A COHORT STUDY OF PERSONS WITH HEMOPHILIA

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by

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Persons with hemophilia, particularly those with severe hemophilia (Factor VIII deficiency), are at high risk of the acquired immunodeficiency syndrome (AIDS).[1] In September 1982, the Environmental Epidemiology Branch (EEB) initiated a series of AIDS related studies of hemophiliacs and their families with Dr. Elaine Eyster and her colleagues at the Hershey Medical Center of the Pennsylvania State University in Hershey, Pennsylvania. To date, this collaboration has been very fruitful, having documented the association between low helper suppressor: T cell ratios and frequent use of Factor VIII concentrate,[2] a very high prevalence of antibodies against the etiologic agent of AIDS, HTLV-III, among frequent users of Factor VIII concentrate,[3] the first appearance of HTLV-III antibodies among hemophiliacs in 1979 and the dramatic increase in prevalence during 1981 and 1982,[4] and the early natural history of HTLV-III seropositive hemophiliacs documenting a close association of prolonged (more than 3 years) seropositivity with lymphadenopathy and low helper T cell counts.[4] One of the early findings of this collaboration was the observation of an abnormal acid-labile alpha interferon circulating in the serum of hemophiliacs 3-10 months before the appearance of AIDS, suggesting that this relatively simple serologic marker might predict eventual development of AIDS.[5]

We now intend to expand these studies with the particular intention of evaluating circulating alpha interferon and other serologic assays as predictive markers in HTLV-III-seropositive hemophiliacs. This study is based on a firm collaborative relationship, dating back more than 10 years, to the multi-center investigation of circulating Factor VIII inhibitors among hemophiliacs that was funded by the National Heart, Lung, and Blood Institute and that was performed at our collaborating centers.[6] The current study was originally proposed and

funded for 1 year by the NHLBI on a grant that was submitted by our interferon collaborator, Dr. Olivia Preble, in response to an RFA for serologic surrogate markers of AIDS. With the discovery of HTLV-III and the development of the antibody assay that has now been licensed and distributed to blood and plasma collection facilities in the United States, the NHLBI has elected to not continue funding this project despite the excellent justification provided in the revised proposal which is attached (Attachment 1). Because of our tremendous interest in continuing this study, we have proposed continuing the relatively low level of support required by the hemophilia centers, and Dr. Preble has agreed to perform the laboratory assays out of other funds. Under this scenario, Dr. Eyster will continue to function as the coordinator with the centers, Dr. Preble will function as the principle testing laboratory, and the EEB will function as the Biospecimen Repository and principle analysis site.

Programmatic Needs

The EEB has been in the forefront of cohort studies of persons at high risk of AIDS since the end of 1981. Such studies have provided virtually all of the data regarding the eventual development of AIDS in HTLV-III seropositive persons. Because most of these data are generated from studies of homosexual men, however, the possibility of different clinical outcomes among persons in different risk groups cannot be evaluated without larger studies of parenteral drug users, hemophiliacs and others. The need to establish a large cohort study of parenteral drug users was accomplished in the autumn of 1984 with a seroprevalence survey of approximately 1,000 drug users in the state of New Jersey.[7] The current multi-center hemophilia study will fulfill at least two

programmatic goals: 1) a better understanding of viral transmission, the natural history of infection, and the risk of clinical outcomes in a different risk group; and 2) an evaluation of circulating interferon as a prodromal condition in a unique population in which it is possible to obtain frequent serial specimens and close to 100% follow-up.

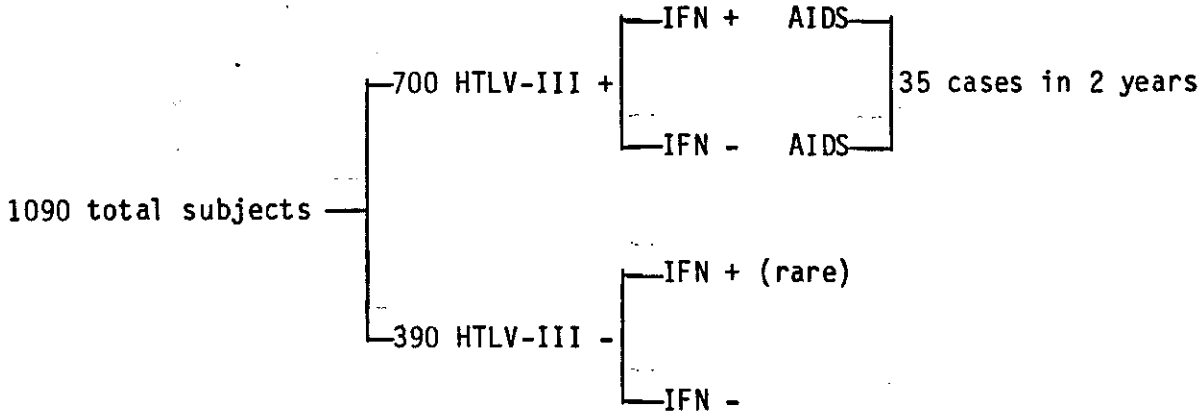
In addition to prospective surveys of persons infected with HTLV-III, the EEB has active investigations of the transmission of HTLV-III to heterosexual partners, to non-sexual contacts, and to newborn infants of seropositive pregnant women. The collaborating hemophilia centers have all indicated a tremendous interest in participating in the ongoing studies of the wives and other family members of hemophiliacs that we have conducted in Hershey, Pennsylvania.[8] In order to obtain a larger sample size, current plans do include expanding our studies of viral transmission and AIDS risk in family members to include at least the wives and children of hemophiliacs, using the procedures and questionnaires that were approved by the technical evaluation of protocols and questionnaires committee (TEPAQ) in March of this year. These studies in family members of hemophiliacs will become a particularly urgent requirement if accrual in our studies of the spouses and non-sexual contacts of drug users in New Jersey continues at a very slow pace.

Given that AIDS has been declared the major problem faced by the Public Health Service, considerable benefit can be anticipated from these studies of the transmission of HTLV-III and the possible early detection of AIDS by serologic tests including circulating interferon.

Sample Size and Background of the Hemophilia Centers

The seven participating hemophilia centers (Table 1) are regional centers for the comprehensive care of patients with hemophilia and related disorders which have been funded under Medicare regulations since 1975. Because patients with hemophilia have a congenital, incurable disorder that can be treated under Medicare through the regional centers, it is possible to obtain nearly complete ascertainment of the disease in the United States in a relatively small number of centers. With modern therapy, both the length and quality of life of hemophiliacs is nearly normal, so it is possible for them to move to other centers which may not be included in our study. Hemophilia is a rare disorder, however, (approximately 12,000 patients with severe hemophilia A in the entire United States) so that communication with regional hemophilia centers in other areas of the United States and follow-up of individual patients with hemophilia are routine practices.

The seven hemophilia centers are located in the geographic region bounded by New York City, Pittsburgh, and Washington, D.C. The 5 centers caring for both adults and children plan to enroll between 150-200 patients each. The two childrens' hospitals each plan to enroll 70 patients, bringing the total sample size to 1,090 study subjects. At least 700 (70%) of the subjects are expected to have HTLV-III antibodies, and of these 35 (5%) can be expected to develop AIDS within 2 years. (See diagram below)



Materials and Methods

Each study subject will be evaluated at the time of his annual or semi-annual visit to the clinic for routine comprehensive hemophilia care. At that time, a modified EEB biospecimen repository form (Attachment 2) will be completed and peripheral blood will be drawn. The blood will be allowed to clot, centrifuged, and aliquoted into 1/2 ml nunc tubes that have been provided by our biospecimen repository. Four vials will be obtained on each study subject, and these will be promptly frozen at each of the centers. Background data forms (Attachment 2) will be forwarded to EEB for editing and keypunching, and the sera will be shipped to the biospecimen repository on dry ice as batches every few months. These sera will be tested for HTLV-III antibodies and will be sent to Dr. Preble for interferon and other potential serologic markers of AIDS.

The modifications of the EEB biospecimen background data forms encompass the essential exposure and clinical information of each study subject. These include the type of hemophilia (hemophilia A, hemophilia B, vonWillebrand's disease, or other clotting factor disorders), the severity of the disorder, and

the type of treatment utilized by the patient (Factor VIII, Factor IX, cryoprecipitate, fresh frozen plasma or no therapy). Also included are clinical diagnoses that encompass the range of AIDS and AIDS-related conditions. Each of the centers has been provided written instructions regarding the completion of the background data form (Attachment 3), and the EEB AIDS research nurse has been in close communication with the nurse coordinator at each of the centers regarding the proper completion of this instrument. Each of these forms is edited prior to keypunching, and the relatively small numbers of errors and omissions noted have been easily corrected by telephone communications between the EEB research nurse and the appropriate nurse coordinator at the center.

Serologic assays will utilize established techniques. Results will be reviewed by the Principal Investigator prior to keypunching and merging with the background data set.

Retrospective and Prospective Studies

Samples of sera or plasma have been stored at the regional hemophilia centers on the vast majority of these study subjects on approximately an annual basis for the past 2 to 10 years. The centers have agreed in principle to provide serial samples on HTLV-III seropositive study subjects in order to document the date of seroconversion and to plot the natural history of HTLV-III infection. Background data for the date that each sample was collected will be obtained by abstracting the clinical records and completing a biospecimen background data form for each serum or plasma sample available.

Prospectively, each study subject will be seen at least once a year and aliquots of serum along with a background data form will be provided to the

study. Serologic and clinical follow-up will be obtained for at least two years. Indefinite follow-up of this group for the long-term consequences of HTLV-III infection, particularly with a view toward outcomes of rare malignancies, may be possible.

Analysis and Reports

Once verified by the Principal Investigators, reports of the laboratory tests will be forwarded to each of the centers for their patients. The EEB will serve as the principle statistical analysis center. Clinical follow-up on the development of AIDS and related conditions from the centers together with the initial seroprevalence survey will provide sufficient data to estimate the cumulative attack rate of AIDS at various points in time. The retrospective and prospective sera will provide an accurate assessment of the natural history of HTLV-III seropositivity in hemophiliacs and will provide the biologic specimens necessary to search for serologic predictors of AIDS (e.g., circulating interferon) in persons with HTLV-III infection. This large cohort of closely followed hemophiliacs will also permit very accurate information regarding eventual development of various life-threatening and non-life-threatening manifestations of HTLV-III infection (e.g., lymphomas, herpes zoster).

Funding

Utilizing the EEB Support Services Contract for studies of AIDS with Westat, Inc., purchase agreements for the specimens and completed background data forms totaling the amounts shown in Table 1 will be arranged with each of the hemophilia centers.

TABLE 1

Estimated number of study subjects and first-year cost of purchase agreements

Collaborator	Institution	No. of Subjects	Cost/Year
M. Elaine Eyster (co-investigator)	Hershey Medical Center Hershey, PA	200	$19,000*
Joel Spero	Hemophilia Center of Western PA, Pittsburgh, PA	200	$ 6000
Margaret Hilgartner	Hemophilia Center Cornell-NY Hospital New York, NY	200	$ 7000
Louis Aledort	Hemophilia Center Mt. Sinai Medical Center New York, NY	200	$ 7000
Sandor Shapiro	Cardeza Hemophilia Center Jefferson Medical College Philadelphia, PA	150	$ 5000
John Kelleher	Hemophilia Center Children's Hospital Washington, DC	70	$ 3000
Frances Gill	Children's Hospital Philadelphia, PA	70	$ 3000
Total		1090	$50,000

* Includes coordination of data collection instruments, specimens, laboratory results, and clinical follow-up with the multiple centers.

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