THE HEMOPHILIA BULLETIN

January, 1983
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## ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) AND HEMOPHILIA

You probably first read about AIDS in hemophilia in the MMWR (Morbidity and Mortality Weekly Report) of the CDC (Center for Disease Control, in Atlanta, Georgia). Your next news probably came in your local newspaper, a national newsmagazine, or television newscast, and the information given may have been scant but probably very frightening. You may have received an appeal from the National Hemophilia Foundation to report cases of suspected AIDS on a protocol form to the CDC. You may have received, in December, minutes of the October 2 meeting of the National Hemophilia Foundation Medical and Scientific Advisory Counsil Meeting, at which AIDS was discussed by Dr. Evatt of the CDC and the Council discussed "what we should tell patients."

While awaiting this dribble of information, you may have been deluged with inquiries from frantic patients who read the alarming newspaper articles. We at Orthopaedic Hospital felt the frustration of too little information and understanding about AIDS, but recognized the necessity of deciding whether we ought to change our treatment approach for patients with hemophilia. We have made a major effort in the past month to get more information. Some of us attended the meeting of the American Society of Hematology in Washington and took notes on presentations and informal comments. Dr. Dietrich attended an unannounced but "open" meeting on January 4 at the CDC in Atlanta. On January 3, we had an evening meeting for our patients and their families and for our health care personnel at which Dr. David Auerbach, an epidemiologist from the CDC, and Dr. Michael Gottlieb, an immunologist from UCLA who has been handling a large number of persons with AIDS in Los Angeles, presented extensive information. Representatives of the Red Cross Blood Bank in Los Angeles and representatives from four manufacturers of concentrate also offered comments. We also have had private conversations with CDC officers.

We should like to share our small amount of additional information with you, our colleagues along the Pacific Rim, who are so far away from the centers of activity at the CDC in Atlanta and the NHF in New York.

First of all, what is AIDS? The CDC defines AIDS quite strictly: Kaposi's sarcoma or an infection moderately to highly predictive of a defect in cell-mediated immunity occurring in a person without a known predisposing cause.

Let us delve into this more deeply. Kaposi's sarcoma usually was seen in the USA in 50 to 150 patients a year. Most patients were elderly and males predominate over females by a margin of 10 to one. Signs and symptoms include skin or mucosal lesions (small tumors) in 87%, lymphadenopathy in 45%, fever in 32%, weight loss in 26%, diarrhea in 24%, dyspnea in 21%, and thrush in 14%.

Kaposi's sarcoma (KS) is endemic in Africa, where the incidence is 20 to

150 tires as high as in the USA, and where it constitutes 10% of all cancers. A larger percentage of children and young adults are affected than in the USA. The geographic distribution of Kaposi's sarcoma in Africa is uneven.

In the USA, prior to the current epidemic which dates from 1979, Kaposi's sarcoma was seen also in organ transplant recipients and other patients receiving immunosuppressant drugs.

The opportunistic infections which have been associated with AIDS have included pneumocystis carinii pneumonia (the most common such infection), Toxoplasmosis of the CNS, cryptococcal meningitis, cytomegalovirus pneumonia, avian tuberculosis, candidiasis, zygomycosis, aspergillosis, nocardiosis, CNS or pulmonary strongyloides, intestinal cryptosporidosis, extensive herpes simplex, and prolonged varicella zoster.

Pneumocystic carinii pneumonia (PCC), the most common opportunistic infection in this group, used to be a rare disease. Before the current epidemic, that is, before 1979, the incidence was 0.03 cases per 100,000 people per year in the USA. In one recent year before this epidemic, 194 cases were reported in the USA and only one occurred in a person who did not have an underlying disorder such as congenital cellular immunodeficiency, a hematologic malignancy, immunosuppressive chemotherapy, prematurity with malnourishment, etc.

In a 23-month period from June 1, 1981, to November 12, 1981, the CDC recorded the following incidence of Kaposi's sarcoma, pneumocystis carinii pneumonia, and other opportunistic infections in persons in the USA:

| | Number of Cases | Number of Deaths | Percent Fatal |
|---|---|---|---|
| KS without PCP | 216 | 43 | 20 |
| PCP with KS | 368 | 165 | 45 |
| Both KS and PCP | 52 | 31 | 60 |
| Other Opportunistic Infections | 96 | 45 | 47 |
| TOTAL: | 732 | 284 | 39 |

The CDC also has records of the number of cases of AIDS (i.e., no predisposing cause) with PCP or KS reported in 1979 through 1982, which show the growth of the epidemic:

| CALENDAR PERIOD | NUMBER OF CASES | NUMBER OF DEATHS | PERCENT FATAL |
|---|---|---|---|
| 1979 Jan-June | 1 | 1 | 100 |
| July-Dec | 6 | 5 | 83 |
| 1980 Jan-June | 17 | 13 | 76 |
| July-Dec | 25 | 22 | 88 |
| 1981 Jan-June | 67 | 48 | 72 |
| July-Dec | 139 | 84 | 60 |
| 1982 Jan-June | 264 | 83 | 31 |
| July-Nov | 205 | 27 | 13 |

By age group, 5% of cases were reported in persons under age 25, 44% in persons age 25 to 34, 36% in persons age 35 to 44, and 15% in persons over the age of 45. Thus, the epidemic is occurring in young adults, primarily.

The geographic distribution of cases is also illuminating, for 48% of cases come from New York City, 13% from San Francisco, 6% from Los Angeles, 4.4% from Miami, 2.5% from Newark, 2% from Houston, and the remaining 23 to 24% are scattered among states along the eastern seaboard, along the Gulf of Mexico, along the West Coast, and bordering the Great Lakes. Some midwestern and mountain states are spared. The condition has been reported from ten foreign countries, mostly in Europe, but also including Haiti.

As of November 12, 1982, the groups at risk for AIDS contained the following representatives:

| RISK GROUP | PERCENT OF AIDS CASES |
|---|---|
| Homosexual or bisexual men | 74.5 |
| IV drug users, not homosexual | 14.1 |
| Haitians, in USA, not homosexual and not IV drug users | 5.7 |
| Hemophiliacs, not homosexual and not users of IV (street) drugs | 0.7 |
| None of above risk factors | 5.0 |

One theme uniting the above groups is that all are also at high risk for hepatitis B. These homosexuals with AIDS had a great many more different sexual partners than homosexuals who have not had AIDS.

The CDC's working hypothesis of the etiology of AIDS is that it is caused by a virus, which may be a new hybrid virus, a new strain of a common virus, or an unusual reaction to a common virus. They strongly suspect that many more persons are exposed to this virus than show signs of infection with it. The

virus may cause injury to T-lymphocytes leading to immune deficiency. This immune deficiency may make the patient more susceptible to opportunistic infections, including perhaps infection with a virus which, in vulnerable hosts (which may include those with HLA type DR5), may induce malignant transformation of endothelial cells into Kaposi's sarcoma. Immunologists hypothesize that in the early stages of infection with the mystery virus, the number of helper lymphocytes is depressed while the number of suppressor lymphocytes remain normal, and as the disease progresses, the number of helper lymphocytes becomes even more depressed while the number of suppressor cells also is somewhat depressed. The absolute number of lymphocytes is low, and the ratio of helper to suppressor cells (usually in the range of 1:1 or 2:1 or higher) reverses, so that there are fewer helper than suppressor cells, i.e., ratios of 0.7 or below. No one knows at this point whether persons infected with the mystery virus who start to develop abnormalities in the lymphocytes progress relentlessly to worse and worse abnormalities, or whether some recover spontaneously. It is not yet known whether all persons who develop marked abnormalities in the helper:suppressor ratio and absolute lymphocyte count will develop opportunistic infections or Kaposi's sarcoma, but certainly many individuals have been observed from the homosexual and hemophilic population studies who have the above-described lymphocyte abnormalities and are robustly healthy. No one knows whether they will become ill, or whether they will recover from a "subclinical" infection, if indeed they are infected with the mystery virus. Such lymphocyte abnormalities are not specific for AIDS, and may be found also in persons with infectious mononucleosis, cytomegalovirus infection, and other conditions. There is no pathognomic laboratory test for AIDS.

Among persons in the risk groups which have been identified, that is, homosexuals, users of IV street drugs, and hemophiliacs receiving blood derivatives, some individuals have been found who have illnesses which may be a prodrome of AIDS, or a minimal manifestation of AIDS. The signs and symptoms have included generalized adenopathy, fever, unusual fatigue, night sweats, prolonged diarrhea, prolonged cough, unexplained weight loss, demyelinating neuropathy, ITP, and Coombs positive hemolytic anemia. Some patients are anergic to all skin tests.

What connection has AIDS with hemophilia? Some epidemiologists feel that the mystery virus originated in Haiti, a cheap and popular vacation resort for New Yorkers. The virus was picked up and rapidly disseminated amongst the more promiscuous members of the homosexual community in New York and thence to the homosexual communities of other large cities. The virus is believed to be transmitted among these persons by intimate sexual contact, and transmitted to users of IV street drugs by contamination of needles and syringes with the blood of infected persons. Homosexuals constitute a notable proportion of plasmapheresis donors in big cities, and they are also generous contributors to volunteer blood banks. Thus, infected plasma may enter the pools from which clotting-factor concentrates are made, and, to a lesser extent, it may form the starting material from which cryoprecipitate is made, particularly in those large cities in which AIDS is epidemic.

How many persons with hemophilia have been afflicted with AIDS? As of this writing, less than ten persons with hemophilia have been reported to have opportunistic infections. We don't know yet how many persons with hemophilia have the symptoms which might represent a prodrome or minimal manifestation of

infection with the mystery virus. Several surveys of persons with hemophilia for lymphocyte count suppressor cells have been performed, although t ec is limited by the fact that these time-consuming e performed on fresh blood, and only a few laboratori s. Dr. Menitove and colleagues reported a study in o of helper to suppressor lymphocytes averaged 1.4 in 14 hemophiliacs taking concentrate, but 2.2 yoprecipitate. Dr. Koerper and colleagues from San F .1 of 13 patients with moderate to severe hemophilia, concentrate intensively, the helper:suppressor rat ford deviation below the mean ratio in control individuals. Dr. Tsoukas and his colleagues from Montreal report that 70% of 34 asymptomatic patients with hemophilia who use concentrate are anergic, and their mean helper:suppressor ratio is 1.1 compared to a mean of 1.8 seen in 22 age-matched normal male controls. Dr. Luban and colleagues from Washington, D.C., studied 25 children with hemophilia who are taking concentrate and found decreased lymphocyte counts in 22, but reversed helper:suppressor ratios in only five. An unidentified physician at the meeting of the American Society of Hematology commented from the floor that he had found a mean helper:suppressor ratio of 1.2 in 51 hemophiliacs on concentrate whereas the mean ratio was 2.1 in ten hemophiliacs on cryoprecipitate and also 2.1 in 39 controls. Dr. Ratnoff from Cleveland also spoke from the floor, stating that among a 100 patients in northern Ohio on home treatment with concentrate, two had died in the past year of opportunistic infections, one died of Burkitt's lymphoma, and three had had ITP.

Thus, a substantial percentage of patients with hemophilia who take concentrate have lymphocyte changes similar to those seen in AIDS or those seen in illnesses which might represent a prodrome of AIDS or minimal manifestation of AIDS (but may also be seen in other infections, as already mentioned). Yet most of these persons with hemophilia and lymphocyte changes appear healthy. What do these findings mean? We do not know whether such lymphocyte aberrations are characteristic of hemophiliacs in general, or characteristic of hemophiliacs who are on concentrates in general (no matter whether the donors of the concentrate included persons with AIDS), or whether these changes are indeed the result of an infection with the mystery virus. It would be most interesting to know the status of the lymphocytes of patients with hemophilia, who take concentrates, in Australia, for AIDS has not been reported from Australia, and Australia makes all its own concentrate from domestic plasma.

If we accept, for the moment, that AIDS is transmitted by a virus through blood products and that it represents a serious threat to the health of persons with hemophilia, what can be done about it?

Immediate action can be taken to reduce the presumed exposure to the mystery virus in some patients by using cryoprecipitate instead of Factor VIII concentrate, to the extent that local blood banks can increase cryoprecipitate production. The advantage of using cryoprecipitate is greatest if the blood bank is NOT located in a big city where there is a large homosexual community, and if the recipient does not have to use Factor VIII often (so that the total number of donors to whom he is exposed is low). We have selected patients who have been using Factor VIII or IX concentrate but who do not use it often or who do not require large doses (such as young children) and have asked the local blood bank to prepare additional cryoprecipitate and fresh-frozen plasma

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for their use. In most patients, concentrate will still be the only feasible therapeutic modality.

We advise patients to treat hemorrhages early, even if concentrate is the only product available to them, in order to avoid developing the large hemorrhages which would require heavy, prolonged concentrate treatment. We advise patients to continue using their usual dosage to treat hemorrhages, to assure hemostasis. We advise a few patients to remain on prophylactic concentrate because we calculate that these patients will use less concentrate on prophylaxis than they would in the treatment of frequent random hemorrhages. We are postponing elective surgery, because it requires very heavy use of concentrate, until we have more information about the risks of acquiring AIDS. We hope that we shall be able to expand our use of DDAVP in patients with mild classic hemophilia and patients with von Willebrand's disease, and we pray for early licensure from the FDA. Some patients with inhibitors to Factor VIII can be treated with porcine Factor VIII concentrate, but this concentrate is still experimental in this country. We hope for rapid expansion of its availability.

The blood banks and the manufacturers of concentrate have recently made attempts to eliminate homosexuals from their donor population, and are increasing their efforts to evaluate donors for possible signs of prodromal AIDS. Spokesmen for homosexual organizations, however, feel that civil rights will be violated if prospective donors are questioned about sexual preference. Some physicians have commented unfavorably about the presence of plasmapheresis centers on "skid rows." Manufacturers state that most plasmapheresis centers are in pleasant neighborhoods and small towns; they admit that some centers are in downtown areas and have no plans to close these centers.

Several manufacturers of concentrate in the USA have developed heat-treated Factor VIII concentrates which are, to some degree, hepatitis-safe. Hyland Laboratories tested a concentrate which contained the virus of non-A non-B hepatitis and was innoculated with the virus of hepatitis B. Unheated concentrate was injected into some chimpanzees who then developed both types of hepatitis. Heated concentrate was injected into other chimps who did not develop non-A non-B hepatitis, and developed hepatitis B only after an unusually long incubation period. This concentrate probably will be licensed in early 1983. Hyland will try to develop an even more hepatitis-safe concentrate. Other companies are also in the process of testing heat-treated concentrates. We hope that the heat treatment which kills or modifies hepatitis viruses also exterminates the mystery virus of AIDS.

Concentrates prepared from plasma pools from which homosexuals have been eliminated will not reach the market for two or three months. Heat-treated concentrates will not reach the market for three or more months in the USA, and they will be more expensive than most current concentrates. There is no heat-treated Factor IX concentrate. Therefore, for the next few months, we must continue to use the cryoprecipitate and concentrate currently available to us. Some hospitals with facilities for blood donors may be able to make cryoprecipitate and fresh-frozen plasma from well-known low-risk donors.

Many patients have asked what they can do to lessen the chance of getting sick from AIDS, in case they are being exposed to it through blood products. Our physicians suggest that patients lead a healthy life, getting normal amounts of rest, eating a good balanced diet, trying to reduce and manage

stress, and exercising properly in order to build up muscle strength so that they bleed less often and, therefore, need treatment with blood products less often. Our physicians also remind our patients to report to the clinic immediately if they have any of the symptoms which have been associated with AIDS (e.g., fever, adenopathy, cough, dyspnea, etc.) because opportunistic infections respond best if treated early.

Many nurses and laboratory workers have asked how they should protect themselves against infection with AIDS when they handle AIDS patients or their body fluids. The CDC has recommended that the same precautions be used when managing patients with AIDS as when managing patients with hepatitis B, that is, that the patient be isolated and that gowns and gloves be used in handling him and his blood. When examing and treating paients who might have a prodrome of AIDS, but do not have an opportunistic infection, some extra common-sense precautions are advisable, such as handling blood with special care, using finger-cots or gloves if the examiner has a cut, washing hands often, and so on.

Some of our patients who take concentrate have asked whether they should continue to have sexual relations with their wives, or cuddle and kiss their small children. Our epidemiology and immunology advisors do not think there is sufficient evidence to justify interruption of the normal family relationships of hemophiliacs who are in good general health. It might be wise to suspend marital relations if a partner falls ill with the symptoms associated with the possible prodrome of AIDS.

If significant further information becomes available to us, we shall transmit it to you in the next Bulletin. We hope that 1983 will be a pleasant and successful year for all of you.