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ACQUIRED IMMUNODEFICIENCY SYNDROME AMONG PATIENTS ATTENDING HEMOPHILIA TREATMENT CENTERS AND MORTALITY EXPERIENCE OF HEMOPHILIACS IN THE UNITED STATES

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The acquired immunodeficiency syndrome (AIDS) was first recognized among hemophiliacs in 1982. The authors have conducted investigations to determine the onset and incidence of AIDS among hemophiliacs and to determine trends in hemophilia mortality since the introduction of clotting-factor concentrates in the late 1960s. A survey of United States hemophilia treatment centers, supported by the Centers for Disease Control and the National Hemophilia Foundation, defined a population of hemophiliacs which was monitored for AIDS cases through June 1984. Death reports from the United States Vital Statistics System and from the hemophilia treatment center survey provided mortality trends for 1968–1979 and for 1978–1982, respectively. The results of these investigations demonstrate the following points. 1) The AIDS epidemic is a new and important cause of illness and mortality among hemophiliacs, although a very low incidence of AIDS among hemophiliacs prior to 1982 cannot be ruled out. 2) The AIDS cases who attended the surveyed hemophilia treatment centers were distributed throughout the United States and were older than hemophilia treatment center patients without AIDS. AIDS cases also used more lyophilized clotting-factor concentrate, but only a small number of cases were reported with this information. 3) Improved care for hemophilia, including the use of clotting-factor concentrates, dramatically reduced hemophilia mortality rates during the 1970s. 4) In 1982, hemorrhage was the major cause of death among hemophiliacs. Deaths from non-alcoholic liver disease were also increased. AIDS incidence among hemophilia treatment center attendees was stable at 0.6 cases per 1,000 hemophilia treatment center attendees per year during 1982 and 1983 but increased sharply to 5.4 cases per 1,000 during the first quarter of 1984.

acquired immunodeficiency syndrome; hemophilia

Following the recognition of the first three cases of the acquired immunodeficiency syndrome (AIDS) in hemophiliacs (1), the Assistant Secretary for Health, Department of Health and Human Services, convened an expert committee on July 27,

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Abbreviation: AIDS, acquired immunodeficiency syndrome.

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1982, to review the risks associated with blood-product usage. One of the committee's recommendations was for the Centers for Disease Control to collaborate with the National Hemophilia Foundation and United States hemophilia treatment centers to institute active surveillance for AIDS in hemophilia treatment center hemophilia patients (2). Between November 1982 and March 1983, the Centers for Disease Control and the National Hemophilia Foundation surveyed 116 US hemophilia treatment centers to identify AIDS patients and to institute AIDS surveillance prospectively.

We report here results of the hemophilia treatment center survey and AIDS trends among the hemophilia treatment center attendees through June 1984. We also report results of an analysis of US hemophilia-related deaths between 1968 and 1979 reported to the National Center for Health Statistics Vital Statistics Program.

Materials and methods

Identification of hemophilia treatment centers and their response rate

The National Hemophilia Foundation identified 116 hemophilia treatment centers located in the contiguous 48 states. In November 1982, the Centers for Disease Control mailed a survey packet to each hemophilia treatment center. By March 1983, ninety-eight (84 per cent) of the hemophilia treatment centers had returned packets that were at least partially completed. The results from these hemophilia treatment centers along with subsequent reports of AIDS cases who attended the participating hemophilia treatment centers are the basis of this report.

Survey packet

The survey packet included two questionnaires. The instructions directed the hemophilia treatment centers to use the first questionnaire 1) to report each death from any cause among hemophilia treatment center patients making visits during 1978 and subsequently, and 2) to report all AIDS-like illnesses among hemophilia treatment center attendees making visits between October 1, 1981 and September 30, 1983. We include results from questionnaires submitted for 1982 and earlier. The first questionnaire included these details: demographic data; dates and causes of death; AIDS-related symptoms, signs, laboratory data, and diagnoses; quantity of cryoprecipitate used in the year preceding the last hemophilia treatment center visit; and date, brand, lot number, and quantity of clotting-factor concentrate dispensed during the two years preceding the last hemophilia treatment center visit. The second questionnaire was designed for hemophilia treatment centers to describe their patients' use of clotting-factor concentrates. Since abnormalities in genes located on the X-chromosome cause factor VIII and IX deficiencies, we assume that essentially all of the hemophilia treatment center patients are male. Personal identifiers were not included on any of the forms.

Classification of causes of death

We ranked the causes of death from most immediate to most remote for each case with multiple causes, using criteria published by the National Center for Health Statistics for completion of death certificates (3). We omitted hemophilia from this ranking, making a separate determination for each case as to the likelihood that hemophilia represented the underlying cause of death. We assigned each cause of death a code from the International Classification of Diseases—Clinical Modification, ninth edition (ICD-9-CM).

We grouped the ICD codes for causes of death into causes of death that are today associated with AIDS, those that may be attributable to a clotting-factor deficiency, and those that may be attributable to adverse effects of factor-concentrate therapy. The following categories, derived from the ICD-9-CM codes, resulted: immunodeficiency, possibly opportunistic infections,

reticulo-endothelial neoplasms, autoimmune and related disorders, hemorrhage unrelated to trauma, hemorrhage-related trauma, viral hepatitis and chronic liver disease unrelated to alcohol, and all other causes. In an effort to detect all possible previous AIDS cases, we included in the "possibly opportunistic infections" category ICD codes only weakly associated with AIDS. Examples include nonbacterial-nonbronchial pneumonia, tuberculosis, and diarrhea of unknown etiology (a complete list of the ICD codes included in each category can be obtained from the authors).

Next, we utilized the National Center for Health Statistics public-use computer tapes containing multiple-cause mortality for the period 1968–1979, the latest period available. The National Center for Health Statistics used the ICD-8 to code causes of death for the period 1968–1978 and the ICD-9 for 1979. All records with factor VIII deficiency or factor IX deficiency as a cause of death were selected from the National Center for Health Statistics tapes for tabulations of AIDS and hemophilia-related deaths. Causes of death on these records were grouped using the same categories described above. We obtained counts of deaths for all US males from published tables (4) or directly from the National Center for Health Statistics.

Statistical analysis

We tested for the statistical significance of differences between the United States male population and hemophilia treatment center hemophilia patients using a chi-square goodness of fit test (5). We used a chi-square test for independence to test the differences between subgroups of hemophilia treatment center hemophilia patients. We used the binomial or Poisson distributions to obtain the probability of observing specified numbers of events among patient groups given a small expected value obtained from the US male population or the total hemophilia treatment center patient population. We used a chi-square test for trends in proportions to test for the significance of trends in the proportion of US male deaths for whom hemophilia was mentioned as a cause of death and linear regression to test for the significance of trends in case counts.

RESULTS

Hemophilia treatment center patients with factor VIII or factor IX deficiency and hemophilia treatment center AIDS cases

A total of 6,717 patients were included in the age tallies. Since an estimated 14,467 hemophiliacs with factor VIII and IX deficiencies resided in the United States in 1980 (6), the patients reported by hemophilia treatment centers represent more than one-third of the hemophiliacs receiving care at hemophilia treatment centers or other facilities.

Place and time of reports

Hemophilia treatment centers which participated in the survey reported eight AIDS cases during the survey. As of June 30, 1984, an additional 18 AIDS cases, who had received care from the participating hemophilia treatment centers, had been reported to the Centers for Disease Control by the hemophilia treatment centers or had been reported by physicians not affiliated with hemophilia treatment centers and linked to a participating hemophilia treatment center during the Centers for Disease Control's investigation of the case. Three cases were excluded from the following analyses because the cases had AIDS risk factors—homosexuality, intravenous drug abuse, Haitian—in addition to hemophilia; all three excluded cases were homosexual. The number of reported cases by calendar quarter of diagnosis was stable between the last quarter of 1981 and the last quarter of 1983, with an average of 1.0 cases per quarter, an annual incidence of 0.6 cases per 1,000 hemophilia treatment center attendees. A sharp increase occurred in 1984 with reports of nine cases diagnosed in the first quarter and five cases diagnosed in the

second quarter. The nine cases per quarter would represent an annual incidence of 5.4 cases per 1,000 hemophilia treatment center attendees.

The reported AIDS cases were geographically dispersed. The 23 cases resided in 14 different states which included eight of the nine United States census regions.

Age

The hemophilia treatment center patients in the survey were substantially younger ($p < 0.001$) than the US male population (table 1). Median age for the hemophilia treatment center patients was approximately 19 years; the median for all US males is a decade older. The AIDS cases were older than the other hemophilia treatment center patients ($p < 0.005$), with a median age of 34 years. Age data were not collected by type of deficiency.

Type of deficiency and clotting-factor usage

As shown in table 2, hemophilia treatment center patients with factor VIII deficiency used more lyophilized clotting-factor concentrate than hemophilia treatment center patients with factor IX deficiency: 34 per cent of factor VIII-deficient patients received more than 50,000 units per year versus 18 per cent for factor IX-deficient patients ($p < 0.001$). Clotting-factor usage was reported only for the seven AIDS cases reported during the survey. Although each of these cases had factor VIII deficiency and five received greater than 50,000 units of lyophilized concentrate per year, neither observation was statistically significant when compared with the other hemophilia treatment center factor VIII-deficient patients.

Deaths of US males with hemophilia mentioned as a cause of death, 1968–1979

Age-specific trends. We compared age-specific trends for the number of factor VIII deficiency deaths reported to the National Center for Health Statistics between 1968

TABLE 1

United States male population, hemophilia treatment center patients with factor VIII or IX deficiency, and hemophilia treatment center acquired immunodeficiency syndrome (AIDS) cases, by age, 1978–June 1984

Age (years)	US male population in millions*		Reported hemophilia treatment center patients†		Reported hemophilia treatment center AIDS cases‡	
	No.	Cumulative %	No.	Cumulative %	No.	Cumulative %
0–9	16.90	15.4	1,519	22.8	0	0.0
10–19	20.07	33.6	1,854	50.6	4	17.4
20–29	20.36	52.1	1,570	74.2	4	34.8
30–39	15.54	66.2	892	87.6	6	60.9
40–49	11.10	76.3	427	94.0	4	78.3
50–59	11.10	86.4	251	97.8	4	95.7
60+	14.97	100.0	148	100.0	1	100.0
Total	110.04		6,661§		23	

* Source: US Bureau of the Census: Statistical Abstract of the United States 1982–1983. 103rd ed. Washington DC: USGPO, 1982, Table 31.

† Significantly different from the US male population ($p < 0.001$, goodness of fit chi-square = 1660, d.f. = 6).

‡ The number of AIDS cases aged +40 years significantly exceeds the number expected among hemophilia treatment center patients ($p < 0.005$, binomial distribution).

§ Age was unknown for 56 patients yielding 6,717 patients included in hemophilia treatment center tallies of ages. Clotting-factor usage and frequency of home therapy were reported for 6,368 and 6,673 patients, respectively. These estimates of total patients in the survey may differ because the required information was not available for some patients, because of tabulating errors, or because of other reasons. We are not able to distinguish among these explanations for the discrepancies.

TABLE 2

Number of United States hemophilia treatment center patients, by factor usage and type of hemophilia, and reported acquired immunodeficiency syndrome (AIDS) cases, 1978–December 1982

Anti-hemophilia therapy	Factor VIII deficiency‡				Factor IX deficiency‡		Reported AIDS cases*
	Without inhibitor†		With inhibitor†				
	No.	%	No.	%	No.	%	
No concentrate	807	15.9	65	12.3	228	21.7	0
Cryoprecipitate only	528	10.4	4	0.8	49	4.7	0
<50,000 units of factor VIII and/or IX in past year	2,067	40.8	237	44.9	584	55.6	2
>50,000 units of factor VIII and/or IX in past year	1,667	32.9	222	42.0	189	18.0	5
Total	5,069	100.0	528	100.0	1,050	100.0	7

* Number of AIDS cases who received no lyophilized concentrate is not significantly less than the expected number among factor VIII-deficient patients ($p = 0.17$, Poisson distribution); among factor VIII-deficient hemophilia treatment center patients who received lyophilized concentrates, the number of AIDS cases who received greater than 50,000 units does not significantly exceed the expected number ($p = 0.21$, Poisson distribution).

† Statistically significant difference between factor VIII-deficient patients with and without inhibitor ($p < 0.001$, chi-square = 75, d.f. = 3).

‡ Statistically significant difference between factor VIII-deficient and factor IX-deficient patients ($p < 0.001$, chi-square = 156, d.f. = 3).

and 1979 with the number of deaths among US males (figure 1). We present only those tabulations of deaths in which factor VIII deficiency was mentioned because of the small number of deaths with factor IX mentioned. Between 1968 and 1979, a dramatic decline occurred in the number of deaths reported to the National Center for Health Statistics with factor VIII deficiency mentioned. The decline in deaths was greatest in the youngest age group, became less pronounced with each older age category, and was not evident among those aged 60 years and older (figure 1). A similar pattern was evident for deaths among all US males, but the decline was significantly greater for hemophilia-related deaths among those aged 0–19 years ($p < 0.001$) and 20–49 years ($p < 0.025$) than for US males. Based on three-year moving averages, the number of deaths with factor VIII deficiency mentioned as a cause of death decreased by 67 per cent in the 0–19 years age group between 1968 and 1979, compared with a decrease of 29 per cent among all US males in that age group.

Cause-specific trends: underlying cause of death. Three-year moving averages for deaths attributed to hemorrhage-related causes (hemophilia, hemorrhage unrelated to trauma, and hemorrhage-related trauma) declined by 33 per cent between 1968 and 1979 ($p < 0.001$) (figure 2). No trend was evident in the number of deaths attributed to possibly AIDS-related causes (possibly opportunistic infections, reticuloendothelial neoplasms, and autoimmune and related disorders) ($p > 0.30$), to viral hepatitis and chronic liver disease unrelated to alcohol ($p > 0.20$), or to all other causes ($p > 0.20$), i.e., those deaths attributed to causes unrelated to hemophilia, to the treatment of hemophilia, or to AIDS.

Cause-specific trends: all mentions of AIDS-related causes of death. In 1968–1979, 37 deaths with possibly opportunistic infec-

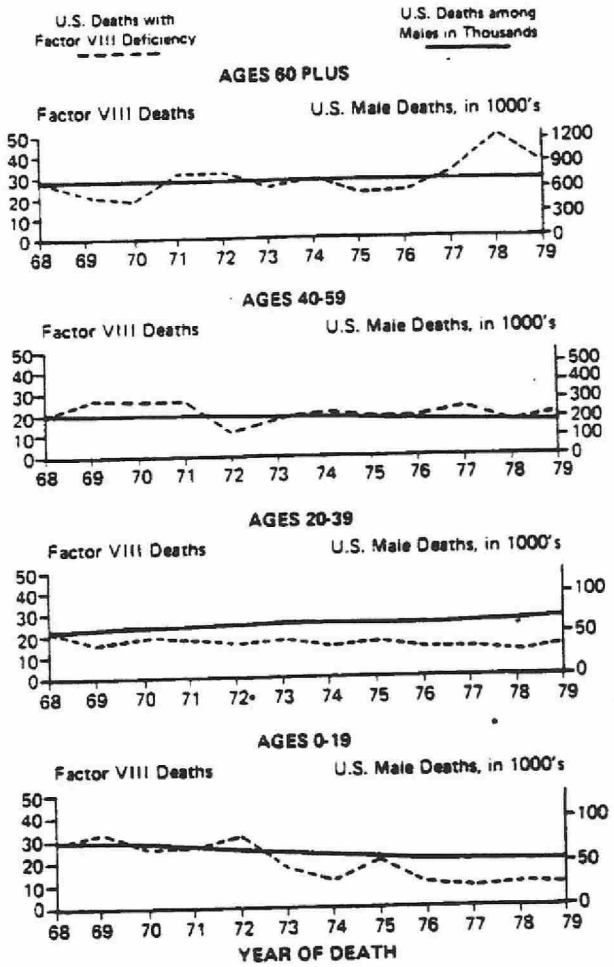

FIGURE 1. Number of US deaths among males and number of US deaths with factor VIII deficiency as a cause of death by year of death (1968–1979) and age (chi-square test for decreasing linear trend in proportion of United States male deaths occurring with factor VIII deficiency mentioned significant for ages 0–19 years (chi-square = 15.9, df = 1, $p < 0.001$) and 20–39 years (chi-square = 6.08, df = 1, $p < 0.025$), not significant for ages 40–59 years (chi-square = 0.03, df = 1, $p > 0.50$), and significant for increasing trend for ages 60+ years (chi-square = 6.2, df = 1, $p < 0.025$)).

tions were reported to the National Center for Health Statistics. These included 21 deaths with nonbronchial pneumonia of unspecified etiology, six with pulmonary and one with disseminated tuberculosis, seven with central nervous system inflammatory disease of unspecified etiology, one with moniliasis, and one with diarrhea of unspecified etiology. Seventeen deaths were reported in 1968–1979 with mentions of reticulo-endothelial neoplasms. Five of these were coded as lymphocytic leukemia, five as myeloid leukemia or multiple myeloma, five as lymphosarcoma or unspecified lymphoma, and two as Hodgkin's disease. Autoimmune and related disorders possibly

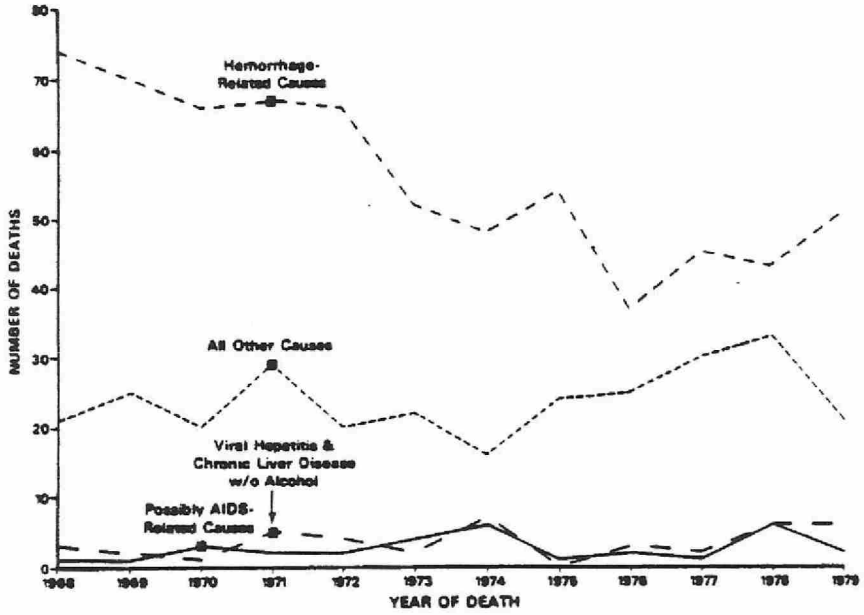

FIGURE 2. Number of US deaths with factor VIII deficiency mentioned as a cause of death by year of death (1968–1979) and underlying cause of death (t test for non-zero least squares regression coefficient significant for hemorrhage-related causes ($t = -5.59$, df = 10, $p < 0.001$) and not significant for possibly AIDS-related causes ($t = 0.93$, df = 10, $p > 0.30$), viral hepatitis and chronic liver disease without alcohol ($t = 1.14$, df = 10, $p > 0.20$), and all other causes ($t = 1.10$, df = 10, $p > 0.20$)).

associated with AIDS were mentioned for an additional 17 deaths during this period. These included five deaths with acute nephritis or nephrotic syndrome, four with rheumatoid arthritis, three with thrombocytopenia, two with unspecified connective tissue disorders, and one each with a mention of agranulocytosis, acquired hemolytic anemia, or progressive systemic sclerosis. No trends were evident for any of these groups. Thus, an average of six deaths were reported to the National Center for Health Statistics annually in 1968–1979 for conditions which could possibly be related to AIDS.

Hemophilia treatment centers survey deaths, 1978–1982

Cause-specific trends: underlying cause of death. Tabulations presented are for hemophilia treatment center patients with factor VIII deficiency because of the small number of deaths among factor IX-deficient patients. The number of deaths reported among factor VIII-deficient patients in the hemophilia treatment center survey decreased from 26 deaths and 24 deaths in 1978 and 1979, respectively, to 18 and 19 deaths in 1980 and 1981, respectively. The number of deaths then more than doubled, with 53 deaths reported for 1982. The two- to three-fold increase in deaths in 1982 include the first five reports of immunodeficiency, an increase in deaths assigned to hemorrhage unrelated to trauma, and an increase in deaths unrelated to AIDS or hemophilia. The sharp increase in deaths across all categories is most likely due to underreporting of deaths, as a result of hemophilia treatment centers inability to identify deaths in previous years.

Cause-specific trends: all mentions of AIDS-related causes of death. We combined deaths reported for factor VIII-deficient and factor IX-deficient hemophilia treatment center patients and tabulated the number of mentions of all causes of death, including the underlying cause of death. The hemophilia treatment center survey deaths included five mentions of immunodeficiency, all occurring in 1982. Four were confirmed AIDS cases and one was a probable AIDS case in an adult with a prior B-lymphocyte deficiency. These five deaths accounted for nine of 10 mentions of possibly opportunistic infections during 1982. Deaths between 1978 and 1981 included four mentions of possibly opportunistic infections: one mention each of pulmonary tuberculosis and of septicemia, meningitis, and pneumonia of unknown etiology. Hemophilia treatment centers reported six deaths involving mentions of reticulo-endothelial neoplasms: two mentions of Burkitt's lymphoma, one in 1978 and one in 1982; two mentions of malignant histiocytosis, one in 1979 and one in 1982; and one mention each of myeloid leukemia and of another, unspecified lymphoma occurring in 1980 and 1979, respectively.

Expected and observed deaths among hemophilia treatment center patients in 1982: comparison of hemophilia treatment center patients and all United States males

In order to compare the mortality experience of hemophiliacs during the first year that AIDS was recognized in this group with the mortality experience of the general US male population, we modified the cause of death categories to permit comparison with the National Center for Health Statistics published results for the US male population (4). Using 10-year age groupings and 1978 mortality rates for US males, we obtained the number of hemophilia treatment center deaths expected among the reported hemophilia treatment center patients with visits in 1982. We compared this figure with the reported number of 1982 hemophilia treatment center patient deaths for each cause of death category (table 3).

For 1982, surveyed hemophilia treatment centers reported 2.3 times the number of deaths predicted from age-adjusted mortality rates for all US males ($p < 0.001$). Cause of death categories with statistically significant increases included AIDS/immunodeficiency ($p < 0.001$), the remaining possibly AIDS-related causes as a group ($p < 0.029$), hemorrhage-related causes ($p < 0.001$), and viral hepatitis and chronic liver disease unrelated to alcohol ($p < 0.028$). Hemorrhage-related causes accounted for most of the excess in mortality in 1982. If the mortality due to hemorrhage-related causes observed for the hemophilia treatment center patients were reduced to that for US males of equivalent age, overall hemophilia treatment center patient mortality would be reduced by 30 per cent. Eliminating the difference for central nervous system hemorrhage alone would reduce overall mortality by 26 per cent. The equivalent percentage for AIDS/immunodeficiency is 9.6 per cent, for the other possibly AIDS-related causes 5.5 per cent, and for viral hepatitis and chronic liver disease unrelated to alcohol 3.3 per cent.

Discussion

AIDS: a new and important cause of illness and mortality among hemophiliacs

The purpose of the Centers for Disease Control-National Hemophilia Foundation survey of hemophilia treatment centers was to document the frequency and onset of AIDS among US hemophilia treatment center patients in 1978–1982. The hemophilia treatment centers reported one AIDS case diagnosed in late 1981. Incidence of AIDS among factor VIII-deficient and IX-deficient attendees remained at 0.6 cases per 1,000 attendees through 1983 but increased sharply to 5.4 cases per 1,000 attendees in the first quarter of 1984. The four deaths among confirmed AIDS cases in 1982 accounted for 7.5 per cent of the

TABLE 3

Number of expected and observed deaths among United States hemophilia treatment center patients, by underlying cause of death, 1978–1982

Underlying cause of death	Hemophilia treatment center deaths*			
	Expected		Observed	
	No.	Confidence interval	No.	p value†
Possibly AIDS-related causes				
AIDS/immunodeficiency	0.00	–	5‡	<0.001
Possibly opportunistic infections	0.48	0–2	1	0.381
Reticulo-endothelial neoplasms	0.47	0–2	2	0.081
Autoimmune and related disorders	0.19	0–1	1	0.173
Hemorrhage-related causes				
Central nervous system hemorrhage	0.27	0–1	14	<0.001
Peptic ulcer disease	0.06	0–1	0	–
Other diseases of circulatory system	0.03	0	2	<0.001
Hemorrhage-related trauma	3.29	0–7	3	–
Viral hepatitis and chronic liver disease unrelated to alcohol	0.26	0–1	2	0.028
Causes common among US population				
Heart disease	5.70	1–10	3	–
Non-reticulo-endothelial neoplasms	3.00	0–6	4	0.353
Influenza and pneumonia	0.24	0–1	0	–
Diabetes	0.23	0–1	0	–
Alcoholic cirrhosis of liver	0.23	0–1	0	–
Arteriosclerosis	0.13	0–1	0	–
Suicide	0.96	0–3	1	–
Trauma unrelated to hemorrhage	1.09	0–3	1	–
All other causes	5.61	1–10	11§	0.029
All causes	22.97	14–32	52‖	<0.001

* Calculated from age-specific United States male mortality for 1978.

† Poisson probability of the observed or more deaths given the expected number.

‡ One patient had T lymphocyte deficiency and long-standing B cell deficiency; the remaining patients were confirmed AIDS cases.

§ Five deaths may have been caused by hemophilia: three due to hemorrhage of gastrointestinal tract, unspecified; one due to shock lung; and one due to cerebral edema.

‖ Cause of death was not reported for two deaths.

deaths. The increase in reported AIDS cases among the hemophilia treatment center attendees in 1984 will, presumably, be followed by an increase in reported deaths. The hemophilia treatment centers reported no AIDS cases among the illnesses and deaths occurring before 1981. An average of six deaths for which AIDS was a possible cause were reported to the National Center for Health Statistics annually during the 12-year period. However, in only one case was the cause of death relatively specific for AIDS. The first AIDS case involving a hemophiliac reported to the Centers for Disease Control was diagnosed in 1981 and this was followed by eight diagnosed in 1982, 13 in 1983 and 30 in the first 10 months of 1984. Mortality rates have been very high among AIDS cases (8). Neither the deaths reported to the National Center for Health Statistics from 1968 to 1979 nor the pre-1982 deaths reported in the hemophilia treatment center survey include sufficient deaths suspect for AIDS to suggest

that the reported AIDS cases are attributable to increased awareness and improved diagnosis.

The onset of AIDS among the other US risk groups—homosexuals, intravenous drug abusers, and Haitians—preceded that for hemophiliacs by approximately 2–2½ years (9). The lag between the onset of the AIDS epidemic in the United States and the first occurrence of AIDS in hemophiliacs is consistent with transmission of AIDS mediated by blood products. Some time would be required following the initiation of transmission in the United States for the prevalence of infecteds to reach a level that transmission through blood donation would be detectable. A newly discovered retrovirus, AIDS virus, is the probable cause of AIDS (10–13). The prevalence of antibody to AIDS virus increased from 1 per cent in 1978 to 25 per cent in 1980 to 65 per cent in 1984 among homosexuals attending a venereal disease clinic in San Francisco (14). One of 22 California factor VIII-deficient patients had antibody to AIDS virus in sera collected in 1978–1980; by 1984, more than 85 per cent of these patients had seroconverted (15). Thus, AIDS trends among hemophiliacs and homosexuals are consistent with trends in the prevalence of AIDS virus antibody.

The United States is an exporter, not an importer, of plasma and plasma products, including clotting-factor concentrates (16). Thus, AIDS among hemophiliacs in the United States cannot be attributed to imported plasma. US donors, however, are a possible source of AIDS among hemophiliacs residing in other countries. To date, we know of 14 AIDS cases that have occurred among hemophiliacs residing outside the United States. Of these cases, 12 resided in one of 10 European countries that collaborate in the reporting of AIDS to the World Health Organization (17) and two resided in Canada (18). Immunologic abnormalities associated with AIDS have been reported among asymptomatic hemophiliacs in Italy (19) and Denmark (20). The United States was the sole source of plasma for the clotting-factor concentrates used by the Italian hemophiliacs. The Danish hemophiliacs could be divided into those treated only with clotting-factor concentrates of Danish origin and those who had received concentrate of US origin. T-cell abnormalities were more prevalent among patients who had received concentrates of US origin. Transmission from European donors is also now a possibility, given the high prevalences of antibody to AIDS virus reported for some groups of European homosexuals (21, 22). With AIDS endemic in Europe, the distinction between concentrates of United States and European origin will probably decrease.

AIDS incidence was higher among older hemophilia treatment center patients who had received larger amounts of clotting-factor concentrate. Hemophilia treatment center AIDS cases were geographically dispersed

The 23 AIDS cases were older than their fellow hemophilia treatment center patients. The reason for the increased age of cases is unknown. Plausible explanations include a cumulative exposure, immunologic changes with age, or a long latent period.

The initial AIDS cases reported in the survey were also more likely to have factor VIII deficiency and to have received larger quantities of lyophilized clotting-factor concentrates than other factor VIII-deficient patients. This result is consistent with studies which correlated factor usage with T-cell abnormalities or with antibody to AIDS virus. Surveys of hemophiliacs for T-cell abnormalities have reported a greater prevalence of abnormalities among factor VIII-deficient patients using lyophilized clotting-factor concentrate than among factor VIII-deficient patients using cryoprecipitate or factor IX-deficient patients (19, 20, 23–27). A weak correlation between quantity of lyophilized factor VIII concentrate administered to factor VIII-

deficient patients and T-cell subsets has been reported from most of the studies which quantified factor usage (19, 20, 25–27). The weakness of these associations may be explained by results from a survey of hemophiliacs for antibody to AIDS virus (28). AIDS virus antibody was detected in 74 per cent of the factor VIII-deficient patients and in 39 per cent of the factor IX-deficient patients. Mean factor usage was substantially greater among patients with AIDS virus antibody. Although almost all heavy users had antibody, the association between antibody and factor usage broke down among patients who used less concentrate; many of these patients were also antibody positive.

Although the survey of hemophilia treatment centers was designed to study the role of individual lots of factor concentrate, this approach to the study of blood products proved to be very inefficient because of the large number of lots used by any given hemophiliac and because of the methods employed to produce factor concentrates. Blood for a single batch of concentrate is pooled from hundreds to thousands of donors. The resulting concentrate is then distributed widely within the United States and abroad. This production and distribution system probably accounts for the geographic dispersion of hemophilia cases which contrasts with the geographic clustering of AIDS cases belonging to the other risk groups (8). The study of the role of blood products in AIDS transmission involving non-hemophiliacs has proven more tractable. These investigations have demonstrated a very strong association between a history of blood transfusion among AIDS cases who do not belong to established risk groups and the existence of a donor who is a risk group member and/or AIDS virus culture or antibody positive (29, 30).

Improved treatment, including the use of concentrates, has dramatically reduced mortality among hemophiliacs

Substantial changes occurred in the treatment of hemophilia between 1971 and 1982, including marked increases in the use of clotting-factor concentrates, utilization of hemophilia treatment centers, and reliance on home therapy. These conclusions are based on a comparison of our 1982 results with those of a survey conducted in 1972 shortly after the introduction of lyophilized clotting-factor concentrates (7).

The 1972 survey was designed to describe hemophiliacs with moderate-to-severe factor VIII or IX deficiency who had visited a US physician during 1970 or 1971. Marked differences existed between the care reported by hemophilia treatment centers in 1982 and that reported for US hemophiliacs in the 1972 US physician survey. Seventy-three per cent of both the factor VIII-deficient and factor IX-deficient hemophilia treatment center patients reported in 1982 received lyophilized concentrates, compared with 46 per cent of factor VIII-deficient and 61 per cent of factor IX-deficient patients treated by US physicians in 1970–1971. Also, 54 per cent of the factor VIII-deficient and 43 per cent of the factor IX-deficient patients reported in 1982 received therapy almost exclusively at home, whereas only 10 per cent of infusions were given outside an institution in 1970–1971.

The median age for factor VIII-deficient and IX-deficient hemophiliacs in the 1972 survey was 11.5 years, compared with a median age of 26.8 years for the US male population in 1970. The median age of the patients reported by hemophilia treatment centers in 1982 was 20 years, compared with a median age of 29.3 years for US males in 1981. The much older median age of hemophilia treatment center hemophiliacs in 1982 and much smaller difference between the median age of hemophilia treatment center hemophiliacs in 1982 and the US male population were consistent with a decrease in the overall mortality rate for US hemophiliacs, probably as a consequence of improved medical management. However, selection bias may have contributed to these differences because neither survey included hemophiliacs who make

infrequent visits to physicians. Also, our 1982 survey did not include hemophiliacs who visited only physicians not affiliated with a hemophilia treatment center. Analysis of US mortality reports for 1968–1978 also suggests a dramatic decline in the mortality rate for hemophiliacs. The decline in deaths, confined to younger age groups, resulted entirely from a reduction in hemophilia-related causes of death. Selection bias may have distorted the results from US mortality reports since only deaths with hemophilia as one of the certified causes of death were included in our analysis. However, it seems improbable that such a bias would account for the decline in reported mortality confined to younger hemophiliacs dying of hemophilia-related causes. Similar declines in mortality for hemophiliacs have been reported in the United Kingdom (31) and in Finland (32).

Spontaneous hemorrhage continues to be the leading cause of death among hemophiliacs attending hemophilia treatment centers. Hemophiliacs are also at increased risk for death caused by liver disease

Overall, the age-adjusted mortality rate for the reported hemophilia treatment center hemophiliacs was approximately twice that for US males. Hemorrhage, particularly central nervous system bleeding, remains, by far, the most important cause of death for hemophiliacs, accounting for 48 per cent of deaths and a 30 per cent increase in mortality compared with US males. This result is consistent with reports from other surveys of mortality among hemophiliacs (33–35).

Hemophiliacs who are treated with blood products are at markedly increased risk for hepatitis B, non-A non-B viral hepatitis and other liver disease. As many as 4 per cent are chronic carriers of HBs antigen and one-fourth have persistently elevated liver enzymes (36). The hemophilia treatment center patient deaths due to viral hepatitis and chronic liver disease unrelated to alcohol reported in the Centers for Disease Control-National Hemophilia Foundation survey represented a 3.3 per cent increase in mortality over that for US males of comparable age. This increase was statistically significant, although only two deaths were reported.

In spite of the increasing use of concentrates during the 1970s, the number of deaths reported to the National Center for Health Statistics with hemophilia and liver disease mentioned as causes of death did not increase between 1968 and 1979. Any of the following explanations may account for these somewhat surprising results: most hemophiliacs were exposed to hepatitis even before the introduction of lyophilized clotting-factor concentrates; the use of concentrates resulted in only a small marginal increase in exposure; the year 1979 is too early for increases in subclinical liver disease to result in increases in mortality; the National Center for Health Statistics death reports are insensitive to trends in hemophilia deaths caused by viral hepatitis and chronic liver disease unrelated to alcohol.

Conclusions

We conclude that AIDS and viral hepatitis are important causes of death, but these possible adverse consequences of clotting-factor usage must be balanced by the benefits of recent improvements in the care of persons with hemophilia, which produced a large decline in hemophilia mortality rates during the 1970s. In March 1983, the US Public Health Service recommended that members of groups at increased risk of acquiring AIDS should refrain from donating blood or plasma (37). Additional steps to prevent blood product-mediated transmission of AIDS and other infections are clearly indicated. Preliminary in vitro studies indicate that heat treatment effectively eliminates viable AIDS virus from factor VIII concentrates (38). A serologic test for screening blood products should be available soon. More

time will be required to develop methods to produce clotting factors from cloned genes.

Results now becoming available from ongoing studies provide added importance to these considerations. Rates of AIDS virus antibody were 74 per cent for factor VIII recipients and 39 per cent for factor IX recipients in one survey of US hemophiliacs (28). AIDS developed during a 24-month follow-up period in two (9 per cent) of 22 initially asymptomatic but AIDS virus antibody-positive Danish homosexuals (21). The individuals tested in these studies were not randomly selected. Larger, better controlled studies of hemophiliacs are clearly needed to adequately define the prognostic significance of a positive AIDS virus antibody test. Nevertheless, the recently revised recommendations of the Medical and Scientific Advisory Council of the National Hemophilia Foundation (39) provide a prudent course pending the accumulation of more information concerning AIDS and the handling of blood products. The Council recommends that 1) cryoprecipitate be used in factor VIII-deficient newborn infants and children under four years of age and in newly identified patients never treated with factor VIII concentrates; 2) fresh frozen plasma be used in factor IX-deficient patients in the same categories; and 3) desmopressin be used whenever possible in patients with mild or moderate hemophilia A. The majority of hemophilia patients do not fit in categories 1–3. For patients requiring clotting-factor concentrates, the Council recommends the use of heat-treated clotting-factor concentrates. These measures are directed towards preventing AIDS and hepatitis and should be followed until alternative measures are developed and evaluated.

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