetoma)
      b. Focal infiltration
    2. Chronic, low grade infection or granuloma
  B. Invasive—usually bronchopneumonic
  C. Disseminated
    1. Endocarditis
    2. Multiple abscesses or granulomas (in the absence of endocarditis)

Multiple sections of lung obtained at autopsy were reviewed and showed severe bronchiectasis and pulmonary fibrosis with organized pneumonitis and superimposed acute bronchopneumonia and recent hemorrhages. No aspergilli were identified and cultures were not made at autopsy.

Comment: Antibiotics and adrenocortical steroids were given to this man for bronchiectasis and pulmonary fibrosis, and were associated with the emergence of A. fumigatus in his sputum. Amphotericin B was given empirically for a short period, but its effects on the aspergillus could not be adequately evaluated.

This case demonstrates the difficulty in making a definitive diagnosis of pulmonary aspergillosis. The presence of aspergillus in the sputum on two occasions, in the presence of bronchiectasis with antibiotic and steroid therapy, seemed to offer sufficient evidence of secondary fungus infection. However, the failure to find the organisms in autopsy material leaves the diagnosis in doubt.

CASE XII. B. B., a sixty-seven year old white man, was admitted to Wadsworth Veterans Hospital in 1958 complaining of cough, night sweats and a 25-pound weight loss of three months' duration. Two years previously a routine annual chest roentgenogram was reported to him as showing "spots on the lung." He remained asymptomatic until the present illness. The patient worked around grains and grain milling dust for many years and raised pheasants for two years, feeding the birds from sacks of mixed grain. The patient had received no steroid or antibacterial therapy.

Physical examination revealed no abnormalities except for evidence of recent weight loss. The hematologic examination was within normal limits except for a moderate anemia and a sedimentation rate of 30 mm. per hour. Chest roentgenograms showed densities in the right hilum extending into the mid-lung field, the lower left lung field and the right first interspace. (Fig. 7.) The initial impression was bronchogenic carcinoma with metastasis. Review of previous chest films showed the three pulmonary lesions noted on this admission to have been present two years before. On bronchoscopy, a small soft tissue mass was noted projecting from the lateral wall of the lower right lobe bronchus. Biopsy of this mass revealed hyphal elements consistent with aspergillus and a culture was identified as A. flavus.

The patient has received 2 gm. of griseofulvin* orally per day for four weeks without evidence of improvement.

Comment: This is an example of primary invasive aspergillosis of the chronic granulomatus variety occurring in a patient exposed to grain and grain dust, who had no underlying disease and who had not received steroids or antibiotics.

COMMENTS

Classification. A new classification of aspergillosis is presented in Table I. The disease has been divided into a primary variety which arises without the presence of an antecedent disorder and a secondary type which is always associated with an underlying local process, debilitating illness, or antibiotic or steroid therapy. Both of these varieties have been further subdivided into localized, invasive or disseminated, depending upon the type and extent of the inflammatory process.

Primary Aspergillosis. Localized, primary aspergillosis is seen primarily in the lung in the form of an abscess, mycetoma [*4*] or granuloma. However, other sites may be involved with similar, non-invasive processes; these include the external ear, skin, nails, nasal sinuses, eye, orbit, nasopharynx, vagina, urethra, pleural cavity, bronchial tree and brain [*1,3,5–8*].

Also included as localized, primary aspergillosis is the allergic variety of Hinson, Moon and Plummer [*3*]. The lesions in this instance are confined to the bronchial tree, at times with the

* Kindly supplied by Dr. G. Hildick-Smith of Johnson and Johnson, Inc., New Brunswick, New Jersey.

clinical picture of Loeffler's syndrome. The basic pathophysiology apparently is sensitization to the fungus, leading to production of an exudate in the bronchial lumen consisting of mycelium, mucus, fibrin, eosinophils, Curschmann's spirals and Charcot-Leyden crystals. This mass leads to bronchial blockage and subsequent collapse or consolidation. Typically there is a marked peripheral eosinophilia, and there may be asthma. One of the patients described by Hinson, Moon and Plummer [*3*] died in status asthmaticus. There are characteristically recurrent episodes of fever, severe cough and purulent sputum containing white or brownish flecks (of mycelium) just visible to the naked eye. Plugs may be expectorated, with subsequent improvement clinically and radiologically (suggesting unblocking of a bronchus). X-ray findings often persist for weeks; the appearance of new shadows in different locations in association with new episodes of clinical illness is common.

Invasive, primary aspergillosis usually takes the form of a pneumonia, with or without abscess formation [*9*], which may be fulminating and fatal [*10*]. Besides the lung, the brain may be involved by extension from the orbit [*11*] and sinuses [*12*].

In addition to acute pneumonic aspergillosis, a chronic granulomatous lung disease occurs which closely simulates pulmonary tuberculosis. This variety is usually an occupational illness of workers exposed to cereal grains. Symptoms include cough, hemoptysis, pleurisy, fever and weight loss. Patients may cough up black or dark granules resembling soot or coal dust which actually represent dislodged conidia [*13*]. Healing may lead to progressive fibrosis [*14*]. One of our patients (Case XII) belongs in this category.

Disseminated, primary aspergillosis apparently is rare. Involvement of the lung, tongue, palate and mesenteric nodes was reported by Wheaton [*15*]. Peet described a patient with pulmonary involvement for seven years and eventual extensive spread to the cerebellum [*16*]. Hertzog, Smith and Goblin [*10*] cited a personal communication from Doub discussing a family of five with diffuse miliary lesions throughout both lungs.

Secondary Aspergillosis. Localized secondary aspergillosis is usually found in the lung, and is associated with some previous disease of local tissue, such as pneumonia (Cases I, II, III, IV, V, VIII and X), lung abscess (Case VIII), carcinoma of the lung (Case VI), pulmonary infarct [*3*], tuberculosis [*17,18*], pneumonoconiosis [*19*], lung cyst [*3,20*], bronchiectasis (Case XI), asbestosis [*3*] or trauma [*21*]. In addition to occurrence in the lung, localized aspergillosis may be present elsewhere, as in the feet [*1*], bowel mucosa [*22*], spinal cord [*23*] and pleural cavity [*21,24*].

Two varieties of localized secondary aspergillosis are recognized; one is a saprophytic process such as a mycetoma or focal growth (Cases II, VIII and possibly XI), and the other a chronic low grade infection, abscess or granulomatous process (Cases III, VI and X). Both types of infection may have serious implications if critically located. Hemoptysis may be found with either mycetomas or solid lesions, and occasionally may be massive [*25*] and affected by position [*26*]. Patients with mycetomas may have a chronic cough; Hemphill [*27*] describes a patient with severe paroxysmal cough apparently precipitated by the fungal mass acting as a ball-valve over a bronchial communication. Mycetomas may be entirely free within the surrounding cavity (Case VIII); this may be established radiologically by roentgenograms taken with the body in various positions.

Secondary aspergillosis may also be invasive in nature (Cases I, IV, V and VII). This type usually presents as a pneumonic process (and may be superimposed on a bacterial pneumonitis) and may lead to multiple abscesses (Case VII). Tissues other than the lung also may be invaded.

The final category of secondary aspergillosis is the generalized or disseminated variety which can be further subdivided into types associated with endocarditis and disseminated infection in the absence of endocarditis.

There are three cases of endocarditis due to aspergillus reported in the literature [*28–30*]. None of the three patients had pre-existing valvular damage; the lesions produced by the aspergilli were quite destructive and involved both sides of the heart. The case cited by Welsh and Buchness [*28*] was extraordinary in that three different species of aspergillus were recovered from different lesions.

Disseminated secondary aspergillosis unassociated with endocarditis has been reported by a number of authors [*31–39*]. In these cases the following tissues of the body were involved in at least one of the patients: lung, pleura, mediastinum, brain, meninges, spleen, liver, kidney, heart, pericardium, aorta, smaller vessels, thyroid, duodenum, bones, lymph nodes and

skin. In our Case IX the uterus also was involved. Generalized aspergillosis results from hematogenous and possibly lymphogenous spread. It is surprising that dissemination is not more common since the organism characteristically invades blood vessels producing vascular necrosis. Histologically the lesions are either abscesses or granulomas. The symptoms and signs depend primarily on the size and site of lesions.

Predisposing Factors. Primary aspergillosis occurs following occupational or other exposure to the fungus [*1–3*]. Aspergillosis is encountered in bird fanciers (it is an important disease in many species of birds), hair sorters, millers, threshers and others who inhale dust or grain particles, and in farmers and other workers who are constantly exposed to any form of dry or powdered vegetable matter. Aspergillus spores may be present in farm homes, stables and barns. Frequent reference has been made to the high incidence of chronic, progressive disease in the pigeon crammers (mouth-to-mouth feeding) of Paris and in hair sorters who are exposed through the use of contaminated rye flour in removing grease from hair. Other areas such as the external ear, the spinal cord and the vagina may be sites of primary infection.

Predisposing factors are of paramount importance in secondary aspergillosis. In addition to a suitable portal of entry, usually the lung or upper respiratory passages, a local lesion is commonly found in the form of an area of inflammation, abscess or bronchiectatic cavity. The vagina and infected uterus were the likely portal of entry in our Case IX. Zimmerman [*38*] has documented hematogenous spread to the lung from secondary invasion of a gastric ulcer. Of increasing importance is the presence of an underlying debilitating illness and iatrogenic factors conducive to fungus infection.

Table II is a summary of the twelve cases herein reported, with emphasis on predisposing factors. Seven of the eleven patients with secondary aspergillosis had carcinoma, leukemia or Hodgkin's disease. Seven patients also had either bacterial pneumonia or pneumonitis of undetermined etiology as an underlying lung disease. Three patients with secondary aspergillosis had had recent surgery, three had chronic pulmonary disease, two had chronic congestive heart failure, and two had serious infections other than pneumonia. Three of the eleven patients had marked leukopenia, two with granulocytopenia. Six of these eleven patients with secondary aspergillosis had received adrenocortical steroids (usually for long periods) and one had also received corticotropin.

The association of mycotic infections with the use of antibiotics and adrenal cortical hormones is well discussed by Torack [*40*] and Zimmerman [*28,38*]. Although we believe that steroids definitely predispose the host to secondary infection, we were unable to demonstrate a relationship between the dose and duration of steroid administration and the severity of secondary aspergillosis. However, Mankowski [*41*] has shown that cortisone-treated mice had a much more rapid death than control animals in experimental aspergillosis. This author also refers to an interesting report by Devillers and Revon which mentioned a woman with chronic membranous aspergillus bronchitis who experienced distinct flareups of her disease a few days prior to each menstruation; this suggests that other hormones also may be important.

Four patients received other "anti-neoplastic" therapy; included was radiation to the spleen, administration of Myleran,® Leukeran® and amethopterin. The possibility that antimetabolites may enhance other types of infections has been discussed by other authors [*42,43*]. Ten of our patients had received extended courses of multiple antibiotics; the other patient with secondary aspergillosis received small amounts of two antibiotics.

Table III summarizes twenty-four cases of aspergillosis from the literature in which the use of antibiotics and/or steroid hormones may have played a role. All patients had received antibiotics and/or sulfonamides. Seven of these twenty-four patients received adrenocortical steroids and/or corticotropin, two received radiation, one nitrogen mustard, and one urethane. As in our series, the presence of malignant or other debilitating diseases or injuries, leukopenia or granulocytopenia, pneumonitis, other infections and underlying pulmonary disease was noted frequently. Zimmerman [*38*] discusses these predisposing conditions and stresses the importance of local lesions as a portal of entry. Other possible factors predisposing to aspergillosis are splenectomy [*30,47*] (one in our series), prematurity [*35*], infancy [*31,38*], old age (our series) and possibly diabetes.

Pathology. In the lung, aspergillosis is most frequently associated with necrosis (probably attributable to both vascular obstruction and

toxin production by the organism), accompanied by acute or chronic inflammatory cellular infiltration [*48*]. Other changes include small granulomatous masses with Langhans-type giant cells (Fig. 1), areas of gray hepatization surrounded by a zone of emphysema, and cavity

TABLE II

SUMMARY OF CASES OF ASPERGILLOSIS BEING REPORTED

Case No.	Age (yr.), Sex	Underlying Disease(s)	Leukopenia?	Steroids (daily dose and duration)	Anti-Neoplastic Therapy	Antibiotics (daily dose and duration)	Type of Aspergillosis
I.	74, M	Squamous carcinoma, anus; recent abdominoperineal resection; bronchopneumonia	No	None	None	Sulfasuxidine, 8 gm. for 12 days; oxytetracycline, 1 gm. for 4 days; penicillin, 600,000 units for 6 days; streptomycin 1 gm. for 6 days; sulfisoxazole, 4 gm. for 9 days	Multiple pulmonary abscesses both upper lobes; up to 1 cm. in diameter; **invasive secondary aspergillosis**
II	62, M	Epidermoid carcinoma, lung; pancytopenia, etiology undetermined; hemolytic anemia; pneumonia, staphylococcic	900–1,800 white cells/cu. mm. 75–87% lymphocytes	Cortisone, 300 mg. for 9 days	None	Penicillin, 1.2 million units/day for 2 days; tetracycline, 1 gm. for 6 days	Necrotizing bronchitis, with superimposed aspergillus infection; **localized secondary aspergillosis**
III	30, M	Acute myelogenous leukemia; pyelonephritis; recent laminectomy; pneumonitis	No	Cortisone, 300 mg. for 23 days; 200 mg. for 8 days; 150 mg. for 17 days	Amethopterin	Penicillin, 3,000,000 units for 5 days; 1,200,000 units for 28 days; streptomycin, 1 gm. for 5 days; sulfisuxazole 4 gm. for 23 days; nitrofurantoin 400 mg. for 38 days; tetracycline, 300 mg. intramuscularly for 30 days; 2 gm. orally for 11 days	Two small granulomatous pulmonary nodules; **localized secondary aspergillosis**
IV	78, M	Fracture, right hip; surgical reduction of fracture; volvulus; bowel resection; surgical parotitis; staphylococcal bacteremia; aspiration pneumonia; chronic congestive heart failure	No	Hydrocortisone, 50–100 mg. for 19 days; ACTH, 15–20 mg. for 19 days	None	Penicillin, 10,000,000 units for 22 days; streptomycin, 2 gm. for 28 days; tetracycline, 1 gm. for 11 days; erythromycin, 1 gm. for 11 days; chloromycetin, 1 gm. for 2 days; bacitracin, 80,000 units for 6 days; sulfisoxazole, 2 gm. for 6 days	1.5 cm. cavity upper lobe of right lung; contains fungus ball; blood vessel invasion; **invasive secondary aspergillosis**

TABLE II (*Continued*)

SUMMARY OF CASES OF ASPERGILLOSIS BEING REPORTED

Case No.	Age (yr.), Sex	Underlying Disease(s)	Leukopenia?	Steroids (daily dose and duration)	Anti-Neoplastic Therapy	Antibiotics (daily dose and duration)	Type of Aspergillosis
V	35, M	Chronic myelogenous leukemia; Pneumonitis	Yes—2 mo. before death (following radiation); white blood cells decreased to 500 and then ran between 1,400 and 2,800 for 1 mo. before returning to normal and higher ranges (approximately 15% neutrophils during period of leukopenia)	Cortisone 75–225 mg. for 11 days	Radiation to spleen; Myleran	Tetracycline, 2 gm. for 45 days; erythromycin, 800 mg. for 11 days; 400 mg. for 4 days	Necrotizing pneumonitis; **invasive secondary aspergillosis**
VI	58, M	Bronchiolar carcinoma with widespread metastases; multiple old pulmonary infarcts (embolic); emphysema, bronchiectasis; cor pulmonale	No	None	None	Penicillin, 600,000 units for 14 days; 900,000 units for 28 days; streptomycin, 0.5 gm. for 16 days	Somewhat loculated 7.0 cm. abscess cavity in upper lobe of left lung at margin of carcinoma; **localized secondary aspergillosis**
VII	58, M	Hodgkin's disease	725–4,000 white cells/cu. mm. 80–90% polymorphonuclear leukocytes	Prednisolone 30–60 mg. for 78 days	Leukeran	Tetracycline, 2 gm. for 28 days; erythromycin, 1.5 gm. for 13 days; nystatin, 1,500,000 units for 13 days	Pneumonitis and numerous small pulmonary cavities with mycelium and fructification characteristic of A. fumigatus on culture; **invasive, secondary aspergillosis**
VIII	68, M	Bacterial pneumonia and lung abscess; congestive failure (hypertensive cardiovascular disease); emphysema	No	None	None	Penicillin, 1,000,000 units for 65 days; 5,000,000 units for 9 days; tetracycline, 1 gm. for 3 days; chloromycetin, 2 gm. for 117 days; erythromycin, 2 gm. for 62 days; streptomycin, 2 gm. for 2 days; sulfisoxazole, 4 gm. for 13 days; nystatin, 1,000,000 units for 11 days	Mycetoma; A. fumigatus found twice on culture; **localized secondary aspergillosis**

TABLE II (*Continued*)

SUMMARY OF CASES OF ASPERGILLOSIS BEING REPORTED

Case No.	Age (yr.), Sex	Underlying Disease(s)	Leukopenia?	Steroids (daily dose and duration)	Anti-Neoplastic Therapy	Antibiotics (daily dose and duration)	Type of Aspergillosis
IX	33, F	Septic abortion; shock, acute renal failure	No	None	None	Penicillin, 3.6–12.5 million units for 26 days; chloromycetin, 0.5–1.0 gm. for 21 days; erythromycin, 1.5 gm. for 5 days	Widely disseminated with involvement of uterus, heart, lungs, spleen, and brain; A. fumigatus on culture; **disseminated secondary aspergillosis**
X	47, M	Chronic lymphatic leukemia; pneumonitis, etiology undetermined	No	None	Leukeran	Penicillin, streptomycin and erythromycin for 1 mo. prior to admission; chloromycetin, 2 gm. for 24 days; novobiocin, 1 gm. for 10 days; sulfisoxazole, 4 gm. for 6 days; penicillin, 2–3 million units for 4 days; neomycin, 1 gm. for 8 days; polymyxin 90 mg. for 7 days; streptomycin, 2 gm. for 5 days; bacitracin, 80,000 units for 5 days; nystatin, 1,000,000 units for 10 days; amphotericin, 25 mg. for 3 days	Small abscesses and granulomas, upper lobe of left lung containing mycelium consistent with aspergillus A. fumigatus previously grown out of sputum 3 times; **localized secondary aspergillosis**
XI	39, M	Chronic pulmonary disease with bronchiectasis and pulmonary fibrosis; cor pulmonale	No	Prednisolone 15–20 mg. for 57 days	None	Oxytetracycline, 2 gm. for 36 days; penicillin, 1,200,000 units for 38 days; streptomycin, 1 gm. for 7 days; amphotericin, 25–50 mg. for 6 days	Localized bronchial infection?, A. fumigatus found on sputum culture two times; **localized secondary aspergillosis**
XII	67, M	None	No	None	None	None prior to onset, (nitrofurantoin subsequently)	Chronic granulomatous pulmonary involvement (bilateral); **invasive primary aspergillosis**

formation. Atherosclerosis in the pulmonary artery is common [*31*]. The fungi, if present, are single wide hyphae or matted masses of branching hyphae, and are usually easily discerned with routine hematoxylin and eosin stains. Kade and Kaplan [*49*] found that aspergilli

TABLE III

SUMMATION OF CASES OF ASPERGILLOSIS FROM LITERATURE IN WHICH ANTIBIOTICS AND/OR STEROIDS MAY HAVE PLAYED A ROLE

Author (Ref.)	Location and Type of Aspergillosis	Associated Fungal Disease	Underlying Disease(s)	Antibacterial Chemotherapy	Steroids	Other Antineoplastic Therapy
Torack [*40*]	Small granulomas of lung; **localized secondary aspergillosis**	Monilial ulceration of epiglottis, pharynx and esophagus	Carcinoma of breast; leukopenia	Nystatin for 36 days; penicillin for 24 days; streptomycin for 39 days; tetracycline for 71 days; erythromycin for 31 days	Cortisone for 65 days	Radiation therapy
Torack [*40*]	Necrotic focus in lung; **localized (?) secondary aspergillosis**	Monilial gastritis	Hodgkin's disease; pancytopenia	Penicillin for 23 days; streptomycin for 23 days	ACTH for 75 days; prednisone for 22 days; hydrocortisone for 76 days	None
Torack [*40*]	Abscess of lung; **localized secondary aspergillosis**	Monilial gastric ulceration	Carcinoma, bladder	Penicillin for 50 days; streptomycin for 50 days; erythromycin for 7 days; neomycin for 5 days; chloromycetin for 45 days; sulfisoxazole for 5 days	None	None
Welsh and Buchness [*29*]	Endocarditis and myocarditis; pulmonary abscesses; **disseminated secondary aspergillosis**	None	"Primary splenic neutropenia"; chronic interstitial pneumonitis; salmonella infection	Penicillin for 1 week; oxytetracycline for 2 weeks	ACTH and cortisone for 3 months	None
Welsh and McClinton [*36*]	Numerous small peribronchial abscesses; duodenal ulcer with extensive aspergillus invasion; **disseminated aspergillosis, either primary or secondary**	None	Swollen hemorrhoids; perianal slough	Sulfadiazine for 9 days; penicillin for 12 days; oxytetracycline for 9 days	None	None
			(Aboard ship carrying grain)			
Cooper [*44*]	Numerous peribronchial abscesses; **invasive secondary aspergillosis**	None	Ruptured duodenal ulcer; peritonitis (2 operations)	Sulfadiazine	None	None
Grekin et al. [*33*]	Disseminated—brain, myocardium, lungs, thyroid, duodenum, and kidneys; **disseminated aspergillosis, either primary or secondary**	None	Respiratory infection (?)	Penicillin; sulfadiazine; chlortetracycline; streptomycin	None	None

TABLE III (*Continued*)

SUMMATION OF CASES OF ASPERGILLOSIS FROM LITERATURE IN WHICH ANTIBIOTICS AND/OR STEROIDS MAY HAVE PLAYED A ROLE

Author (Ref.)	Location and Type of Aspergillosis	Associated Fungal Disease	Underlying Disease(s)	Antibacterial Chemotherapy	Steroids	Other Antineoplastic Therapy
Wybel [*23*]	2.5 granuloma surrounding and distorting spinal cord; quadriplegia; **localized secondary aspergillosis (fatal by virtue of location)**	None(?)	Pneumococcal meningitis	Sulfadiazine; penicillin intramuscularly for 16 days; penicillin, intrathecally for 12 days	None	None
Darke et al. [*39*]	Extensive bilateral pneumonia with scattered abscesses; involvement of spleen; **disseminated secondary aspergillosis**	None	Pneumonia	Sulfonamides; tetracycline; chloromycetin	None	None
Zimmerman [*28*]	Endocarditis, ruptured intraventricular septum; **disseminated secondary aspergillosis**	None	Multiple injuries	Penicillin for 7 weeks (?)	None	None
Zimmerman [*38*]	Disseminated—lung, pleura, pericardium, brain, liver; **disseminated secondary aspergillosis**	None	(Newborn) Staphylococcal pneumonia	Penicillin; streptomycin	DOCA; cortisone 1 mo. (?)	None
Zimmerman [*38*]	Lung abscess; **localized secondary aspergillosis**	None(?)	Hodgkin's disease; pancytopenia	Yes—not specified	None	X-ray; nitrogen mustard
Zimmerman [*38*]	Invasion of gastric ulcer and metastatic lung abscesses; **disseminated secondary aspergillosis**	None(?)	Chronic lymphatic leukemia	Penicillin	ACTH; cortisone	None
Abbott et al. [*45*]	Extensive bronchopneumonia, 2 lobes with one 5 cm. cavity; **invasive secondary aspergillosis**	None	Postinfluenzal bronchopneumonia	Penicillin for 5 days; chloromycetin for 11 days; streptomycin for 5 days	None	None
Cawley [*31*]	Chronic pulmonary, later disseminated—brain, heart, lungs, spleen, liver, kidneys, ankle, dura, nodes; **disseminated secondary aspergillosis**	None	(Newborn) Pneumonitis(?)	Sulfonamides; penicillin	None	None

TABLE III (*Continued*)

SUMMATION OF CASES OF ASPERGILLOSIS FROM LITERATURE IN WHICH ANTIBIOTICS AND/OR STEROIDS MAY HAVE PLAYED A ROLE

Author (Ref.)	Location and Type of Aspergillosis	Associated Fungal Disease	Underlying Disease(s)	Antibacterial Chemotherapy	Steroids	Other Antineoplastic Therapy
Rankin [*34*]	Disseminated—lung (thrombi→infarcts), liver, spleen, kidney; **disseminated secondary aspergillosis**	Generalized moniliasis, chiefly in gastrointestinal tract	Agranulocytosis (chloromycetin)	Sulfonamides; penicillin; chloromycetin	None	None
Kirschstein and Sidransky [*30*]	Endocarditis tricuspid valve, myocarditis, pulmonary granulomas with necrosis, involvement of many pulmonary arteries and veins; **disseminated secondary aspergillosis**	None	Pancytopenia; chronic lymphatic leukemia(?); splenectomy	Tetracycline and oxytetracycline for 2 mo; penicillin for 16 days; streptomycin for 16 days	ACTH 20–30 units for 2 mo.	None
Levy and Cohen [*37*]	Generalized abscesses brain, heart, lung; **disseminated secondary aspergillosis**	Generalized moniliasis, lung, lymph nodes, spleen	Anemia and thrombocytopenia, etiology(?); staphylococcal sepsis	Penicillin for 14 days; sulfadiazine for 5 days	ACTH 25 units to 100 units for 4 months	None
Tobler and Minder [*35*]	Generalized—abscesses in lungs, lymph nodes, cerebellum, vertebrae, rib; **disseminated secondary aspergillosis**	None	Prematurity; ascariasis; hemolytic anemia	Chlortetracycline, 7.7 gm.; chloromycetin, 32 gm.	None	Urethane
Yesner and Hurwitz [*46*]	Pulmonary cavity, solitary; **localized aspergillosis, either primary or secondary**	None	Lung abscess(?)	Sulfonamide	None	None
Kligman [*22*]	Local infection in bowel mucosa (two patients)—not clinically manifest; **localized secondary aspergillosis**	None	Severe, chronic diarrhea, etiology(?)	Sulfasuxidine; oral streptomycin	None	None
Friedman et al. [*18*]	Localized pulmonary mycetoma; **localized secondary aspergillosis**	None	Pulmonary tuberculosis	Streptomycin; and PAS for 8 months	None	None
Golebiowski [*24*]	Empyema; **localized secondary aspergillosis**	None	Pulmonary tuberculosis; recent gastrectomy; segmental pulmonary resection	Streptomycin for 11 months; INH for 14 months	None	None

stained well also with Giemsa and Schiff reagent stains, of which the Gridley stain was best.

Occasionally, a cavity may contain a branching matted mass of hyphae, the so-called "fungus ball" or mycetoma. A fibrotic capsule is associated with this cavity formation and only rarely are fungi noted in the wall or in the surrounding tissue. It is uncertain whether bronchial dilatation or bronchiectasis precedes or follows the fungus infection; it is probable that both occur. In the report by Pesle and Monod [*26*] two patients did show bronchiectasis in other areas of the lung not involved by aspergillus. In the non-cavitary necrotic type of pulmonary disease, the fungi invade the surrounding alveolar walls and show some predilection for the walls of blood vessels, at times causing thrombosis.

On occasion (Case VII) one may see conidiophores in preparations of pulmonary aspergillosis, usually in association with cavities. (Fig. 3.) It should be emphasized that, strictly speaking, a tissue diagnosis of aspergillosis is justified only if recognizable conidiophores are seen. The hyphal elements are difficult to distinguish from those of penicillium, candida or mucor, but typically the mycelium of mucor is non-septated and exhibits marked irregularity of width, and candida tends to have considerably smaller septate hyphae with less lateral branching and more uniform staining; with candida, furthermore, small rounded spore forms are usually present in large numbers. However, it is possible to confuse hyphae cut in cross-section with spores. Penicillium and aspergillus cannot be distinguished in tissues in the absence of typical conidiophores and spores; penicillium, however, rarely causes deep-seated infection. Cryptococcus can be eliminated from practical consideration if true mycelial structures are demonstrable in tissues [*28*]. Occasionally in aspergillosis one sees "actinomycetoid bodies" resembling the sulfur granules of actinomycosis or nocardiosis [*6*]; however, the filaments are much larger than those of actinomyces or nocardia.

In disseminated aspergillosis the histopathologic appearance is similar to that described in the lung except that cavity formation is seldom encountered; abscess formation is characteristic. Dissemination is primarily hematogenous and in metastatic sites the fungi are most often noted growing through the walls of small vessels into the surrounding tissue.

Diagnosis. Pulmonary aspergillosis is usually diagnosed at autopsy, although if the disease is suspected it may be tentatively diagnosed with relative ease during life by mycologic examination of the sputum or bronchial lavage specimen. Direct microscopic examination of sputum may reveal fragments of septate hyphae that are often branched. Identification usually depends on culture.

Aspergillus species grow rapidly on a wide variety of simple media. Media containing penicillin and streptomycin or chloramphenicol are satisfactory, but cycloheximide (Actidione®) must not be used. Speciation in the genus aspergillus is a complex problem requiring considerable mycologic experience. A. fumigatus is the most common pathogen but the following species have been implicated in human disease: A. niger, A. versicolor, A. clavatus, A. nidulans, A. flavus, A. oryzae, A. glaucus and A. sydowi. Henrici [*48*] isolated an endotoxin from A. fumigatus which is pathogenic for rabbits receiving intravenous injection.

Aspergilli are not only common laboratory contaminants but also, because of their ubiquitous nature, may be found in a wide variety of clinical specimens. In the absence of histologic material care is required in making a diagnosis of aspergillosis. The presence of the fungus may represent the overgrowing of a more obscure but primary infectious agent or a contaminant introduced in the specimen collection or laboratory. The *repeated* isolation of aspergillus from clinical material in the absence of a more obvious pathogen is good evidence of aspergillosis but is still inconclusive. Recovery of the organism from unexposed sources (such as empyema fluid) or from tissues helps provide definitive diagnosis.

Cases VII, VIII, IX, X and XII can be considered as diagnosed unequivocally because of morphologically typical fungi noted in biopsy, operative or autopsy specimens, together with recovery of aspergillus on culture on one or more occasions from each patient. In Case XI the diagnosis must be considered questionable; although the fungus was recovered twice on culture of the sputum there was no clinical evidence of aspergillosis outside the bronchial tree and we were unable to find fungi in a review of lung tissue obtained elsewhere. Cases I, II, III, IV, V and VI are clinically and pathologically suggestive of aspergillus infection, and fungi consistent with (but not diagnostic of) aspergillus were seen in the tissue sections; unfortunately, no cultures were made in these cases.

The protean manifestations of the disease make it difficult to diagnose. However, primary aspergillosis localized to the bronchial tree is easily recognized by the finding of the fungus in the expectorated mucous plugs [*3*]. The primary forms should be looked for in patients exposed to grains, dry vegetable matter or birds. Aspergillosis should be considered in the differential diagnosis of granulomatous diseases and it should be thought of especially (along with other fungus diseases) in patients with debilitating illnesses who have received antibiotics or adrenocortical steroids.

Skin tests and serologic studies give inconsistent results and are not useful diagnostically. X-ray findings are variable and not diagnostic. Infiltration into the lungs is usually basal in location. A suggestive x-ray feature is an increase of the hilar shadows with radiating spider-web appearance—the "sun-burst" effect [*50*]; this finding may be seen in various fungus diseases as well as in other conditions. The x-ray picture of pulmonary mycetoma is quite unique. The literature on mycetomas has been reviewed by Levin [*51*] and by Lodin [*52*] who point out that mycetomas can be caused by candida or streptomyces occasionally. However, most pulmonary mycetomas are due to aspergillus and the typical x-ray picture warrants a tentative diagnosis of aspergillosis. The typical mycetoma as seen on roentgenograms is a mass with a thin, crescentic aerated area at the upper pole; the cavity is enclosed by a thin line, as in an air cyst. (Fig. 5.)

Treatment. Drug therapy for aspergillosis has not been generally effective. Iodides have been recommended for a number of years but it is clear that the results have often been disappointing. Desensitization is recommended for the allergic type of migrating pneumonitis by Smith [*53*]. Although transitory improvement has been reported with the intravenous administration of hydroxystilbamidine [*54*], others have reported treatment failure [*55,56*]. Riddell [*57*] found that inhalations of nystatin in suspension, solutions of brilliant green or hydroxystilbamidine were effective in suppressing or removing A. fumigatus from the bronchial secretions.

Nystatin will probably not be useful except in unusual cases in which it might be used topically. Parenterally administered amphotericin [*58*] and pimaricin have not had an adequate trial and probably offer the best possibilities for treatment at present. Eulicin [*59*] is very active *in vitro*, but toxicity may limit its usefulness. Cycloheximide (Actidione) is no longer available for parenteral use. Griseofulvin showed no promise in the one patient we treated (Case XII).

Although currently available medical therapy for aspergillosis leaves much to be desired, it is likely that more favorable results would be obtained if patients were diagnosed and treated earlier. Prophylaxis in the form of rational use of antibiotics and adrenocortical steroids is an important consideration.

Surgical therapy is indicated for drainage of abscesses and excision of localized lesions. Apparently the first successful surgery for a pulmonary mycetoma in the United States was reported by Gerstl, Weidman and Newmann [*32*] in 1948. Many others have since been noted in the literature. Surgical treatment has been used in solid pulmonary lesions [*25*], empyema [*21,24*] and abscess of the brain [*16,60*].

Prognosis. The prognosis in primary aspergillosis is poor in cases of the invasive or generalized variety, but is usually good in localized disease. The prognosis in secondary aspergillosis is further modified by the nature and extent of the underlying disease. All eleven patients with secondary aspergillosis in our series died; the aspergillosis was considered to be either the primary cause of death or a significant contributing factor in Cases I, V, VII and IX.

Associated Fungus Diseases. Table III lists five patients with aspergillosis and co-existing candida infections (all invasive); our Case II was similar, and in our Case V the patient may have had an associated Candida ulceration.

SUMMARY AND CONCLUSIONS

The clinical and pathologic data in twelve cases of aspergillosis are presented. Eleven patients came to autopsy; one is still living. One of the patients had primary aspergillosis; the others all had secondary involvement. The eleven patients with secondary aspergillosis all had debilitating underlying diseases and had received antibiotic therapy, usually multiple drugs, for a prolonged period. Six of these patients had received adrenocortical steroids or corticotropin. Three were leukopenic. Similar cases of aspergillosis from the literature in which the use of antibiotics and/or steroids may have played a role are tabulated. Possible predisposing causes other than these are listed.

A new classification of aspergillosis is presented.

The diagnosis of aspergillosis is difficult.

Early diagnosis would probably improve results of medical treatment. Surgery is effective in drainage of abscesses and resection of localized lesions. Prophylaxis through more judicious use of antibiotics and steroid hormones is most important even though the use of antibiotics and steroid hormones may be unavoidable; in these situations one should be alert to the possibility of superimposed aspergillus (as well as other fungal and bacterial) infection.

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ADDENDUM

Since the manuscript was completed we have encountered another case of disseminated aspergillosis, in this instance associated with other mycoses. A twenty-eight year old student entered Wadsworth General Hospital in 1959 for treatment of lymphosarcoma established six months previously. The past history included a diagnosis of coccidioidomycosis in 1956 (confirmed by a complement fixation test) that apparently healed without incident. Treatment for his lymphoma consisted of high doses of prednisolone, prolonged use of a wide variety of antibiotics, radiation, nitrogen mustard, chlorambucil, 5-fluorouracil and 6-mercaptopurine. A persistent infiltration was seen on his chest roentgenogram. Oral ulcerations repeatedly yielded cultures of Candida albicans, and sputum cultures grew aspergillus twice and Coccidioides immitis once. Two blood cultures revealed aspergillus and one of them in addition grew C. immitis. These disseminated mycoses were the immediate cause of death. Autopsy findings and further laboratory studies will be reported when more complete data are available.

Two additional cases of secondary aspergillosis in the form of large pulmonary abscess cavities have recently been reported [*61*]; iodide therapy cleared the sputum of aspergillus but also produced toxic manifestations.

An additional experimental study has recently been published by Sidransky and Friedman [*62*]; this study demonstrates increased susceptibility to aspergillosis in mice treated with cortisone or with cortisone plus antibiotics.

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