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ASPERGILLOSIS AND THE ASPERGILLI

Report of a Unique Case of the Disease

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PLEBEIANS among fungi, members of the great group Aspergillus have attained chief notoriety as vexatious laboratory contaminants. Considerably less attention has been focused on their aptitude as instigators of disease, while their role as serviceable implements of medicine has received minimal consideration.

Aptly labeled "weeds" of the culture room,[1] over three hundred and fifty authenticated strains of aspergilli have been identified and delineated subsequent to their initial description in 1729. To warrant classification as an Aspergillus, a microscopic fungus must be comprised fundamentally of a stalk and a spore-bearing head. Innate minor variations occur in profusion, and though a species may be tentatively identified without undue difficulty, precise designation not infrequently entails recourse to a monograph devoted to this genus of molds exclusively.[1]

The aspergilli prosper in diverse circumstances, and their ability to thrive on foodstuffs, soil and a host of seemingly barren mediums is attested to by detailed laboratory precautions often maintained for their exclusion. Though species of this mold almost invariably throttle bacteria and other fungi attempting to proliferate on the same culture medium, the morphologic response of the former in such circumstances is at times so atypical as to render identification a laborious and protracted task. Little difficulty need be anticipated in culturing and grossly classifying material from clinical sources, however, since the colony may be readily recognized as a component of this genus on the basis of its resemblance to a field of ripening grain, in which stalks and heads predominate.[1] Examination of the aerial growth under a low power of the microscope reveals details of the spore-bearing or fruiting head and other features of taxonomic significance. A preponderance of species grow best at a temperature of 37 C., although

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1. Thom, C., and Church, M. B.: The Aspergilli, Baltimore, Williams & Wilkins Company, 1926.

Aspergillus fumigatus has adequately demonstrated its ability to survive prolonged temperatures as low as —12 C., and certain of the aspergilli were, before the advent of modern refrigeration, commonly the derivation of distinctive molds on meat in storage room. Adequate oxygen tension is a prerequisite to the development of fruiting heads, though mycelium apparently proliferates under relatively anaerobic conditions. This doubtless accounts for the abundance of filamentous forms, often accompanied with chlamydospores and occasionally with bulbous terminal structures representing abortive heads, which may be discerned infiltrating the tissues in microscopic sections in cases of aspergillosis.

THE ASPERGILLI AS IMPLEMENTS OF MEDICINE

Flavicin, extracted from a strain of Aspergillus flavus and penicillin, both purified by the same method to an activity of 500 Oxford units per milligram, are reputedly similar in their chemical and antibiotic properties.[2] Another product of A. flavus, aspergillic acid, in contrast, to flavicin, has been shown to inhibit the growth of human strains of Mycobacterium tuberculosis, and suggestive evidence is presented to indicate that the mode of action of aspergillic acid can be explained on the basis of interference with the utilization of iron by the tubercle bacillus.[3]

Derivation of a partially purified preparation from A. fumigatus and the subsequent experimental study demonstrated the material to have bacteriostatic activity against M. tuberculosis BCG in a 1 : 1,400,000 dilution and bacteriocidal efficacy against the same organism in a dilution of approximately 1 : 700,000.[4] The authors reporting these results were not inclined to consider animal experiments concerned with toxicity and activity of the product until preparations of greater purity were available. It was postulated that the active substance may have been allied to helvolic acid, or purified fumigacin.

Other observers have determined that the mold Aspergillus fumigatus Fresenius affords several crystalline metabolic products, no less than three of which possess high antibacterial activity.[5]

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2. Bush, M. T.; Goth, A., and Dickinson, H. L.: Flavicin: An Antibacterial Substance Produced by an Aspergillus Flavus, J. Pharmacol. & Exper. Therap. **84**:262 (July) 1945.

3. Goth, A.: The Antitubercular Activity of Aspergillic Acid and Its Probable Mode of Action, J. Lab. & Clin. Med. **30**: 899 (Nov.) 1945.

4. Asheshov, I. N., and Strelitz, F.: An Antibiotic Substance Active Against Mycobacterium Tuberculosis, Science **101**:119 (Feb. 2) 1945.

5. Birkinshaw, J. H.; Bracken, A., and Raistrick, H.: Studies in the Biochemistry of Micro-Organisms: Metabolic Products of A. Fumigatus Fresenius, Biochem. J. **39**:70, 1945.

On the basis of these and a few other reports already available, enthusiastic prognostications as regards the future of antibiotics derived from the aspergilli appear to be well founded.

THE DISEASE ASPERGILLOSIS

Relatively few species of aspergilli have manifested pathogenicity for human beings. Perusal of available authentic data indicates that A. fumigatus has been isolated with greatest frequency from infections caused by the fungus, succeeded rather closely by Aspergillus niger. Aspergillus glaucus, A. flavus and Aspergillus nidulans are others implicated on occasion. Of worldwide consequence, the disease has been unearthed most often in warm, damp climates, and, as with other mycoses, more males than females are affected.[6] Aspergillosis has been disclosed in a child of 30 months and in an adult aged 77 years, though in most cases it apparently occurs in the decades of middle life. Asymptomatic infections caused by these fungi have been encountered on occasion.[7]

Pathologic alterations incited by the aspergilli are hardly unique. Microscopic scrutiny of the granulomatous lesions which eventuate reveals focal zones of necrosis containing the organism in varied stages of maturity and attended by a multifarious cellular infiltrate. Abscesses of diverse configuration and magnitude may supervene after coalescence of such lesions. Although metastatic dispersal of the fungi has not been verified in man, there is ample presumptive evidence to denote such an occurrence.

DIAGNOSIS

The reputation maintained by these fungi as frequent contaminants militates against a diagnosis of aspergillosis unless the evidence for such a conclusion is well founded and steadfast. Direct examination of suspected material may reveal filaments and spore-bearing heads. Presence of only the former, however, does not exclude this disease from the realm of diagnostic possibilities and may merely signify an oxygen supply which is inadequate for fruition. Repeated cultures of the organism in conjunction with stringent efforts to eliminate the likelihood of it being simply a contaminant are estimable and, in combination with the occurrence of fungi in biopsy specimens, of diagnostic import. The significance of immunologic reactions is equivocal. There is a paucity of precise information concerned with antibody response to

6. Conant, N. F., and others: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1945.

7. Donaldson, J. M., Jr.; Koerth, C. J., and McCorkle, R. G.: Pulmonary Aspergillosis, J. Lab. & Clin. Med. **27**:740 (March) 1942.

aspergillus infections,[6] although some authors have expressed the opinion that this fungus, in contrast to certain others designated, does not provoke the development of agglutinins.[8] A positive cutaneous reaction to an extract or vaccine does not discriminate between mere presence of the organism within the body and its role as an instigator of disease. Successful inoculation of animals lends credence to the belief that this fungus is causing a given infection, while failure does not exclude pathogenicity in other situations and in varied circumstances.[1] Roentgenograms, especially in pulmonary aspergillosis, may furnish presumptive evidence of mycotic etiology. In essence, a forthright and indisputable diagnosis of aspergillosis may be difficult of attainment. Microscopic specimens revealing the organism in tissues, combined with repeatedly positive cultures, are adequate for practical purposes.

CLINICAL MANIFESTATIONS

There is considerable speculation as to when aspergillosis may be labeled primary and when it is engrafted on tissues previously impaired by other disease processes. Inadequately controlled diabetes, carcinomatosis, tuberculosis, bronchiectasis, sepsis, cirrhosis of the liver, dysentery, enteritis [9] and even syphilis [8] have been cited as predisposing factors, and a proportion of patients with bronchial asthma and allergic rhinitis are reputedly sensitive to this mold. The term primary aspergillosis would appear to be best suited for cases in which the patients acquired the condition after prolonged exposure to massive doses of the organism and are without discernible evidence of other diseases. In a preponderance of recorded cases the disease has been of the secondary variety.

Once the organism has gained a foothold in the human host, a varied clinical picture may eventuate. Otomycosis has been publicized as the most frequently encountered manifestation of aspergillosis, although there is ample corroboration for the expressed opinion that the organism thrives in the cerumen of the external auditory canal most often as an ingenuous saprophyte,[10] accompanied on occasion with erythema, scaling and crusting merely as sequels to mechanical irritation.

Pulmonary aspergillosis is prone to occur, because of vocational hazard, in farmers, feed mill workers, fur cleaners utilizing rye flour for removal of grease, threshers and others having protracted and intimate

8. Wahl, E. F., and Erickson, M. J.: Primary Pulmonary Aspergillosis, J. M. A. Georgia **17**:341 (Aug.) 1928.

9. Van Ordstrand, H. S.: Pulmonary Aspergillosis with Report of a Case, Cleveland Clin. Quart. **7**:66 (Jan.) 1940.

10. Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935.

contact with birds or grains, and pneumomycoses instigated by the aspergilli have recently been dignified by their legal accession to the category of occupational diseases.[11] Onset of the disease is usually insidious, although it may on occasion be brusque. The course of chronic pulmonary aspergillosis may, and not infrequently does, simulate that of pulmonary tuberculosis, while the acute variety is most often reminiscent of either bronchitis or pneumonia.[9] Varied roentgenologic patterns have been described, the early changes being at times indistinguishable from those of tuberculosis.[9] In an aggregation of 61 patients suspected of having pulmonary tuberculosis, painstaking scrutiny of sputum disclosed aspergillosis in 1,[8] and there appears to be general concurrence of opinion that the disease, masquerading under the guise of tuberculosis, may be more frequent than was previously suspected. The possibility of mycelial fragments retaining acid-fast stain, resulting in confusion with Koch's bacillus, is one to be borne in mind.[8]

Attention has been directed to the aspergilli as a cause of onychomycosis within recent years, a series of 13 cases having been cited in one communication.[12] Nails of both hands and feet may be involved, the clinical picture closely simulating that caused by other fungi. Greenish discoloration of the nail plate contingent on growth of the mold is at times helpful in gross differentiation. Simultaneous infection of nails with both a species of Aspergillus and Trichophyton rubrum has been reported.[12]

Protean manifestations of aspergillosis exclusive of those previously described may, on occasion, challenge the most astute clinician. Osseous involvement has been recorded, though infrequently. Subsequent to extrusion of a small foreign body from the swollen finger of a 13 year old Negro, there developed a fluctuant swelling on the back accompanied with roentgenographic evidence of destructive changes in several vertebrae and ribs. Culture of purulent material aspirated from the lesion on the back resulted in a pure growth of A. fumigatus.[13] An abscess of the cerebrum instigated by a species of this genus has been encountered,[14] as has also a fatal aspergillosis of the meninges.[15] Dacro-

11. Coe, G. C.: Primary Bronchopulmonary Aspergillosis, an Occupational Disease, Ann. Int. Med. **23**:423 (Sept.) 1945.

12. Bereston, E. S., and Waring, W. S.: Aspergillus Infection of the Nails, Arch. Dermat. & Syph. **54**:552 (Nov.) 1946.

13. Shaw, F. W., and Warthen, H. J.: Aspergillosis of Bone, South. M. J. **29**:1070 (Nov.) 1936.

14. Just, E.: Aspergillus Abscess of the Cerebrum, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**:540, 1931.

15. Linck, K.: Fatal Aspergillus Meningitis in Man, Virchows Arch. f. path. Anat. **304**:408, 1931.

cystitis occurring in 1 patient and blepharitis in another were depicted as ophthalmic complications of aspergillus infections primary in the nose.[16] Deep black pigmentation of the vaginal wall distinguished such a mycotic infection involving this portion of the reproductive tract in an 8 year old girl, and the recorders unearthed only one comparable report in the literature.[17] Further illustrative of this fungus in the role of mimic was the case of a patient manifesting cervical and axillary adenopathy in combination with pulmonary pathologic symptoms who was regarded originally as being afflicted with tuberculosis, subsequently regarded as having Hodgkin's disease and ultimately proved to have aspergillosis of both lymph nodes and of the pulmonary structures.[8] Complete occlusion of the pulmonary artery by an elongated thrombus comprised essentially of this mold has been encountered at autopsy. The filiform structure pursued smaller arteries to their terminal branches, and the walls of the vessels were perforated at numerous sites by mycelium.[8] Aspergilli were isolated from a pericecal abscess on one occasion, and lesions of the spleen, kidneys and duodenum have been described, the majority occurring in conjunction with fatal pulmonary aspergillosis.[8] The diagnosis of primary cutaneous aspergillosis is difficult of establishment, and the condition is probably of relatively infrequent occurrence. Mycetomas have, however, been ascribed to this organism on occasion, and A. fumigatus has been demonstrated as a secondary invader in a gunshot wound of the chest.[8]

Discovery of aspergilli in the feces of patients with pellagra occasioned a furor in medical circles at one time. The strain isolated was productive of strong fluorescence when cultured, and it was postulated that absorption from the gastrointestinal tract of photodynamic substances evolved by these fungi might be a factor in the causation of pellagra.[18] Though alluring, this theory has not received widespread recognition. As concerns the danger associated with ingestion of mold-tainted foods, it is more than probable that these fungi are the conspicuous but usually harmless cause of damage or decay, in which situation, however, they are accompanied with bacteria or other organisms which are not grossly apparent yet which may be and often are dangerous.[1] The presence of mold in such situations is interpreted, therefore, as a warning.

Evidence has been adduced within recent years which indicates that many cases of reputed arsenical wallpaper poisoning, seldom an indis-

16. Rosenvold, L. K.: Dacrocystitis and Blepharitis Due to Infection by Aspergillus Niger, Am. J. Ophth. **25**:588 (May) 1942.

17. Weinstein, L., and Lewis, R. M.: A Case of Fungus Infection of the Vagina, Yale J. Biol. & Med. **11**:85 (Oct.) 1938.

18. Jobling, J. W., and Arnold, L.: The Etiology of Pellagra, J. A. M. A. **80**:365 (Feb. 10) 1923.

putable medical entity at best, were actually examples of infection with aspergillosis.[19] Chemical analyses performed in at least 2 cases labeled as instances of this type of poisoning did not reveal sufficient quantities of the chemical to warrant an etiologic relationship, and numerous investigators have noted an abundant growth of mold on wallpaper which supposedly was implicated as the source of the arsenic. Clinical manifestations on frequent occasions have been analogous to those encountered with pulmonary aspergillosis, and the green particles, supposedly arsenic, inhaled by the patients were probably in many instances the green spores of A. fumigatus.[19]

Notwithstanding the alleged efficacy of an imposing array of reputed therapeutic agents, treatment of aspergillosis is often unsatisfactory. The sulfonamide compounds and the newer antibiotics have not, so far as can be ascertained, proved especially valuable, and reliance must continue to be placed on intensive and prolonged administration of the iodides. An established diagnosis of this disease, especially as it concerns visceral cases of long standing, must entail in most instances a circumspect prognosis.

REPORT OF A CASE

B. O., a white infant, was born on July 15, 1938. No physical abnormalities were detected when the child was examined shortly after birth, but a roentgenogram of the chest at the age of two weeks demonstrated bronchopneumonia.

On Dec. 28, 1940, the child was admitted to the Pediatrics Service of the University of Michigan Hospital because of an apparently inflammatory consolidation of the medial portion of the lower lobe of the right lung, which had been manifest since resolution of the bronchopneumonia at the approximate age of six weeks. At no time had the patient been severely ill, and sulfonamide compounds by mouth had on numerous occasions effected an apparently evanescent amelioration in objective manifestations. There were no abnormal physical findings other than the area of consolidation, and the roentgenologist was of the opinion that tuberculosis, suppurative pneumonitis and pulmonary abscess could not be excluded from the realm of diagnostic possibilities. The results of laboratory studies were well within normal limits, and after two weeks of hospitalization, a course of sulfonamide drugs having been administered, the child was discharged, the film of his chest showing a moderate amount of clearing at the involved site.

By midyear of 1942 the patient had had oft repeated bouts of slight fever accompanying manifestations of a mild respiratory infection, the roentgenogram of his chest on each occasion exhibiting consolidation of the lower lobe of the right lung. One episode was associated with pleural effusion on the right side. Direct examination, culture and inoculation of the exudate into guinea pigs were not productive of etiologic clues. In August 1942 the child was readmitted to the hospital with a tender, fluctuant mass approximately the size and shape of a child's hand located at the lower costal margin in the left anterior axillary line. A roent-

19. Hay, H. R.: Arsenical Wallpaper Poisoning or Aspergillosis, J. Trop. Med. & Hyg. **42**:126 (May 1) 1939.

genogram of the chest revealed an unidentified but localized periosteal lesion involving the sternal portion of the left seventh rib and underlying the soft tissue tumor. Culture of purulent material aspirated from the lesion on two occasions resulted in the growth of a mold, subsequently identified as A. fumigatus.[20] Incision and drainage of the abscess demonstrated it to be of a multilocular structure.

At the age of 5, after two years of moderately good health, the child was found on roentgenologic examination to have pneumonia of the lower lobe of

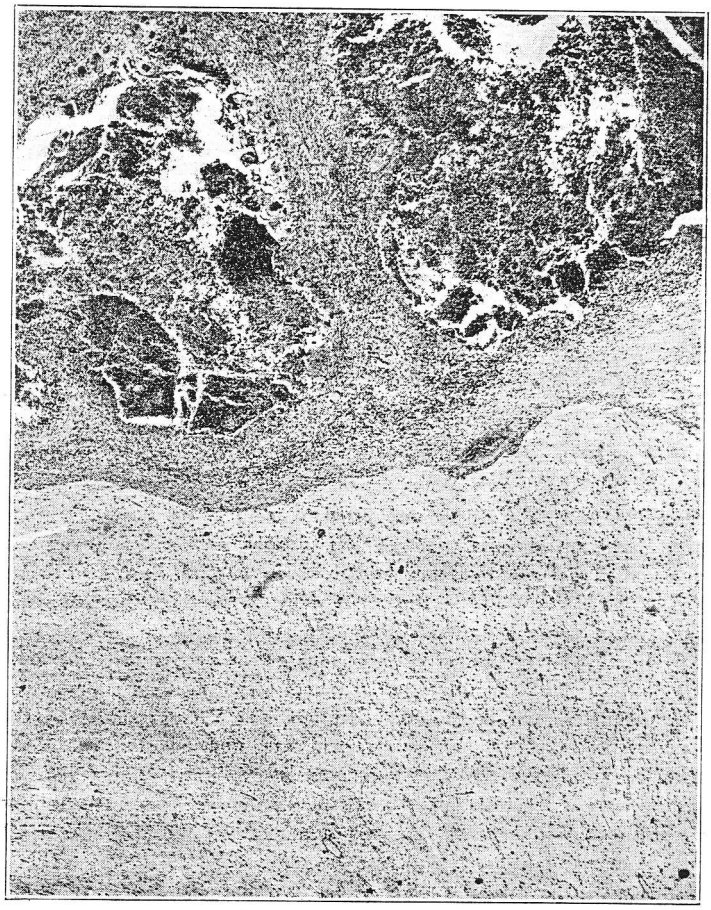

Fig. 1.—Granulomatous foci involving the leptomeninges. These lesions contained an abundance of mycelial and filamentous structures but did not encroach on the cerebral cortex in this area. (Low power.)

the left lung, with minimal accumulation of pleural fluid at the left base. During subsequent months he had a persistent fever, the temperature ranging as high as 102 F. Administration of sulfonamide drugs appeared to be ineffective, and

20. Dr. C. W. Emmons, Principal Mycologist, United States Public Health Service, identified the organism.

a course of penicillin resulted in no notable improvement. Comprehensive laboratory studies, with exception of the cultures previously described, had been consistently noncontributory.

As a semi-invalid, the patient remained at home until January 1946, when, at the age of 7½ years, he began to have frequent episodes of dizziness, occipital headache, projectile vomiting and staggering gait. On admission to the hospital he had pneumonia of both lower lobes and demonstrable evidence of a cerebellar lesion, which was found at operation to be an abscess and from which A. fumigatus was again cultured. Despite intensive and protracted treatment which included administration of penicillin, various sulfonamide compounds, potassium iodide and inhalations of ethyl iodide, the child's condition became progressively worse

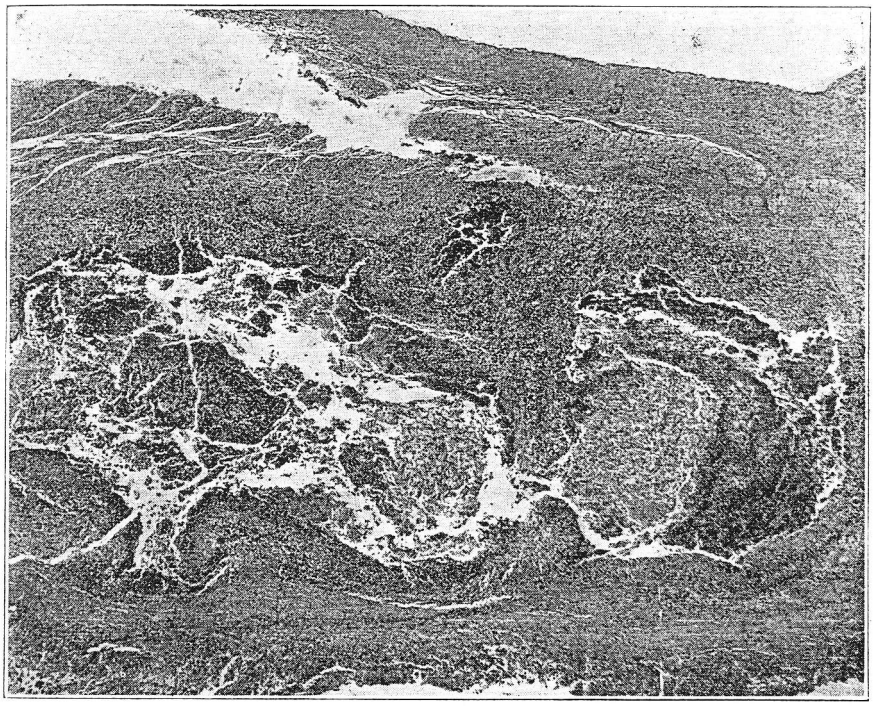

Fig. 2.—Mycotic myocardial abscesses involving the entire thickness of the wall of the left ventricle. (Low power.) The photomicrograph presented as figure 4 was made from the lesion at the left.

and recurrent abscesses, from several of which A. fumigatus was isolated, developed on the thoracic wall, the forehead and the right ankle. Death intervened on Sept. 6, 1946.

Complete necropsy was performed under the direction of Dr. C. V. Weller, Professor of Pathology, University of Michigan Medical School. Abscesses of variable size involving the brain, dura, heart, lungs, mediastinum, lymph nodes, spleen, liver, right kidney and right ankle were noted grossly. There was fibrinopurulent bronchitis, lobular pneumonia, obliterative fibrous pleuritis and an old perforation of the left thoracic wall, with associated abscess formation. Decubital

ulcers were present over the sacrum and the right posterior-superior iliac region of the spine. Early generalized atherosclerosis was apparent, as was also serous atrophy of all adipose tissue. Numerous cultures inoculated from various sites were productive of a growth of A. fumigatus.

Subsequent microscopic changes were especially notable. The dura mater showed an organizing subacute pachymeningitis, with frequent hemosiderin-laden phagocytes, an abundance of granulation tissue and surface necrosis. In the purulent exudate were numerous mycelial and filamentous structures, possessed of terminal and intercalary bulbous dilatations. Beneath areas in which the fungus was apparent in profusion there occurred a layer of multinucleate giant cells of the Langhans type, with, in addition, abundant lipid histiocytes.

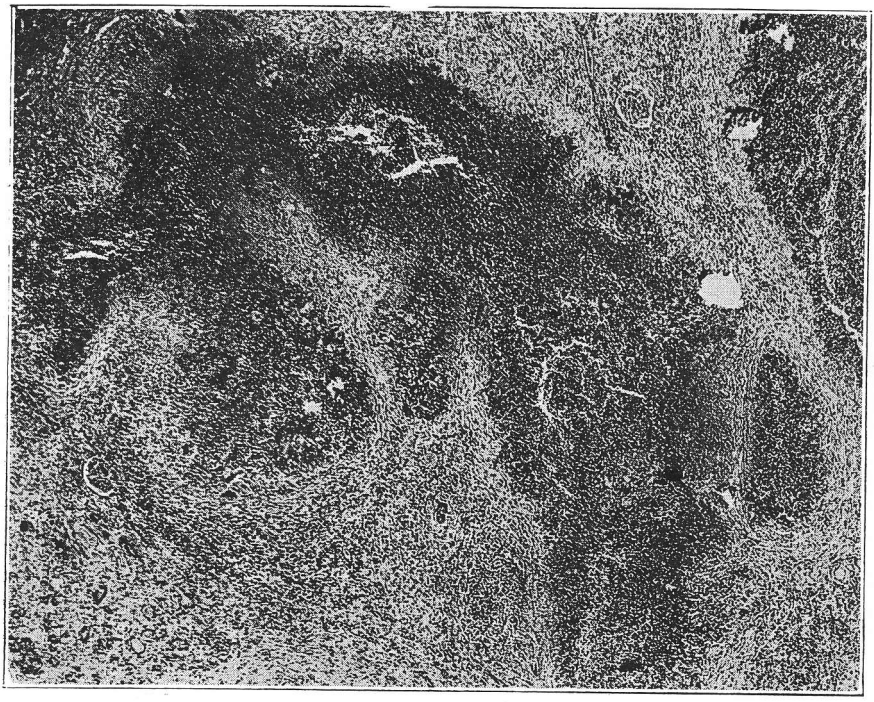

Fig. 3.—A moderately large granulomatous renal lesion. Numerous such foci were present in the kidneys, but myceliums occurred in sparse numbers. Partially destroyed glomeruli are apparent in the upper right and lower left hand corners with, in addition, a few tubules at the latter site. (Low power.)

The leptomeninges of the brain were markedly thickened, and there was an associated exudate similar to that noted in conjunction with the dura (fig. 1). An active base of granulation tissue partially limited abscessed areas containing the fungus from the brain itself, but there was patchy involvement of the cerebral cortex. Occasional foci exhibited a caseous type of necrosis. The cortex of the brain also revealed pronounced acute passive congestion and edema.

Microscopic sections of the heart showed granulomatous tissue involving the subepicardial adipose layer, the root of the aorta and the wall of the right atrium

in addition to relatively large myocardial and subendocardial abscesses which had ruptured into the left ventricle (fig. 2). Several of these same sites were infiltrated by variable numbers of organisms comparable to those previously described. Early coronary artery atherosclerosis was apparent.

The lungs revealed a widespread fungus-instigated pneumonitis accompanied with granulomatous masses similar to those previously described as occurring in the meninges. Mycotic abscesses were apparent in the spleen, liver, kidneys (fig. 3) and lymph nodes.

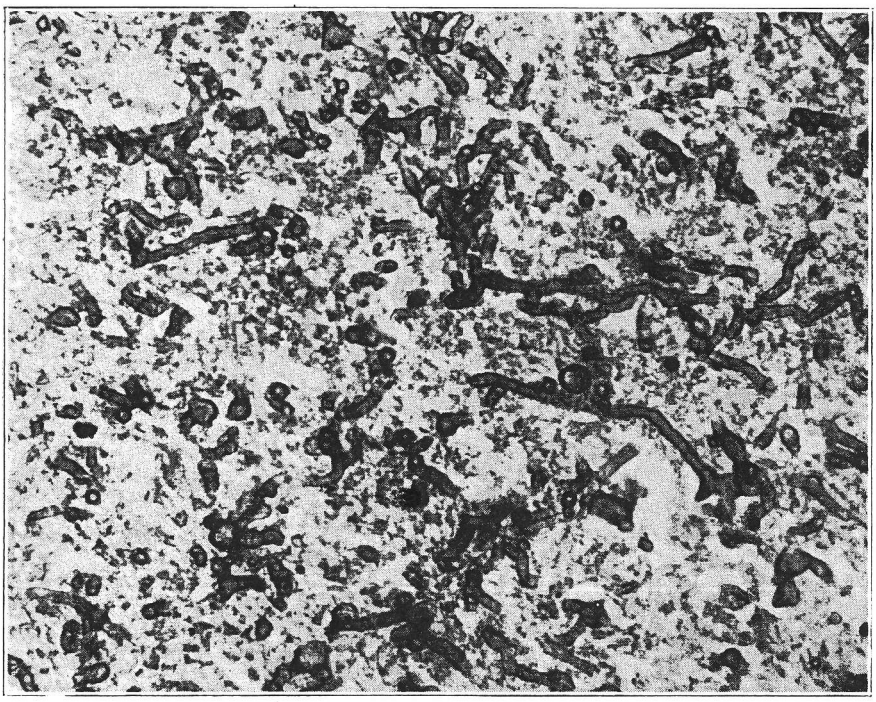

Fig. 4.—Numerous mycelial and filamentous structures, having terminal and intercalary bulbous dilatations, as they occurred in the abscesses involving the left ventricular wall. (High power.)

COMMENT

Though admittedly not verified, it would appear that this child's aspergillosis may have been implanted at the time of or shortly after birth. Indisputable, however, is the possibility that the disease was superimposed at a later date on pulmonary structures adequately prepared for such an invasion by a previously existent lesion.

Consistently normal results from laboratory studies, with the exception of cultures positive for A. fumigatus, were a feature of the disease process. Pneumonia, tuberculosis, suppurative pneumonitis and

pulmonary abscess were the roentgenologic diagnoses which appeared to be among the most logical explanations for a pulmonary lesion which in retrospect may well have been caused by A. fumigatus.

Aspergillosis involving virtually every major structure of the body to a variable extent has not previously been recorded, so far as can be ascertained, and suggests hematogenous dissemination of the organism. Invasion by the mold of such structures as the myocardium and kidneys was especially remarkable.

The frequent presence of atheromatous lesions throughout the arterial tree of the bronchopulmonary system is a feature common to all types of pulmonary aspergillosis [21] and emphasizes the probable cause of a grossly demonstrable atherosclerosis in the case reported.

SUMMARY

The aspergilli, a genus of molds, are notorious as laboratory contaminants. On rare occasion they may be the etiologic agent in production of a specific disease, and in other circumstances they may, as a source of antibiotics, function as serviceable implements of medicine.

Manifestations of the disease aspergillosis are protean, and the diagnosis may be difficult of establishment. The lungs are most frequently the site of primary involvement. Treatment is often disconcerting, there being no specific therapeutic agent.

A unique case of aspergillosis with extensive and widespread involvement of various structures is reported, accompanied with details of the gross and microscopic pathologic changes.

21. Jacobson, H. P.: Fungous Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1932.