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## AN OUTBREAK OF COMMUNITY-ACQUIRED *PNEUMOCYSTIS CARINII* PNEUMONIA

### Initial Manifestation of Cellular Immune Dysfunction

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**Abstract** Eleven cases of community-acquired *Pneumocystis carinii* pneumonia occurred between 1979 and 1981 and prompted clinical and immunologic evaluation of the patients. Young men who were drug abusers (seven patients), homosexuals (six), or both (two) presented with pneumonia. Immunologic testing revealed that absolute lymphocyte counts, T-cell counts, and lymphocyte proliferation were depressed, and that humoral immunity was intact. Of the 11 patients, one was found to have Kaposi's sarcoma,

and another had angioimmunoblastic lymphadenopathy. Eight patients died. In the remaining three, no diagnosis of an immunosuppressive disease was established, despite persistence of immune defects. These cases of pneumocystosis suggest the importance of cell-mediated immune function in the defense against *P. carinii*. The occurrence of this infection among drug abusers and homosexuals indicates that these groups may be at high risk for this infection. (*N Engl J Med*. 1981; 305:1431-8.)

*PNEUMOCYSTIS CARINII* is a ubiquitous organism that infects human beings by a respiratory route. The organism appears to be relatively avirulent, since it rarely if ever causes disease in immunologically competent persons.<sup>1,2</sup> In North America, almost all cases have occurred in patients who have had diagnoses of primary congenital immunodeficiencies or who have received immunosuppressive chemotherapy for malignant neoplastic disease or organ transplantation.<sup>1,2</sup>

Despite the rarity of *P. carinii* pneumonia in previously healthy persons, we recently recognized 11 cases

of this disease in young men with no previous history to suggest immunologic dysfunction. All 11 men were drug abusers or homosexuals or both. Each was found to have similar immunologic defects indicative of abnormal cell-mediated immunity. The clinical, epidemiologic, and immunologic features of this population are the subject of this report.

### METHODS

#### Selection of Patients

Between July 1979 and April 1981, infectious-disease consultants in the New York metropolitan area became aware of several cases of *P. carinii* pneumonia in adults with no history suggestive of immunologic incompetence. Consultants from several medical institutions, who regularly meet at an intercity infectious-disease conference, were queried about similar cases. Thirteen patients were reported from nine hospitals: 11 patients at seven hospitals were made available for this study. A diagnosis of *P. carinii* pneumonia was accepted only if abundant *P. carinii* organisms (identified by methanamine silver or Gram-Weigert stain) were present in areas of lung tissue, if an inflammatory cellular or exudative response was present, and if no other coexistent organisms were demonstrated by pathological examination, by cultivation (for bacteria, fungi, and

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mycobacteria), or by serology. Serologic studies for infectious agents were performed as indicated by the clinical situation. Nine patients were evaluated by complement-fixation testing for titers of cytomegalovirus antibody more than two weeks after lung biopsy. Viral cultivations were not attempted. The pathological features of any available nonpulmonary tissue were also reviewed in order to assess the presence or absence of underlying systemic disease.

#### Selection of Controls

The control group for in vitro mononuclear-cell studies consisted of healthy hospital personnel (matched for age, but not for sex or race) who were not known to be drug addicts or homosexuals and who were not taking medications. Subjects were excluded if they had had an acute illness during the week before testing. Historical control values were used for other studies.

#### Immunologic Testing

Ten of the 11 patients had all immunologic testing performed at the same laboratories of the New York Hospital, Rockefeller University, and Memorial Sloan-Kettering Cancer Center. Patient 8 was studied only at Downstate Medical Center and the Brooklyn Veterans Administration Medical Center. At the time of testing, nine patients had received no immunosuppressive chemotherapy; a single patient had received a two-day course of prednisone (60 mg per day) 10 days before his first test, and another had received a nine-day course of prednisone that ended 11 days before his first test. Five patients who survived their initial hospitalization (Patients 1, 2, 6, 7, and 10) were tested on at least two occasions, the last of which occurred one month or more after discharge from the hospital, when they appeared to be well. Two patients (Patients 3 and 4) who survived the initial hospitalization but died subsequently had their only testing performed at least two months after the resolution of their pneumocystosis. Among four patients who did not survive the initial hospitalization, one was studied on two occasions separated by more than two weeks (Patient 5) and three were studied only once during the acute illness (Patients 8, 9 and 11).

Mononuclear cells were separated from heparinized venous blood

by centrifugation on a Ficoll-Hypaque cushion. T cells were counted by rosette formation with sheep erythrocytes after incubation at 4°C for one hour. B cells were enumerated by detection of cells bearing surface immunoglobulins, with a polyvalent rabbit (ab)-fragment antiserum to human immunoglobulin. The number of monocytes was determined as the percentage of mononuclear cells ingesting latex particles. The viability of cells, as determined by exclusion of trypan blue dye, always exceeded 90 per cent of the total. Enumeration of these different mononuclear-cell populations, as previously described,<sup>3</sup> was kindly performed by Dr. B. Koziner. Monocyte antitoxoplasmic activity was assessed as previously described.<sup>4</sup> T-cell function was measured in vivo by delayed cutaneous reactivity after intradermal administration of at least four of the following antigens: candida, mumps, tetanus-toxoid, trichophyton, tuberculin, and streptokinase-streptodornase. Lymphocyte transformation was measured by incorporation of [<sup>14</sup>C]thymidine in response to stimulation with mitogens, antigens, and allogeneic cells, as previously described.<sup>5,6</sup> The mitogens used and the final concentrations were as follows: phytohemagglutinin at 175-3 µg per milliliter, concanavalin A at 114-3 µg per milliliter, and pokeweed mitogen at 142-3 µg per milliliter. Antigens used included the following microbial activators, prepared as previously described<sup>7</sup> and used in multiple dilutions of their respective stock solutions: ultracentrifuged and sonicated extract of *Candida albicans* Type A at 1 g per milliliter (wet weight), pools of treated extracts of common *Escherichia coli* and common *Staphylococcus aureus*, each resuspended at 10<sup>9</sup> cells per milliliter, and purified protein derivative of tuberculin at a range of final concentrations of 0.5 to 4.5 µg per milliliter. Allogeneic cells pooled from donors who were of at least six different HLA types were also used as stimulators, added (in concentrations ranging from 3000 to 50,000 cells per milliliter) to 50,000 responder cells from patients or controls. Results of lymphocyte-proliferation studies are expressed as the net counts per minute: those in a stimulated culture minus those in the unstimulated culture.

For statistical evaluation, lymphoproliferative responses were analyzed with the median counts per minute of the maximal response elicited to a range of concentrations of each cell activator. P values as given in the text were determined by the paired t-test, comparing each patient's response with his simultaneously tested control's response.<sup>8</sup>

Table 1. Clinical Features of 11 Men with *Pneumocystis carinii* Pneumonia.\*

CLINICAL FEATURE	PATIENT NO.				
	1	2	3	4	5
Age (yr)	27	37	39	40	34
Race/ethnic group	Black	White	Black	Black	White
Occupation	Hospital guard	Drug dealer	Hospital clerk	Mover	Teacher
Sexual preference	Homosexual	Heterosexual	Heterosexual	Heterosexual	Homosexual
Drugs abused	None	Heroin	Alcohol	Heroin	None
Onset of PCP (mo/yr)	4/79	4/80	2/80	6/80	11/80
Duration of symptoms	2 mo	5 mo	5 mo	1 mo	3 days
Date of lung biopsy (mo/yr)	6/79	9/80	7/80	7/80	11/80
Outcome of PCP	Survived	Survived	Survived	Survived	Survived
Other infections Before PCP	Oral candidiasis	None	Epididymitis	None	Oral candidiasis
After PCP	Candida esophagitis, amebiasis, PCP	<i>Mycobacterium avium</i>	Klebsiella sepsis	None	Cryptococcosis, CMV, polybacterial sepsis, PCP
Follow-up (mo after biopsy)	6	10	8	8	3
Current status	Dead	Dead	Dead	Alive	Dead
Clinical and pathological findings	Autopsy: candida esophagitis, PCP	LAP: <i>mycobacterium avium</i>	Marrow biopsy, CTT of abdomen, lymph-node biopsy: ALLD	CTT of abdomen, LSS, LAP, marrow biopsy: NAD	Autopsy: Kaposi's sarcoma, CMV, PCP, cryptococcosis

(Table continues on next page.)

The preformed-antibody response was determined by measurement of isohemagglutinin titers to antigens of the ABO blood group. Most of the patients were tested for the ability to make a specific antibody response by determination of antibody levels after administration of diphtheria-tetanus vaccine with a hemagglutination assay (kindly performed by the Centers for Disease Control, Atlanta) or after administration of pneumococcal polysaccharide vaccine with a radioimmunoassay (kindly performed by Dr. Gerald Schiffman) or with both procedures.

Standard techniques were used for measurement of serum immunoglobulins, absolute lymphocyte number, serum complement, resting-cell nitroblue tetrazolium testing, and myeloperoxidase staining. Latex fixation for rheumatoid factor and indirect immunofluorescence for antinuclear antibody were also performed.

## RESULTS

### Patient Population

The clinical features of these 11 patients are summarized in Table 1. The 11 patients were all men 27 to 40 years old. Four were black, five were white, and two were Hispanic. Each patient was a drug user (seven patients), a homosexual (six), or both (two). Abused substances at the time of illness included heroin (four patients), methadone (one), alcohol (one), and alcohol plus cocaine (one). All patients were residents of New York City who had no social or occupational contacts with one another. The time of lung biopsy was randomly distributed (as calculated by Poisson distribution) over a 21-month period for the group as a whole, although four homosexual men presented to one hospital between February and April 1981. None of the patients had a history of unusual, severe, or recurrent infections in themselves or their

families. Four patients had had oral candidiasis several weeks before the onset of *P. carinii* pneumonia, and one had had localized herpes zoster eight months before his pulmonary disease.

### Clinical Illness

Four patients (Patients 3, 5, 6, and 8) had had non-respiratory symptoms for three to 19 months before presenting with a pulmonary syndrome. These symptoms included fever, anorexia, and weight loss in each patient and voluminous diarrhea in Patient 5. All patients eventually had a respiratory illness characterized by nonproductive cough. Seven of the patients also had marked dyspnea. One patient had pleuritic chest pain, and one had rigors. The pulmonary syndrome had persisted for two to eight months before lung biopsy in eight patients and for three to seven days in three. Ten of the 11 patients had a history of fever before admission.

Initial physical examination revealed that 10 of these patients had fever (temperatures above 38.0°C) and that all had either diffuse fine rales or rhonchi. Two patients who were found to have neoplastic disorders were the only ones with remarkable extrapulmonary findings. Patient 5, who had malabsorption, was markedly cachectic on admission; Patient 3 had both generalized lymphadenopathy and epididymitis.

### Routine Laboratory Evaluation

Seven patients had mild anemia (hematocrit, 31 to 39 per cent), but all had normal granulocyte and

Table 1. (Continued.)

PATIENT NO.					
6	7	8	9	10	11
31	27	34	31	35	27
Black	White	Hispanic	Hispanic	White	White
Carpenter	Waiter	Clerk	None	Horticulturist	None
Heterosexual	Homosexual	Heterosexual	Homosexual	Homosexual	Homosexual
Alcohol, cocaine	None	Methadone	Heroin	None	Heroin
11/80	9/80	7/80	2/81	4/81	1/81
7 days	5 mo	6 mo	2 mo	21 days	2 mo
11/80	2/81	12/80	4/81	4/81	3/81
Survived	Survived	Died	Died	Survived	Died
Herpes zoster	Oral candidiasis	None	None	Oral candidiasis	None
None	PCP, CMV	Candida and aspergillus	Gram-negative bacillary	Oral candidiasis	Gram-negative bacillary
		esophagitis, gram-negative bacillary	pneumonia, CMV, herpes esophagitis, PCP		pneumonia
10	7	1	1	5	1
Alive	Dead	Dead	Dead	Alive	Dead
Marrow biopsy, CTT of chest: NAD	Autopsy: PCP, CMV	LSS, marrow biopsy, CTT of abdomen, IVP, LAG, gallium scan: NAD	Autopsy: CMV, herpes esophagitis, PCP	Marrow biopsy, LSS, CTT of abdomen: NAD	None

\*PCP denotes *Pneumocystis carinii* pneumonia. CTT computed transaxial tomography, LAG lymphangiogram, LSS liver-spleen scan, LAP laparotomy, IVP intravenous pyelogram, AILD angioimmunoblastic lymphadenopathy, CMV cytomegalovirus, and NAD no apparent disease.



platelet counts on admission. Lymphopenia was detected in all patients except one (Patient 4). Leukopenia (1060 to 3000 white cells per cubic millimeter) subsequently developed in five patients (Patients 1, 4, 5, 7, and 10) after therapy with trimethoprim-sulfamethoxazole. Patient 5's chemistry profile was consistent with marked malabsorption, as evidenced by hypoalbuminemia (2.3 g per deciliter) and reduced folate and vitamin B<sub>12</sub> stores. The other patients' chemistry profiles were remarkable only for mild elevations in transaminases (less than twice normal) in three patients, mild hypoalbuminemia (3.0 to 3.3 g per deciliter) in three, and hypocalcemia (4.2 mg per deciliter [1.0 mmol per liter]) in one. Measurements of arterial blood gases while patients were breathing room air showed that the partial pressure of oxygen at admission ranged from 33 to 91 mm Hg. Chest radiographs at admission showed a diffuse interstitial or reticulonodular pattern in 10 cases, three of which were initially asymmetrical. Patient 6 presented with a 3-by-3-cm right-lower-lobe nodule, which progressed to a diffuse reticulonodular pattern after lung biopsy.

#### Diagnosis of *P. carinii* Pneumonia

Ten patients were initially treated with a broad-spectrum antibacterial regimen without resolution of their pulmonary illness. Patient 6 underwent a lung biopsy before the institution of antimicrobial therapy. The diagnosis of *P. carinii* pneumonia was established by transbronchial biopsy in five patients and by open-lung biopsy in six. In 10 patients there was a patchy distribution of mononuclear-cell infiltration with eosinophilic intra-alveolar exudate. Patient 6, who presented with a nodular lesion, had areas of necrosis, infarction, and atypical granulomas surrounding abundant *P. carinii* organisms.

#### Treatment and Outcome

All 11 patients were initially treated for pneumocystosis with oral or intravenous trimethoprim-sulfamethoxazole. Five patients responded promptly, whereas five responded poorly and were treated with pentamidine instead of the trimethoprim-sulfamethoxazole or in addition to it. Patient 6, who initially presented with a nodular lesion, had diffuse infiltrates, which resolved spontaneously before trimethoprim-sulfamethoxazole was instituted.

All patients had extensive serologic, radiologic, and histologic evaluations for the presence of immunosuppressive diseases. Patient 3 had angioimmunoblastic lymphadenopathy documented by lymph-node and bone-marrow biopsy. In Patient 5, a cutaneous lesion was noted during hospitalization; this lesion was demonstrated by biopsy to be Kaposi's sarcoma. Both patients survived their pneumocystosis but died of other infectious processes eight months and three months later, respectively.

Three patients died early in the course of their disease: Patient 9 of autopsy-proved progressive pneu-

mocystosis and Patients 8 and 11 after acquiring nosocomial gram-negative pneumonia. Five others died after more prolonged illnesses. Patient 1 apparently responded promptly to therapy, with clearance of infiltrates and improvement in blood gases, but he continued to have debilitating fever for six months. The only diseases identified during this period were esophageal candidiasis and intestinal amebiasis. The patient died suddenly at home; at autopsy he was found to have extensive pneumocystis pneumonia but no evidence of an immunosuppressive disease. Patient 2 died 10 months after lung biopsy because of a progressive febrile disease (disseminated *Mycobacterium avium* infection), but no underlying disease was found at laparotomy. Fatal klebsiella sepsis developed in Patient 3, and an autopsy was not performed. Patient 5 died of an overwhelming cryptococcal infection that developed after his initial presentation. At autopsy, pneumocystis and cytomegalovirus were also present in the lungs. Patient 7 died seven months after lung biopsy because of another episode of *P. carinii* pneumonia; autopsy did not reveal an underlying disease.

The three survivors have been well and free of severe infectious diseases since discharge. One has had persistent oral candidiasis. These three patients include one homosexual and two drug abusers. They have been followed for five to 10 months.

#### Immunologic Evaluation

None of the patients had cutaneous reactivity to any of the antigens tested. This anergy was present during the acute illness, and it persisted in the patients who were tested for delayed hypersensitivity more than two weeks after the *P. carinii* pneumonia had clinically resolved (Patients 1 to 4 and 6 to 8). Patients 1, 2, 3, 4, 6, 7, and 10 underwent lymphocyte-transformation studies after the clinical resolution of the pneumocystosis. Patients 5, 8, 9, and 11 were studied during their acute illness, as described above.

As seen in Figure 1, the patients had lower proliferative responses to various mitogens, antigens, and allogeneic cells than did a simultaneously tested age-matched control group. These responses represent the maximal lymphocyte proliferation that could be elicited with a range of concentrations of stimulating substances and cells. Since only pooled normal human serum was used to supplement the lymphocyte-culture mediums, it is not possible that serum suppressor factors had a role in these abnormally low responses. An impaired cellular immune response in the patients, as compared with the controls, was observed in *in vitro* studies of lymphocytes cultured with nonspecific inducers of T-lymphocyte activation: phytohemagglutinin ( $P < 0.0001$ ), concanavalin A ( $P < 0.0001$ ), and the T-cell-dependent inducer of mitosis in B lymphocytes, pokeweed mitogen ( $P < 0.0001$ ) (Fig. 1A). Lymphocyte responses to the microbial activators *C. albicans* ( $P < 0.0001$ ), *Staph. aureus* ( $P < 0.003$ ), *Esch. coli* ( $P < 0.004$ ), and purified

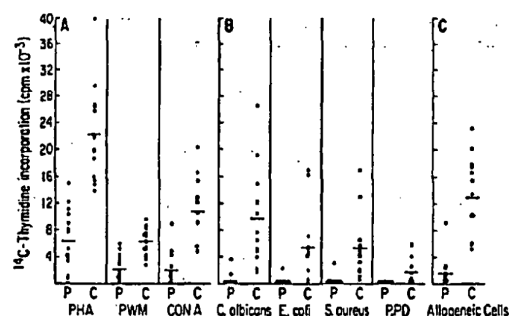


Figure 1. Maximal Proliferation of Lymphocytes from Patients with *Pneumocystis carinii* Pneumonia and from Healthy Controls in Response to Several Mitogens (A), Antigens (B), and Pooled Allogeneic Cells (C).

Five patients were studied once, and six were studied twice. Lymphocytes ( $5 \times 10^4$ ) were cultured in triplicate with multiple dilutions for each cell activator tested. Each culture was pulse-labeled with  $0.04 \mu\text{Ci}$  of  $^{14}\text{C}$ -thymidine at time points predetermined from normal control studies to represent the time of maximum proliferative activity for the particular cell activator used. Cells were harvested 16 to 18 hours later onto glass-fiber filter paper and counted in a scintillation counter. Data are given as net counts per minute (cpm). Bars indicate the arithmetic mean in each group for each activator tested. PHA denotes phytohemagglutinin, PWM pokeweed mitogen, CON A concanavalin A, PPD purified protein derivative of tuberculin, P patients, and C controls.

protein derivative of tuberculin ( $P < 0.025$ ) were also depressed, as seen in Figure 1B. Alloreactivity (Fig. 1C) was similarly depressed in these patients ( $P < 0.0001$ ), as indicated by their low response to pooled lymphocytes as compared with that of the controls. With the exception of Patients 5, 8, 9, and 11, these tests of lymphocyte proliferation were per-

formed when the patients were not acutely ill. In addition, repeated evaluation in Patients 1, 2, 5, 6, 7, and 10 more than one month after the first evaluation confirmed the same type of abnormally depressed responses.

In Table 2, the responses of patients with *P. carinii* pneumonia to phytohemagglutinin are compared with the total lymphocyte count, the percentage of sheep-erythrocyte-rosetting lymphocytes, and the percentage of mononuclear phagocytic cells. These data illustrate that the depressed phytohemagglutinin responses in the patients with pneumocystis infection were associated with low lymphocyte counts, ranging from 82 to 1444 cells per cubic millimeter in all but Patient 4, whose lymphocyte count of 2065 was normal. Nine of the 11 patients had a diminished sheep-erythrocyte-rosetting population on one or more determinations. It is important to note that the degree of impairment of an individual patient's phytohemagglutinin response did not directly relate to the level of reduction of sheep-erythrocyte-rosetting lymphocytes or to the number of mononuclear phagocytic cells. The impaired phytohemagglutinin responses in these patients are consistent with a defect in T cells, T-cell subsets, monocytes, or a combination of these cells.

The evaluation of antibody-mediated immunity in these patients is presented in Table 3. Quantitation of serum immunoglobulins revealed normal or elevated levels of some of the immunoglobulin classes in nine patients. Two patients had slight decreases in their IgG or IgM levels. No monoclonal proteins were detected by serum immunoelectrophoresis. Isohemagglutinins to antigens of the ABO blood group were present in normal titers. Protective levels of tetanus antitoxin were found in Patients 2 to 7 and 9 to 11; protective levels of diphtheria antitoxin were found in

Table 2. Comparison of Maximal Response to Phytohemagglutinin with Lymphocyte Count, Percentage of T-Cell Rosettes, and Percentage of Mononuclear Phagocytic Cells in Patients with *Pneumocystis carinii* Pneumonia.

PATIENT NO.	TIME OF TEST AFTER DIAGNOSIS	TOTAL LYMPHOCYTE COUNT *	SHEEP-ERYTHROCYTE ROSETTES †	MONONUCLEAR PHAGOCYTIC CELLS ‡	PATIENT'S PHYTOHEMAGGLUTININ RESPONSE §	CONTROL'S PHYTOHEMAGGLUTININ RESPONSE §
	mo	cells/mm <sup>3</sup>	%	%		cpm $\times 10^{-3}$
1	1	225	44	29	9,025	15,415
1	2½	1444	67	13	14,988	21,772
2	1	220	63	21	11,113	15,975
2	4	576	19	ND	10,396	14,768
3	3¼	825	55	27	4,220	19,698
4	4	2065	73	3	8,013	13,810
5	½	540	24	25	3,504	21,975
5	1½	480	12	6	100	26,330
6	2	972	71	20	5,235	29,500
6	5	1002	40	33	4,252	19,838
7	1	630	67	12	1,198	18,635
7	3	480	46	ND	908	26,678
8	2	588	22	ND	12,229	39,784
9	<1	735	10	0	3,987	22,150
10	<1	665	75	4	7,780	22,150
10	2	983	71	7	3,920	25,738
11	<1	82	11	0	ND	—

\*Normal range, 1500 to 4000 cells per cubic millimeter.

†Normal mean range  $\pm$ S.D.,  $17 \pm 8$ . ND denotes not determined.

‡Normal mean range  $\pm$ S.D.,  $72 \pm 11$ .

§Value represents  $^{14}\text{C}$ -thymidine incorporation.

Table 3. Evaluation of Antibody-Mediated Immunity in Patients with *Pneumocystis carinii* Pneumonia.\*

VARIABLE (NORMAL RANGE)	PATIENT No.										
	1	2	3	4	5	6	7	8	9	10	11
Serum immunoglobulins											
IgG (616-1647 mg/100 ml)	817	1150	2400	1560	600	1700	560	1390	1590	1360	1300
IgA (59-371 mg/100 ml)	93	370	320	780	200	260	195	710	410	640	220
IgM (57-343 mg/100 ml)	115	170	160	310	100	478	40	380	362	360	146
IgE (<41.0 µg/ml)	15	5.5	83	82	ND	ND	109	0	44	833	20
Isohemagglutinins (titer > 1:4 after 1 yr of age)											
Anti-A	1:32	—	1:32	—	0 †	ND	—	ND	1:32	1:128	1:8
Anti-B	—	1:64	—	1:64	0 †	—	1:32	—	1:32	1:64	1:4
Specific antibody response											
Tetanus (>0.01 antitoxin units/ml)	ND	>0.35	0.09	>0.35	0.04	>0.35	>0.35	ND	>2.8	0.18	1.4
Diphtheria (>0.01 antitoxin units/ml)	ND	>6.0	0.05	>6.0	0.02	<0.01	0.38	ND	0.05	0.09	<0.01
Pneumococcal polysaccharides (substantial antibody rise in 12 serotypes tested)	Present	Present	Present	Present	ND	ND	ND	ND	ND	ND	ND
Pneumocystis	1:16	1:64	1:16	1:16	1:16	Negative	Negative	ND	Negative	1:32	Negative
B-cell quantitation											
Ig-bearing lymphocytes (150-950 cells/mm <sup>3</sup> )	217	196	388	620	418	156	214	ND	ND	147	73

\*ND denotes not done.

†Blood type AB.

Patients 2 to 5, 7, 9, and 10. Patients 1 to 4, who were immunized with pneumococcal vaccine, acquired a substantial level of antibody to at least 11 serotypes two weeks after immunization. More important, six of the 10 patients had titers of anti-pneumocystis antibody  $\geq 1:16$ . B-cell quantitation, determined as the number of surface-immunoglobulin-positive cells, showed normal B-lymphocyte counts in seven patients. Plasma cells were detected by marrow examination in eight patients (Patients 1 and 3 to 9).

The phagocytic cells of these patients were assessed by the neutrophil count, nitroblue tetrazolium testing of unstimulated neutrophils and monocytes, and tests of the monocytes' ability to phagocytose and kill *Toxoplasma gondii*; these cells were found to be normal in all patients. Total hemolytic complement, C3 and C4, or both were also measured, and the levels were not depressed. Rheumatoid factor and antinuclear antibodies were absent in all patients.

### DISCUSSION

*P. carinii* pneumonia is usually a disease of persons with previously recognized immunosuppressive disorders. In adults, pneumocystosis is usually associated with hematologic neoplasia or organ transplantation, although the widespread use of immunosuppressive chemotherapy (especially corticosteroids) has facilitated its occurrence in patients with a wide range of malignant neoplastic and inflammatory diseases.<sup>1,2</sup> In children, pneumocystosis has also been associated with primary congenital immunodeficiency syndromes and protein-calorie malnutrition.<sup>1,2,9,10</sup>

Pneumocystosis has only rarely been recognized as the initial manifestation of an immunologic abnormality. Five infants have had pneumocystosis during

the first year of life, and each was found to have a congenital hypogammaglobulinemia.<sup>11-14</sup> Infants and young children with severe protein-calorie malnutrition but no history of severe or recurrent infection have also had *P. carinii* pneumonia either during nursery epidemics in Eastern Europe or, more recently, as isolated cases among Asian refugees.<sup>1,2,15</sup> In a recent preliminary report, five homosexual men had *P. carinii* pneumonia with evidence of cytomegalovirus infection, and three of these patients had cellular immune dysfunction.<sup>16</sup> Six of our 11 patients were homosexuals, but only two of the five homosexuals tested had serologic evidence of cytomegalovirus.

The 11 patients in this series all had profound defects in the cell-mediated immune response. All patients were anergic, had T-lymphocyte depletion, and had markedly depressed lymphoproliferative responses to mitogens, antigens, and allogeneic cells. The reduction in the response of these patients' lymphocytes to phytohemagglutinin could not be correlated with the percentage of sheep-erythrocyte settes or with the percentage of latex-ingesting cells, suggesting that the impaired phytohemagglutinin response was more probably related to T-cell or monocyte dysfunction than to the cell number. Repeat testing in some of these patients, months after the acute *P. carinii* pneumonia, demonstrated persistence of immunologic abnormalities. In addition, five of these patients had oral candidiasis or herpes zoster before the *P. carinii* pneumonia, at least three had histopathologic evidence of concurrent cytomegalovirus infection, and five had mycobacterial, protozoan, or invasive fungal disease after their initial presentation with pneumocystosis. Infection with these opportunistic agents in vivo clearly supports the in vitro evidence of defective cellular immunity.

In contrast to cellular immunity, humoral immu-



nity, phagocytosis, and complement levels all appeared intact in the persons tested.

Evaluation of the relative importance of cell-mediated and humoral immunity in adults with *P. carinii* pneumonia has previously been difficult, because both are usually suppressed by the complex interaction of effects of the underlying immunosuppressive disease, chemotherapy, or protein-calorie malnutrition.<sup>1,2,8</sup> In children with primary congenital immunodeficiencies, pure B-cell defects have clearly been associated with pneumocystis disease.<sup>1,2,10</sup> However, patients with combined T-cell and B-cell deficiencies seem more predisposed to pneumocystosis than patients with pure B-cell dysfunction.<sup>9</sup> There has been only one reported case of a pure T-cell defect associated with pneumocystosis.<sup>17</sup>

Our study supports the importance of cell-mediated immune function in host defenses against pneumocystis infection. This concurs with studies that have shown in vitro that the human-lymphocyte-antibody response to pneumocystis antigen is dependent on the presence of both T lymphocytes and adherent cells.<sup>18</sup> These observations supplement previous studies that have shown that the degradation of pneumocystis trophozoites by murine cells is dependent on specific anti-pneumocystis serum for opsonization and on intact mononuclear phagocytes for killing.<sup>19</sup>

In two of the 11 patients, the observed immune dysfunction could have been associated with malignant neoplastic disorders: angioimmunoblastic lymphadenopathy and Kaposi's sarcoma. The cause of the immune abnormalities in the remaining nine patients has not been established. Perhaps, given sufficient time, all would have had a recognizable disease that caused their immunosuppression. A common environmental substance that might have been a factor in the immunosuppression in this group of young men could not be identified. They did not live near each other or use similar medications; their close associates were not clinically affected. Narcotic abuse has been reported to cause in vitro immune defects similar to those described here,<sup>20,21</sup> yet it has not previously been associated with pneumocystosis. Certain viral diseases common in the homosexual community, such as cytomegalovirus, can depress the immune response; yet, these viral processes have not previously been associated with opportunistic superinfection in this population.<sup>22,24</sup> Moreover, in patients with evidence of cytomegalovirus infection, it is unclear whether the viral process was the precipitating cause of the immune depression or the result of reactivation subsequent to the initial immunosuppressive process. We are not aware of previous data suggesting that immunosuppression has been frequent among homosexuals. The results of this study and of other preliminary reports suggest that immunologic evaluation of homosexuals and drug abusers should be reassessed in conjunction with epidemiologic investigations of factors that could subject subpopulations to unusual

risks for neoplastic disease or opportunistic infections.<sup>16,22</sup>

Serologic data and limited autopsy studies have suggested that pneumocystis is a ubiquitous organism to which many people are exposed early in life.<sup>25,26</sup> Studies in animals have demonstrated that murine transmission can occur through a respiratory route.<sup>27</sup> Nursery epidemics in economically disadvantaged regions and clusters of cases of pneumocystis pneumonia among oncology patients at three separate hospitals have suggested that person-to-person spread does occur, probably by a respiratory route, and that normal, healthy persons can serve as vectors.<sup>1,28,29</sup> Healthy medical personnel and family contacts of patients have not been documented to have *P. carinii* pneumonia, despite close contact with sporadic cases or hospital epidemics, although Watanabe et al. described an intriguing cluster of respiratory illnesses in two healthy family members of a patient who died of pneumocystosis.<sup>30</sup> In fact, diffuse *P. carinii* pneumonia has never been convincingly demonstrated to occur in an immunologically normal adult. Three adults and two children have been reported to have *P. carinii* pneumonia and to have had no immunosuppressive disease discovered at autopsy.<sup>30-34</sup> However, these patients had only limited immunologic studies performed. Subsequently, one seven-month-old child survived *P. carinii* pneumonia and was found by Rao et al. to have several normal markers of cell-mediated and humoral immunity.<sup>35</sup>

At present, there is insufficient evidence to determine whether the *P. carinii* pneumonia in these patients was due to pneumocystis infection that was latent and then reactivated or to infection that was recently acquired. Since homosexuals are suddenly contracting a variety of opportunistic fungal, viral, and mycobacterial infections, it seems unlikely that this outbreak has been due exclusively to a new virulent or resistant strain of pneumocystis. This outbreak was more probably related to the immunologic consequences of some unknown process. The high mortality rate also seems more likely to have been due to the immunologic lesion than to virulence or resistance of the specific organism or to peculiarities of clinical management.

This outbreak of community-acquired *P. carinii* pneumonia among young male homosexuals and drug abusers raises questions about increased exposure to pneumocystis as well as about the prevalence and origin of abnormal cellular immune responses in these populations. An awareness of the association should prompt further study of the epidemiology of pneumocystis infection and an aggressive diagnostic approach to diffuse pneumonias that occur in these groups of patients.

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