APPENDIX FIFTEEN

WORLD FEDERATION OF HEMOPHILIA

MAY 18 1983

I. DEFINITION AND DESCRIPTION - Acquired immune deficiency syndrome (AIDS), as defined by the Centers for Disease Control (CDC) of the United States Public Health Service is the occurrence of Kaposi's sarcoma and/or an infection, moderately to highly predictive, of a defect in cell-mediated immunity in a person without a known predisposing cause. Although the present U.S. epidemic seems to have begun in 1979, the first report on AIDS appeared in the Mortality and Morbidity Weekly Report of the CDC (MMWR) on June 5, 1981, listing five cases of pneumocystis carinii pneumonia (PCP) in homosexual males. Since the initial report in MMWR, new cases of PCP as well as Kaposi's sarcoma and other rare infections and malignancies have been reported in certain high-risk groups and are summarized in Table 1. The first cases in patients with hemophilia were reported in the July 16, 1982, issue of MMWR, and currently total 12. All AIDS cases in hemophiliacs have been associated with opportunistic infections.

A number of hemophilia patients have manifested prodromal (or "incomplete") AIDS signs and symptoms which may include one or more of the following: generalized lymphadenopathy, fever, unusual fatigue, nightsweats, prolonged diarrhea, prolonged cough, unexplained weight loss, idiopathic thrombocytopenic purpura, and Coomb's positive hemolytic anemia. Some patients are anergic to all skin tests. The CDC has conducted a survey of the United States hemophilia treatment centers for patients with these possible AIDS-associated findings (results pending), and the complete description of the clinical spectrum (Table 2) is attached.

The prognostic significance of these findings is unclear; in many patients the clinical course is marked by waxing and waning of the generalized lymphadenopathy. Lymph node biopsies performed on hemophilia patients with generalized lymphadenopathy have generally shown changes characteristic of reactive hyperplasia.

II. ETIOLOGIC THEORIES

A. It must be emphasized that as yet no scientific evidence of the putative transmissible agent causing AIDS, whether a new or known viral agent, has yet been identified in the laboratory or clinically. Some researchers believe evidence points strongly to the acquired immune deficiency state arising as a result of multiple antigenic exposure which is high in the male homosexual or bisexual populations because of sexual practices by which semen and sperm enter the blood stream through breaks in the mucosal barrier. Still others involved in this mystery hold that both the above theories are tenable, and that a two-step process combined with genetic susceptibility may result in the onset of AIDS.

B. Dr. Carol Kasper has summarized the CDC position as follows:

"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 remains 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."

Several studies have confirmed immunologic abnormalities in a substantial percentage of hemophilia patients who use concentrate, yet most of these individuals appear healthy. Therefore, the significance of these findings will be determined by prospective, serial studies. Immunologic changes of a lesser degree and frequency have been reported in hemophilia patients on cryoprecipitate.

Theories of pathogenesis include:

? Multiple antigenic exposure
? Specific transmitted agent (e.g., virus)
? Chronic exposure to immune complexes
? Genetic susceptibility
? Combination of the above

Laboratory findings include the following immunoregulation disturbances:

Cellular (T cell) immunodepression - characterized by:

1. Lymphopenia
2. Skin-test anergy
3. Depressed <u>in vitro</u> T-cell responsiveness to mitogen
4. Reduction in T-helper subset with reduction in T-helper/T-suppressor ratio
5. Increase in absolute T-suppressor subset

Humoral (B cell) immunity

1. Generally remains intact
2. <u>Hypergammaglobulinemia</u> is often found

III. BLOOD/PLASMA DONATION - Because the possibility of acquiring AIDS through blood components or blood exists, there is intense concern about donation of blood or plasma by person belonging to the high-risk groups.

Recommendations are summarized in MMWR (March 4, 1983, Vol.32, No.8):

"As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma and/or blood. This recommendation

includes all individuals belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma and/or blood should inform potential donors of this recommendation. The Food and Drug Administration (FDA) is preparing new recommendations for manufacturers of plasma derivatives and for establishments collecting plasma or blood. This is an interim measure to protect recipients of blood products and blood until specific laboratory tests are available.

"Studies should be conducted to evaluate screening procedures for their effectiveness in identifying and excluding plasma and blood with high probability of transmitting AIDS. These procedures should include specific laboratory tests as well as careful histories and physical examinations.

"Physicians should adhere strictly to medical indications for transfusions, and autologous blood transfusions are encouraged.

"Work should continue toward development of safer blood products for use by hemophilia patients."

The interim recommendation requesting that persons in high-risk groups refrain from donating plasma and/or blood is especially important for donors whose plasma is recovered from plasmapheresis centers or other sources and pooled to make products that are not inactivated and may transmit infections, such as hepatitis B. The clear intent of this recommendation is to eliminate plasma and blood potentially containing the putative AIDS agent from the supply. Since no specific test is known to detect AIDS at an early stage in a potential donor, the recommendation to discourage donation must encompass all members of groups at increased risk for AIDS, even though it includes many individuals who may be at little risk of transmitting AIDS."

The pharmaceutical industry has been extremely concerned and cooperative in attempts to exclude plasma donors at high risk for AIDS. These efforts are summarized in a public service brochure recently issued by Alpha Therapeutic Corporation.

"Q: What are manufacturers doing to diminish our risk?

"A: All commerical producers of concentrate, following Alpha's lead, have taken steps to eliminate members of high-risk groups from their donor pools. Alpha now educates donors about the risk of AIDS and specifically indentifies high-risk donors such as male homosexuals, intravenous drug users, and travellers from Haiti. Staff personnel back up a self-exclusion option with questions designed to identify and exclude high-risk donors. All donors are screened via medical history, physical examinations, and questionnaires for early signs of AIDS, such as unexplained weight loss and swollen glands. Alpha does not accept plasma from any suspect donor.

"Many Community Blood Banks like the New York Blood Center, which provide some 20% of raw material for concentrates, also are instituting policies to exclude high-risk donors."

Community and volunteer blood banks are instituting educational and self-exclusion systems. Persons who have had symptoms of AIDS, persons who consider themselves at high risk for AIDS, and persons who have had intimate contact with someone who may have had AIDS are asked to refrain from donating blood.

IV. AIDS AND THE USE OF BLOOD PRODUCTS FOR THE TREATMENT OF HEMOPHILIA

The patient with hemophilia and the patient's physician is presently faced with the necessity for immediate decision regarding treatment of hemophilia and use of blood products, decisions which cannot be deferred until further scientific data is available.

The National Hemophilia Foundation in the United States and its Medical and Scientific Advisory Council (MASAC) has issued recommendations regarding AIDS in patients with hemophilia which are summarized below:

"A. It is recommended that cryoprecipitate be used to treat patients in the following groups except when there is an overriding medical indication:

* new born infants and children under 4
* newly identified patients never treated with Factor VIII concentrate
* patients with clinically mild hemophilia who require infrequent treatment

"B. The potential advantages and disadvantages of cryoprecipitate versus Factor VIII concentrate therapy for severe hemophilia A are not clear at the present time and are controversial. The Medical and Scientific Advisory Council does not offer a specific recommendation at this time, but will continue to review the data.

"C. DDAVP (synthetic vasopressin analogue) should be used whenever possible in patients with mild or moderate hemophilia A. (Editorial note: Licensure of DDAVP in the U.S. is expected shortly.)

"D. All elective surgical procedures should be evaluated with respect to the possible advantages or disadvantages of a delay."

It is painfully evident that hemophilia is a chronic, life-long disease with well documented morbidity and mortality. Treatment of hemophilia rests basically in replacement of the missing coagulation factors, Factor VIII or IX, from human source blood or plasma products.

The next table lists currently available coagulation factor replacement products.

BLOOD/PLASMA PRODUCTS USED IN TREATMENT OF HEMOPHILIA

1. Whole Blood - Effective in Factor VIII or IX replacement only if fresh and use limited by volume.
   Indicated principally for red cell and volume replacement.

2. Fresh plasma and fresh frozen plasma - Use limited by volume.
   Indicated for replacement of Factors I, II, V, VII, VIII, IX, X, and XI, and von Willebrand's disease.

3. Cryoprecipitate - Indicated for replacement of Factors I and VIII and von Willebrand's disease.

   a. Single donor
   b. Pooled lots - 12 donors or less
   c. Pooled cryoprecipitate from greater than 12 donor lots.
   d. Lyophilized cryoprecipitate

4. Lyophilized Factor VIII concentrates (from large-donor pools)
   Trade names: Alpha (Profilate), Armour (Factorate & Generation II), Cutter (Koate), and Hyland (Hemofil)

   a. Intermediate purity
   b. High purity
   c. Heat-treated

   Manufacturers offer various ranges of protein content as well as volume and number of AHF units per ml.

5. Factor IX concentrates

   a. Regular - Trade names: Cutter (Konyne), Hyland (Proplex), and Alpha (Profilnine)
   b. "Activated" - Trade names: FEIBA and Autoplex used in Factor VIII inhibitor patients.

6. Porcine Factor VIII - Trade name: Hyate
   Indicated for Factor VIII inhibitor patients.

7. DDAVP - Synthetic vasopressin analogue
   Indication: Von Willebrand's or mild Factor VIII deficient patients.

The patient and physician must weigh and balance various modes of treatment including choice of factor replacement product and intensity of use against potential risks/problems as opposed to medical and psychologic benefits. Table 3 outlines various modes of treatment and the risks/problems and benefits/positives associated with each.

The recognition and description of the acquired immune deficiency syndrome in the hemophiliac population is a major challenge for all those involved in the professional and personal aspects of this disease. Because modern treatment has revolutionized the life quality as well as life expectancy of most persons with hemophilia, the implied threat to the safety and purity of blood and plasma products is causing deep distress. All segments of the blood banking system and plasma product producers are challenged to assure as safe a product as possible in the light of present incomplete knowledge. In the best of circumstances physicians and patients together will weigh the relative benefits/assets and risks/problems of various modes of treatment and reach a decision beset with ambiguities and uncertainties. Hemophilia per se is a

life-threatening and crippling disease and will remain that way until genetic prevention or engineering becomes a reality. Adult patients with hemophilia have already experienced in their lifetimes the range of minimal treatment to inadequate treatment to modern treatment. The threat of complications and potential side effects (real or not) of inhibitor stimulation, hepatitis, and now AIDS has been part of that experience. Members of the medical profession more than ever before need to establish and maintain close patient-physician relationships and cooperate in the scientific community by discussion, data collection, and sharing of information.

The Medical Advisory Board is asked to consider the following questions or situations:

1. Impact of AIDS on volunteer blood donations and commercial plasmapheresis and fractionation.

2. Impact of AIDS on hemophilia treatment.

3. Impact of AIDS on international hemophilia data collection efforts.

    a. Identification and tabulation of number of hemophilia cases per country.
    b. Identification and tabulation of number of deaths annually from hemophilia per country by cause.
    c. Treatment modes available by country.
    d. Reporting mechanisms of actual or suspected AIDS cases.

TABLE 1

AIDS DIAGNOSED CASES

Total Cases 1,300* to date **Overall Mortality Rate 37.6%**

Homosexual or Bisexual Men: **933 Cases, 35% Mortality**

AIDS first struck extremely promiscuous "fast-lane" gays. Many of the early victims had had more than 1,000 different sex partners, were frequent users of recreational drugs and had long histories of sexually transmitted diseases. The epidemic has now spread to include more conservative, even monogamous gays.

Intravenous Drug Users: **217 Cases, 40% Mortality**

Both male and female drug users have developed AIDS. Researchers suspect an infectious agent is getting into the victims' blood through the use of shared needles in "shooting galleries." The majority of cases have been diagnosed in New York City.

Haitians: **64 Cases, 55% Mortality**

The outbreak of opportunistic infections among recent Haitian immigrants of both sexes in New York and Miami is one of the biggest mysteries puzzling AIDS researchers. Nearly all of the victims deny IV drug use and are vehement about their heterosexuality, but a deep-rooted anti-homosexual bias in Haitian culture makes sexual orientation difficult to determine. Early theories linking AIDS to Haitian animal sacrifice and voodoo rituals have been discarded.

Hemophiliacs: **11 Cases, 73% Mortality**

AIDS poses a serious threat to the nation's 20,000 hemophiliacs, some of whom require 30 to 40 transfusions of blood-clotting concentrates each year. Because a single dose of clotting agent may be drawn from thousands of donors, hemophiliacs are extremely susceptible to blood-borne infections. To reduce the likelihood of AIDS transmission by this route, major blood-collecting organizations have urged people who are at high risk for the disease to refrain from donating blood.

Children: **20 Cases (under investigation), 50% Mortality**

The CDC has been receiving reports of immunologically deficient children for the last six months, but has hesitated to classify them as AIDS victims because certain immunological deficiencies do occur at birth. Still, the evidence suggesting AIDS is compelling. Most of the infants have parents who are members of high-risk groups. In San Francisco, one child developed opportunistic infections after receiving a blood transfusion from a man who later died of AIDS.

Others: 75 Cases, 43% Mortality

While still under investigation, these cases do not now belong to any of the above risk groups. They include other transfusion cases, female sex partners of IV drug users and Haitians, and a group of 36 seemingly risk-free heterosexual men.

*Figures as of April 7, 1983

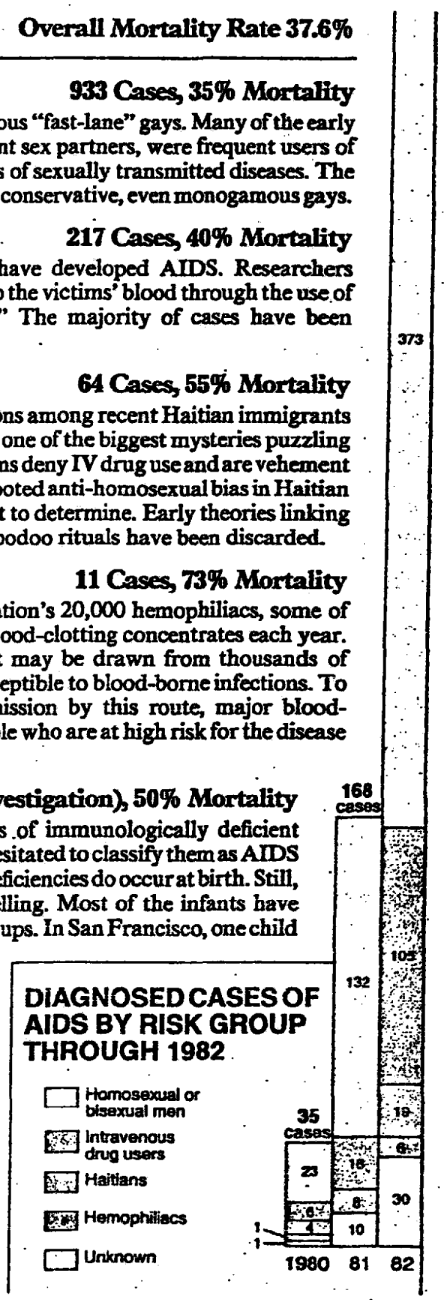

TABLE 2

Acquired Immune Deficiency Survey
Hemophilia Treatment Centers

Attachment 5

SPECTRUM OF DISEASE PRESENTATION IN THE
ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Please report to the Centers for Disease Control (CDC) all hemophilia patients visiting your Center who fulfill any of the following criteria. Although some patients meeting the following criteria may have other underlying conditions and/or immunosuppressive therapy accounting for AIDS-related findings, please report these patients anyway. Use the ILL OR DEAD PATIENT SURVEY/SURVEILLANCE REPORT to report these AIDS-suspect patients to the CDC address provided in the instructions.

1. Diseases Specific for AIDS

The following diseases may be specific manifestations of or associated with AIDS. Report all patients with these diseases:

Malignancies
- Kaposi's sarcoma
- Lymphocytic leukemia
- Lymphoma
- Other lymphoreticular neoplasms

Infections

Parasitic
- Pneumocystis carinii pneumonia
- Toxoplasmosis (CNS or pulmonary)
- Strongyloidosis (CNS or pulmonary)
- Cryptosporidiosis (intestinal disease lasting longer than one month)

Fungal
- Candidiasis - "thrush" (oral, pharyngeal, esophageal or systemic)
- Cryptococcosis (CNS or pulmonary)
- Zygomycosis (CNS or pulmonary)
- Aspergillosis (CNS or pulmonary)
- Nocardiosis (CNS or pulmonary)

Viral
- Cytomegalovirus disease (CNS, pulmonary or esophageal)
- Herpes simplex virus (extensive oral or genital disease or persisting longer than one month)
- Varicella zoster virus- herpes zoster, "shingles" (involving more than one dermatome or persisting longer than one month)

Bacterial

Tuberculosis (active, reactivated, and/or disseminated)
Non-tuberculosis mycobacterial disease (e.g., M. avium [intracellulare]/Battey bacillus)

2. AIDS-Related Diseases: Nonspecific Diagnoses

The following "diseases" are non-specific diagnoses for which AIDS-specific diagnoses must be considered until a specific diagnosis is made.

Pneumonia
Central nervous system dysfunction

3. AIDS-Related Prodromal Symptoms and Signs

The following symptoms and signs have been common among AIDS cases prior to the diagnosis of the specific diseases listed above. Report all patients with any of these symptoms or signs:

Throat pain and difficulty swallowing (lasting more than a week)
Shortness of breath
Fever (lasting more than a week)
Diarrhea (lasting more than a week)
Swollen lymph glands (lasting more than a month)
Cough (lasting more than two weeks)
Unexplained weight loss

4. Hematologic/Immunologic Abnormalities

The underlying defect leading to AIDS appears to be a loss of the "helper" subset of the T cell population of lymphocytes. The following laboratory test abnormalities are seen in a variable (depending on the test) proportion of AIDS cases. Please report all patients with the following abnormalities:

Lymphopenia (WBC x % lymphs in differential e.g., 4500 x .20 = 800)
(consistently less than 1,000 lymphocytes per mm^3 on at least two occasions at least two weeks apart)
In vitro lymphocyte stimulation test responses abnormally low
Skin test anergy to delayed type hypersensitivity antigens
T lymphocytes percent or absolute number abnormally low
T-helper lymphocytes percent or absolute number abnormally low
T-helper:T-suppressor lymphocyte ratio abnormally low (below 1.0)

5. Autoimmune Disorders

Idiopathic thrombocytopenia purpura
Coombs positive hemolytic anemia
Demyelinating neuropathy (recent onset, unexplained)

HHS,PHS,CDC

TABLE 3

HEMOPHILIA TREATMENT - MODES AND PRODUCTS

TYPE	RISKS/PROBLEMS	BENEFITS/ASSETS
No Treatment or Minimal		
Indication: Life-saving, severe pain, prolonged bleeding Products Used: Blood, FFP, very limited cryo & concentrates	1. Death, severe pain & disability 2. "Invalid" life-style 3. Shortened life-span 4. Economic & physical dependence on others 5. Nonproductive member of society	1. Cost: None to low 2. Exposure to blood products is minimal as is exposure to hepatitis & AIDS 3. Other iatrogenic treatment complications nil to minimal
Crisis Treatment		
Indication: Significant pain, joint swelling, bleeding Treatment usually hospital or M.D. based Products Used: Whole blood, FFP (cryo, concentrate in limited degree)	1. Same as above but less intense & severe 2. Productivity problematic	1. Moderate cost 2. Some decrease in morbidity & mortality 3. Moderate exposure to blood products 4. ? lower incidence of hepatitis, etc.
Early "p.r.n." Rx or Prophylactic		
Usually on SST	1. High $$$ 2. Intense exposure to plasma products 3. ? increase in hepatitis, cirrhosis	1. Normal life-style 2. Normal vocational/professional opportunities 3. Prevention of arthropathy 4. Productive member of society
Elective Orthopedic Surgery		
	1. Usual surgical & anesthetic risks 2. Bleeding & infection 3. Failure of surgical procedure 4. High cost $$$ Dollar days hospitalized & missed days from school/work 5. Intense concentrate exposure	1. Relief of pain 2. Improvement of physical functioning 3. Decreased need for analgesic & anti-inflammatory medication 4. Potential long-term decrease in concentrate/cryoprecipitate use