Fungal Infection in Chronic Granulomatous Disease

The Importance of the Phagocyte in Defense Against Fungi

MYRON S. COHEN, M.D.*
RAUL E. ISTURIZ, M.D.†
HARRY L. MALECH, M.D.
RICHARD K. ROOT, M.D.
New Haven, Connecticut

CATHERINE M. WILFERT, M.D.
LAURA GUTMAN, M.D.
REBECCA H. BUCKLEY, M.D.
Durham, North Carolina

Among 245 cases of chronic granulomatous disease which were evaluated, fungal infection occurred in 20.4 percent. Fungi encountered include Aspergillus, Torulopsis and Candida. In 18 percent of the patients with fungal infection, the disease was limited to soft tissue or bone; all did well. Most of the patients had fungal pneumonia and/or widely disseminated disease; diagnosis was usually confirmed by open lung biopsy. Patients with pneumonia or disseminated disease who received no therapy succumbed to infection, whereas more than half the patients who received antifungal therapy were cured. Modalities of treatment included antifungal chemotherapy, surgical removal of infected tissue and granulocyte transfusion. Although several patients showed dramatic improvement during granulocyte transfusions given in combination with antifungal chemotherapy, the improvement achieved was not statistically significant when compared with that achieved with chemotherapy alone. These results emphasize the importance of phagocytic cells in defense against fungi and the need for further evaluation of granulocyte transfusion therapy in compromised hosts in whom fungal infections develop.

Opportunistic fungal infections are a major source of morbidity and mortality in the compromised host [1–6]. Factors which contribute to the development of such infections include neutropenia, lymphocyte abnormalities, corticosteroid and antineoplastic therapy, prolonged antimicrobial therapy, invasive devices and hyperalimentation [4,6]. The prognosis associated with fungal infection has remained dismal [5] regardless of aggressive diagnostic [7] and therapeutic approach [8].

Recently, in vivo [9] and in vitro [10] experimental data have supported the idea that polymorphonuclear leukocytes are an essential defense against fungi. This contribution is difficult to assess in patients with neoplastic disease because of widespread abnormalities which occur as a result of the disease and therapy.

In order to better assess the role of phagocytic cells in the defense against fungal infections, we reviewed the infectious complications associated with chronic granulomatous disease of childhood. This illness is characterized by recurrent purulent infections of the skin, reticuloendothelial system and lungs [11,12]. Neutrophils from the patients with chronic granulomatous disease have a killing defect which results from their failure to form bactericidal oxygen metabolites (e.g., superoxide, singlet oxygen and hydrogen peroxide) during phagocytosis [13].

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* Present address: Department of Medicine, 547 Clinical Sciences Building, University of North Carolina School of Medicine, Chapel Hill, NC 27514.

† Present address: Central Medical School of Caracas, Consultant No. 175, Caracas 1011, Venezuela.

Because even small amounts of exogenous hydrogen peroxide can be utilized by chronic granulomatous disease cells to destroy microorganisms [14], only those pathogens which possess the enzyme catalase (which will destroy hydrogen peroxide) survive inside the chronic granulomatous disease phagosome [15]. Catalase-positive fungi, therefore, are not killed by chronic granulomatous disease neutrophils [16]. Although most patients with chronic granulomatous disease have hyperglobulinemia, antibody and complement function are normal as is cell-mediated immunity [17].

In this report we demonstrate that fungal infections are common and severe in patients with chronic granulomatous disease, and the findings underscore the phagocytic cell as a primary defense against fungal pathogens. The potential role of granulocyte transfusion therapy in this setting will be discussed.

MATERIALS AND METHODS

Patient Source. Patient records and results of leukocyte function tests were obtained from our own experience and through the cooperation of physicians with a known interest in chronic granulomatous disease (see "Acknowledgments"). Cases of chronic granulomatous disease previously reported in the English literature were found through the bibliography of review series [13,18,19] and computerized searches (Medlars II and Bibliographic Retrieval Services, Inc., Scotia, New York).

Criteria for the Diagnosis of Chronic Granulomatous Disease. In patients studied after 1966, the diagnosis of chronic granulomatous disease was established by a failure of their neutrophils to reduce nitroblue tetrazolium dye to formazan, a reaction dependent on superoxide formation [13]. Further investigations of neutrophil function revealed defects in one or more of the following areas: bactericidal activity, hexose monophosphate shunt stimulation, oxygen consumption, and superoxide and peroxide release.

Patients who were diagnosed as having chronic granulomatous disease before the nature of the neutrophil defect was known had an appropriate clinicopathologic syndrome as described by Berendes et al. [11], Landing and Shirkey [12], and Carson et al. [20]. This included recurrent infections of the skin and lungs with lymphadenitis and hepatosplenomegaly; tissue examination revealed diffuse granulomas and pigmented lipid histocytes in involved organs.

SELECTED CASE REPORTS (See Table I)

Case 6. In this patient, a white female born in 1968, the diagnosis of chronic granulomatous disease was established at nine months of age. Her health was excellent until 1970 when pain developed in her left lateral malleolus. Roentgenologic examination revealed osteomyelitis of the left fibula, and needle aspiration yielded Aspergillus fumigatus. The patient was treated with 5-fluorocytosine for 23 weeks. During repeated examinations the bone lesion demonstrated progressive healing, and the patient remained well over one and a half years of re-evaluation.

Comment: This patient is typical of patients with chronic granulomatous disease and fungal infection localized to bone. She responded well to antifungal therapy alone, and her bone lesion healed gradually. Other patients with abscesses and/or osteomyelitis have undergone surgical drainage, and most have received amphotericin B (see "Results" section).

Case 4. This patient was a 30 year old white man. The diagnosis of chronic granulomatous disease was made at age 21 subsequent to recurrent episodes of staphylococcal lymphadenitis, pneumonia and liver abscess. In August 1977 the patient had a fever, anorexia and cough; chest roentgenogram revealed a diffuse reticulonodular infiltrate, but transbronchoscopic biopsy was nondiagnostic. The patient was given antituberculous therapy and was transferred to Yale-New Haven Hospital in December 1977 for further evaluation. At that time he was afebrile, but tachypnea, tachycardia and inanition were observed. He was treated with cephalothin, gentamicin, amphotericin B, rifampicin and bactrim, but he died four days after admission. Torulopsis glabrata, Escherichia coli and Pseudomonas were grown from several sites, and Torulopsis alone was recovered from the lung and kidney.

Comment: An untreated disseminated fungal infection (which may have developed as early as August 1977) was recognized after the patient's death. Uncontrolled gram-negative sepsis most likely contributed to his death.

Case 2. In this patient, a black boy born in 1971, the diagnosis of chronic granulomatous disease was established at age nine months subsequent to recurrent staphylococcal pneumonia. In 1977 he was admitted to Yale-New Haven Hospital with a cough and temperature of 104°F. Chest roentgenogram showed consolidation of the upper lobe of the right lung, but specimens of blood, sputum and urine were not diagnostic. Assessment of Aspergillus antibody by countercurrent immunoelectrophoresis revealed a titer of 1:32. After a brief hospitalization a diagnostic and therapeutic lobectomy of the upper lobe of the right lung was performed; A. fumigatus was grown from the pathologic specimen. Regardless of therapy, which included rifampin, amphotericin B and 5-fluorocytosine, new areas of pulmonary involvement developed. Granulocyte transfusions were given for 28 days. During this latter therapy, the patient's condition improved remarkably. He has remained well without relapse of infection over the last three years.

Comment: In this situation the patient did not respond to surgery and antifungal chemotherapy. Granulocyte transfusions appeared to have a dramatic therapeutic effect.

Case 17. In this six and a half year old white boy the diagnosis of chronic granulomatous disease was made at age three and a half subsequent to recurrent infections. In 1975 he had pneumonia; an open lung biopsy revealed invasive A. fumigatus, and a lobectomy of the upper lobe of the right lung was performed. He subsequently received a six-week course of amphotericin B therapy. Purulent material continued to drain from the thoracotomy scar, and Aspergillus osteomyelitis of the anterior fourth through sixth ribs developed.

TABLE I 50 Patients with Fungal Infection as a Complication of Chronic Granulomatous Disease

Case No.	Age (yr) and Sex	Organisms	Site of Infection	Institution and/or Reference
1	5, M	Aspergillus flavus	Left kidney, bone marrow	Yale [23]
2	8, M	Aspergillus fumigatus	Pneumonia in upper and lower lobe of right lung	Yale
3	5, M	Aspergillus fumigatus	Bilateral pneumonia	Yale
4	30, M	Torulopsis glabrata	Lungs, liver, kidney, spleen, bone marrow and lymph nodes	Yale
5	5, M	Aspergillus fumigatus	Pneumonia in upper lobe of right lung	Duke [24]
6	2, F	Aspergillus fumigatus	Left fibula	Duke [24]
7	20, M	Aspergillus (? species)	Paravertebral abscess and osteomyelitis (–T2)	Duke [24,25]
8	21, M	Aspergillus fumigatus	Bilateral pneumonia with chest wall penetration	Duke
9	6, M	Aspergillus niger	Pneumonia in upper lobe of right lung	Duke [25]
10	7, M	Aspergillus fumigatus and nidulans	Pneumonia in upper lobe of right lung and adjacent rib involvement	NIH [21]
Recurrence	9, M	Aspergillus fumigatus	Right paraspinal abscess T2–4 and osteomyelitis T2–4, T5–6	. . .
11	17, M	Aspergillus fumigatus	Bilateral pneumonia	NIH [22]
12	5, M	Candida albicans	Lungs, liver, brain, intestines, blood	Rhode Island Hospital
13	4, M	Aspergillus fumigatus	Bilateral pneumonia	Rhode Island Hospital
14	13, F	Aspergillus (? species)	Bilateral pneumonia, osteomyelitis, 3rd and 4th ribs, breast abscess	University of Manitoba
15	9 mo, F	Probable Aspergillus (? species)	Lungs, possibly kidney, and bone	University of Manitoba
16	12, M	Aspergillus (? species)	Left lung, pleura, osteomyelitis, C4–7, T4	University of Manitoba
17	6, M	Aspergillus fumigatus	Upper, middle, lower lobes of right lung, osteomyelitis right anterior ribs	University of Vermont
18	7, M	Aspergillus fumigatus	Pneumonia in lower lobe of left lung, osteomyelitis; 7,8,9th ribs, adjacent abscess	National Jewish Hospital
19	12½, M	Aspergillus fumigatus and Torulopsis glabrata	Bilateral pneumonia	Childrens Memorial Hospital
20	9½, M	Aspergillus fumigatus	Pneumonia in upper lobe of left lung, osteomyelitis left 3rd rib	Childrens Memorial Hospital
21	13, M	Aspergillus fumigatus	Bilateral pneumonia	University of Minnesota
22*	11, M	Probable Aspergillus*	Bilateral pneumonia	University of Minnesota
23†	10, F	Aspergillus fumigatus	Bilateral pneumonia	University of Minnesota
24	19, M	Aspergillus fumigatus	Right-sided pneumonia	Hospital Claude-Bernard
25	10, M	Aspergillus (? species)	Pneumonia	Hospital Claude-Bernard
26	4½, M	Aspergillus (? species)	Pneumonia	Hospital Claude-Bernard
27	16, F	Aspergillus (? species)	Pneumonia	Hospital Claude-Bernard
28	12, M	Aspergillus (? species)	Pneumonia	Hospital Claude-Bernard
29	10½, M	Aspergillus nidulans	Pneumonia in upper lobe of right lung, osteomyelitis 2nd, 3rd ribs, axillary abscess	[26], Case T.D.
30	2, M	Aspergillus fumigatus	Pneumonia in upper lobe of right lung, osteomyelitis right 3rd rib	[26], Case A.M.
31	12, M	Aspergillus fumigatus	Pneumonia	[27]
32	5, M	Candida albicans and Staph. aureus	Lungs, liver, spleen, kidney	[28], Case 3
33	4, M	Candida albicans and micrococcus	Submandibular abscess	[20], Case F1
34	17, M	Candida albicans and Staph. aureus	Bilateral pneumonia	[29], Case B.P.
35	2½,	Candida albicans	Ulcerative stomatitis	[30]
36	n/a,n/a	Aspergillus fumigatus	Pneumonia	[31]
37	n/a,n/a	Aspergillus fumigatus	Pneumonia	
38	n/a,n/a	Asperigillus fumigatus	Pneumonia	
39	n/a,n/a	Aspergillus fumigatus and niger	Pneumonia	[31]
40	11, M	Aspergillus fumigatus	Thyroid gland abscess	[32]
41	8 wk, M	Candida albicans	Cervical lymphadenitis	[33]
42	3, M	Aspergillus fumigatus	Thoracic abscess, probable pneumonia	[34]

Continued

TABLE I (Cont'd) 50 Patients with Fungal Infection as a Complication of Chronic Granulomatous Disease

Case No.	Age (yr) and Sex	Organisms	Site of Infection	Institution and/ or Reference
43	2 mo, M	Torulopsis (? species)	Lungs, spleen, kidney, liver	[35]
44	8, M	Aspergillus fumigatus	Bilateral pneumonia	[36], Case D.D.
45	4, M	Candida albicans	Bilateral pneumonia, ? kidneys	[37], Case 5
46	14, M	Aspergillus fumigatus	Osteomyelitis, left tarsal bone	[37], Case 3, Case 9
47	?, M	Aspergillus fumigatus	Bilateral pneumonia	[38], Case L.J.
48	4, ?	Aspergillus fumigatus	Pneumonia and osteomyelitis involving T3, T4 and ribs	[39], Case G.H.
49	13, M	Candida albicans Aspergillus (? species) Pseudomonas, enterococcus	Lung, pleural and pericardial abscesses	[20], Case A
50	2, M	Aspergillus fumigatus	Chest wall abscess	[20], Case D

NOTE: n/a = not available.
* This patient was included because (1) biopsy-proved Aspergillus pneumonia developed in his brother after both patients were exposed to material believed to be contaminated with Aspergillus and (2) the patient was cured with amphotericin B.
† This patient also had an Aspergillus fumigatus infection at age two years.

These ribs were resected, and he received a second and third course of amphotericin B therapy in combination with 5-fluorocytosine. New bony lesions of the ribs and thoracic vertebrate developed which resulted in increased pain and deformity. The patient received two short courses of granulocyte transfusions, which did not result in improvement. He died on February 17, 1977, approximately two years after the onset of Aspergillus pneumonia.

Comment: This case demonstrates the chronic, unremitting nature of fungal infections, which are often unresponsive to antifungal chemotherapy.

Case 8. This patient is a 20 year old white man with chronic granulomatous disease. In 1977 he had pneumonia of the lower lobe of the left lung and of the middle lobe of the right lung produced by Aspergillus; subsequently, a lesion of the left anterior chest wall developed which revealed Aspergillus upon biopsy. He was treated with antibacterial agents and clotrimazole; because fever persisted, clotrimazole was replaced with amphotericin B. The patient received a total of 2.0 g of amphotericin B and his pulmonary infiltrates gradually resolved. Persistant osteomyelitis of the chest wall developed for which a second course of amphotericin B therapy and excisional biopsy were required. For a more recent exacerbation, the patient has been treated with improvement with oral ketoconazole (personal communication, Dr. Harry Gallis).

Comment: This patient is one of several with Aspergillus pneumonia with involvement of adjacent ribs or chest wall.

RESULTS

Clinical Findings. A total of 245 cases of chronic granulomatous disease were evaluated. Fifty of these patients (20.4 percent) had a history of fungal infection (Table I). Twenty-eight patients were hospitalized in the institutions surveyed for this study (eight of whom have previously been described in less detail) [21–25]; one patient (Case 10) had recurrent infection. Another 22 patients have been described in the literature reviewed (Table I).

Ages of the patients at the time of admission ranged from two months to 30 years. All but four of the patients were male. Forty-seven patients were Caucasian, three were Black, one was Japanese and one Chinese.

The fungi encountered were restricted to Aspergillus (several species), Candida albicans and Torulopsis glabrata (see "Addendum"). Aspergillus infections were most common (78.4 percent) and usually produced pneumonia or widely disseminated disease (**Table II**). Local extension of disease from the lungs to the pleura, soft tissue and/or bony structures of the chest wall occurred in almost one third of the patients with Aspergillus pneumonia. Candida infections were less common (13.7 percent), and in 43 percent of the patients with Candida the disease was limited to soft tissue or bone. Torulopsis was found in two patients with disseminated disease, and several patients had mixed infections.

The nature of the disease was recognized antemortem in 86.3 percent of the patients. Biopsy of tissue (open lung, bone, kidney) led to the correct diagnosis in 43 percent of them. In three patients, however, this method initially failed to reveal the fungal infection, and the diagnosis was ultimately made by repeat open lung biopsy (one patient) or bronchoscopy (two patients). Other procedures employed included aspiration of pus from abscess foci (seven patients), percutaneous lung aspiration (one patient), sputum assessment (one patient) and blood culture (one patient). In one patient (Case 21), fungal infection was presumed when Aspergillus pneumonia was documented in the patient's brother who was concomitantly exposed to contaminated material. The means of diagnosis are unknown in 13.7 percent of the cases.

Host factors which might have predisposed to fungal infection [4,6] were assessed. Four patients were exposed to material proved [22] or presumed to be contaminated with Aspergillus, including hay or marijuana. One patient received hyperalimentation several days

TABLE II Fungi Responsible for 51 Infections Among 50 Patients with Chronic Granulomatous Disease

Fungus	Soft Tissue		Osteomyelitis		Pneumonia		Pneumonia and Extrapulmonary Extension*		Dissemination†		Total
	No.	%	No.	%	No.	%	No.	%	No.	%	(no.)
Aspergillus‡	2	3.9	4	7.8	21	41.2	9	17.7	4	7.8	40
Candida albicans	3	5.8	0	0	1	2	0	0	3	5.8	7
Torulopsis glabrata	0	0	0	0	0	0	0	0	2	3.9	2
Combined§	0	0	0	0	1	2	0	0	1	2	2
Total	5		4		23		9		10		

* Extension of disease into the pleural space, or soft tissue or bony structure of the chest wall.
† Dissemination is defined as recovery of fungus from blood or parenchymal organ other than, or in addition to, the lung.
‡ Aspergillus species including fumigatus [27], niger [1], nidulans [1] and flavus [1], species unknown [10].
§ One patient with Aspergillus fumigatus and Torulopsis glabrata, one patient with Aspergillus (? species) and Candida albicans.

prior to the onset of Candida sepsis. Ten patients were receiving long-term antimicrobial therapy including sulfonamides (five patients), trimethoprim sulfamethoxazole (four patients) and chloramphenicol (one patient). Cell-mediated immunity as assessed by cutaneous hypersensitivity was normal in 14 of 18 patients (77 percent) in whom this was assessed. Serum immune globulin (immunoglobulin G (IgG) or immunoglobulin A (IgA)) concentrations were greater than normal in six of seven (85.7 percent) patients examined with fungal infection. Humoral response to Aspergillus antigens by a variety of techniques was assessed in 12 patients with aspergillosis, and some increase in titer over controls was reported in eight (67 percent) of them.

Outcome of Infection/Limited Infection. All patients with fungal infections of the bone or soft tissue survived. Cure was achieved in one patient with surgery only, in three patients with amphotericin B, in one patient with amphotericin B and 5-fluorocytosine, in one patient with 5-fluorocytosine alone, and in two patients with surgery and amphotericin B. In two patients, the mode of therapy is unknown.

Outcome of Infection/"Pneumonia or Dissemination." Among 43 patients with more widespread fungal infections, 20 patients (16.5 percent) survived, 19 (44.2 percent) died, and in the remainder the outcome is unknown. The therapy employed is summarized in **Table III**. Patients could be divided into three groups: (1) those who showed dramatic improvement; (2) those whose infection persisted regardless of therapy over several months; and (3) those who died shortly after the diagnosis was made. One hundred percent of the patients who received no therapy died. One patient (Case 9) with Aspergillus producing a chronic pneumonia in the upper lobe of the right lung was cured by surgical resection

TABLE III Outcome of Therapy for 29 Pulmonary or Disseminated Infections Complicating Chronic Granulomatous Disease

	Improved or Cured*		Persistent Infection		Death		
	No.	%†	No.	%	No.	%	Total (100%)‡
No therapy	0	0	0	0	4	100	4
Surgery only	1	100	0	0	0	0	1
Antifungal chemotherapy‡	9	56.3	1	6.3	6	37.5	16
Antifungal chemotherapy and granulocyte transfusions§	4	50	2	25	2	25	8
Total	14		3		12		

* One patient with pneumonia and chest wall extension (Case 8) showed improvement with initial amphotericin B therapy but has had several exacerbations of Aspergillus osteomyelitis of the ribs most recently treated with improvement with ketoconazole (Gallis H: Personal communication).
† Percent values refer to percent of patients who received a particular mode of therapy.
‡ All patients in this group received amphotericin B. Total dosage ranged from 0.5 to 4.0 g (1.2 ± 0.7, mean ± SD). In addition, five patients received 5-fluorocytosine, one patient rifampicin, two patients 5-fluorocytosine and rifampicin, one patient clotrimazole and 5-fluorocytosine, one patient rifampicin, 5-fluorocytosine and clotrimazole.
§ All patients in this group received amphotericin B. Dosage ranged from 0.34 to 4.7 g (2.1 ± 1.8, mean ± SD). Two patients also received 5-fluorocytosine and rifampicin. Duration of granulocyte transfusion therapy ranged from five to 28 days (11.3 ± 8, mean ± SD), two patients underwent surgical procedures including a partial lung resection ("cure category") and a nephrectomy ("persistent" category). One patient had a severe adverse reaction in association with granulocyte transfusions and subsequently died with Salmonella sepsis.

of infected tissue. Twenty-four patients received antifungal therapy which included amphotericin B with a variety of combinations of 5-fluorocytosine, rifampicin, miconazole, clotrimazole, granulocyte transfusions and surgery. Although in some cases granulocyte transfusions seemed to have a dramatic impact on the clinical course, there was no significant difference in survival between patients treated with granulocytes and antifungal chemotherapy or those given antifungal chemotherapy alone. One patient (Case 5) had a severe reaction to a granulocyte infusion.

COMMENTS

Chronic granulomatous disease is characterized by recurrent infections with bacteria and fungi which produce catalase [15], an enzyme which detoxifies endogenous or exogenous hydrogen peroxide to oxygen and water. Since other host defense mechanisms are intact in chronic granulomatous disease, those patients provide a model to examine the role of phagocytic cells in defense against specific pathogens.

Among 245 patients with chronic granulomatous disease available for review, 20.4 percent had a history of fungal infection. This incidence is only a rough estimate because our sampling technique was in no way random or complete. Organisms encountered include A. flavus, fumigatus and niger, C. albicans and T. glabrata. These results are consistent with other reports with respect to the frequency and organisms producing such infections [13,18,19,40,41].

The proper diagnosis was made with difficulty and only at autopsy in 14 percent of the patients with fungal infection. Because these organisms may act as contaminants of the tracheobronchial tree [6], evidence of tissue invasion was generally sought; the diagnosis was most frequently confirmed by open lung or tissue biopsy. This vigorous diagnostic approach has been advocated in other immunocompromised patients with pulmonary infection [7].

We attempted to assess other risk factors which might have predisposed to fungal infection [4,6]. No patients were receiving corticosteroids. All patients had normal or increased immunoglobulins when this parameter was examined, as has been previously reported [11,17,20,28]. In addition, more than half of the patients examined had some increase (often slight) in antibodies directed against Aspergillus antigens. This observation is in disagreement with the careful study of Greenberg and his co-workers [31] who detected no increase in Aspergillus antibodies as measured by immunoprecipitation, immunofluorescence and hemagglutination. Recently, more sensitive tests including counter immunoelectrophoresis and the enzyme linked immunoabsorbent assay (ELISA) have demonstrated the formation of antibodies directed against Aspergillus in granulocytopenic patients with invasive fungal disease [42]. The role that such antibodies play in defense against fungal infections [10] (or protection from recurrent infection [31]) and their usage in serodiagnosis will require further evaluation.

Cell-mediated immunity assessed by cutaneous delayed hypersensitivity was normal in the majority of patients examined as has been previously reported [11,17,20,28,31]. Information regarding delayed hypersensitivity to Aspergillus antigens was not available.

Several environmental risk factors were examined. Four patients were exposed to material proved or believed to be contaminated with Aspergillus prior to the onset of fungal pneumonia. One patient received hyperalimentation nutrition before candidemia developed. This type of exposure has been implicated as a source of fungal infection in other compromised hosts [6].

Available records suggested that 20 percent of the patients in whom fungal infection developed were receiving long-term, broad spectrum antimicrobial therapy. Philippart and his colleagues [43] reported a decreased incidence of infection in patients with chronic granulomatous disease who received nafcillin in an uncontrolled trial. More recently, Johnston and his colleagues [24] reported enhanced bactericidal activity of chronic granulomatous disease cells exposed in vitro to sulphisoxazole, as well as decreased incidence of bacterial infection in children given this drug [24].

Although we were unable to assess whether antimicrobial therapy predisposed to fungal infection, such therapy may enhance fungal colonization [6]. Furthermore, Lehrer [44] observed that sulphonamides inhibit the candidacidal activity of normal neutrophils in vitro, perhaps secondary to inhibition of myeloperoxidase.

No uniform therapy was given to patients with chronic granulomatous disease and fungal infection. Treatment included surgery, antifungal agents and granulocyte transfusions. Patients with infection limited to soft tissue and bone responded well to all forms of therapy. Patients with pulmonary or disseminated infection, however, had a high mortality. Among this latter group, those who were untreated did not survive. In one patient cure was achieved with the removal of infected tissue only, and two other patients responded to a combination of surgical and antifungal therapy. In an uncontrolled study of 25 patients with chronic granulomatous disease, Robach and his colleagues [45] noted that in 85 percent of the patients surgical intervention was required. These investigators also reported cure of a bacterial pneumonia with resection of infected tissues in combination with antimicrobial therapy.

Amphotericin B is the cornerstone of antifungal therapy [8]. Most of the patients were given ampho-

tericin B, often in combination with other agents [46]. Unfortunately, there were too few patients in our study to allow adequate comparison of single (amphotericin B) and combination drug therapy.

One third of the patients who were given antifungal chemotherapy for fungal pneumonia or dissemination were also given granulocyte transfusions. Although in individual patients (e.g., [21,36] Cases 2 and 10) granulocyte transfusions seemed to have a dramatic impact on the clinical course, no statistically significant benefit was observed.

Controlled therapeutic trials of granulocytes for a variety of infections in patients with neoplasms [47,48] and isolated reports of granulocytes given to children with chronic granulomatous disease ([49,50] Case 2) have been encouraging. These studies have not, however, specifically assessed the efficacy of such therapy for patients with fungal infection. In an animal model, Ruthe et al. [9] observed reduced numbers of Candida in tissues harvested from leukopenic dogs after four days of granulocyte transfusions when compared to a second leukopenic population inoculated with this fungi.

Granulocyte transfusions for patients with chronic granulomatous disease introduce special considerations. First, in a recent report by Wright and co-workers [51] it has been suggested that transfusion reactions may be more frequent when leukocytes are administered with subsequent addition of amphotericin B. Second, some patients with chronic granulomatous disease have a rare red blood cell and leukocyte antigenic phenotype (the McLeod blood type) wherein these cells do not express Kx antigen. In these patients anti-Kx antibodies may form which may interfere with the function of transfused granulocytes and lead to adverse reactions [50].

In conclusion, the frequency with which fungal infections occur in patients with chronic granulomatous disease emphasizes the importance of the phagocyte in defense against these pathogens. As with other compromised hosts [7,52], aggressive evaluation leading to early diagnosis is optimal. Treatment should include antifungal chemotherapy, and surgical removal of infected tissue should be considered. The value of granulocyte transfusions as a defense against fungal infection in granulocyte-compromised hosts will require further evaluation.

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ADDENDUM

Since the preparation of this manuscript, we have learned of three other cases of Aspergillus infection as a complication of chronic granulomatous disease, and Chusid et al. [53] have described a patient with a defect of leukocyte oxidative metabolism in whom Aspergillus pneumonia developed after smoking marijuana contaminated with this fungus. Finally, McGinnis and coworkers [54] have reported a Hansenula polymorpha mediastinal node infection in a child with chronic granulomatous disease.

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