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## The Acquired Immunodeficiency Syndrome in Patients with Hemophilia

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Since mid-1981 the Centers for Disease Control (CDC) has received reports of more than 1900 cases of the acquired immunodeficiency syndrome. These patients had either Kaposi's sarcoma confirmed by biopsy or a life-threatening opportunistic infection confirmed by biopsy or culture. In January 1982 a case of a hemophiliac with *Pneumocystis carinii* pneumonia was reported to the CDC, and by July 1982 two other hemophiliacs had developed *P. carinii* pneumonia. During the next 12 months a total of 22 confirmed cases of the acquired immunodeficiency syndrome occurred in hemophiliacs; 17 in the United States and 5 outside the United States. We report the nature of the epidemic of the acquired immunodeficiency syndrome in hemophiliacs and summarize pertinent clinical aspects.

THE ACQUIRED IMMUNODEFICIENCY SYNDROME first appeared in sexually active homosexual men (1, 2) and by 26 July 1983, the epidemic had totaled 1922 cases in the United States (3). All cases had either biopsy-confirmed Kaposi's sarcoma or a life-threatening opportunistic infection confirmed by culture or biopsy and under the conditions suggested by the Centers for Disease Control (CDC) case criteria (4). Patients who had the appropriate immunologic studies done had a similar pattern of immune dysfunction, associated with a decreased number of T-helper lymphocytes. Several factors have implicated a transmissible agent as the cause of the syndrome. These factors have included the sudden appearance of cases in a geographic distribution of specific localized areas; the association with a prolonged prodrome that includes generalized lymphadenopathy, recurrent fever, and weight loss; and epidemiologic studies of case clusters, suggesting that the syndrome may be sexually transmitted among sexually active homosexual men (5, 6).

The preponderance of homosexual men and intravenous drug abusers among the first groups affected suggested hepatitis B as a possible model of transmission of any proposed agent (6, 7). The occurrence of the syndrome in patients with hemophilia has been consistent with that model (8-15). The first hemophiliac with *Pneumocystis carinii* pneumonia was reported to the CDC in

January 1982, and the second and third patients were found by the CDC through routine surveillance of requests in June and July 1982 for drugs available only from the CDC to treat *P. carinii* pneumonia. Since then, a total of 22 cases of the acquired immunodeficiency syndrome in patients with hemophilia have been identified, 17 in the United States and 5 in other countries (8-15). In all but two cases, inquiries about patients' sexual activities, drug usage, ethnicity, and travel or residence provided little evidence that the disease could have been acquired by contact with homosexuals, illicit drug abusers, or Haitian immigrants. On the other hand, all of these patients had been exposed to either factor VIII or factor IX concentrates, and all but one had received other blood components. We report the current status of the acquired immunodeficiency syndrome in patients with hemophilia and summarize current epidemiologic aspects.

### Materials and Methods

As part of the ongoing surveillance for the acquired immunodeficiency syndrome, case report forms were completed on all life-threatening or fatal opportunistic infections documented by biopsy or culture for patients with no known underlying illness or history of immunosuppression. In addition, reports were also completed for patients with Kaposi's sarcoma confirmed by biopsy in patients under 60 years of age without underlying immunosuppressive disease or therapy. Cases of the acquired immunodeficiency syndrome in patients with hemophilia were found by interviewing attending physicians, reviewing reports of suspected cases of the syndrome in hemophiliacs from the Centers for Disease Control (CDC)-National Hemophilia Foundation Surveillance program, or by routinely reviewing requests to the CDC for pentamidine isethionate to treat *P. carinii* pneumonia.

Once a case was identified, a CDC staff member interviewed the patient or the attending physician by telephone or in person, and reviewed all obtainable clinical information—for example, types of illnesses; dates and methods of diagnosis; dates of onset of signs or symptoms; history of predisposing conditions; types of treatment; dates and types of blood transfusion or blood product transfusion; and demographic data such as age, race, marital status, sexual preference, travel history, and residence. Attempts were made to obtain laboratory data in all suspected cases of the acquired immunodeficiency syndrome in patients with hemophilia. If possible, complete blood counts, differential counts, platelet counts, lymphocyte subset enumeration, lymphocyte helper to suppressor subset ratios, in-vitro lymphocyte responses to mitogens and antigens, skin tests, and immuno-

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Table 1. The Acquired Immunodeficiency Syndrome in Patients with Hemophilia

Patient	Age	Severity*	Onset of Symptoms	Date of Diagnosis	Diagnosis†	Date of Death
yrs						
Cases in the United States						
1	62	S	7/81	1/82	PCP‡	1/82
2	59	S	6/81	5/82	PCP, pulmonary CMV, esophageal candidiasis	7/82
3	27	S	7/81	10/81	PCP, MAI	9/82
4	55	S	11/81	9/82	PCP, MAI	Alive§
5	52	S	3/82	10/82	PCP, esophageal candidiasis, disseminated histoplasmosis	11/82
6	26	S	8/82	11/82	PCP	Alive§
7	49	M	11/82	11/82	PCP	11/82
8	10	S	10/82	10/82	PCP, cryptococcal pneumonitis	Alive§
9	24	S	9/82	12/82	PCP	12/82
10	46	S	12/82	2/83	PCP	2/83
11	29	S	1/83	2/83	PCP	Alive§
12	11	M	9/82	2/83	PCP	2/83
13	53	S	11/82	4/83	PCP, esophageal candidiasis, MAI	Alive§
14	37	S	3/83	4/83	Esophageal candidiasis	Alive§
15	39	S	3/83	5/83	PCP	7/83
16	33	S	5/83	6/83	PCP	Alive§
17	74	...	1/83	4/83	PCP	4/83
Cases not in the United States						
1	9	S	5/81	2/83	Pulmonary CMV	2/83
2	16	S	3/82	3/83	Pulmonary CMV, esophageal candidiasis	4/83
3	19	S	1/83	3/83	Esophageal candidiasis	Alive§
4	38	S	6/82	2/83	PCP	4/83
5	29	S	2/83	3/83	Central nervous system toxoplasmosis, pulmonary CMV	3/83

\* S=severe hemophilia; M=mild.

† PCP=*Pneumocystis carinii* pneumonia; CMV=cytomegalovirus; MAI=*Mycobacterium avium-intracellulare*.

‡ Not available.

§ Alive as of 26 July 1983.

globulin levels were obtained. When these results were not available from the patients' records, tests were done when possible at the CDC using standard techniques (16-20).

## Results

The acquired immunodeficiency syndrome was documented in 22 hemophiliacs between 1 January 1982 and 26 July 1983. Seventeen of the cases were in the United States, 4 in Europe (Spain and Wales), and 1 in Canada. Two other patients with symptoms of immunodeficiency were excluded because of a possible predisposing illness or because the strict criteria of case definition could not be confirmed. As of 26 July 1983, 14 of the patients had died, including 10 from the United States. Most cases were found through active surveillance of hemophilia treatment centers in collaboration with the National Hemophilia Foundation or through follow-up on requests for pentamidine isethionate. Cases not in the United States were confirmed by follow-up on reports to the CDC by other sources.

The 17 cases in this country were reported from 13 states: Alabama, Colorado, Connecticut, Florida, Georgia, Illinois, Iowa, Maryland, Missouri, New Jersey, New York, Ohio, and Pennsylvania. Approximately 66% of all reported cases in non-hemophiliacs have been in New York City, San Francisco, and Los Angeles, whereas none of the cases of hemophilia has occurred in those three cities.

Twenty-one of the twenty-two patients had hemophilia A, one had hemophilia B. Only one patient with hemophilia A had an inhibitor. The inhibitor was found in low titer, and the patient was treated during bleeding episodes with high doses of factor VIII concentrate. The ages of the 22 patients have ranged from 9 to 74 years with a median of 35 years (Table 1). Twenty were white, and two were black. The number of cases was too small to determine if significant differences existed in age or race among the disease categories. Two of the patients in this country had other risk factors; one was homosexual, and the other had a history of intravenous drug abuse. The second patient, however, used disposable needles, had no history of sharing needles with other drug abusers, and did not use "street drugs."

Data generated by the CDC surveillance showed a steady increase in the number of confirmed cases (Figure 1). There was an interval of 1 to 12 months between onset of symptoms and date of diagnosis in all but two cases (median, 3 months) and this interval was associated with failure to recognize nonspecific symptoms as related to the acquired immunodeficiency syndrome. Seventeen of the patients had *P. carinii* pneumonia, and 8 had more than one infection (Table 1). Other opportunistic infections included *Mycobacterium avium-intracellulare* infection, histoplasmosis, disseminated cytomegalovirus, cerebral toxoplasmosis, and esophageal candidiasis. In one instance, *Mycobacterium tuberculosis*

Table 1. (Continued)

T-helper to T-suppressor Ratio	Lymphocyte Count	Platelet Count	Skin Test	IgG	IgA	IgM	In-vitro Lymphocyte Response
	/ $\mu$ L						
...	288	201 000	†	Normal	†	Normal	...
1.3	112	84 000	†	Normal	†	Normal	†
0.25	390	...	†	Normal	†	Normal	†
0.10	540	86 000	†	Normal	†	Normal	†
0.10	450	...	...	...	...	...	...
0.80	1740	"Adequate"	...	†	†	Normal	...
0.30	212	354 000	†	Normal	†	Normal	...
0.10	580	171 000	†	†	†	†	...
0.50	846	102 000	†	Normal	†	Normal	...
0.21	860	264 000	...	...	...	...	...
0.20	900	...	...	...	...	...	...
0.00	500	...	...	Normal	†	Normal	†
0.12	328	200 000	Normal	...	...	...	†
0.16	1200	100 000	...	...	...	...	...
0.15	858	120 000	†	†	Normal	†	†
0.40	340	...	...	...	...	...	...
0.40	340	...	...	Normal	†	Normal	...
0.17	...	...	†	†	†	†	...
0.26	...	...	...	†	†	†	...
0.11	931	...	...	...	...	...	...
0.31	...	...	†	†	†	†	...
0.00	100	...	...	...	...	...	...

infection occurred before *P. carinii* pneumonia.

Patients with hemophilia with the acquired immunodeficiency syndrome had a complex illness identical in its clinical manifestation to the syndrome as seen in other affected groups. Most patients have had a prodromal episode lasting for a few weeks to months, characterized by malaise, weight loss, fever, and lymphadenopathy. After the onset of opportunistic infections, most of the patients did poorly. Of the 14 patients who are known to have died, survival time after the date of diagnosis of opportunistic infection was a few days to 11 months. Most of the patients survived no longer than 2 months.

The most consistent laboratory finding in the patients has been a markedly depressed lymphocyte helper-to-suppressor ratio. In all but two cases this ratio has been less than 0.5. In addition, all but one of the patients have developed lymphopenia with their illness. In 18 of the cases, absolute lymphocyte counts ranged from 100/ $\mu$ L to 1200/ $\mu$ L at the time of diagnosis of the initial opportunistic infection. The late phase of disease may coincide with a drop in lymphocyte count as shown by a comparison of the lymphocyte count and clinical manifestations seen in Patient 3 (Figure 2). This patient developed non-specific symptoms at a time when his circulating lymphocyte count was just below the lower limits of normal (1500/ $\mu$ L). Throughout the next 12 months the patient had a progressive decline in circulating lymphocytes associated with recurrent episodes of opportunistic infections, and had very few circulating lymphocytes when he died in September 1982.

When measured in hemophiliacs with the acquired im-

munodeficiency syndrome, the in-vitro lymphocyte functions have been abnormal, and skin tests have shown a high degree of anergy to common antigens. Patients have had elevated immunoglobulin levels; especially IgA and IgG. Three of the patients have had thrombocytopenia (100 000/ $\mu$ L or less) at the time of diagnosis.

#### Discussion

The hypothesis that the acquired immunodeficiency syndrome developed in these patients as a result of an infectious agent transmitted by blood product administration seems logical. The transfusion of blood products is known to be associated with the transmission of other viruses, especially hepatitis B virus, non-A, non-B hepatitis virus, cytomegalovirus, and Epstein-Barr virus. Patients with hemophilia have a significant risk of developing hepatitis; in fact, approximately 85% of these patients will eventually have serum markers for an infection with hepatitis B (21). The evidence of increased incidence of hepatitis B infection in the other populations that have a high risk of contracting the acquired immunodeficiency syndrome (male homosexuals, intravenous drug abusers, and recent Haitian immigrants to the United States) suggests hepatitis B as a model for transmission of the disease (22; CURRAN J.W. Unpublished observations).

Although the number of reported cases of the acquired immunodeficiency syndrome in hemophiliacs is low, it represents an attack rate of about 1 per 1000 of the 12 000 to 17 000 patients with hemophilia in the United States (23). All but five of the hemophiliacs with the syndrome had *P. carinii* pneumonia. The annual inci-

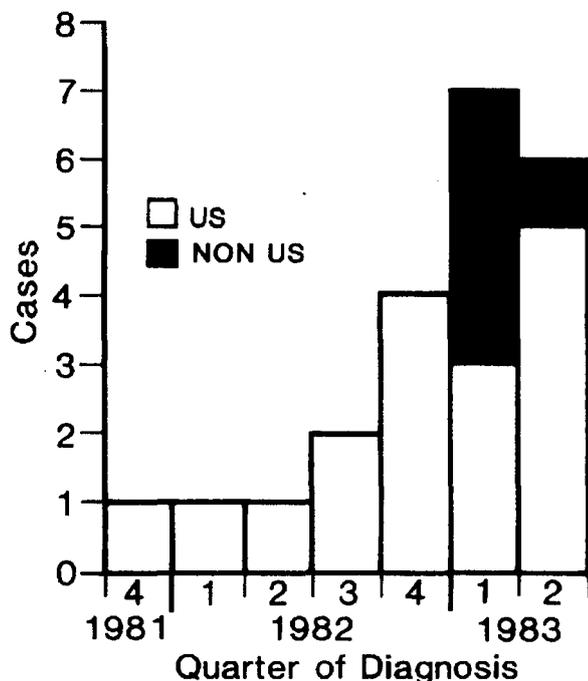


Figure 1. Incidence of the acquired immunodeficiency syndrome in hemophiliacs, 1981 to June 1983.

dence of *P. carinii* pneumonia in the United States has been estimated to be about 0.30 cases per 1 000 000 population (24). The present attack rate of *P. carinii* pneumonia among patients with hemophilia represents about a 5000-fold increase over that in the general population. The outbreak among patients with hemophilia appears to be a recent occurrence. We can find only one report of a case of *P. carinii* pneumonia in a hemophiliac before 1981 (25). The patient was a 7-year-old boy with hemophilia A who had *P. carinii* pneumonia after a 2-month course of high-dose corticosteroids for joint problems. The immunosuppression produced by the extended steroid treatment may have been responsible for his *P. carinii* pneumonia, and he would not qualify as having the acquired immunodeficiency syndrome. In addition, an extensive review of requests for pentamidine isethionate in the period 1967 to 1983 for treatment of patients with *P. carinii* pneumonia failed to show a single patient with underlying hemophilia.

For patients with hemophilia, the initial part of the epidemic curve resembles the early phase of the epidemic as seen for the other groups affected. For the period from October 1981 to July 1982, 3 patients were found; from July through December 1982, 6 more were reported; and from January through June 1983, 13 were reported. An extensive review of the 7600 patients seen in hemophilia treatment centers in the United States with ten or more patients failed to uncover other patients from 1978 to 1982. There is an apparent lag phase of 2 to 2.5 years between the original epidemic beginning with homosexuals (mid-1979) and the appearance of the acquired immunodeficiency syndrome in patients with hemophilia

(January 1982). If these two epidemics are related, and if the acquired immunodeficiency syndrome is indeed transmitted by an agent found in blood or blood products, then the time lag may partly represent latency after the introduction of the agent into blood products, plus any processing time of the blood products before they reached a susceptible population. The 2 to 2.5 years would be compatible with what is known about the latency seen after possible exposure (7 to 14 months) in the sexually transmitted acquired immunodeficiency syndrome in homosexual men (26) plus the average processing time of plasma factor concentrates (12 to 15 months [RODELL M. Unpublished data]) from blood acquisition to consumption.

The patients with hemophilia, of course, receive other blood products besides plasma factor concentrates, including blood and plasma transfusions at the time of bleeding episodes. The possibility that some or all of the cases in patients with hemophilia may be related to transfused blood rather than to plasma factor concentrates cannot be ruled out. Only one of the patients received plasma factor concentrates and had no history of blood or plasma transfusions. Most of the blood used for transfusion is obtained in the region where it is used, and any diseases produced by possible transmissible agents would be expected to appear in that region, that is, an area having high endemic rates; with respect to the acquired immunodeficiency syndrome, therefore, New York, San Francisco, and Los Angeles would be expected to have the highest incidence of association with a blood-transfused agent. The random geographic distribution of the syndrome in patients with hemophilia is not inconsistent with this expectation, because plasma factor concentrates are manufactured in only a few locations and then widely distributed.

Although the epidemiologic evidence suggests that the acquired immunodeficiency syndrome is caused by a transmissible infectious organism, the possibility that a noninfectious agent, such as a protein that affects the immune system, is transmitted in plasma factor concentrates cannot be ruled out. Plasma factor concentrates

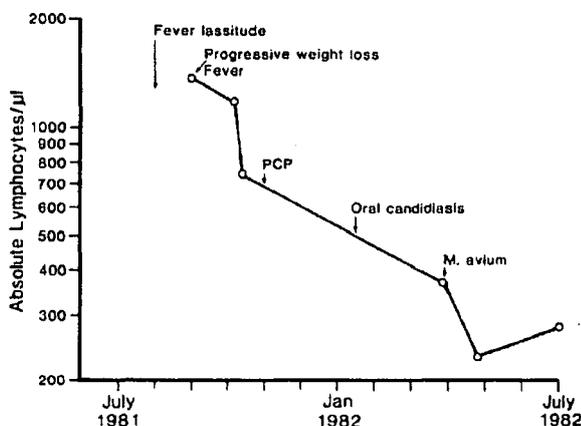


Figure 2. Lymphocyte count and clinical symptoms of a hemophiliac with the acquired immunodeficiency syndrome.

first became widely used in the late 1960s; therefore, if such an agent was responsible for the syndrome, the appearance of the syndrome might have been expected before 1982. In addition, the syndrome has occurred in young hemophiliacs who have received plasma factor concentrate only during the last few years; thus, the age distribution of hemophiliacs with the acquired immunodeficiency syndrome does not support the necessity of long-term exposure to a potential agent. Finally, the recent appearance of the syndrome in patients who have received blood transfusions but who otherwise have no known risk factors suggests that a single exposure may be all that is necessary to transmit the disease (27, 28).

The use of concentrates rather than cryoprecipitates has been associated with phenotypic changes in T lymphocytes in patients with hemophilia (29, 30). All the above patients had used factor concentrates within the past 5 years and none used routine cryoprecipitate. Because a small group of patients in the United States are treated exclusively with cryoprecipitate, the relative safety of these products will need to be evaluated by a different approach.

Although the median age of patients with hemophilia with the acquired immunodeficiency syndrome was 35, there was an increased attack rate of the syndrome among patients in the older age groups. When the incidence was adjusted for age based on population data obtained in a recent CDC-National Hemophilia Foundation survey of hemophilia treatment centers (unpublished data) the attack rate for hemophiliacs over the age of 40 was at least five times higher than that for younger patients. This age bias may be due to differences in duration of exposure to blood products; however, five of the patients are less than 20 years of age, and two of the patients (ages 10 and 11) have mild hemophilia and have received little factor concentrate. Patients with hemophilia have been reported to have abnormalities in cellular immunity associated with age when compared with normal controls (31; LAWRENCE D. Unpublished observation). Whether this difference is a result of treatment, is related to the acquired immunodeficiency syndrome, or is a result of an unrelated factor has not been determined. Additionally or alternatively, age may be a host susceptibility factor. Further data are needed to clarify these observations.

Most patients with hemophilia have died a few months after the onset of opportunistic infections. Clinically these patients are more difficult to manage because any invasive procedure is complicated by their bleeding diathesis. In addition, these patients have frequently had the first case of the acquired immunodeficiency syndrome to appear in a given locale.

The evidence so far suggests that it is prudent to take measures to reduce the risk of acquiring and transmitting the acquired immunodeficiency syndrome via blood and blood products. Specific recommendations concerning the treatment of hemophiliacs with blood and blood products have been issued by the Medical and Scientific Advisory Committee of the National Hemophilia Foundation (32). The Public Health Service is requesting that

high-risk groups refrain from donating plasma or blood and that an extensive effort be made to develop and evaluate the use of laboratory tests for screening out blood or blood products obtained from these high-risk groups (33). Although these are interim measures until the cause of the acquired immunodeficiency syndrome is found, they are all anyone can do until the situation is clarified.

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## Cryptosporidiosis in Homosexual Men

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Between April 1982 and June 1983, cryptosporidiosis was diagnosed in six homosexual men. Four patients with the acquired immunodeficiency syndrome had lymphopenia, cutaneous anergy, and profoundly impaired cellular immunity; their cryptosporidiosis was severe, unremitting, and refractory to all therapy. Two patients without other opportunistic infections or Kaposi's sarcoma had moderately impaired cellular immunity but not lymphopenia or anergy; their enteric illness was self-limited. *Cryptosporidium* recently has been recognized as a human pathogen that is transmitted through fecal-oral contamination. The severity of human cryptosporidiosis appears to be determined primarily by immunocompetence of the patient. These six homosexual men, with different degrees of immunologic impairment, had two clinically divergent forms of cryptosporidiosis. Their cases raise questions about human transmission of *Cryptosporidium* and the prognostic significance of this disease in patients who are at high risk for developing the acquired immunodeficiency syndrome.

**CRYPTOSPORIDIUM**, a coccidian parasite, is a well-recognized cause of diarrheal illness in animals. Animal cryptosporidiosis is usually a short-lived, acute illness that may be either self-limited or rapidly fatal (1). Before 1982, approximately seven cases of cryptosporidiosis had been reported in humans (2-8). Five of the seven patients were immunocompromised, and in four patients, the disease lasted for more than 8 weeks. These findings suggested that, in contrast to animal cryptosporidiosis, infection in humans is opportunistic and chronic.

In 1982, in addition to 3 sporadic cases (9-11), 56 cases of human cryptosporidiosis were reported to the Centers for Disease Control (12). Forty of these patients had the acquired immunodeficiency syndrome (13) and a prolonged diarrheal illness, whereas 12 were previously

healthy animal handlers in whom immunologic parameters were normal and resolution occurred in less than 2 weeks (14). Thus, the spectrum of clinical illness due to *Cryptosporidium* appears to be closely related to the immunologic competence of the patient. We report the clinical features, treatment, and outcome of cryptosporidiosis in 6 homosexual men with different degrees of immunologic impairment.

### Methods

#### MICROBIOLOGIC STUDIES

At least four unformed stool specimens from each patient were examined for bacterial pathogens, including *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, and *Mycobacterium*, by routine microbiologic techniques. Stool was also examined for rotavirus antigen, ova, and parasites. Isolation of viruses from stool was not attempted.

*Cryptosporidium* oocysts were identified in the stool by using a three-step procedure that included the Sheather's sugar cover-slip flotation technique for concentration, an iodine stain, and a modified Kinyoun acid-fast stain (15). All three procedures were done on each stool specimen in laboratories at both The New York and St. Vincent's Hospitals.

#### SEROLOGIC ASSAYS

Antibody titers to cytomegalovirus (M.A. Bioproducts, Walkersville, Maryland) were determined by complement fixation, as previously described (16). Antibody titers to Epstein-Barr viral capsid antigen were measured by complement fixation with a commercially available kit (Litton Bionetics, Charleston, South Carolina). Surface antigen of hepatitis B virus and antibody to hepatitis B virus surface antigen were detected with a radioimmunoassay (Abbott Laboratory, North Chicago, Illinois).

#### IMMUNOLOGIC STUDIES

Cutaneous delayed hypersensitivity was evaluated with intradermal injections of the following recall antigens: intermediate-strength purified protein derivative, *Candida albicans*, mumps, and trichophyton. Test results were checked at 24, 48, and 72 hours and were considered positive if induration of 5

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