ANNALS of Internal Medicine
Volume 98 • Number 3
March 1983

PUBLISHED monthly by the American College of Physicians under the direction of the Publications Subcommittee of the Board of Regents; see advertising page I-5 for listing of the Subcommittee, the Editorial Department, the Editorial Board, and the Business Department.

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Annals of Internal Medicine
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Philadelphia, PA 19104 USA
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Acquired Immune Deficiency Syndrome: The Past as Prologue

IN JUNE 1981, five cases of *Pneumocystis carinii* pneumonia in young homosexual men were reported to the Centers for Disease Control (1). Since then, over 1000 definite cases of life-threatening opportunistic infections with or without Kaposi's sarcoma have been reported from 33 states and 13 foreign countries. Recognition that a similar pattern of immune dysfunction underlies each of these conditions resulted in their designation as the acquired immune deficiency syndrome.

From the outset, several factors implicated a transmissible agent as the cause of the severe alterations in immune regulation found in the syndrome. These lethal illnesses appeared suddenly and were remarkable in their geographic distribution. Careful retrospective reviews failed to detect cases diagnosed before 1979 (2). Even now over 90% of the reported cases have occurred in the United States, of which 70% have been reported from New York and California (Centers for Disease Control. Unpublished data). Physicians considered an infectious cause for the syndrome because of the nature of the prolonged prodrome described by many patients, including generalized lymphadenopathy, recurrent fever, and weight loss. The preponderance of homosexual men and intravenous drug abusers (3-6) among the first patients was reminiscent of the distribution of hepatitis B. Consistent with the hepatitis B model are epidemiologic studies suggesting that a causal agent for the syndrome may be sexually transmitted among sexually active homosexual men (7; Jaffe HW. National case-control study of Kaposi's sarcoma and *Pneumocystis carini* pneumonia in homosexual men: epidemiologic results. In preparation).

Six articles in this issue lend further support to the transmissible agent hypothesis and extend our knowledge about the clinical and epidemiologic aspects of the syndrome. The reports of cases in patients with hemophilia A (8-10) portray with excellent detail a complex illness identical in its clinical and laboratory manifestations to those reported in other groups. Since the first reports of the syndrome in three persons with hemophilia, several additional cases have been diagnosed among the 12 000 to 15 000 persons with hemophilia in the United States (11, 12). Although patients with hemophilia frequently receive both blood and blood products, most attention has been given to the clotting factor concentrates as the likely source of transmission. Each year, approximately 800 lots of these products are produced in the United States by further pooling and processing the cryoprecipitated antihemophilic protein factor remaining after plasma is separated from whole blood and frozen. Each lot contains material pooled from 2500 to 22 500 individual donations and contains approximately 500 000 U of antihemophilic factor. The average patient with severe hemophilia needs 30 000 to 50 000 U/yr, which is obtained from five to ten separate lots. Approximately 100 individual patients receive material from a given lot (Food and Drug Administration, Bureau of Biologics. Unpublished data). Thus a person with severe hemophilia using clotting factor concentrates is potentially exposed to tens of thousands of donors per year, and a given donor may potentially expose

approximately 100 persons.

We agree with Goldsmith and associates (13) that their finding of reduced helper-to-suppressor ratios in 9 of 12 healthy persons with hemophilia is of uncertain cause and significance, but disturbing in light of a similar proportion of reduced ratios among homosexual men in New York City (14). In both groups, whether these nonspecific alterations signify "early" or "mild" manifestation of the syndrome or merely result from other immune-altering exposures will remain unclear until the specific cause of the syndrome is discovered or longer-term longitudinal studies are completed.

Wormser and associates (15) describe cases of the syndrome in intravenous drug abusers who are inmates in New York State prisons and carefully document the absence of cases before 1981. Additional cases in New York and New Jersey prisoners have recently been detected (16). Because over 90% of the 120 reported cases in intravenous drug abusers have been reported from New York and New Jersey (Centers for Disease Control. Unpublished data), cases among prisoners in these states should not be surprising. The finding of leukopenia in some of the patients several months before diagnosis is consistent with a prolonged incubation period for the syndrome. Such a hypothesis is supported by the finding that patients linked by homosexual contact to another patient with the syndrome developed symptoms 9 to 22 months after contact (7; Auerbach DM, Darrow WW, Jaffe HW, et al. A cluster of AIDS: patients linked by sexual contact. In preparation). Because homosexual contact and intravenous drug use among male prison inmates has been frequently reported, further spread of the syndrome within prisons might be anticipated.

Factors underlying the occurrence of the syndrome in Haitians remain to be identified, but the prodrome and clinical manifestations described by Pitchenik and colleagues (17) are similar to the disease among other groups. Reports of cases in Haiti indicate that cases of the syndrome are occurring in that country, but little is known about specific risk factors. The recent report of the syndrome in a female sexual partner of a man with the syndrome suggests that this illness may be sexually transmissible among heterosexuals (18). This mode of transmission may have occurred among the Haitian patients.

What are the implications if the transmissible-agent hypothesis is correct? First, we should expect a continued occurrence of cases, but the increase in incidence should be gradual if the "incubation period" is as prolonged as it appears. As observed during the past 2 years, the syndrome will probably continue to be recognized in new risk groups. The highest incidence of new cases, however, will probably continue to be among sexually active homosexual men because the current prevalence of disease and risk factors are greatest in this group. The extent of geographic spread will depend on the mobility and sexual behavior of those persons affected and the distribution of blood and blood products. Among patients receiving blood products, those with hemophilia will continue to be at highest risk. However, one case has been reported in an infant who received a platelet transfusion from a man who subsequently was diagnosed as having the syndrome (19) and others can be anticipated.

Even in the absence of certainty about the cause of the acquired immune deficiency syndrome, there are opportunities for prevention. Because sexual transmission of a causal agent appears likely, sexual contact with known or suspected patients should be avoided. Because the syndrome (and presumably the "agent") is more prevalent among sexually active homosexual men, persons in this group could further reduce their risk by minimizing the number of their sexual contacts, specifically avoiding all casual and anonymous contacts. Prevention of the syndrome in recipients of blood and blood products may call for restricting use of blood from high-risk donors, improving preparation and processing of these products, and disseminating guidelines for their use. (JAMES W. CURRAN, M.D., M.P.H.; BRUCE L. EVATT, M.D.; and DALE N. LAWRENCE, M.D.; *Acquired Immune Deficiency Syndrome Activity and the Host Factors Division, Center for Infectious Diseases Centers for Disease Control, Atlanta, Georgia*)

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(Recommendations from the Centers for Disease Control on precautions that should be taken by clinical and laboratory staffs caring for, or handling specimens from, patients with the acquired immunodeficiency syndrome have been published in Morbidity and Mortality Weekly Report [Morbid Mortal Weekly Rep. *1982; 31:577-9] and this journal* [Ann Intern Med. *1983;98(1):I-139, I-143].—The Editor)

Hemophilia, Hepatitis, and the Acquired Immunodeficiency Syndrome

PREPARATIONS OF blood fractions for transfusion contain various infectious agents that may be transmitted to the recipient. Cytomegalovirus, hepatitis B virus, and non-A, non-B viruses are among the many agents that may be contained in these fractions. The risk of infection with these agents is increased in patients with hemophilia who receive concentrates of plasma derived from many donors and who receive such concentrates on repeated occasions. Approximately 85% of patients with clinically severe hemophilia needing frequent transfusions with concentrates of factor VIII or IX have serologic evidence of previous exposure to hepatitis B antigen (HBsAg), and up to 10% will be HBsAg carriers (1). The incidence of liver dysfunction is high, and liver biopsies from patients with hemophilia have shown a spectrum of liver diseases, from mild focal inflammation to chronic active hepatitis, cirrhosis, and even hepatic malignancies (2-4).

Reports from the Centers for Disease Control of the acquired immunodeficiency syndrome in seven patients with hemophilia A (5, 6) raise the possibility of an additional complication that may be related to transfusions. Three of these cases are reported in detail in this issue by Davis and associates (7), Poon and coworkers (8), and Elliot and associates (9). The features in the affected hemophilic patients are similar to those reported in homosexuals and include *Pneumocystis carinii* pneumonia and other opportunistic infections, lymphocyte abnormalities with an absolute lymphopenia and abnormal T-cell subpopulations, and, in some patients, a lymphadenopathy-fever syndrome which precedes the development of more severe opportunistic infection.

Although the incidence of the acquired immunodeficiency syndrome in the hemophiliac population is low, the report by Goldsmith and coworkers (10) in this issue of a series of patients with hemophilia with T-cell abnormalities but no evidence of opportunistic infections suggests that we may be seeing only the tip of the iceberg. Although this finding is of enormous concern, we should note that the relationship between T-cell abnormalities and the acquired immunodeficiency syndrome is uncertain. Immunofluorescent staining of T-cell populations using monoclonal antibodies shows only phenotypic cell-surface markers and may not predict functional abnormalities. Thus, these changes do not necessarily indicate a state of immune deficiency. Furthermore, abnormal lymphocyte subpopulations such as these have been described in patients with a number of illnesses, including several that are endemic to patients with hemophilia such as cytomegalovirus (11) and hepatitis B infections (12, 13). While it may be true that all reported patients with the acquired immunodeficiency syndrome have abnormal lymphocyte studies, not all abnormal lymphocyte studies are necessarily indicative of the syndrome. Longitudinal studies of hemophilic patients with abnormal T-cell ratios will be needed to assess the relation between this abnormality and the tendency to develop the acquired immunodeficiency syndrome.

Given the low incidence of the acquired immunodeficiency syndrome so far and the fact that many patients have been treated with the same lots of factor VIII but have not developed the syndrome, what can be said about some of the factors that predispose to or protect against the acquired immunodeficiency syndrome? Liver disease may be an important factor. The incidence of liver disease is high in both hemophilic patients and homosexuals, and forms of liver disease, especially hepatitis due to hepatitis B virus, are associated with at least transient defects in cellular immunity as manifest by cutaneous anergy, decreased numbers of E-rosette cells, and reduced responsiveness of T cells to mitogens (13, 14). Repeated exposure to hepatitis viruses may lead to more or less permanent immune suppression and may therefore contribute to the development of the acquired immunodeficiency syndrome or may even be responsible for the development of opportunistic infections.

Where does this leave physicians faced with the dilemma of treating a patient with hemophilia, knowing that an infusion of concentrates may cause the acquired immunodeficiency syndrome and that withholding concentrates may result in uncontrolled bleeding? Before this dilemma can be solved, a number of crucial questions need to be answered and answered quickly. Do all concentrates of clotting factors have a risk of transmitting a hypothetic agent causing the syndrome? In studies at our center, patients on prothrombin complex concentrates have had normal findings in lymphocyte studies, raising the possibility that the responsible material may not fractionate with the vitamin K-dependent factors. It is interesting that of the three patients with normal T-cell studies in the report of Goldsmith and associates (10), two were receiving prothrombin complex concentrates. If these observations are confirmed, they may provide valuable clues about preparation of material free of the hypothetic causal agent. Can preparations of factor VIII free of the acquired immunodeficiency syndrome agent be made? Preliminary studies suggest that lymphocyte subpopulations in patients with hemophilia treated with cryoprecipitate are normal compared with a group treat-