MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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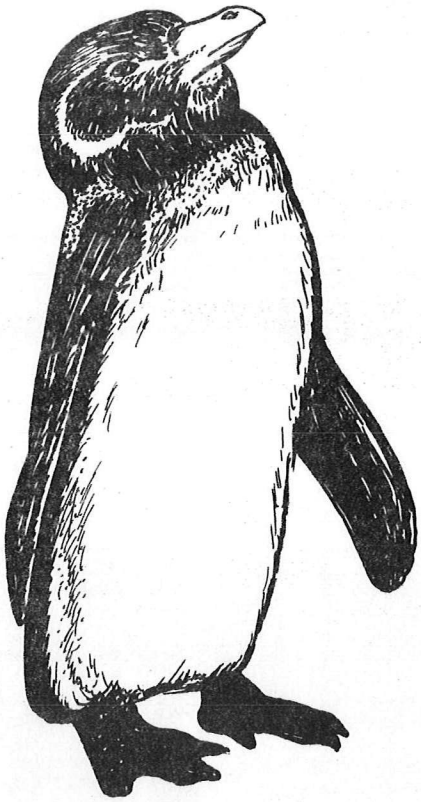
Jay P. Sanford, M.D.

ASPERGILLOSIS



Aspergillosis, which has been classically defined as a comparatively rare disease in man caused by species of the genus aspergillus, is beginning to emerge as an important and perhaps common mycotic infection. Although speculative, there is a basis on which to suggest that aspergillosis will emerge in the 1970s as histoplasmosis unfolded in the last 20 years. Infection varies in severity from an incidental, saprophytic relationship to a fulminating fatal infection, with the lungs being the most common site of significant infection. The spectrum of disease has been fragmentary and hard to define and even harder to diagnose. This difficulty relates to ubiquitous occurrence of species of aspergilli in the general environment so that it can be isolated from the sputum of normal persons. Previously a patient was considered to have aspergillosis if he had an aspergilloma or if the fungus was demonstrated histologically to invade tissue or was grown from organs or body fluids which are normally sterile. The increasing frequency of occurrence of invasive fungal infections in the compromised host, the more widespread use of diagnostic procedures such as transtracheal aspiration and lung biopsy and aspiration, the recognition of the association of serum precipitins to aspergillus extract and the development of a complement fixation test have each contributed to the recognition of an increasingly important role of aspergillosis as a significant mycotic infection of man.

HISTORICAL:

The aspergilli, as part of moldiness of things, have always been a factor in man's environment, but for ages were brushed away as white, green or black mold. Micheli, in 1729, was said to have distinguished conidiophores and heads of this mold. He noted that the heads were rough, hence he applied the name aspergillus (L. rough-head) (1). The organisms also resemble an aspergillum, which is a perforated globe holding a sponge and used for sprinkling holy water (L. aspergere--to sprinkle) (Fig. 1). The first reference to invasion of animals by the fungus was by Mayer (1815), who observed it in the lungs of a jay (2). The first human case in which aspergilli were definitely identified was described by Sluyter (1847) in a woman dying of an unspecified pulmonary infection (2). Subsequently, Virchow (1856) described 4 cases of pulmonary aspergillus infection in patients dying of other conditions (3). Dieulafoy and associates (1890) were the first to describe the disease in pigeon-crammers and they called it "maladie des gaveurs" (2). The pigeon-crammers of Paris performed gavage by taking a mouthful of grain and water and spitting it into the mouth of a pigeon. Each man fed about 2000 pigeons a day and it was accepted that they would succumb to a chronic pulmonary disease. Rénon amplified on these observations and also reported two new cases in hair-combers who used rye flour for removing grease from hair before making it into wigs. He also referred to primary and secondary aspergillosis (2). Rénon was also the first to mention the occurrence of asthma in aspergillosis.

Fig. 1

GEOGRAPHIC DISTRIBUTION:

Aspergillosis is found in all parts of the world.

SOURCE OF INFECTION:

Aspergilli are ubiquitous in nature. Many species are pathogenic for plants, especially figs. Some species infect insects such as bees, birds and domestic animals. Birds are particularly susceptible and 40% of necropsies on penguins showed evidence of infection with aspergillus (4,5).

AGE, SEX, RACE AND OCCUPATIONAL INCIDENCE:

Adults are infected more frequently than children, although the disease has been reported in individuals between the ages of 2 days and 78 years (6,7). The disease is recognized more frequently in men than it is in women. Since the early descriptions by Rénon, many texts and papers have listed aspergillosis as an occupational disease among persons in close contact with birds, grain, flour and agriculture. In detailed analysis of these original cases, Maccartney concludes: "It cannot be accepted that there is any convincing evidence to date connecting pulmonary aspergillosis with certain occupations." (8)

CLINICAL FEATURES:

The respiratory tract, external auditory canal, skin and nails are common sites of infection. Less common sites include ocular involvement. Occasionally the infection becomes disseminated with resultant widespread involvement of many organs: meningitis, encephalitis, osteomyelitis, endocarditis, ophthalmitis, the kidneys, the thyroid gland, and infection of the paranasal sinuses and orbits (9-12). Consideration of these features is facilitated by a classification. The following classification is modified slightly from that of Finegold, Will and Murray by using the term opportunistic in place of secondary to meet the criticism that the term secondary is somewhat ambiguous (7,13) (Table I).

TABLE I

Classification of Aspergillosis

I. Primary Aspergillosis
   - A. Localized
     1. Mycetoma or abscesses
     2. Allergic--bronchitis with asthma and/or eosinophilia
   - B. Invasive
     1. Acute--usually bronchopneumonic
     2. Chronic granulomatous disease--usually pulmonary
   - C. Disseminated

II. Opportunistic (Secondary) Aspergillosis
   - A. Localized--usually pulmonary
   - B. Invasive
   - C. Disseminated

Primary Aspergillosis:

Localized primary aspergillosis is seen mainly in the lung in the form of mycetoma or "allergic pneumonitis", although other sites may be involved in non-invasive processes; these include the external ear, skin, nails, and paranasal sinuses.

Pulmonary Aspergillosis (Mycetoma) or Intracavitary Fungus Ball:

Aspergillomas, fungus balls of the lung, develop in pre-existing areas of disease, e.g., bullae, old tuberculous cavities, healed cavitary histoplasmosis, bronchiectasis, sarcoidosis and neoplastic cavities of the lung (14-17). In a review of 58 cases, Schwarz and associates have summarized the salient clinical features (14). Location of fungus balls was as follows: right upper lobe 30, left upper lobe 23, right middle lobe 2, lower lobes 2. In two instances, the lobes were not specified and two patients had cavities in two lobes. The cause of the cavity was bronchiectasis in 21, tuberculosis 11, histoplasmosis 5, and malignancy 2. The age range in this group of cases was 19 to 82 years with most of the patients in the 51 to 60 year decile. There were 42 men, 15 women, and in one case the sex was not noted. The commonest symptom is a productive cough. Hemoptysis was a symptom in 45%. In 48 cases aspergillus was the fungus producing the fungus ball; 27 were diagnosed by histology alone, while 21 were proven by culture. Only one case of candida and one case of mucorales were noted. The typical roentgenographic finding is that of a rounded density capped or surrounded by air translucency. Contrary to some opinions, these fungus balls are not loose in the cavities, but are attached to the cavity wall in most patients (19). The air crescent sign was once considered pathognomonic of echinococcus or hydatid cysts (20). The morphologic identification may be difficult because the character of hyphae in the mycelial conglomerate is greater than the width seen in culture mounts (14). Pepys and associates have measured precipitating antibody against extracts of Aspergillus fumigatus in the sera of patients with aspergillosis using both agar diffusion and immunoelectrophoresis (21). Of the sera of 57 patients with a mycetoma in situ, 98% contained precipitins and the degree of positivity was greater than in other groups of patients (Table 2). After removal of the mycetoma, 5 of 9 sera remained positive but the reactions were less marked.

TABLE 2

Reactions of Sera of Patients and Healthy Persons to Aspergillus fumigatus (22)

Group	No. of Sera	No. Positive	No. Sera Positive With ≥ 6 Arcs
Asthma without pulmonary eosinophilia	307	29	3
Asthma with pulmonary infiltrates and eosinophilia	93	59	2
Pulmonary mycetoma in situ	57	56	44
removed	9	5	0
Other lung diseases	185	14	1
Healthy persons	60	0	0

There is no accepted form of treatment for pulmonary aspergilloma. Once diagnosed, the tendency has been to resect the mycetoma. Since the first successful resection of a mycetoma (23), several others have reported satisfactory surgical results (24,25). Various drugs have been used in the treatment of pulmonary aspergillosis including amphotericin B, nystatin, hydroxystilbamidine and iodides (26-30). Most consist of isolated case reports, hence evaluation of efficacy is not possible. Reddy and associates from the Missouri State Sanatorium have analyzed the clinical features and the results of treatment in 16 patients who have been followed for 6 months to 10 years (average follow-up about 4 years) (Table 3) (18).

TABLE 3

Outcome in Three Groups of Patients With Aspergilloma (18)

Type of Treatment	No. of Patients	Sputum Conversion to Negative*	Progression of Disease (No. Pts.)	No. of Deaths	Mortality (%)	Side-Effects or Complications of Therapy (No. Pts.)‡
Surgical Resection	5	1/2	1	1	20	3
Amphotericin B	8	6/8	1	1	13	2
No Specific Rx	3	2/3	0	2	67	0

* Number of sputa negative per number positive at start of therapy

‡ In the surgical group this includes postoperative complications (one bronchopleural fistula, two empyema); in the amphotericin B group these are severe uncontrollable side-effects

While this is a small series, it does provide an indication of the potential seriousness of the infection. Amphotericin B has been recommended as the drug of choice for treatment of aspergillosis (31); however, the effectiveness is still uncertain. A randomized prospective study is proposed as necessary and feasible to evaluate therapy in aspergillosis (32).

In addition, there is an investigational antifungal agent, 5-fluorocytosine, which can be taken orally with minimal toxicity. While primarily active against Cryptococcus neoformans and Candida albicans, a strain of Aspergillus flavus and A. niger were also susceptible in vitro (33,34). Studies in mice infected with A. fumigatus have been equivocal.

Primary Localized Abscesses:

Other sites which may be involved with non-invasive aspergillosis include the external ear, skin, nails, paranasal sinuses (35,36). The symptoms are not specific but compatible with chronic infection in these areas.

Allergic Pneumonitis (Bronchopulmonary Aspergillosis or Hypersensitivity Aspergillosis):

Hinson, Moon and Plummer called attention to three patients with broncho-

pulmonary aspergillosis, who had evidence of sensitization to the fungus and resembled patients with "pulmonary eosinophilia" (2). Most of the patients have had a long history of asthma (37). The clinical picture is then that of developing febrile episodes which occur episodically over intervals of months to years with variable periods between attacks (2,19,37). The febrile episodes are associated with wheezing, cough, expectoration of purulent sputum which often contains plugs. Blood streaking of sputum can occur, but is not a prominent feature. During the acute episode, the patient may experience dyspnea and chest discomfort, but typical pleural pain is unusual. The sputum produced during the acute episodes has diagnostic characteristics. It is purulent and typically contains white or brownish flecks. These flecks contain mycelia aggregated together with Charcot-Leyden crystals, Curschmann's spirals, mucus, eosinophils and neutrophils into rounded masses which are dull brownish and measure about 1 cm in diameter and have been called "plugs". An eosinophilia in the peripheral blood (usually of greater than $1000/mm^3$) is frequently found. Serial chest roentgenographs reveal transient, migratory lobar or segmental collapse and consolidation. The infiltrates may clear within a week, but more often they persist for 4 to 6 weeks. In one patient reported by Hinson et al. the collapse persisted for almost one year (2). Involvement of new areas usually coincides with a febrile episode. Bronchoscopy has shown a polypoid mass obstructing the lumen of a bronchus or edema of the mucosa and occlusion of the lumen with tenacious material. Longbottom and Pepys demonstrated that sera from 9% of a group of patients with asthma but without eosinophilia contained precipitins against Aspergillus fumigatus (Table 2) (21). Skin tests revealed immediate wheal and flare reactions in 38% including 10 of 13 patients (77%) with precipitins. In patients with the syndrome of "hypersensitivity aspergillosis", i.e., asthmatics with transient shadows in chest roentgenograms associated with eosinophilia in the peripheral blood, 63% contained precipitins (Table 2) and skin tests were positive in 87%. Slavin and Cherry have further studied this syndrome and demonstrated the occurrence of wheezing and a significant decrease in $FEV_{1.0}$ in a patient with this clinical syndrome when challenged with an aerosol of A. fumigatus (38). They also demonstrated that the precipitating antibody was IgG and that it elicited a direct "late" arthus type skin reaction.

In the United States, this syndrome has been very rare, even when groups of patients with asthma are specifically screened (39).

Hinson and associates reported that iodides were not an effective form of treatment (2). Slavin and Cherry reported that treatment with oral corticosteroids and amphotericin B by aerosol resulted in marked improvement in both patients with clearing of infiltrates, decrease in eosinophilia, weight gain, increase in vital capacity and eventual negative sputum cultures for aspergillus.

Invasive Primary Aspergillosis:

Invasive, primary aspergillosis usually takes the form of pneumonia, with or without abscess formation (40). In this group, the aspergilli produce a definite bronchitis with invasion of bronchial walls and subsequent pneumonitis. The result is destruction of lung tissue with abscess formation and the production of foul-smelling sputum. Despite efforts to isolate fungi from the sputum and bronchial secretions, the organism often was not isolated except from the tissue itself (17). Besides the lung, the brain may be involved by extension from the orbit and sinuses (41-45).

Chronic Granulomatous Disease:

In addition to acute pneumonic aspergillosis, a chronic granulomatous lung disease occurs which may closely simulate tuberculosis. Symptoms include cough, hemoptysis, pleurisy, fever and weight loss. Patients may cough up black granules which actually represent dislodged conidia.

The report by Parker and associates is pertinent to the understanding of the actual incidence of aspergillosis (32). Seven chest hospitals in the south central part of the United States participated in the study. For one year, a serum sample was obtained from each patient who was admitted to the hospitals and complement fixation tests for aspergillosis were performed (46). Newly admitted patients with complement fixation titers of 1:8 or greater were admitted to the study. Of the 3,227 patients in the study, 54, or 1.7%, had aspergillin titers of 1:8 or greater. The clinical course of 50 of these patients was followed. Twenty-eight were found to have cultures yielding A. fumigatus and 20 were thought to have aspergillosis on the basis of the presence of aspergillomas on chest film, multiple sputum cultures yielding A. fumigatus, or the presence of aspergillus in the lung by pathologic examination. Of note, during the same period of time, 34 cases of chronic pulmonary histoplasmosis were identified in these sanatoriums, i.e., in the "histo belt" of the U.S., the prevalence of aspergillosis is 60% that of histoplasmosis. The patients with positive aspergillin complement fixation tests had symptoms similar to the matched controls, i.e., anorexia, weight loss, cough productive of sputum and fever; however, the aspergillin positive patients had significantly more hemoptysis. While the report of this study did not emphasize the clinical features, it provides one of the bases for the initial speculation regarding the importance of aspergillosis.

Primary Disseminated Aspergillosis:

Disseminated primary aspergillosis is rare. Involvement of the tongue is rare. Involvement of the lung, tongue, palate and mesenteric nodes has been reported (46). Patients may cough up black or dark granules which represent dislodged conidia.

Opportunistic (Secondary) Aspergillosis:

Infection is a frequent complication of acute leukemia. In recent years, the frequency of fungal infections has increased, being responsible for 14% of deaths in a large series of leukemic patients (47). To place aspergillosis in perspective as an opportunistic infection, the report by Bodey summarizing the experience at the National Institutes of Health where 189 fungal infections were observed in 161 patients with acute leukemia during a 10-1/2 year period provides much data (47). (Table 4). Aspergillosis ranked second to candidiasis in this series. Subsequently, Young and associates have reviewed the spectrum of aspergillosis in 98 patients seen at the NIH since 1953 (48). The types of underlying diseases are listed in Table 5. The diagnosis of aspergillosis in this group of patients is difficult. While 82% of the patients had antemortem fungal cultures, only 34% had one antemortem culture positive for aspergillus and only 9% had more than one positive culture. The sites of infection in these 98 patients are presented in Table 6, Figure 2.

TABLE 4

Types of Fungal Infection and Incidence in Patients With Acute Leukemia* (47)

Type	No. of Episodes	Incidence‡
Candidiasis		
Focal	62	13.6
Severe	71	15.6
Total	133	29.2
Aspergillosis	38	8.0
Mucormycosis	6	1.0
Cryptococcosis	5	1.0
Histoplasmosis	5	1.0
Torulopsis glabeata	2	0.4
	189	

* Total number of patients with fungal infections 161 (107 major infections), with 454 total fatalities.

‡ Expressed as number of cases of fungus infection per 100 fatalities.

TABLE 5

Pre-Existent Diseases Associated With Aspergillosis
98 Patients

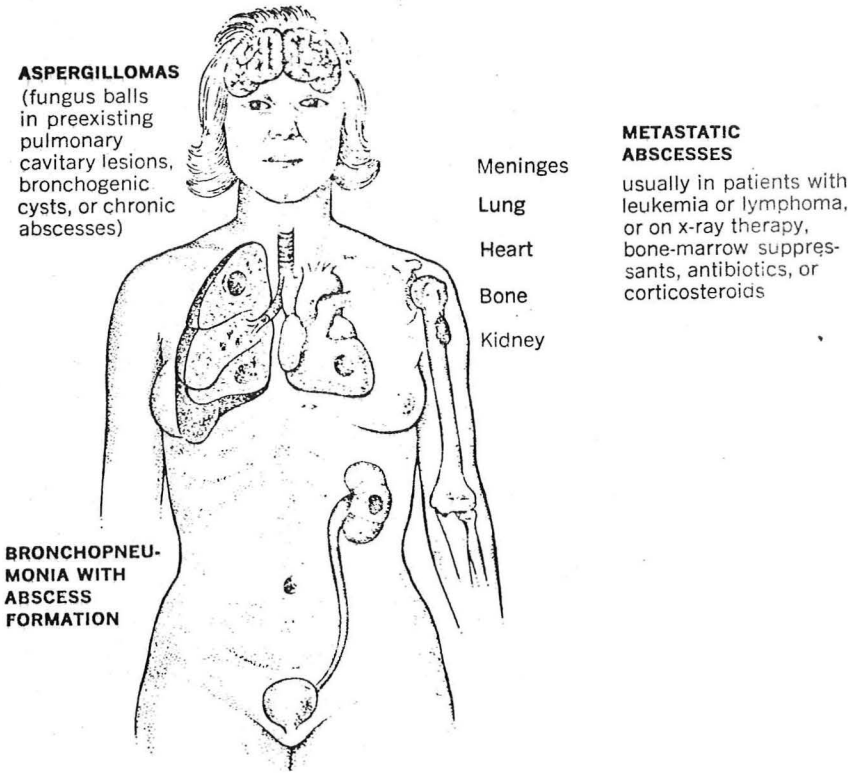
Diagnosis	No. of Patients
Acute lymphocytic leukemia	41
Acute myelogenous leukemia	21
Chronic myelogenous leukemia with blastic transformation	9
Hodgkin's disease	5
Lymphosarcoma	5
Aplastic anemia	3
Systemic lupus erythematosus	3
Chronic lymphocytic leukemia	2
Agnogenic myeloid metaplasia	1
Carcinoma of the rectum	1
Periarteritis nodosa	1
Mycosis fungoides	1
Multiple myeloma	1
Prostatic carcinoma	1
Saccular bronchiectasis	1
Rheumatic heart disease	1
Hypertensive cardiovascular disease	1

TABLE 6

Organ Involvement in Aspergillosis
98 Patients

Organ	No. of Patients
Lungs	92
Gastrointestinal tract	21
Brain	13
Liver	12
Kidney	12
Thyroid	9
Heart	7
Diaphragm	5
Sinuses	3
Skin	2
Testis	1
Adrenal	1

FIGURE 2



Pulmonary Aspergillosis:

Of the 92 patients with pulmonary aspergillosis, 60 had pulmonary aspergillosis as their only site of infection. The pattern of pulmonary aspergillosis is unusual in this patient population and is summarized in Table 7.

TABLE 7

Pulmonary Manifestations of Aspergillosis
92 Patients

	No. of Patients
Necrotizing bronchopneumonia	30
Hemorrhagic pulmonary infarction	29
Miliary microabscesses	9
Focal lung abscesses	3
Solitary lung abscess	3
Lobar pneumonia	8
Aspergillary bronchitis	8
Aspergilloma	1
Solitary granuloma	1

The two commonly reported primary forms, mycetoma and allergic bronchopulmonary aspergillosis, were essentially absent. The most common manifestation was that of necrotizing bronchopneumonia. All but three of the patients had symptoms, usually dyspnea, fever and tachycardia. Cough was commonly non-productive. Only 3 patients (10%) had hemoptysis and 6 had pleuritic chest pain (20%). Roentgenographic evidence was varied. Five patients (17%) had no x-ray evidence of pneumonia, even shortly before death. In those patients with positive x-rays, patchy pneumonitis was often first noticed in the last week of life. Twenty-nine patients (32%) had hemorrhagic pulmonary infarctions. At necropsy, each of these 29 patients had prominent vascular invasion by mycelial elements with occlusion and thrombosis of pulmonary vessels. In this group of patients, pleuritic chest pain occurred in 61% and was often associated with a pleural friction rub. Fifteen patients had pulmonary lesions characterized primarily by abscess formation. Eight patients had lobar pneumonia caused by aspergillus (49). The clinical and roentgenographic findings of dense lobar consolidation suggested specific bacterial agents such as klebsiella and pneumococcus.

Disseminated Aspergillosis:

In the review by Young et al., 34 patients had disseminated aspergillosis (Table 8). Of these patients, aspergillosis was the primary cause of death in 62%. Within the gastrointestinal tract, the esophagus was most frequently involved. The usual lesion was ulcerative esophagitis with areas of confluent necrosis. Gastrointestinal bleeding was detected by positive stool guaiac studies in 80%, while in 6 patients massive GI bleeding related to aspergillus ulceration occurred. Multiple lesions were found in the CNS of 7 patients and solitary lesions in 6. Ten patients (77%) had prominent vascular invasion and infarction. Examination of cerebrospinal fluid was normal in 7 of 11 patients. In the 4 patients with abnormalities in CSF,

TABLE 8

Organ Involvement Identified in Disseminated Aspergillosis
34 Patients

Organ	No. of Patients
Lung	32
Intestines	16
Brain	15
Kidneys	13
Liver	12
Esophagus	10
Thyroid	9
Heart	5
Stomach	5
Spleen	5
Diaphragm	5
Tongue	4
Sinus	3
Skin	2
Palate	2
Pericardium	2
Adrenal	1
Testis	1

3 had elevated protein concentrations (118 to 148 mg.%), 3 had slight increases in neutrophils (3 to 8 cells/mm^3), and one patient had a CSF glucose of 28 mg.%. No patient had diffuse meningeal involvement. These findings are consistent with those reported in other reports based on smaller groups of patients (12,50,51).

In 20 patients who underwent cardiac transplantation, 41 separate postoperative infections occurred in 12 patients (52). In this series, there were two instances of disseminated aspergillosis, and three cases of aspergillus pneumonia characterized by single or multifocal nodular infiltrates which rapidly progressed to cavitary lesions. One patient responded well to endocavitary treatment with amphotericin B and sodium iodide.

Aspergillus Endocarditis:

Aspergillus endocarditis has been reported, and more recently several instances have occurred after open heart surgery (53-55). The patient reported by Mahvi et al. presented with fever, migratory polyarthritis and painful swelling of the thighs and calves three months postoperatively. He subsequently had a typical massive saddle embolus to the bifurcation of the abdominal aorta.

MYCOLOGY:

Aspergilli are very commonly found in soil and decaying organic matter. The ubiquity of its spores is responsible for frequent contamination of laboratory cultures. In sputum, it appears as short branching hyphael elements, often with many small (2 to 4 μ) round green spores scattered throughout the field. The fungus grows well on simple media such as Sabouraud's glucose agar and on ordinary blood agar plates, which can be incubated at room temperature up to 45°C. A colony of aspergillus has a basal white felt consisting of an interwoven mycelium of septate hyphae (Fig. 3). Occasional cells of the hyphae enlarge and are designated as foot cells. A foot cell gives off a shoot which, enlongating upward, is known as a conidiophore and bears at its free extremity a swollen vesicle. From this vesicle, shorter stalks (phialides) arise and each stalk bears a row of conidia or spores which may be colored. The compact slow growing colony is at first white, then becomes bluish-green with sulfur yellow areas scattered over the surface.

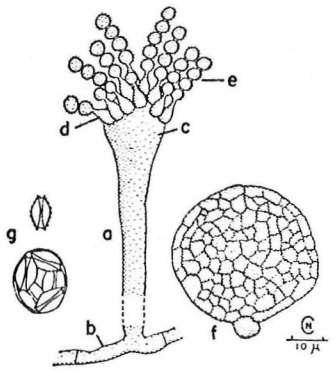


FIG. 3

Some 350 names have been used to designate aspergilli, but the actual number of species is probably 69 (1). Of these, only a few have been incriminated in human infections: Aspergillus fumigatus (most common), A. niger, A. clavatus, A. versicolor, A. flavus, A. nidulans, A. sydowi and A. glaucus. Differentiation between species is based on morphology of the conidiophore (Fig. 4). Isolation of multiple species of aspergillus from a single patient has been described (56).

At least five toxic products (aflatoxins) have been isolated from A. flavus. These are potent carcinogens. Heffernan and Asper concluded that there was no evidence that aspergilli produced substances damaging to the liver of the host when in vivo growth occurred (51).

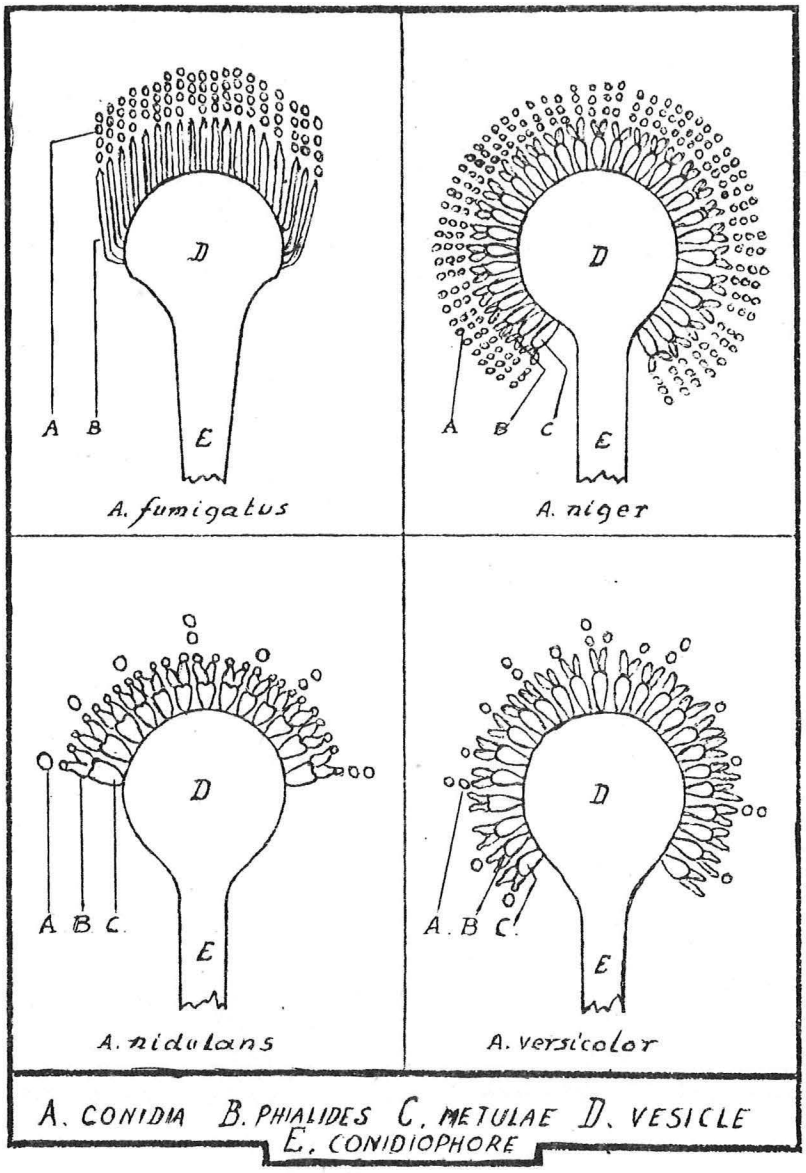


FIG. 4

PATHOLOGY:

Morphologic identification of hyphae in tissue is best accomplished when materials are stained by periodic acid Schiff or Gomori-methenamine silver techniques. Aspergillus hyphae are characteristically uniform, about 4 μ in diameter, septate and often branched. Occasionally the characteristic conidiophore may be seen. Candida pseudohyphae are usually smaller and can be distinguished by the presence of yeast-like as well as filamentous forms and by the absence of true branching. Phycomycete (mucor) hyphae are distinguished by great breadth, irregular thickness and absence of septae. The most difficult distinction arises between aspergillus and penicillium (57). To complicate the distinction, the hallmark of invasive aspergillosis and of mucormycosis, i.e., vascular invasion and thrombosis, was present in the patient with penicilliosis.

CASE REPORTS:

1. Primary Aspergillosis, Localized, Mycetoma:

[redacted]

The patient was a 67-year-old [redacted] who was seen in the emergency room in [redacted] 1963 because of a series of vague complaints. Examination at that time revealed evidence of a chronic brain syndrome, hypertension with hypertensive cardiovascular disease, left facial weakness and a positive serology. Chest film revealed a lesion in the left upper lobe with a "meniscus sign". Leucocyte count was 4,000/mm^3 with 2% eosinophils. The patient was admitted to the hospital for evaluation of these many problems. Although a clearcut history could not be obtained, she gave a questionable history of cough and sweats, but denied dyspnea and orthopnea. Skin tests including atypical mycobacteria and histoplasmin were negative except for a 6x6 mm nonchromogen reaction. Ten sputum cultures were negative for fungal pathogens and bronchoscopy was negative.

Comment: Although the diagnosis of aspergilloma was not confirmed in this patient, the x-ray is typical of that which one would expect.

2. Allergic Bronchopulmonary Aspergillosis:

[redacted]

The patient is a 44-year-old [redacted] whose history dates back to 1952, when she was diagnosed as having allergic rhinitis and sinusitis. In 1954, surgical drainage of the left maxillary sinus was performed with removal of a degenerating polyp. In 1956, she underwent an allergy evaluation and was found to have a 3+ reaction to aspergillus. She then received a series of hyposensitization injections with extracts of mold, dust, trees and grasses. In 1958, she developed right middle lobe pneumonia for which she was treated as an outpatient, although there was a question of infiltrate remaining at the level of the left second interspace. In [redacted] 1965, she had "snowball" infiltrates involving both apices and both mid-lung fields. These were associated with a two-week episode characterized by productive cough, weight loss, and burning substernal chest pain. In [redacted] 1966, she had extensive involvement of the right upper lung field and both hilar regions. At that time, the left maxillary sinus was completely opacified. Pulmonary function studies revealed the vital capacity to be 70% of predicted. Blood smears revealed 21% eosinophils. Work-up included bronchoscopy with bronchial washings. From one sputum, Aspergillus flavus was grown. Biopsy obtained from the right bronchus revealed chronic bronchitis. Fungal complement fixations including histoplasmin, coccidioidin and blastomycin were negative. In [redacted] 1966, she developed a "flu-like syndrome" with a 3-day history of cough, foul-tasting sputum which was blood-streaked, chills and fever. X-ray revealed consolidation in the area of the right upper lobe with a questionable abscess. In [redacted] 1967, the allergy work-up was repeated and it was concluded that she had perennial allergic rhinitis, sinusitis and nasal polyposis and pulmonary aspergillosis associated with the hypersensitivity syndrome. In [redacted] 1968, she underwent right thoracotomy at [redacted] Hospital. On pathology from a biopsy of the right upper lobe, Aspergillus species were noted. Sensitivity studies revealed the organism to be sensitive to 1.5 µg/ml of amphotericin B. In [redacted] 1969, she developed dyspnea and was hospitalized. At that time, sinus films revealed pansinusitis. In [redacted] 1969, a right nasal

antral window revealed Aspergillus species. She subsequently was treated with 522 mg of amphotericin B over a 90-day course. In [redacted] 1969, she developed left pleuritic chest pain and foul green sputum without associated fever or chills. Chest examination was negative. This episode cleared quite promptly. At present, symptoms have recurred and she has bilateral pulmonary infiltrates and an Aspergillus species has again been isolated on sputum culture.

Comment: This patient represents a combination of allergic bronchopulmonary aspergillosis, although precipitins have not been measured in her serum, and invasive aspergillosis, in that on biopsy the organisms actually had invaded.

3. Invasive, Chronic Aspergillosis:

[redacted]

The patient was a 54-year-old [redacted] woman who was initially seen in the emergency room in [redacted] 1955 because of asthma. She was next seen in [redacted] 1959, when admitted to the [redacted] for cervical biopsy. In [redacted] 1960, she was again seen in the emergency room and admitted to the Surgical Service for biopsy of a right axillary node which revealed chronic granulomatous inflammation with negative fungal stains. At that time, it was noted on x-ray that her right maxillary antrum was clouded. In [redacted] 1962, repeat x-rays revealed clouding of both the maxillary and ethmoid sinuses. In November 1962, she underwent nasal polypectomy. At that time, she had no blood eosinophilia. In [redacted] 1963, x-rays again revealed pansinusitis and at this time there was bony erosion of the sphenoid. In [redacted] 1963, she underwent surgical exploration. On biopsy septate hyphae and typical conidiophores were noted. The patient was treated with 1.505 gm of amphotericin B intravenously between [redacted] and [redacted] 1963. She has subsequently been lost to follow-up.

Comment: This patient represents a fairly typical example of aspergillosis involving the paranasal sinuses and associated with nasal polyposis.

4. Invasive, Chronic Aspergillosis:

[redacted]

When first seen, the patient was a 32-year-old [redacted] man. In [redacted] 1944, he came to the emergency room with the chief complaint of a headache. At that time, he gave a history of having been admitted to [redacted] Hospital in [redacted] and in [redacted] 1943 underwent surgery for a tumor of the right maxillary area, at which time a giant cell tumor, epulis type, was removed which contained multiple abscesses. Over the subsequent years, he has had a prolonged course with osteo of the right maxillary sinus being demonstrated in [redacted] 1948. In [redacted] 1956, he was seen in the emergency room with a questionable brain abscess. At that time, he had decreased vision in his left eye and seizures. Septate hyphae were seen on smear, but the culture revealed candida. In [redacted] 1957, he underwent incision and drainage of a left frontotemporal extradural abscess. The biopsy revealed granulomatous inflammatory tissue with epitheloid giant cells. In [redacted] 1957, he developed a fistula from the mouth to the right cheek. In [redacted] 1958, he was admitted for plastic procedures to his face. In [redacted] 1959, he underwent left temporal craniotomy for decompression. The following month, he had a biopsy of the lesion which revealed a foreign body granulomata. In [redacted] 1959, he was seen in the emergency room with "bronchial asthma". At that time, he had a mass in the left lower lobe which was considered a probable

granulomatous process and 4% eosinophils in his peripheral blood. In [redacted] 1960, he was seen in the emergency room with an abscess involving the left forehead. Culture of this revealed no fungi. In [redacted] 1960, he was re-explored and loculated pus was found in the epidural area extending into the temporal lobe, frontal sinus and left orbit. GMS stain at that time revealed septate branching hyphae with bulbous enlargements of the hyphae. No conidiophores were seen. Re-stain of the 1957 and 1959 biopsies revealed the organisms. Culture revealed mucor species. Between [redacted] 1961 and [redacted] 1961, he received 2.385 gm of amphotericin B intravenously. Since that time, he was admitted in June 1965 for evaluation of seizures, in [redacted] 1967 for repair of a right inguinal hernia and a bladder diverticulum, and was last seen in [redacted] 1968 in the emergency room following a seizure.

Comment: This patient has had progressive, invasive chronic aspergillosis associated with paranasal sinuses, orbits and extending into the brain. It would appear that the course of amphotericin B modified the progression, so that he has had relatively less difficulty with this.

5. Miscellaneous Aspergillosis

[redacted]

The patient was a 55-year-old [redacted] who underwent a vaginal hysterectomy for long-standing uterine prolapse in [redacted] 1969. During the post-operative period, she received an IV of 5% glucose and water which was apparently cloudy and subsequently had a febrile reaction. The solution and the patient's blood subsequently grew Aspergillus species. The patient remained febrile over the next four days. At the time of admission, her temperature was 100°, blood pressure 128/76, and the physical examination was otherwise normal. Studies included hemoglobin 14.2 gm.%, white count 8,200 with 59% neutrophils, 32% lymphocytes, 4% monocytes, 4% eosinophils. BUN was 8, creatinine 0.7, glucose 110. Serum bilirubin was 0.4, alkaline phosphatase 13.0, SGOT 45. The patient became afebrile within 36 hours. Blood cultures were all negative. Chest x-ray was normal.

Comment: This is an interesting case in that the patient received a massive intravenous inoculation with aspergillus, had moderately persistent fungemia, maintained fever for 5 days, but recovered spontaneously. She has subsequently remained well, hence the organism was unable to establish itself.

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