

## Chronic Fungal Sinusitis in Apparently Normal Hosts

RONALD G. WASHBURN,<sup>1</sup> DAVID W. KENNEDY,<sup>3</sup> MARTIN G. BEGLEY,<sup>2</sup>  
DAVID K. HENDERSON<sup>1</sup> AND JOHN E. BENNETT<sup>1</sup>

### Introduction

Fungal infection of the paranasal sinuses is being recognized and reported with increasing frequency worldwide (1, 3, 30, 50, 74, 75). Plaignaud (60) reported the first case of possible fungal sinusitis in 1791; a 22-year old soldier with maxillary pain had a "fungus tumor" which was said to be cured by cautery. A more specific diagnosis of noninvasive aspergillosis of the paranasal sinus was established in a case reported in 1885 (69). The first well-documented case of invasive fungal sinusitis was reported by Oppe in 1897 (54); in this patient, an *Aspergillus* infection eroded through the bony walls of the sphenoid sinus into the cerebrum. The invasive form of fungal sinusitis was again reported in 1927 by Wright (85) in 2 cases with extension into the orbit. These patients were treated with irradiation and were then lost to follow-up.

Today, 2 types of fungal sinusitis are recognized: 1) chronic noninvasive disease (3, 37, 38, 45, 58, 61, 64, 71, 74-77), and 2) invasive disease which may be either chronic (2, 5, 8, 14, 21, 23, 27, 28, 30, 31, 39, 43, 50, 51, 59, 63, 64, 66, 70, 72, 80, 83, 87, 89) or acute (13, 44, 51, 88) depending upon the host. Chronic noninvasive fungal sinusitis may be defined as the presence for months or years of a mycelial mass which remains confined to the lumen of the sinus cavity. A local inflammatory response may accompany the mass, but fungi do not destroy the local architecture. In contrast, invasive fungal sinusitis is characterized by insidious extension across the mucosa into bone and other contiguous structures such as the orbit and brain. Recently,

Katzenstein and coworkers (33, 34, 82) proposed yet another diagnostic category in patients with histories of asthma and recurrent sinusitis: allergic *Aspergillus* sinusitis. Their retrospective analysis of sinus biopsy slides revealed hyphae within mucin which also contained eosinophils and Charcot-Leyden crystals. The unresolved issue is whether the hyphae are simply saprophytes growing in inspissated mucus of a poorly drained paranasal sinus or are antigens which are crucial in the allergic process. In either case, surgical removal of inspissated mucus and improved drainage would seem essential in management. Only in the latter case might antifungal therapy be useful theoretically to decrease fungal growth in mucus. Critical case studies with prolonged follow-up would be helpful in resolving these issues. The well known entities of invasive acute paranasal sinusitis due to mucormycosis and aspergillosis have been amply described in this journal (57, 88) and elsewhere (4, 6, 13, 24, 43, 44, 46, 47, 51, 64, 78); no further attention will be given here. Rather, our report will concern the chronic forms of fungal sinusitis.

The array of fungi which have caused fungal sinusitis is broad (Table 1). It should be noted that hyphal organisms were responsible in nearly all of the reported cases. In the only described exceptions of which we are aware, *Sporothrix schenckii*, a *Candida* species, and *Rhinosporidium seberi* were the responsible organisms. Finally, it is important to note that most of these same fungi in Table 1 are commonly cultured from the mucosal surfaces of the nose and sinuses as normal commensals. Their presence probably results from adherence of inhaled ubiquitous fungal spores to mucus secretions, and is generally not considered to indicate an etiologic role.

We report here our experience with 10 immunologically normal patients having chronic fungal infections of the paranasal sinuses. Included are 7 patients with chronic invasive fungal sinusitis caused by *Aspergillus avenaceus*, *Aspergillus flavus*, or the dematiaceous molds *Bipolaris (Drechslera)* spp., *Curvularia lunata*, and *Exserohilum rostratum*. Dematiaceous or brown-walled fungi are hyphal organisms which produce pigment in culture and

From the Clinical Mycology Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases<sup>1</sup> and Department of Radiology,<sup>2</sup> National Institutes of Health, Bethesda, Maryland; and Department of Otolaryngology—Head and Neck Surgery,<sup>3</sup> The Johns Hopkins University, Baltimore, Maryland.

Dr. Washburn's current address: Division of Infectious Diseases, Bowman Gray School of Medicine, 300 S. Hawthorne Road, Winston-Salem, NC 27103.

Address reprint request to: John E. Bennett, M.D., Head, Clinical Mycology Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Room 11N107, Building 10, Bethesda, MD 20892.

TABLE 1. Agents of chronic fungal sinusitis: Appearance in tissue

Current Name	Other Names	Reference
<b>Broad Nonseptate Hyphae</b>		
<i>Rhizopus oryzae</i>	<i>Rhizopus arrhizus</i>	4, 18, 19, 24, 29, 46, 57
<i>Rhizomucor pusillus</i>	<i>Mucor pusillus</i>	
<i>Rhizopus microsporus</i> var. <i>rhizopodiformis</i>	<i>Rhizopus rhizopodiformis</i>	
<i>Cunninghamella bertholletiae</i>		7
<i>Conidiobolus coronatus</i>	<i>Entomophthora coronata</i>	12
<i>Basidiobolus haptosporus</i>	<i>Basidiobolus ranarum</i>	15
<i>Absidia corymbifera</i>		65
<b>Narrower Septate Hyphae</b>		
<b>Nonpigmented fungi</b>		
<i>Aspergillus</i> spp.		3, 14, 17, 21, 25-27, 30, 31, 37-39, 41, 45, 49, 50, 58, 64, 66, 75, 76, 80, 83, 88, 89
<i>Pseudallescheria boydii</i>	<i>Allescheria boydii</i> <i>Petriellidium boydii</i>	9, 30, 51, 68
<i>Scedosporium apiospermum</i>	<i>Monosporium apiospermum</i>	
<i>Penicillium</i> spp.		52
<i>Fusarium</i> spp.		79
<i>Paecilomyces</i> spp.		55, 61
<i>Schizophyllum commune</i>		36
<b>Dematiaceous fungi</b>		
<i>Bipolaris</i> spp.	<i>Drechslera</i> <i>Helminthosporium</i>	1, 28, 63, 72, 77, 87
<i>Exserohilum rostratum</i>	<i>Drechslera rostrata</i>	1, 56
<i>Curvularia</i> spp.		40, 59
<i>Alternaria</i> spp.		1, 5, 23, 40, 51, 53, 70
<i>Cladosporium</i> spp.		8, 37
<b>Rounded Forms</b>		
<i>Candida</i> sp.		32
<i>Sporothrix schenckii</i>		51
<i>Rhinosporidium seeberi</i>		67

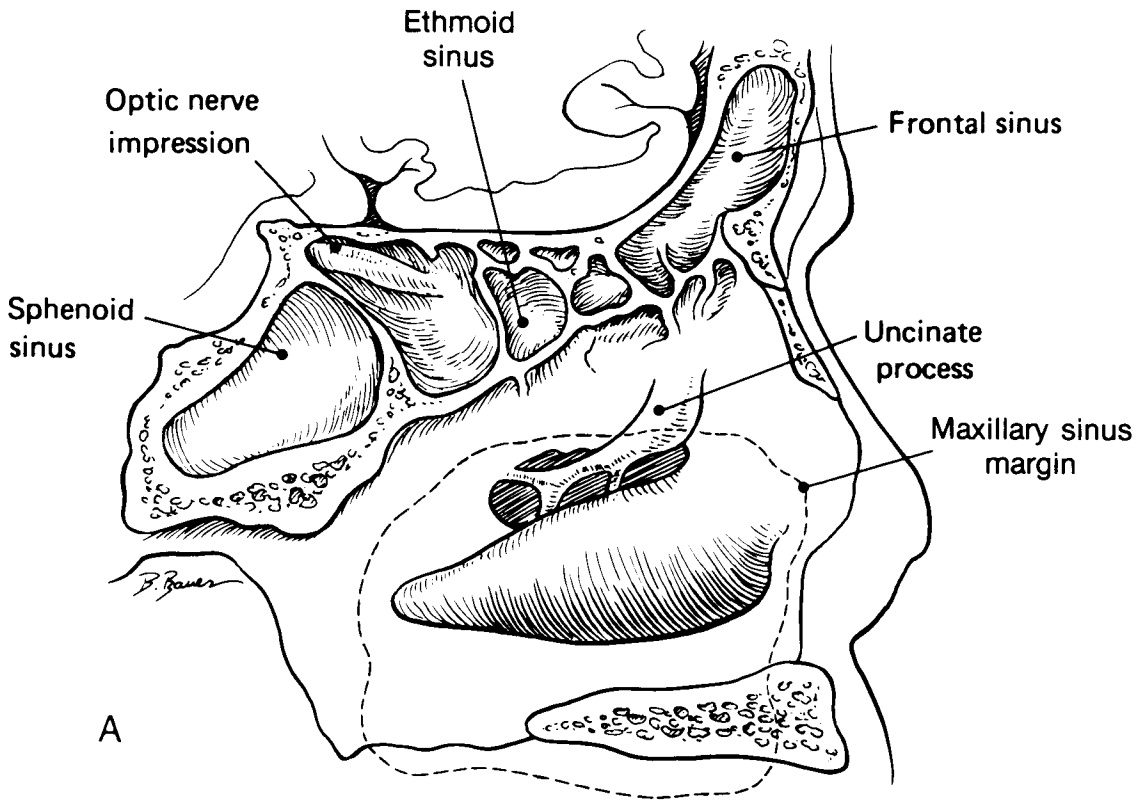
usually also in invasive human infections. For comparison with invasive disease, we report 3 patients with noninvasive fungal sinusitis caused by either *Aspergillus* spp. or *Pseudallescheria boydii*. After reviewing the anatomy of the paranasal sinuses and neighboring structures, we shall outline the clinical course of each patient in our series, and discuss pertinent histopathologic and radiographic findings, as well as approaches to therapy.

### Anatomy

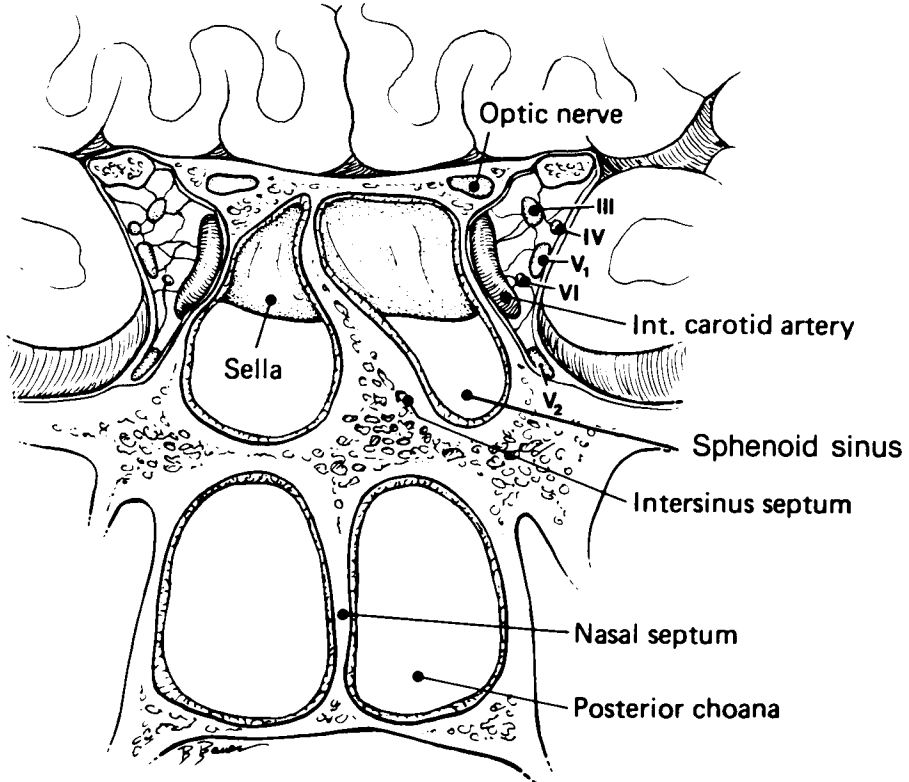
An understanding of the clinical manifestations of chronic invasive fungal sinusitis requires familiarity with the anatomy of the paranasal sinuses and neighboring structures (Fig. 1). Given the fact that this slowly progressive infection can cross local anatomic barriers, one may observe lesions arising from extension through the walls of a sinus into any of the structures listed in Table 2. For example, erosion of the infection through the superior wall of the sphenoid sinus could lead to invasion of the sella turcica (21, 25, 43); violation of the lateral wall could result in unilateral blindness due to compression of the optic nerve (14). Extension of infection peripherally along the optic nerve might give rise to orbital apex syndrome, superior orbital fissure syndrome, or orbital abscess. In 3 cases of probable chronic invasive

aspergillosis of the sphenoid sinus, lateral extension compressed the cavernous sinus (21, 43, 83). Erosion from the ethmoid air cells laterally through the lamina papyracea could displace the eye, resulting in either hypertelorism or proptosis (41, 64). Invasion superiorly through the ethmoid sinus has resulted in frontal lobe abscess formation (41). Proptosis can also arise from invasion through the roof of the maxillary sinus (31, 43, 50, 66, 80, 89). When infection erodes through the floor of the maxillary sinus, lesions of the hard palate may be produced (23, 70). Traversal of chronic fungal infection through the posterior wall of the frontal sinus has initiated abscess formation in the frontal lobes (8). Chronic fungal meningitis, an infection which is difficult to cure even with prolonged courses of amphotericin B, has resulted when meninges have been seeded by extension of fungal infection either from the frontal sinuses or from the sphenoid sinus (2, 17, 25, 43). One reported case of probable chronic frontal sinusitis was believed to erode along the ventral surface of the brain, ultimately producing a fungal mycotic aneurysm at the junction between the posterior cerebral artery and internal carotid artery (2).

The frontal and maxillary sinuses communicate with the nose via the ostiomeatal complex, a term used to describe the narrow passages within the anterior ethmoid and middle meatus. Thus the maxillary sinus opens into the narrow channel of the ethmoidal infundibulum. The ethmoidal infundibulum drains into the inferior portion of the hiatus semilunaris and this, in turn, opens into the middle meatus and subsequently into the nose.



A



B

FIG. 1. A. Sagittal section demonstrating the relative anatomy of the frontal, ethmoid, and sphenoid sinuses. The maxillary sinus (dashed line) ostium opens lateral to the uncinete process. B. Coronal section demonstrating the sphenoid sinus and its relationships.

TABLE 2. Structures that may be involved by contiguous extension of fungal sinusitis

Paranasal Sinus	Adjacent Structure
Maxillary	Maxillary bone, skin of cheek Orbit, orbital floor, infraorbital vessels and nerve Lateral wall of nose, including turbinates Ethmoid sinus Hard palate Pterygopalatine space
Ethmoid	Cribriform plate, olfactory bulb Orbital plate of frontal bone, frontal lobe of brain Frontal sinus Sphenoid sinus Lamina papyracea, orbit, and skin near inner canthus Maxillary sinus
Sphenoid	Frontal lobe of brain Dorsum sella, pituitary gland Clivus, brainstem Optic nerve, cranial nerves III, IV, V, and VI Sphenopalatine canal, artery, nerve, and ganglion Internal carotid artery, cavernous sinus Ethmoid sinus
Frontal	Frontal lobe of brain Ethmoid sinus Orbit Skin of forehead

Similarly, the frontal sinus typically opens into the superior aspect of the middle meatus by a tortuous communication. This channel is deflected in its course by the most anterior ethmoid cells and the medial wall of the ethmoidal infundibulum (Fig. 1).

There is increasing evidence that the primary cause of maxillary and frontal sinusitis is obstruction within the narrow passages of the ostiomeatal complex (10, 35, 73). It has been suggested that a similar mechanism is also important in the pathogenesis of noninvasive fungal disease of the maxillary and frontal sinuses (74). Thus, the underlying problem in invasive fungal maxillary sinusitis may be obstruction within the narrow passages of the ostiomeatal complex as a result of chronic inflammation, allergy, or anatomic deformity. The fungal growth then begins on retained secretions within the affected sinus.

More posteriorly, the sphenoid sinus and the posterior ethmoid sinuses communicate directly with the spheno-ethmoidal recess of the nose via their individual ostia. As the ostium is the primary area for obstruction in these cells, non-invasive fungal disease is typically confined to the sphenoid sinus or to one cell of the posterior ethmoid. Extension of sphenoid fungal disease into the posterior ethmoid strongly suggests invasion.

## Case Reports

### *Chronic invasive fungal sinusitis*

#### *Case 1*

A 38-year-old Sudanese woman presented in July 1982 with a 1-year history of left-sided headache, nasal congestion, impaired vision on the left, and left-sided hearing loss associated with serous otitis. A computerized tomographic (CT) scan obtained while she was in Indiana disclosed a mass occupying the left retro-orbital and pterygopalatine regions. A nasopharyngeal biopsy performed at an outside hospital revealed septate hyphae within

granulomatous inflammation (Fig. 2), and a culture grew *Aspergillus avenaceus*. Serous otitis due to obstruction of the left eustachian tube was treated by placement of a myringotomy tube.



FIG. 2. Case 1. High-power view of *Aspergillus* hyphae within granulomatous inflammation of patient with subtemporal extension of chronic invasive disease (hematoxylin and eosin, and Gomori methenamine stain,  $\times 1000$ ).

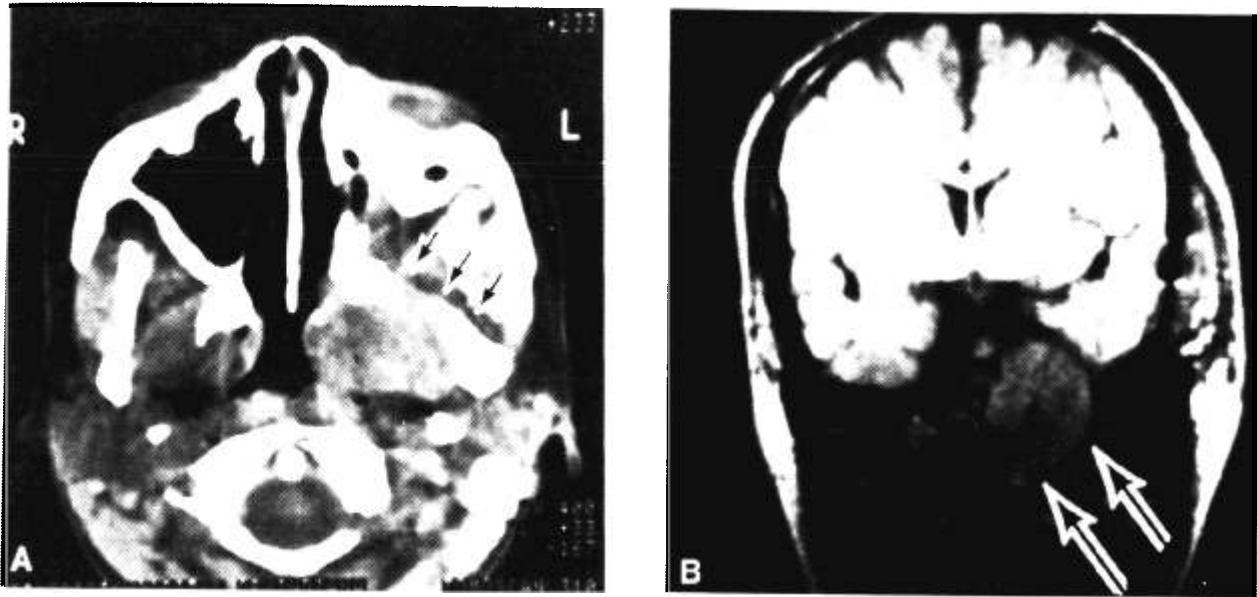


FIG. 3. Case 1. A. CT scan axial image showing invasive mass in left pterygopalatine fossa, and erosion of sphenoid bone, anterior clinoid process, and pterygoid bone. B. MRI coronal view of left subtemporal mass, with superior displacement of temporal lobe.

A repeat CT scan in September 1982 showed erosion of the clivus, pterygoid plate, and left lateral wall of the sphenoid sinus. A soft-tissue mass involved the left nasal cavity and maxillary, ethmoid, and sphenoid sinuses, extending across the midline. Resection of a large mass of granulomatous tissue was achieved via a left frontotemporal craniotomy and partial lateral rhinotomy with left external ethmoidectomy and sphenoidectomy. Postoperatively, the patient received a 3-g course of amphotericin B along with flucytosine over 3 months.

The patient's headache began to recur towards the end of treatment, and the development of left facial pain in June 1983 prompted repeat CT scanning which showed a mass in the pterygopalatine fossa; this invaded the pterygoid muscle and showed enhancement adjacent to the cavernous sinus on the left. A partial resection was achieved by a transmaxillary approach, and a culture was again positive for *A. avenaceus*. The patient was retreated with 2.5 g amphotericin B and flucytosine over 2 months.

A year later, in September 1984, she experienced recurrent left-sided headaches, associated with new ipsilateral ptosis and onset of difficulty in swallowing due to a sense of fullness in the left pharyngeal area. A CT scan showed a left peripharyngeal mass extending anteriorly and superiorly into the left ethmoid, maxillary, and sphenoid sinuses, and retro-orbital area; posterior extension was into the sphenoid bone, pterygopalatine fossa, infratemporal fossa, and middle cranial fossa (Fig. 3A). A Caldwell-Luc procedure was performed, and the nasopharyngeal area and left pterygopalatine fossa were explored. The lesion again contained septate hyphae and was culture positive for *A. avenaceus*; another gram of amphotericin B was administered. Adherence of dura to adjacent bone prevented resection of the intracranial mass during a second craniotomy in January 1985.

Following the patient's transfer to the National Institutes of Health (NIH) in February 1985, a CT scan failed to clearly delineate whether the mass actually invaded parenchyma of the left temporal lobe, but a magnetic resonance image (MRI) showed that it was extradural, displacing the temporal lobe super-

iorly (Fig. 3B). The only notable laboratory finding was a peripheral blood eosinophilia of 7% (total white blood cell count, 6,000/mm<sup>3</sup>). Oral therapy was initiated with an investigational antifungal agent, terbinafine, 500 mg daily (Sandoz, Vienna, Austria). In November 1985, the patient developed severe left facial pain, headache, and left 3rd and 4th cranial nerve palsies. Radiographically, there was some increase in the degree of elevation of the dura in the middle cranial fossa. The patient was started on a regimen of amphotericin B and underwent a facial-degloving approach with subtotal resection of the infratemporal fossa mass. The lesion consisted primarily of granulation tissue, but superiorly an abscess was present, extending into the middle fossa, under the dura. Medially, the eroded clivus and posteriorly-exposed posterior fossa dura were identified from within the mass. The area was drained into the nose. The patient's pain and cranial nerve palsies resolved; however, radiographically the lesion was not dramatically reduced in size.

The patient did well subsequently, continuing with occasional headaches; however, by February 1987, her headaches began to be incapacitating. It was therefore decided to discontinue treatment with terbinafine and substitute 200 mg of itraconazole daily. Failure of the headaches to improve by May, 1987 led us to further debulk the area with laser treatment, gaining access endoscopically through the nose. Infiltrating hyphae consistent with *Aspergillus* were again found on pathology. Treatment with itraconazole was continued. Surgery led to a temporary reduction in pain. Six months postoperatively, the patient had moderately severe headaches but no neurological abnormalities.

*Comment:* Most cases of invasive *Aspergillus* sinusitis in the United States have been caused by *A. fumigatus* (11, 88), *A. oryzae* (11, 27) or *A. flavus* (27, 31, 89), but for reasons not entirely clear, *A. flavus* has caused nearly all cases in the Sudan (42, 50, 66, 80). This ubiquitous saprophyte (50) can be cultured from the environment in the northern portion of the Sudan, including straw-thatched roofs

and cereal grains commonly eaten by the inhabitants (80). The infection is rare in the more humid southern part of the country. It has been postulated that nasal polyp formation in the many natives of the arid and windy northern area favors overgrowth of fungus in the upper airways (66, 80). Combined with poor sinus drainage, the increased organism burden may eventually lead to invasive infection.

Infection in Case 1 was caused not by *A. flavus* but by a closely related organism, *A. avenaceus*. The patient never resided in the rural areas of northern Sudan. Her sinusitis was apparently acquired while she was living in the arid city of Khartoum, as was thought to be true for 2 patients discussed by Veress and coworkers (80). Her disease then became clinically apparent only after she moved to Indiana. It seemed likely that the infection began in the ethmoid air cells or maxillary sinuses and then extended into the sphenoid sinus and neighboring structures. Such a sequence of events would be consistent with the observation by others that invasive aspergillosis of the sphenoid sinus was usually associated with infection in the ethmoidal and maxillary sinuses (14, 21, 30, 39, 43, 49, 50, 83).

After surgical debridement of diseased tissue, our patient's infection relapsed several times. The tendency for invasive *Aspergillus* sinusitis to recur has been previously noted (31, 43, 64, 89). Surgical procedures became increasingly difficult due to distortion of normal anatomical landmarks by chronic infection or scar tissue. This problem arose also in several patients in the series of Milosev and coworkers (50). In Case 1, the size and location of the intracranial lesion prohibited complete surgical resection, an unfortunate circumstance also encountered in several patients reported by Green (27) and McGill (43); however, in a few cases where intracranial extension was better circumscribed and the location permitted surgical removal, long-term cures were achieved (50).

In our patient, repeated surgery and a large total dose of amphotericin B combined with flucytosine seemingly exerted little impact upon progression of the disease. During 2 years of investigational antifungal therapy with terbinafine, the size of her subtemporal mass did not change but fungi remained visible in the mass. The patient is currently receiving another experimental systemic antifungal drug, itraconazole.

### Case 2

A 44-year-old white school principal from New York developed rhinorrhea and a slightly tender swelling of the soft palate in 1976. Initially, this appeared to resolve, but recurred about 3 months later associated with pain in the right eye and diplopia. Sinus films demonstrated haziness of the right maxillary and ethmoid sinuses. The patient underwent an intranasal ethmoidec-

tomy. Histopathology revealed an inflammatory cell infiltrate with a predominance of plasma cells plus granulation tissue and fibrous connective tissue. The diagnosis of plasmacytoma was entertained, but serum protein electrophoresis was normal.

A subsequent CT scan showed a persistent mass in the ethmoid area. Examination at that time demonstrated a mass completely obliterating the superior portion of the nasal cavity, surrounded by yellowish pus. The patient had a significant septal deformity. Polytomography revealed an opacified right ethmoid and maxillary sinus, with the mass extending into the right nasal chamber. The right frontal sinus showed mucosal thickening. Findings in the right sphenoid sinus included opacification, possible erosion of the anterior wall, and moderate elevation of the planum sphenoidale.

The patient underwent a right Caldwell-Luc procedure, external ethmoidectomy, and sphenoidotomy with the finding of inflamed hypertrophic tissue throughout. The tissue contained necrotic and fibrinopurulent material, but no evidence of tumor. Fungal stains were negative. The patient's symptoms subsequently resolved and he later underwent a nasal septal reconstruction.

He did well until 1978, when the diplopia recurred. Examination revealed regrowth of the intranasal mass, but purulence was now less evident. CT confirmed regrowth of the mass, with opacification of all the sinuses on the right side and erosion of the roof of the ethmoid sinuses posteriorly. Extensive intranasal biopsy revealed infiltrating *Aspergillus*, and this was confirmed as *Aspergillus flavus* on culture.

After 2 weeks of treatment with amphotericin B, the patient underwent resection of the area through a Weber-Ferguson lip splitting incision and lateral rhinotomy. At surgery, the disease consisted of masses of hypertrophic and fibrous tissue, with inspissated area of thick brown jelly-like fungal material. The orbital periosteum was largely intact and the orbital fat was not invaded. In the posterior ethmoid the dura was exposed, and the sphenoid sinus was expanded in the region of the optic nerve. The bone over the optic nerve was eroded and some residual disease remained in this area. The presence of fluorescence under ultraviolet light proved to be helpful in determining the extent of fungal bony invasion during the procedure. All grossly involved bone was drilled away and the frontal sinus was surgically collapsed.

The patient initially refused further therapy, but eventually reconsidered when persistent disease became evident on the optic nerve. Beginning 4 months postoperatively, the patient received 1.2 g of amphotericin B over 2 months. His residual disease slowly resolved, and the patient remained free of disease during 9 years of follow-up.

*Comment:* Mature plasmacytes were so abundant within the submucosal infiltrate that the patient was initially believed to have a plasmacytoma. The case illustrates the important point that chronic invasive fungal sinusitis may escape diagnosis for years. Not until the third surgical procedure were invasive hyphae demonstrated by careful examination of many mucosal sections stained with methenamine silver.

### Case 3

A 44-year-old woman from Florida with a history of nasal polyps and congestion developed severe headaches, lightheadedness, leg weakness, and diminished sense of smell beginning in December

1981. In February 1982, a CT scan performed at a local hospital was said to demonstrate a soft-tissue mass which invaded both frontal lobes, with midline shift, obliteration of the frontal horn of the right lateral ventricle, and cerebral edema, plus bilateral soft-tissue densities within the ethmoid sinus. A frontal craniotomy was performed and a dark reddish-brown mass was resected from the frontal lobes and left frontal sinus, both of which contained wide irregular hyphae and a granulomatous inflammatory response. Some hyphae appeared to be intracellular. Abundant eosinophils and plasmacytes were also present. The specimen from the frontal lobe grew *Drechslera biseptata*, and material from the frontal sinus yielded another dematiaceous mold, *Curvularia lunata*. Both isolates were identified by Dr. K. J. Kwon-Chung and the identity of *D. biseptata* was confirmed by Dr. M. B. Ellis. Isolation of 2 different potential pathogens from adjacent infected sites raised the question whether 1 isolate might be a contaminant. Both were obtained in pure culture and with heavy growth. Unfortunately, the 2 cannot be distinguished morphologically in tissue. No portal of entry for the *D. biseptata* could be found outside the paranasal sinuses. Therapy was initiated with amphotericin B and a brief course of parenteral dexamethasone.

Upon the patient's transfer to the NIH in March 1982, a CT scan showed more extensive opacification on the left than on the right of the frontal, sphenoid, ethmoid, and maxillary sinuses. There were no symptoms referable to the paranasal sinuses. Laboratory testing was notable for 16% eosinophils in the differential count of 8,400/mm<sup>3</sup> peripheral white blood cells. Bilateral external ethmoidectomies and sphenoidectomies with frontal sinotomy again yielded cultures positive for *C. lunata*, and treatment with amphotericin B to a total dose of 4 g intravenously was administered. A CT scan in May 1982 showed no recurrence of soft tissue in the sinuses. The patient was discharged in June 1982 taking ketoconazole 600 mg daily. This treatment was continued through April 1983 and discontinued; unfortunately, the infection recurred in the left maxillary and ethmoid sinuses with cultures positive for *C. lunata* in June 1983. Despite reinstitution of ketoconazole at a dose of 900 mg daily, the infection progressed to involve all paranasal sinuses on the left by June 1984. Infected mucosal tissue was surgically extirpated and therapy with terbinafine 500 mg daily was begun. In July 1985, the patient underwent a revision left Caldwell-Luc procedure for recurrent maxillary sinus opacification. A thick brown mass of inspissated fungal material was found, but there was no evidence of mucosal invasion. The hyphae were reported as morphologically consistent with *Drechslera* spp.

In October 1985, 1 month after completing her course of terbinafine, follow-up CT demonstrated a mass in the right ethmoid area. Endoscopic intranasal examination revealed polypoid disease with brownish discharge in the right ethmoid area and the patient underwent a revision external ethmoidectomy. Again no fungal tissue invasion was identified, but hyphae were present in the inspissated material. The patient did well during the next 2 years. Regular endoscopic and MRI follow-up showed no evidence of recurrent disease.

**Comment:** Isolation of *D. biseptata* from brain tissue in this case made this the first report of invasive infection caused by this organism; however, 3 different patients with invasive infections due to *Curvularia* spp. have previously been described, 1 of whom had sinusitis (20, 59, 62). We concluded that our patient's culture findings could best be explained by probable

mixed infection in the sinus, with only 1 pathogen extending to the brain. Infection by 2 different dematiaceous molds in the same patient was unusual, but this was reported previously in 2 well-documented cases. Adam and coworkers (1) isolated both *Exserohilum rostratum* and *Alternaria* from a child with chronic invasive fungal sinusitis, and Loveless et al (40) cultured species of *Curvularia* as well as *Alternaria* from the submucosa of a nasal lesion in a patient with chronic granulocytic leukemia.

Case 3 was the only other reported case of brain abscess (besides that of Brown [8]) caused by a dematiaceous mold where the paranasal sinuses appeared to have served as the portal of entry. Though other cases of brain masses due to brown-walled fungi have been described, the role played by the sinuses has not always been clear (48). Our patient's fungal infection probably originated in the ethmoid sinuses and eroded superiorly and anteriorly into the frontal sinuses, and thence posteriorly into the frontal lobes. Unlike Case 1, the intracranial mass in Case 3 actually invaded brain parenchyma. Fortunately, the margins of the mass were well-defined, and the patient remained free of relapse within the brain 5 years after complete surgical excision; however, the case illustrated 1) the tendency for invasive fungal infection to relapse within the sinuses in an asymptomatic fashion detectable with CT scans, and 2) the need for prolonged antifungal chemotherapy and vigilant follow-up.

#### Case 4

A 27-year-old man from Texas developed left-sided proptosis and right shoulder weakness in December 1983. Progression of these symptoms led to CT scanning at an outside hospital in March 1984, which showed areas of decreased attenuation in both frontal lobes with a serpiginous pattern of enhancement and enlargement of the frontal horns of the lateral cerebral ventricles. Abnormal soft-tissue densities and destruction of bone were evident in the left nasal cavity (Fig. 4A) as well as the left maxillary, ethmoid, and frontal sinuses. A biopsy obtained from the left middle turbinate contained granulomatous inflammation and grew *Exserohilum rostratum* (*D. halodes*). A diagnosis of invasive fungal sinusitis was made and the patient was treated with amphotericin B to an eventual dose of 3 g over 2 months. Generalized seizures were controlled with phenytoin. Unfortunately, evidence of bilateral frontal lobe cerebritis persisted on CT scans despite amphotericin therapy and subsequent treatment for 1 month with ketoconazole 800 mg daily.

The patient was transferred to the NIH in June 1984. Repeat CT scanning showed persistent sinus abnormalities; cerebral enhancement was more prominent in the left than in the right frontal lobe (Fig. 4B). A magnetic resonance image also demonstrated the areas of cerebritis (Fig. 4C).

Specimens obtained during left external ethmoidectomy, sphenoidectomy, and Caldwell-Luc procedure again contained pleomorphic hyphae consistent with *Exserohilum*, but cultures were negative. A tan hemorrhagic fibrotic mass bulged from the left ethmoid sinus superiorly into the floor of the frontal sinus

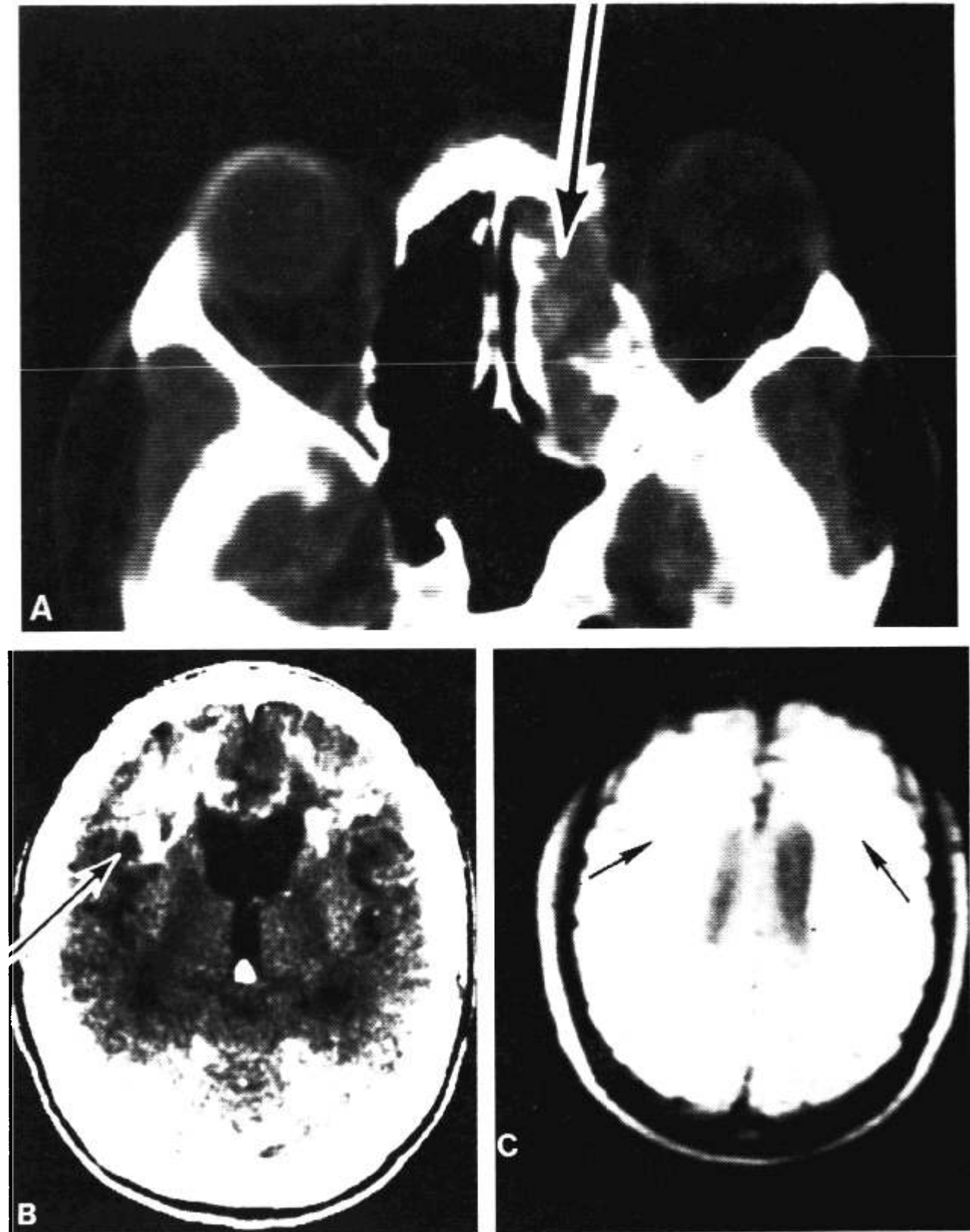


FIG. 4. Case 4. A. CT scan revealing soft-tissue opacity in left nasal cavity and ethmoid sinus. B. Serpiginous pattern of enhancement is seen on CT scan of patient with cerebritis caused by *E. rostratum*. C. MRI delineating bilateral areas of frontal lobe cerebritis.



and eroded the lamina papyracea laterally. In the left maxillary sinus, the medial wall was eroded.

Following resumption of therapy with amphotericin B 2.5 g over 2 mo, monthly CT scans showed improvement, with decreasing enhancement of the frontal lobes. The search for a satisfactory oral drug for this patient led to a brief trial of terbinafine. Unfortunately, the ensuing clinical and CT evidence of worsening cerebral edema necessitated reinstitution of amphotericin B treatment. The drug was administered for 3 months following transfer of the patient back to a hospital close to home. During 30 months of follow-up without antifungal chemotherapy, no evidence of recurrent infection was observed, and a CT scan obtained in 1986 showed nearly complete resolution of frontal lobe lesions; however, the seizure disorder persisted, necessitating long-term therapy with phenytoin.

*Comment:* One other reported case of invasive fungal sinusitis caused by *E. rostratum* appeared in the series of Adam et al (1). Seventeen months following local extirpative sinus surgery and 6 weeks of amphotericin B therapy, that patient appeared to be cured of his infection. Case 4 already had extensive areas of encephalitis bilaterally at the time of his initial presentation, and his infection responded very slowly to amphotericin B.

Two other cases of diffuse encephalitis due to dematiaceous molds have been reported. Yoshimori (86) described a case of *B. spicifera* encephalitis in an immunologically competent 21-year-old woman who appeared cured immediately following treatment with amphotericin B 2 g intravenously, but the infection subsequently relapsed and the patient died. A severe clinical course also ensued in a case of *B. hawaiiensis* meningoencephalitis in a patient with metastatic well-differentiated lymphosarcoma reported by Fuste (22). This case progressed rapidly to a fatal outcome. Neither report mentioned the paranasal sinuses.

#### Case 5

A 32-year-old woman from Florida with a history of allergic rhinitis noted worsening nasal congestion and a foul odor in her nose in 1981. By December 1982 she developed anosmia and began to experience episodes of left visual blurring provoked by Valsalva-like maneuvers. In May 1983 a large, dark-brown, friable mass was surgically removed from her left ethmoid and sphenoid sinuses at an outside hospital. The mass was said to resemble a mucocele. Methenamine silver stain of this mass disclosed irregular hyphae in the submucosal tissue. The surrounding submucosal infiltrate contained abundant eosinophils and plasmacytes, with occasional Langhans' giant cells and histiocytes. Cultures subsequently grew a dematiaceous mold, *Bipolaris spicifera*. Recurrence of the foul odor and visual disturbance in June 1983 prompted referral to the NIH where a CT scan demonstrated a soft-tissue mass occupying the left lateral superior region of the sphenoid sinus and the ethmoid sinus, with bony erosion extending along the medial aspect of the left orbit. Routine laboratory testing was remarkable for 87 peripheral eosinophilia with a total white count of 5,900 mm<sup>3</sup>. In July 1983, bilateral external ethmoidectomies and sphenoidectomy yielded necrotic tissue which again grew *B. spicifera* and the pa-

tient was treated with amphotericin B 2.4 g intravenously over 2 months. During that time her visual and olfactory symptoms resolved and the appearance of her sinuses on CT scan normalized almost completely. Ketoconazole 800 mg per day was administered prophylactically following amphotericin B, beginning in September 1983 and ending in November 1985. Repeat CT scans showed some fluctuation in mucosal thickness related to flares in allergic symptoms and 2 episodes of bacterial sinusitis caused by *Hemophilus influenzae* but there was no evidence of recurrent fungal sinusitis during the period of ketoconazole therapy or in the subsequent 22 months.

*Comment:* The ability of *B. spicifera* to invade paranasal sinus tissues in normal hosts has been noted previously (1, 63). Fortunately, unlike Cases 1, 3, and 4, the infection in Case 5 was diagnosed before any extension to structures within the cranial vault. The curious symptom of unilateral visual blurring during such Valsalva-like maneuvers as bending forwards may have been due to pressure-induced compression of the left optic nerve or ophthalmic artery coursing supero-laterally to the sphenoid sinus.

An aggressive surgical approach, a large total dose of amphotericin B, and prophylactic use of ketoconazole for more than 2 years was rewarded with probable long-term cure.

#### Case 6

A 22-year-old previously healthy black man noted protrusion of his left eye and nasal congestion in November 1982. Computerized tomography in January 1983 was said to show soft-tissue masses in both nasal airways and maxillary sinuses as well as the ethmoid and sphenoid sinuses bilaterally, prompting bilateral Caldwell-Luc procedures and external ethmoidectomies and sphenoidectomies at an outside hospital. The material which was removed was said to have a foul odor, and to have a greasy consistency. It contained branching hyphae on histopathology, but no cultures were obtained.

From February through September 1983, the patient experienced progressive facial pain and nasal congestion and developed the appearance of hypertelorism. A follow-up CT scan in October 1983 apparently showed erosion of the right lamina papyracea in addition to soft-tissue densities throughout all the paranasal sinuses. Repeat bilateral Caldwell-Luc procedures and bilateral external ethmoidectomies yielded foul-smelling greasy material containing broad, branching hyphae. Despite negative cultures, the patient was judged at that point to have fungal sinusitis and was treated with amphotericin B 2.4 g over the next 3 months.

From January 1984 through March 1985 the patient was asymptomatic, but then developed increasing left nasal congestion and lateral displacement of the left eye. A repeat CT scan in September 1985 demonstrated reappearance of soft-tissue densities in all the left paranasal sinuses with erosion of the left lamina papyracea and extension of soft tissue across the midline at the level of the ethmoid sinus. Specimens obtained at left medial inferior tubinectomy, left Caldwell-Luc procedure, left ethmoidectomy and left sphenoidectomy revealed invasion of sinus mucosa by only a few hyphae; cultures grew *B. spicifera*.

A CT scan performed in December 1985 after the patient was transferred to the NIH showed recurrent soft-tissue densities in all paranasal sinuses bilaterally plus erosion of the clivus. A



FIG. 5. Hypertelorism following chronic fungal sinusitis and bilateral external ethmoidectomies in (A) Case 6 and (B) Case 7.

peripheral blood eosinophilia was noted, with 10% of 8,900/mm<sup>3</sup> leukocytes being eosinophils. In January 1986, copious thick mucus secretions and polypoid mucosa were removed during bilateral ethmoidectomies and sphenoidectomies, frontal sinus exploration, and lateral rhinotomy. Histopathology and cultures were again positive. The posterior and lateral walls of the sphenoid sinus were felt to be abnormally softened. Investigational therapy with terbinafine 500 mg daily was administered from January 1986 through February 1987. Despite questionable compliance with this regimen, the patient remained free of radiographic and clinical evidence of recurrent invasive fungal sinusitis during that interval and during 3 subsequent months without antifungal therapy.

*Comment:* Case 6 illustrates the difficulty sometimes encountered in diagnosing chronic invasive fungal sinusitis. Following the first surgical procedure, the patient's physician apparently did not understand the significance of hyphae within the necrotic debris filling the sinus cavities. The eventual appearance of hypertelorism (Fig. 5A) and evidence of extensive bony rearrangement on CT

scans were clues that the patient likely had invasive disease. Careful retrospective examination of many fragments of biopsied mucosa was required before a limited number of hyphae could be identified within submucosal areas.

#### Case 7

This 31-year-old man from South Carolina presented in November 1983 with clinical and roentgenographic evidence of left frontal and maxillary sinusitis. A left Caldwell-Luc procedure performed at a local hospital in March 1984 yielded tissue which was said to resemble a mucocele. A postoperative CT scan obtained later that same month revealed abnormal soft-tissue densities bilaterally in the ethmoid and sphenoid sinuses as well as the left frontal and maxillary sinuses. This prompted bilateral ethmoidectomy and sphenoidectomy plus left frontal sinotomy and a repeat left Caldwell-Luc procedure with excision of tissue which was again thought to represent mucocele formation. The significance of hyphae within mucin on specimens stained with methenamine silver was evidently unclear to the patient's physician, and a single fungal culture was negative.

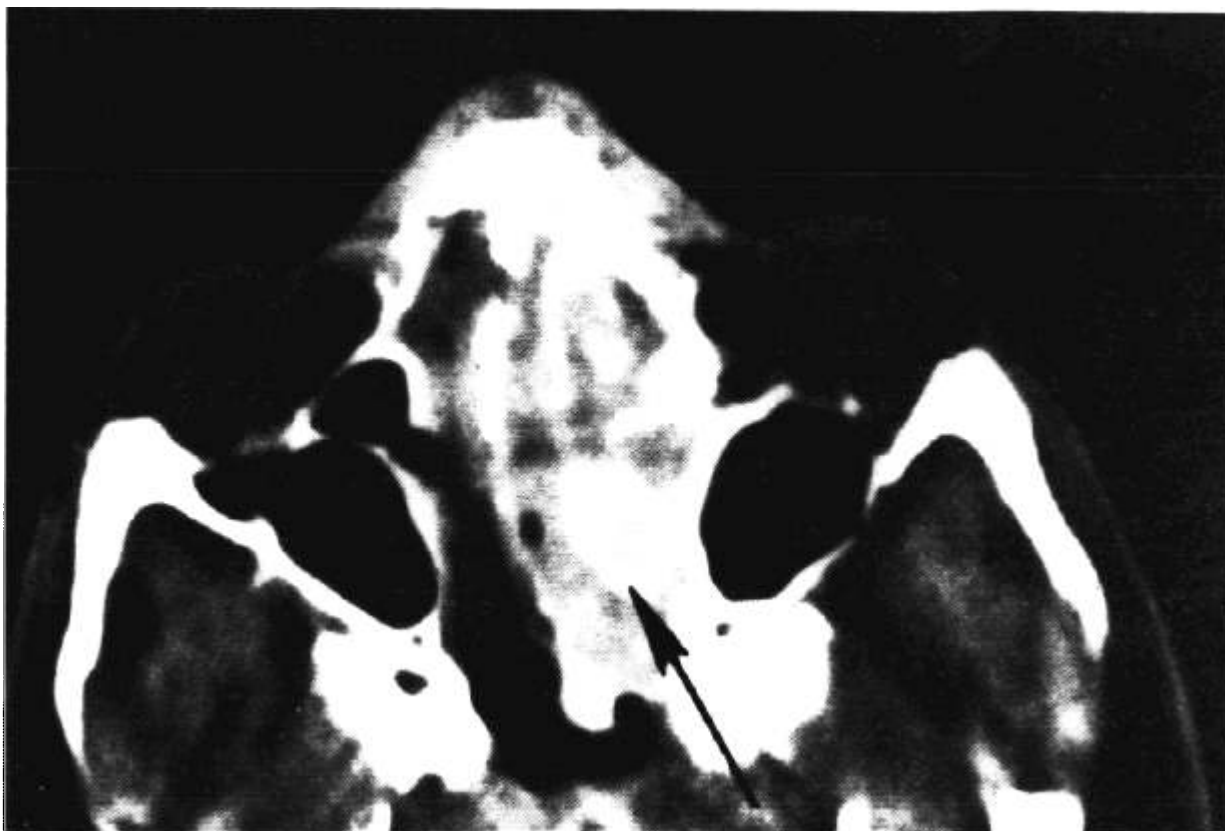


FIG. 6. Case 7. CT scan showing extensive remodeling of nasal septum and bony margins of sinuses, plus soft-tissue densities in nasal cavity and left ethmoid sinus.

Following the recurrence of soft-tissue abnormalities within the paranasal sinuses on 2 subsequent CT scans, the patient underwent left frontal sinotomy, and left Caldwell-Luc operation with bilateral external ethmoidectomies in February 1985. A diagnosis of fungal sinusitis was based upon a combination of extensive bony remodeling on CT scan (Fig. 6) and the presence of broad branching septate hyphae within the mucinous material and necrotic debris which was removed surgically; cultures grew *B. hawaiiensis*. Inflammatory cells within the polypoid mucosa were predominantly eosinophils and plasmacytes. Additional evidence of the invasive nature of the disease was softening of the sinus walls, such that curettage of both the frontal and sphenoidal sinuses was said to have exposed dura mater.

From February through May 1985, the patient received intravenous amphotericin B 3 g, but fungal sinusitis due to the original organism recurred in all paranasal sinuses. Between May 1985 and January 1986 the patient developed the appearance of hypertelorism (Fig. 5b) and he began to note anosmia. Upon referral to the NIH in January 1986, laboratory studies revealed an eosinophilia (11% of 5,900/mm<sup>3</sup> leukocytes). The patient refused further surgery but his disease remained clinically stable during 17 months of therapy with 500 mg daily of terbinafine. Follow-up CT scans during the last 5 months of that treatment period showed improving aeration within all sinuses on the left, and the patient's anosmia resolved. Subsequently, sinus pain recurred and *Bipolaris* was again found on histology and culture of the sinus contents. No mucosal invasion was demonstrated but the bony roof of the ethmoid appeared softened.

*Comment:* Careful examination of the multiple mucosal specimens revealed no hyphal invasion. Yet, a chronic relapsing clinical course and extensive rearrangement of bone on CT scans raised the specter of progressive invasion and even a fatal outcome. The decision to administer antifungal chemotherapy was based upon these considerations. Prolonged treatment first with amphotericin B intravenously and then oral terbinafine was followed by a 17-month period of clinical stability and then deterioration.

The only other reported case of chronic *B. hawaiiensis* sinusitis (87) shared several features in common with Case 7. Hyphae were seen only within necrotic debris filling the sinus cavities, but extensive bony erosion was documented, and intravenous amphotericin B was required for eventual remission following relapse.

#### *Chronic noninvasive fungal sinusitis*

##### *Case 8*

A 37-year-old woman from Georgia with deviation of the nasal septum and chronic nasal congestion developed discomfort in the region of the right maxillary sinus in 1978. Plain roentgenograms

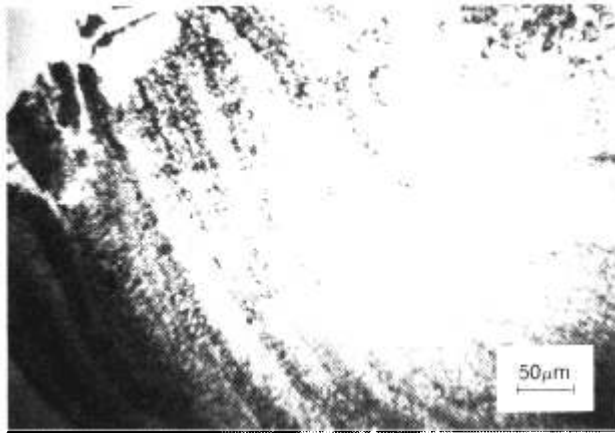


FIG. 7. Case 8. Mass of entangled hyphae in maxillary sinus of patient with noninvasive disease, concentric rings reflect chronicity (Gomori methenamine stain,  $\times 150$ ).

obtained during an exacerbation of the discomfort in June 1979 disclosed opacification of the right maxillary sinus. Intermittent oral antibacterial therapy resulted in no lasting clinical improvement, and a right Caldwell-Luc procedure performed in November 1979 yielded a friable mass of brownish-red material from the maxillary sinus. Review of pathology slides at the NIH disclosed a noninvasive hyphal mass caused by *Aspergillus* (Fig. 7) and hypertrophic submucosa (Fig. 8). Conidia and conidiophores seen on histopathology were consistent with *A. flavus*.

The patient's discomfort abated postoperatively and a CT scan which was obtained in March 1981 showed only minimal mucosal thickening in the superiolateral aspect of the right maxillary antrum.

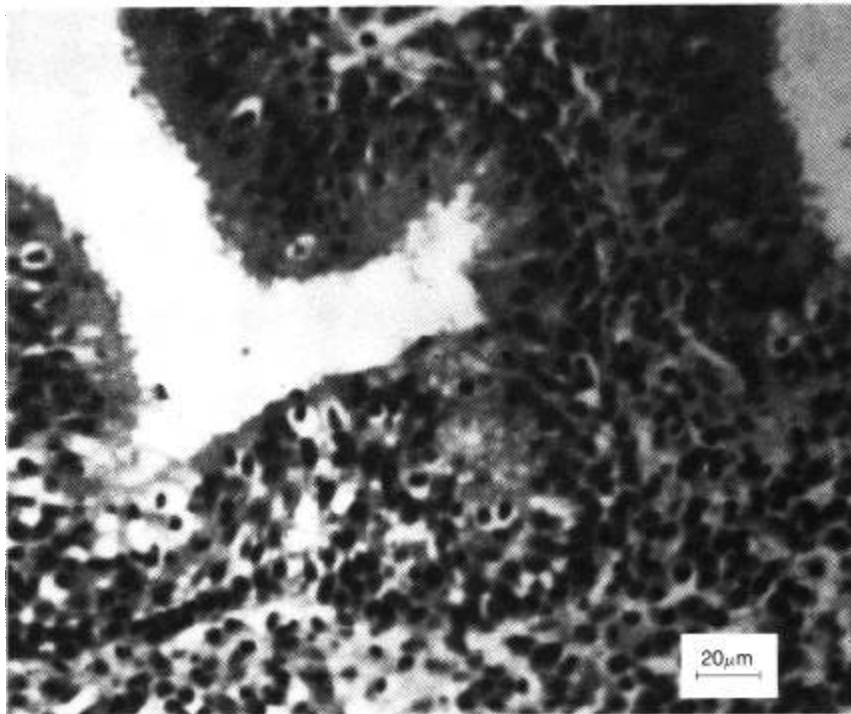


FIG. 8. Case 8. Hypertrophic submucosa of maxillary sinus from patient with noninvasive disease. Note dense submucosal infiltrate with chronic inflammatory cells (hematoxylin and eosin,  $\times 400$ ).

### Case 9

A 55-year-old woman from North Carolina with a long history of allergic rhinitis developed deep right maxillary pain in December 1980. Plain roentgenograms demonstrated opacification of the right maxillary sinus, and a Caldwell-Luc procedure was performed. *Aspergillus fumigatus* was cultured from the friable mass of entangled hyphae which was removed. The submucosa was hypertrophied.

Following the first surgical procedure, the patient initially experienced relief of pain; however, recurrent discomfort prompted a second Caldwell-Luc operation in February 1981. No fungi were found on histopathology, and her pain was temporarily relieved.

After a third recurrence of pain, the patient was referred to the NIH in July 1981. Computerized tomography of the sinuses disclosed extensive soft-tissue density within the right maxillary antrum. This tissue was surgically exenterated and contained no fungus. The patient remained free of recurrent fungal sinusitis during 6 years of follow-up.

### Case 10

A 77-year-old woman from Maryland with a history of recurrent sinusitis beginning in 1951 noted the onset of persistent pain over the right maxillary sinus early in 1986. Despite treatment with nasal decongestants and a course of trimethoprim/sulfamethoxazole, the pain continued and a right naso-antral window was created in September 1986. A needle aspirate of the right maxillary sinus contained cheese-like greenish material in which branching septate hyphae were observed. Mucosal invasion was not seen; the specimen was not cultured.

The pain persisted and a CT scan performed in December 1986 showed opacification of the right maxillary sinus. During a right Caldwell-Luc procedure a large volume of greenish material was completely removed from the sinus cavity and a mucosal biopsy was obtained. Staining with hematoxylin and eosin revealed a

mass of entangled septate hyphae with 45° angle branching, and normal respiratory mucosa with minimal round cell infiltration. A culture grew *Pseudallescheria boydii*. A follow-up CT scan in March 1987 showed that the right maxillary sinus was clear, and the patient remained asymptomatic during 7 months of observation in the postoperative period.

### Assessment of Immunologic Function

Several tests were performed to evaluate host defenses in patients with chronic fungal sinusitis. Phagocytic and fungicidal activity of peripheral blood mononuclear cells from Cases 1 and 3–7 were normal, using conidia of *Aspergillus fumigatus* as fungal target particles in a 1:10 effector:target ratio (81). Additional indications that peripheral blood phagocyte function was normal included superoxide generation (Cases 3 and 7), reduction of nitroblue tetrazolium (Case 6), and chemotaxis (Cases 3 and 7). Furthermore, a normal percentage of mononuclear cells stained positively for nonspecific esterase in Cases 3, 4, 5 and 7, and for myeloperoxidase in Cases 3 and 7. Lymphocyte subpopulations and natural killer cell functional activity, assessed in Cases 6 and 7, were normal. Delayed-type hypersensitivity skin testing revealed no positive reactions in Case 6, but Cases 7 and 8 had normal positive reactions to mumps antigen. The serum concentrations of immunoglobulin classes G, A, and M, measured in Cases 1 and 3 through 9, were within normal limits. Human immunodeficiency virus enzyme-linked immunosorbent assay and Western blot analysis were negative in Case 6. A firm judgment concerning the immunologic competence of our patients was not possible because the immunologic studies were not uniformly applied in all patients. Within the limitations of the studies, however, our patients appeared to be immunologically normal, with the possible exception of Case 6, who may have been anergic. This absence of detectable immune defects was consistent with other evidence that patients with chronic fungal sinusitis possessed normal immunologic function (1, 5, 8, 11, 12, 15, 16, 23, 28, 41, 51, 59, 63, 64, 70, 76, 77, 87).

### Discussion

Central attention of this study is devoted to chronic invasive fungal sinusitis. Our reading of the literature and experience with cases indicated frequent confusion about the features of patients with chronic fungal sinusitis which merit aggressive treatment and prolonged follow-up. In contrast, the management of acute fungal sinusitis in immunocompromised hosts and of paranasal mucormycosis is fairly well defined, even though prognosis is often poor. Previous attempts to understand

chronic fungal sinusitis have been rendered difficult by the infrequency of the infection, the prolonged follow-up necessary to understand the natural history of the illness, and the frustrating lack of crucial details in many of the reported cases. On the positive side, availability of computerized axial tomography and magnetic resonance imaging have provided a wealth of diagnostic and anatomic detail that was heretofore unavailable. Although many features about prognosis and management of fungal sinusitis remain to be learned and very little is known about pathogenesis, we believe that logical management plans can be devised from knowledge currently available. Strategy often depends very little on exact identification of the fungus or upon *in vitro* susceptibility testing with antifungal agents. This relative independence is fortunate because both these issues have the potential of sinking the physician's decision-making process into a quagmire of conflicting opinion and delay.

#### *Distinction between invasive and noninvasive fungal sinusitis*

The single most important principle in caring for patients with chronic fungal sinusitis is to distinguish between invasive and noninvasive disease. This distinction may be easy when clinically apparent invasion of contiguous structures has occurred. More often, invasion is detected by diagnostic imaging (CT or MRI) and findings at surgery. During procedures on the sinus, the surgeon may note loss of bony integrity in some part of the sinus wall; or careful scrutiny of excised tissue may show invasion of the submucosa. The distinction between invasive and noninvasive fungal sinusitis will be elaborated further in the discussion which follows.

Noninvasive fungal sinusitis is a relatively benign condition. Diagnosis is based upon discovery at surgery of a mass of mycelia embedded in mucus within the sinus cavity. More details of the pathology and radiologic findings will be given later. The symptoms prompting surgery are usually nasal congestion, postnasal drip, and chronic sinus pain (1, 11, 36–38, 58, 64, 74–77), accompanied by increased pain and fever during intermittent episodes of acute bacterial sinusitis. Fungi within the sinus may contribute soluble antigens or irritants which increase mucosal inflammation. Conceivably, a mycelia-containing mass could obstruct the sinus ostium, favoring episodes of acute bacterial sinusitis. Alternatively, the fungus may be simply growing in the nutritionally ample source of sinus mucus and not causing any of the clinical manifestations. The operating surgeon finds a thick or cheesy mass within the sinus, readily separated from a sometimes thickened or hypertrophic mucosa, and bony structures are intact. With adequate sinus drainage and

the restoration of mucociliary clearance, recurrence is unusual. In contrast to this relatively trivial condition, invasive fungal sinusitis is a morbid disease.

Invasive chronic fungal sinusitis may follow a relentless course, over months or years, of insidious erosion through the anatomic barriers which normally separate the paranasal sinuses from one another (Cases 1 and 3-7; 30, 63, 70, 87), from the hard palate (23, 70), from the face (53), and from such vital contiguous structures as the eye (Cases 2 and 4-7; 8, 14, 27, 30, 31, 43, 64, 83, 89), brain (Cases 1, 3, and 4; 27, 28, 41, 43, 50, 51, 56, 66, 80) or pituitary (21, 25, 43). Cases 1, 2, and 5 noted visual impairment early in their clinical courses, and ocular symptoms actually overshadowed sinus discomfort in several reported cases (14, 27, 31, 41, 43, 50, 64, 66, 80, 83, 87, 89). Cases 1, 3, and 4 and a few previously reported cases manifested signs or symptoms of frontal lobe disease at some time during their illness, including chronic headaches, lateralizing neurologic findings, seizures, altered sensorium, and urinary incontinence (14, 27, 41, 43, 66). Distortion of normal sinus architecture by chronic invasive fungal sinusitis may also contribute to poor drainage and superimposed bacterial sinusitis as in our Case 5.

### Pathology

The material found in sinuses of patients with noninvasive fungal sinusitis is usually said to be cheese-like or friable (Cases 8-10; 5, 58, 61), but can also have a rubbery consistency (74). It may be green (Case 10), dark reddish-brown (38), black (45), or yellow (61), and may have a foul odor (5, 26, 38, 45). When the material is surgically removed, the underlying mucosa may appear normal, thickened, or polypoid. Biopsy can show submucosal edema and lymphocytic infiltration (Case 10; 3, 38, 61, 76) or frank hypertrophy (Cases 8 and 9; 37, 58). Hyphae are never seen within the mucosa, submucosa, or bone of patients with noninvasive fungal sinusitis (1, 36-38, 61, 74). The fungal mass itself routinely can be seen on hematoxylin and eosin stains as a dense mat of entangled hyphae (Cases 8-10). As can be the case with fungus balls of the lung, sporulation can occasionally be observed at the periphery of fungal masses in the paranasal sinuses (Case 8; 3, 26, 38, 75).

Typically, sinus mucosa of patients with invasive fungal sinusitis shows more pronounced changes than that of patients with noninvasive disease. The mucosa usually appears hypertrophic or polypoid as in our Cases 6 and 7. This feature has also been discussed in previous literature (1, 5, 11, 23, 28, 56, 63, 77, 87). Occasionally, the sinus cavity may seem to contain a mucocele or mucus-filled cyst, as in our

Cases 5 and 7, and that of Miglets (49). As with extramucosal disease, a large volume of tenacious or rubbery mucus or greasy material may fill the sinus cavity. This was seen in our Cases 2, 5, and 6, and the reported cases of Miglets (49), Romett (64), Sobol (72), and Weinstein (83). This brown (83) or greenish (1, 64) material can be so thick and inspissated that curettage is required for removal at the time of surgical exploration, as in Cases 5 and 6. Foul odor may result in the complaint of cacosmia (Case 5; 5). Hyphal fragments can nearly always be identified within submucosa or bone in deep biopsies of the nose or paranasal specimens (Cases 1-6; 1, 5, 23, 27, 28, 39, 49, 51, 56, 66, 70, 80, 87, 89) or other affected tissues (43). This finding may be missed because the pathologist's attention is focused on hyphae within the mucus, or the organisms are present in the submucosa in only small numbers. Occasionally, a very careful search of mucosal fragments using methenamine silver or periodic acid-Schiff stains is required before hyphae can be found, as illustrated by Cases 2 and 6. Case 7 presented a special problem in this regard. Though the history of repeated relapses, multiple surgical procedures, and eventual remodeling of bone combined to produce a clinical picture of invasive infection, no submucosal organisms could be seen despite careful examination by several observers of many different properly stained tissue specimens. Ultimately, therapeutic decisions were guided by the compelling clinical evidence of invasion.

The surrounding inflammatory response, as demonstrated by Cases 1, 3, and 4 and others from the literature, is often granulomatous with Langhans' giant cells present (23, 25, 27, 31, 41, 43, 50, 64, 66, 70, 80). Hyphae within giant cells were seen in Case 1 and patients reported by Veress (80). Palisading histiocytes (25, 50), plasmacytes (Case 2; 25, 49, 56, 66, 87) and often eosinophils (1, 56, 66, 80, 87) mixed with collagenous scar tissue (Case 2; 43, 50, 80) may be found.

### Radiology

Among several available radiologic techniques, computerized tomography (CT scanning) has proven most helpful in distinguishing between noninvasive and invasive fungal sinusitis (1, 21, 28, 37, 41, 56, 63). Patients with noninvasive fungal masses generally exhibit increased soft-tissue density in only 1 sinus. The maxillary sinus is most frequently involved (Cases 8-10; 1, 36, 37, 58, 75), though fungal masses of the frontal (76) or sphenoid sinuses (49, 71) have also been encountered. Kopp (37) and Stammberger (75) demonstrated in patients with noninvasive fungal sinusitis that calcium phosphate deposition within *Aspergillus* masses can produce

dense opacities on CT scans. Extension of soft tissue into contiguous structures such as orbit or brain is indicative of invasion. If soft-tissue densities occur in more than 1 sinus, the presence of invasive infection is strongly suggested because normal structures constitute natural barriers to spread of noninvasive fungal masses along mucosal surfaces between sinuses (see Anatomy). Magnetic resonance imaging (MRI) played an especially important role in Case 1, in defining the extradural location of the intracranial mass. The resolution obtained with CT was insufficient to establish that critical fact. Although T1 and T2 weighted MRI has been excellent for resolving soft-tissue structures, inability to see bony details has prevented MRI from replacing CT for diagnostic imaging in fungal sinusitis.

#### *Differential diagnosis*

Diagnosis of fungal sinusitis requires demonstration of fungi in tissue or, in the case of noninvasive sinusitis, within the sinus contents. The diagnosis of extramucosal disease requires a high index of suspicion whenever thick brown tenacious secretions, or dried masses of cheesy material, are seen at exploration. Pathologic examination and staining of the material is usually diagnostic. Culture of the nose, sinus contents, or sinus tissue removed at surgery is not diagnostic alone because almost all the pathogens (Table 1) also exist as airborne contaminants. Heavy growth of fungus on culture of a sinus aspirate would certainly be suggestive. A positive fungal culture should prompt special stains for fungi on any removed mucosa.

The most common problem in differential diagnosis is failure to consider the possibility of fungal sinusitis in a patient with a chronic destructive lesion in the paranasal sinus, orbit, or frontal lobe of the brain. for Wegener's granulomatosis. Chronic but less granulomatous inflammation raises the question of granulomatous inflammation raises the question of a malignant plasmacytoma, lymphoma, or other cancer. Properly done silver stains will resolve this confusion.

Sinus-occupying masses of fungi embedded in mucin may be confused with mucocoeles, mucin impactions (84), inclusion cysts, or Pindborg tumors. Again, silver or periodic acid-Schiff stains readily demonstrate fungal elements.

Both invasive and noninvasive fungal sinusitis cases exemplify the value of obtaining tissue and, in selected cases, using CT or MRI to define the extent of disease in patients with chronic undiagnosed disease of the paranasal sinuses. Without tissue, fungal sinusitis can be confused with a host of clinically similar diseases, largely malignancies, in this area. Without appropriate imaging techniques, invasion across bony barriers is easily missed.

#### *Therapy*

Successful treatment of patients with noninvasive fungal sinusitis requires only surgical removal of the fungal mass itself and establishment of adequate sinus drainage. No local or systemic antifungal chemotherapy is required (Cases 8–10; 1, 3, 11, 37, 38, 45, 58, 64, 72, 74–76). Even during prolonged follow-up, recurrence is infrequent (1, 74, 75).

The eventual outcome of patients with invasive infection is far less predictable. Several reports suggested that patients with invasive disease could be cured by surgical removal of abnormal tissue (50, 66, 72), perhaps followed by a course of antifungal chemotherapy such as amphotericin B (14, 21, 30, 87, 89). The short duration of follow-up in some of these reports (51, 63, 72, 87) rendered difficult any judgment about the likelihood of eventual relapse. Surgery should consist of wide excision of bone and soft tissue, but it is important to preserve the natural barriers (dura, orbital periosteum). In our series, these structures typically provided a good boundary to limit the further spread of infection, even when clinically involved with disease. Several reported cases with careful long-term follow-up relapsed despite aggressive surgical intervention followed by more prolonged courses of antifungal chemotherapy (23, 27, 31, 43, 53, 64, 70, 89). This experience led us to conclude that most if not all patients with chronic invasive fungal sinusitis should be treated with a combination of surgical extirpation of diseased tissue and a total dose of amphotericin B exceeding 2 g for adults (64, 83, 89). Initial treatment with an imidazole, such as ketoconazole, would be preferable for patients infected with *Pseudallescheria boydii* (30). When cultures are not available, sporulating forms should be sought in the hyphal masses removed from the sinus cavity. Histologic clues to the presence of *P. boydii* include a longitudinal fascicle of hyphae called a coremium, and brownish pear-shaped truncated spores. The former possesses such a distinctive appearance that it is easily identified, but the spores may be mistaken for erythrocytes on H&E stain. Conversely, presence of the sporulating structures of other fungi are helpful in excluding *P. boydii*. The darker, rough conidia of *A. niger*, asci of *A. nidulans*, or fruiting heads of *Aspergillus* are sometimes discernible in histopathology slides of paranasal sinus tissue.

After a period of intensive intravenous antifungal chemotherapy, the frequency of relapse has prompted us to give an oral systemic antifungal drug, such as ketoconazole or terbinafine, for a year or longer. The long-term clinical stability of Cases 3, 5, and 6 supports the use of this approach.

The most realistic goal in some patients who fail to benefit from multiple therapeutic maneuvers is palliation, as in Case 1. For those more fortunate pa-

tients whose diseased tissues can be completely or almost completely removed, and who then receive a generous course of antifungal therapy, CT should be performed approximately one month after surgery as a baseline examination followed by repeat studies every 3 to 4 months looking for new soft-tissue densities, loss of bony architecture, or abnormal tissue in contiguous structures. In our patients, early reintervention directed against a small burden of infected tissue seemed to exert more clinical impact than later measures aimed at more extensive disease.

### Summary

Several fungal species are capable of causing either noninvasive fungal sinusitis or invasive disease characterized by erosion into mucosa, submucosa, bone, and deeper contiguous structures. The diagnosis of invasive infection becomes firmly established only after histologic demonstration of hyphae within these areas. Computerized tomography and magnetic resonance imaging can assist in distinguishing between invasive and noninvasive disease by outlining bone and adjacent structures.

The 2 forms of chronic fungal sinusitis mandate different therapeutic approaches. While patients with noninvasive infection require only surgical removal of hyphal masses and the reestablishment of sinus drainage for a successful outcome, invasive infection necessitates not only thorough surgical debridement of abnormal tissues but may also require prolonged antifungal chemotherapy. All patients require long-term follow-up. Even the combined approach has sometimes proven disappointing during long-term follow-up of disease, rendering investigational therapy appropriate in some patients.

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