Courtesy of Linda Nelson.

Michael S. Gottlieb, MD.

Pneumocystis Pneumonia—Los Angeles

Note. This paper, from the *Morbidity and Mortality Weekly Report* of June 5, 1981, is reprinted in its entirety.

In the period October 1980–May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33 y-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; May 1981 it was 32. The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30 y-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28 in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30 y-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29 y-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

Patient 5: a previously healthy 36 y-old man with a clinically diagnosed CMV infection in September 1980 was seen in April 1981 because of a 4-month history of fever, dyspnea, and cough. On admission he was found to have *P. carinii* pneumonia, oral candidiasis, and CMV retinitis. A complement-fixation CMV titer in April 1981 was 128. The patient has been treated with 2 short courses of TMP/SMX that have been limited because of a sulfa-induced neutropenia. He is being treated for candidiasis with topical nystatin.

The diagnosis of *Pneumocystis* pneumonia was confirmed for all 5 patients ante-mortem by closed or open lung biopsy. The patients did not know each other and had no known common contacts or knowledge of sexual partners who had had similar illnesses. The 5 did not have comparable histories of sexually transmitted disease. Four had serologic evidence of past hepatitis B infection but had no evidence of current hepatitis B surface antigen. Two of the 5 reported having frequent homosexual contacts with various partners. All 5 reported using inhalant drugs, and 1 reported parenteral drug abuse. Three patients had profoundly depressed numbers of thymus-dependent lymphocyte cells and profoundly depressed *in vitro* proliferative responses to mitogens and antigens. Lymphocyte studies were not performed on the other 2 patients.

Reported by MS Gottlieb, MD, HM Schanker, MD, PT Fan, MD, A Saxon, MD, JD Weisman, DO, Div of Clinical Immunology-Allergy, Dept of Medicine, UCLA School of Medicine; I Pozalski, MD, Cedars-Mt. Sinai Hospital, Los Angeles; Field Services Div, Epidemiology Program Office, CDC.

Editorial Note

Pneumocystis pneumonia in the United States is almost

exclusively limited to severely immunosuppressed patients.[1] The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual conduct and *Pneumocystis* pneumonia in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months of the diagnosis of *Pneumocystis* pneumonia. CMV infection has been shown to induce transient abnormalities of *in vitro* cellular-immune function in otherwise healthy human hosts.[2,3] Although all 3 patients tested had abnormal cellular-immune function, no definitive conclusion regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV antibody. In 1 report, 7 (3.6%) of 194 patients with pneumocystosis also had CMV infection; 40 (21%) of the same group had at least 1 other major concurrent infection.[1] A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) of 190 males reported to be exclusively homosexual had serum antibody to CMV, and 14 (7.4%) had CMV viruria; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero for viruria.[4] In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than in urine, but also that seminal fluid may be an important vehicle of CMV transmission.[5]

All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia. ■

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Editor's Note:

With this "Voices from the Past," we are abandoning our self-imposed rule about the age of excerpts reprinted in this department. Previously, and with only one exception (in the case of Walter Lear), we had stated that excerpts reprinted here should be at least 50 years old. We now find the rule overly restrictive and we intend—very selectively—to allow the choice of excerpts at least 10 years old. What better way to initiate this change than with the 25-year-old *Morbidity and Mortality Weekly Report* (*MMWR*) paper reprinted here, marking the first official notice of a new disease, later to become known as HIV/AIDS. This paper, based on a report of 5 patients, has become a classic, a reference point for medical and public recognition of the start of an epidemic that is perhaps the defining public health issue of our times.

Michael S. Gottlieb
and the Identification of AIDS

THE LEAD AUTHOR OF THIS paper, Michael S. Gottlieb, was, in 1981, a 33 year-old assistant professor specializing in immunology at the University of California Los Angeles (UCLA) Medical Center. When he asked one of his immunology fellows to look for interesting "teaching cases," he learned of a young gay man with unexplained fevers, dramatic weight loss, and a severely damaged immune system. His mouth was full of thrush, or candidiasis, which was usually seen in patients with a defect in one particular component of the immune system, the T-lymphocytes. Gottlieb later described a process of reasoning that led him to conclude that that this patient was suffering from some syndrome that had not previously been reported.[1] He discussed the unusual case with his clinical immunology postdoctoral fellows and internal medicine residents. Additional blood tests confirmed a marked deficiency of T-lymphocyte numbers and functions. Then a postdoctoral fellow who was using a series of new monoclonal antibodies to identify subclasses of T-lymphocytes was asked to examine a sample of the patient's blood and found that the T-cells bearing the surface marker CD4, the "helper" cells, were virtually absent.

The patient was discharged from hospital without a definite diagnosis but 1 week later was readmitted, this time with fever and pneumonia. The resident physician was concerned about an opportunistic infection in this individual, who was known to have an immune deficiency, and he convinced a pulmonary specialist to perform a bronchoscopy and retrieve a sample of lung tissue for analysis. This procedure is commonly done in immune-deficient patients to identify particular microorganisms, thus allowing for rapid specific diagnosis and treatment. The diagnosis was *Pneumocystis carinii*, a rare but well-known cause of pneumonia found in some organ transplant patients and children with immune deficiency. The patient was treated and again discharged.

Soon thereafter, Gottlieb heard about 2 patients of Joel Weisman. Weisman and his partner were gay physicians with a largely gay practice.[2] Both patients had chronic fevers, swollen lymph nodes, diarrhea, and thrush. Gottlieb tested the T-cells of Weisman's patients and found they had the same abnormality as his original patient. Over the next several months, both were diagnosed by bronchoscopy with *Pneumocystis carinii*. Both also had the DNA virus cytomegalovirus (CMV).

The fourth case came to Gottlieb through a former student, Wayne Shandera, who had become the CDC's Epidemic Control Officer in Los Angeles. Gottlieb told him that there was a new disease in gay men that seemed to have something to do with CMV and pneumocystis pneumonia and asked Shandera to see what he could find out. Shandera had a report sitting on his desk about a man in Santa Monica who had been diagnosed with pneumocystis pneumonia. Shandera went to see the patient and found that the man was deathly ill. The patient died soon after the visit; on autopsy, CMV was found in his lungs. A fifth case came from a Beverly Hills internist. This patient too had *Pneumocystis carinii* and CMV. Several of these patients went on to develop Kaposi's sarcoma, a rare skin cancer sometimes found in older men or immunosuppressed kidney transplant recipients.

Gottlieb, an ambitious young man, was excited to think he might have made a significant discovery. He telephoned Arnold Relman, the editor of the *New England Journal of Medicine*, and declared that he had a story that was "possibly a bigger story than Legionnaire's disease."[3(p1788)] When Gottlieb described his patients suffering from this complicated new malady, Relman advised that, because publication in the *New England Journal* would take a minimum of three months, Gottlieb should first submit a brief article to the CDC *Morbidity and Mortality Weekly Report*. This would serve the dual function of alerting public health officials and physicians to the new disease and also stake Gottlieb's claim to be its "discoverer." A longer and more detailed account could then be submitted to the *New England Journal*.

Gottlieb followed this good advice and the result was the rather terse announcement reprinted here. It was generally overlooked; few physicians bothered to read the *MMWR*. A few weeks later, however, when Alvin Friedman-Kien published a description of twenty-six cases of Karposi's sarcoma in gay men in New York and California, the media began to pay more attention.[4] National Public Radio, the Cable News Network, the Associated Press, the *New York Times*, and the *Washington Post* all followed with stories. Gottlieb's article in the *New England Journal of Medicine* was published a few months later and attracted

enormous attention.[5] As Gottlieb said later, the publication of this article changed his life. For several years, it was one of the most heavily quoted papers in the medical literature. The story would unfortunately prove to be a great deal more important than Legionnaire's Disease.

In the *New England Journal* article, Gottlieb and his co-authors described a "potentially transmissible immune deficiency"[5(p1425)] and suggested that a sexually transmissible agent contracted at different times by the patients was the common factor. Asymptomatic infection with CMV had recently been found to be common among the male homosexual population, and acute CMV infection had been associated with immunologic abnormalities, including reduction in CD4 cells. They therefore hypothesized that a new strain of CMV had emerged in the homosexual population and was causing immune deficiency. They also acknowledged the possibility that CMV was a result rather than a cause of the T-cell deficiency and that some other undetected microorganism, drug, or toxin might be making these patients susceptible to opportunistic organisms, including CMV. In an editorial accompanying the publication of the article, DT Durack asserted that CMV infection was more likely to be an opportunistic consequence of immune deficiency than its cause.[6]

In the early 1980s, Gottlieb treated a growing number of patients with AIDS and continued his clinical research at UCLA, publishing over 50 papers on various aspects of HIV infection and treatment. He obtained one of the earliest National Institutes of Health grants for AIDS research, served on many AIDS-related boards, and became physician to the stars: Rock Hudson, perhaps the most famous of all people with AIDS, was his patient. Gottlieb was also one of the few scientists who were willing to talk openly to reporters in the early years of the epidemic. His colleagues and superiors let it be known that his frequent appearances in the media were unbecoming to an academic.[7] Part of the problem, said Gottlieb, was that the UCLA Medical Center aspired to develop cardiac and liver transplant programs, and the physicians feared that if the hospital became too well known for AIDS, transplant patients might stay away.[2(p98)] They also foresaw that there would ultimately be a lot of AIDS patients without good health care coverage. AIDS loomed as a threat to the well-being of the hospital and Gottlieb, so publicly and professionally identified with the disease, was becoming a nuisance. Despite or perhaps because of his fame, Gottlieb was denied tenure at UCLA and went into private practice in 1987.

In 1985, Gottlieb and Mathilde Krim became the Founding Chairmen of the American Foundation for AIDS Research (amfAR), with Elizabeth Taylor as its Founding National Chairman. AmfAR would make a crucial contribution to AIDS research by supporting innovative projects; it would also help craft AIDS legislation, accelerate research on new treatments, and argue for rapid access to experimental HIV/AIDS drugs. ■

Elizabeth Fee and Theodore M. Brown

About the Authors

Elizabeth Fee is with the History of Medicine Division, National Library of Medicine, National Institutes of Health, Bethesda, Md. Theodore M. Brown is with the Department of History and the Department of Community and Preventive Medicine, University of Rochester, Rochester, NY.

Requests for reprints should be sent to Elizabeth Fee, History of Medicine Division, National Library of Medicine, National Institutes of Health, 8600 Rockville Pike, Bethesda, MD 20894 (feee@mail.nih.gov).

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