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THE TRAGIC HISTORY OF AIDS IN THE HEMOPHILIA POPULATION, 1982–1984

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Treatment for All

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HISTORICAL SKETCH

The tragic history of AIDS in the hemophilia population, 1982–1984

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Introduction: building the paradigm of hemophilia care

During the first four decades of the 20th century, life for patients with hemophilia was at best miserable. Usually disabled before the age of 20, life expectancy for these patients averaged 27 years because of early deaths, often from bleeding into vital organs [1]. Because of the improvements in transfusion technology made during World War II [2–3], hemophilic patients could receive infusions of fresh whole blood or fresh frozen plasma containing the missing clotting factor. As a result, the life expectancy for a severe hemophilic patient reached 39.7 years by 1960, but the crippling effects of repeated bleeds left a substantial proportion of the population disabled and unemployed. Development of cryoprecipitate and subsequent fractionation procedures in the 1960s allowed storage of a therapeutic form of clotting factor VIII (FVIII), the missing clotting factor in hemophilia A [4–6]. Commercial adaptation yielded lyophilized clotting factor concentrates that immediately raised the missing clotting factor to normal levels, could be carried with patients on trips and could be self-administered.

Both patients and physicians regarded clotting factor concentrates as the ultimate solution to hemophilia. Home care programs grew and comprehensive hemophilia treatment centres (HTC) developed [7–9]. Patients attending HTCs experienced substantial improvement of medical care and better quality of life as dependency on the medical community decreased. Mortality rates fell dramatically, employment levels increased, and school and work absences diminished greatly as hospitalizations and complications of hemophilia decreased [10–11]. Life expectancy reached 60 by 1980, nearly that of normal males.

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Consequently, plasma demand rose significantly, and the need for volume rather than quality drove the plasma industry. Plasma was often obtained from paid donors who had high risks of blood-borne diseases (those who were extremely poor, prisoners, alcoholics, etc.) [2]. As a result, clotting factor concentrates, derived from pools of up to 20 000 donors with inadequate donor screening and infective agent testing, almost uniformly infected patients with hepatitis [12–13]. Considering the enhanced quality of life and increased longevity, these high infectivity rates were deemed an acceptable risk by patients, physicians, industry and government; viral inactivation technology was not vigorously pursued.

The epidemic begins

It was in this setting that a new blood-borne disease, acquired immune deficiency syndrome (AIDS), was spawned in Africa and transmitted by social and sexual intercourse of populations at high risk for blood-borne disease into the Caribbean, the USA and other countries of the developed world.

First apparent in the homosexual population in the USA in the last quarter of 1980, the disease possessed unusual properties that initially obscured it as a distinct infectious disease. Previously healthy victims had no specific symptoms but presented with either secondary infections or tumors associated with immune deficiency [i.e. *Pneumocystis carinii* pneumonia (PCP) or Kaposi's sarcoma] [14,15]. A long incubation time made it difficult to identify person-to-person spread. Laboratory methods needed to culture and identify the etiologic agent were lacking. Leading scientists focused on non-infectious causes, such as antibodies to sperm or reaction of the immune system to chemicals such as inhaled amyl nitrites that homosexuals used to maintain prolonged erections [16,17].

The course of the investigation began to change in 1982. The Centers for Disease Control (CDC), the federal agency responsible for investigating new infectious diseases, had just experienced a major reorganization and severe budgetary and staff reductions. The author directed the Division of Host Factors, which was responsible for investigation of new drugs, one of which was pentamidine, the drug used to treat

the PCP common in AIDS patients. Epidemiologists at the CDC were already investigating the new disorder in homosexual men.

In early 1982, the author received a call reporting a hemophilic patient who, treated with FVIII concentrates, had died of PCP. The physician reasoned that the clotting factor was contaminated with *P. carinii* and was transmitted directly to the patient. However, the manufacturing process would have removed contaminating *P. carinii*, and the rarity of PCP in hemophilia suggested the possibility that the patient had acquired the same syndrome that was affecting homosexuals. After investigating, the author determined that the patient's clinical record was consistent with the new disorder, but the patient's death precluded confirmatory tests.

Almost simultaneously, the CDC received reports of a similar immune disorder in Haitian patients and i.v. drug abusers. As anal intercourse or use of amyl nitrites, prevailing theories regarding the cause of the homosexual disease, were not common practices for hemophilic patients, Haitians or i.v. drug abusers, the author reasoned that these four groups had very little in common except for one thing, a risk for blood-borne diseases (Table 1).

My division began to vigorously pursue the possibility that the new syndrome was blood borne. The author requested a review of the pentamidine request files, in search of other hemophilic patients with PCP. None had ever been received. A thorough search of scientific journals identified only one hemophilic patient who had developed PCP following high-dose ACTH injections a decade earlier. Calls to Dr David Aronson at the Food and Drug Administration (FDA) also confirmed that that agency had received no prior reports of hemophilia PCP cases in routine adverse drug reaction reports. The CDC established a surveillance program using pentamidine drug requests.

June and July 1982 became pivotal months in CDC thinking about AIDS. During the second week of June, The University of Colorado Medical Center, Denver, requested pentamidine for a hemophilic patient. Dr Dale Lawrence was dispatched to conduct the field investigation. He confirmed that the patient had a clinical course compatible with AIDS, ruled out the possibility that the patient was a member of the three known risk groups, and informed the Medical Center that the patient had the same syndrome that affected the homosexual population [16].

On 2 July 1982, a request for pentamidine was received for a third hemophilic patient infected with PCP in Ohio.

Table 1 Distribution of possible AIDS indicators among target populations. From author's personal slide collection, 1982

Population	Anti-sperm antibodies	Amyl nitrates inhalants	Hepatitis B-core +
Drug abuser	0	0	+
Haitians	0	0	+
Hemophilia	0	0	+
Homosexual	+	+	+

Investigation confirmed the presence of the immune disorder. We were now reasonably convinced that hemophilic patients were another risk group for AIDS. The author notified Dr William Foege, Director of the CDC, and drafted a letter for him to warn all the HTC directors. The Executive Director of the National Hemophilia Foundation (NHF) was notified of the implications and NHF's cooperation was enlisted to provide support for further surveillance and investigations. The CDC published a *Morbidity and Mortality Weekly Report* (MMWR) article reporting the three patients and suggesting the probability of a blood-borne infection as a cause of AIDS [18].

In July 1982, we reasoned that the time had come to shift US investigations towards a blood-borne and sexually transmitted infection as a cause of AIDS [19]. The members of the blood banking and plasma industry, the affected patient groups, the hematology professional organizations and government agencies needed to be briefed and an attempt made to reach a consensus position, and ideally, to concur on preventive action, such as blood donor deferral guidelines directed toward excluding high-risk groups from donating blood.

However, these actions could not be easily achieved. Although the implications of finding the syndrome in the four risk groups provided a strong suggestion of a possible blood-borne disease, no direct proof existed that showed the syndrome was infectious or transmitted by blood. No agent had been found and no tests existed to screen potentially infected persons.

Confronting 'existing wisdom'

On 27 July 1982, CDC representatives met with a group of leaders from the blood industry, hemophilia groups, gay community organizations, and representatives from the NIH and FDA, to present the evidence of a possible transmission by a blood-borne agent [18]. If the attendees accepted this possibility, we reasoned that high-risk groups should be prohibited from donating blood until the issue could be clarified by future studies.

It was a long day. Detailed histories of the hemophilia cases were systematically presented, followed by data from the other risk groups and comparison of hypothetical risks posed by various etiologic theories to each risk groups (Table 1) [12,20]. Only the high risk for blood-borne infections could explain a risk common to all four groups. But, rather than expressing alarm at a possible blood-borne infection and suggesting ways to reduce a blood-borne risk, the audience expressed an almost universal reluctance to act. The scientific community had yet to see 'published evidence that the syndrome was indeed an infectious disease', let alone blood borne and sexually transmitted. Homosexuals were major blood donors in the large cities on the east and west coasts. It was thought that singling out homosexuals for exclusion would unnecessarily stigmatize them without evidence that they were indeed transmitting the disease. The blood industry, threatened by losing a large donor pool, strongly supported the position of the gay groups on this

issue; 'three hemophilia patients with the syndrome did not mean that they should spend millions of dollars' changing recruitment and screening practices. The hemophilia groups expressed concerns that the data showing immune suppression in hemophilic patients could have reflected the effects of prolonged use of blood products and did not necessarily mean they had the new syndrome. They also feared the stigma of having a disease associated with homosexual patients and were concerned that reducing the use of clotting factor concentrates would bring back old issues of deformities and early death, the fate of hemophilic patients before concentrate treatment. The FDA, which had regulatory authority over the blood industry, had not yet accepted the collection of disorders related to immune deficiency as a single disease, and was also skeptical that hemophilic patients represented another risk group. Thus, no consensus was reached concerning blood donors.

However, two important steps were accomplished. The official name of the disease, the AIDS, was established. The new name facilitated an expansion of investigations beyond that of solely a homosexual problem. In addition, the CDC was encouraged to continue the studies of hemophilic patients [20].

In the fall of 1982, we identified four additional and one probable case of AIDS in hemophilic patients, two of whom were children. In addition, we investigated and identified AIDS in a number of individuals who had received transfusions. Invoking donor confidentiality, some blood banks severely hampered investigations by refusing to share donor lists of persons who contributed blood given to recipients who later developed AIDS. They feared we would unduly alarm or embarrass donors with sexual questions, thereby discouraging donations. Without linking an AIDS patient's donation to the recipient of a blood component, it was impossible to show transmission. Also, transfused patients often received transfusions for other underlying illnesses (i.e. cancer surgery), conditions that were possible sources of secondary immunodeficiency. As these cases accumulated, the author routinely provided briefings to the blood industry, FDA panels and NIH conferences of blood banking experts, who seemed only to request more patients and proof, without yielding on recommendations for changes in blood policy [2,12]. Frustration and impatience grew at the CDC.

During this period, we worked extensively with the NHF by providing them with current information regarding the investigations. NHF's Medical and Scientific Advisory Council (MASAC) and the MASAC's new subcommittee, AIDS Task Force, reviewed this material, made recommendations and submitted them to NHF's Board of Directors for final approval and distribution to the hemophilia community. The MASAC, recognized as an international authority on hemophilia care, was comprised of internationally known physician experts in hemophilia, well-informed hemophilic patients, and other medical personnel that staffed HTCs. Not authorized to issue guidelines on clinical care, the CDC relied on the MASAC to review new data and develop management guidelines.

During 1982, individual members of the MASAC possessed widely divergent, often strongly held, opinions on AIDS. For example, a proportion (and other imminent physicians such as Drs Oscar Ratnoff, Jeanne Lusher, Charles Abildgaard and Harold Roberts) voiced the need for immediate action to reduce exposure to concentrates, while others expressed doubt that the syndrome was a defined disease and urged NHF to ignore the issue. The situation was, and continued to be, emotionally stressful. As a result, the MASAC's recommendations were compromises, attempting to accommodate the opinion spectrum. In this divisive atmosphere, Alan Brownstein, the Executive Director of NHF, worked to keep the community united and informed of the new cases. Ultimately, the MASAC and the NHF would prove to be critical in building support for CDC studies and human immunodeficiency virus (HIV) prevention efforts in the hemophilia community and in obtaining additional Congressional funding for these efforts.

Meanwhile, the CDC's immunological studies on AIDS patients showed an extremely high incidence of antibodies to the blood-borne virus hepatitis B in affected patients and risk groups and a high incidence of circulating immune complexes in AIDS patients compared with controls (Table 2). These data suggested, in the absence of a specific screening test for blood donors, that such surrogate markers might be useful in reducing the risk to blood recipients [12].

Finally, by December 1982, we identified an unequivocal transfusion case, a 20-month-old infant who developed AIDS following multiple transfusions, including a transfusion of platelets derived from the blood of a male subsequently found to have AIDS. We were now convinced that in spite of the absence of an identified agent, the pattern of the epidemiological evidence was sufficient to implicate a blood-borne disease [21,22]. This evidence could no longer be ignored; in our opinion urgent changes in blood policy were needed to reduce the risk.

The blood-borne epidemic is defined

At the CDC's urging, the Assistant Secretary for Health, Dr Edward Brandt Jr, convened an advisory committee to address

Table 2 Frequency of abnormal tests by group. From author's personal slide collection, 1982

	Anti-HB_C% positive (*n*)	Anti-HB_S% positive (*n*)
Aids cases		
Homosexuals/bisexuals	88.2 (93)	81.9 (94)
I.v. drug users	100.0 (21)	61.9 (21)
Haitians	86.7 (15)	66.7 (15)
Others	42.9 (7)	33.3 (6)
Probable AIDS		
Lymphadenopathy	81.3 (64)	75.4 (61)
Risk group 'Controls'		
Homosexuals/bisexuals	79.2 (149)	79.5 (149)
Haitians	36.2 (116)	39.3 (107)
Normal controls	5	5

questions regarding the disease, on 4 January 1983 in Atlanta, chaired by Dr Jeffrey Koplan of the CDC [23]. Naively, we reasoned that the meeting would be routine and produce a *pro forma* stamp for action, that is, review the data, accept the evidence as significantly supporting the case for a blood-borne infection and produce recommendations that high-risk groups be excluded from the donor pool and/or adopt a surrogate test, for example hepatitis B core testing, or immune complex tests to exclude possible infected donors. Attendees at the meeting included every group with an interest in the epidemic: the American Red Cross (ARC), the American Association of Blood Banks (AABB), the NHF, the National Gay Task Force, the Pharmaceutical Manufacturers Association, The Council of Community Blood Centers, the State and Territorial Epidemiologists, the NIH and the FDA. Also attending were individuals (patients, physicians, media) with other interests.

Unfortunately, 4 January 1983 became possibly the most discouraging and frustrating day of the epidemic for CDC staff. Rather than a rational discussion of the data, the meeting quickly became a forum to advance individual agendas and 'turf protection'. In the presence of (and perhaps in reaction to) news reporters and TV cameras, each group voiced essentially the same skeptical reasoning they had at the earlier meeting in July1982. On this occasion some were less polite, sometimes attacking CDC data as inadequate and over stated. The particularly vocal blood bank organizations still strongly adhered to the philosophy that transfusions were a life saving procedure; some adverse reactions were acceptable to save a life. A 'rare disorder' that affected only eight hemophilia patients and one transfusion patient should not force a change in blood policy. Calls were to 'Show us the agent... subject it to Koch's postulates' [24]. The attendees regarded the data as only anecdotal evidence, without merit. Two views emerged. To us, the attendees' reactions seemed to be those of a group approaching an idealized science problem in an abstract world; to the audience, their position was that of a group acting as careful scientists in accordance with their training.

All attendees underestimated the already high disease incidence in the population because AIDS was obscured by a long, still undetermined incubation time. Dismissed as inadequate were our data on the high frequency of immune disorders affecting the hemophilia population that were identical to those found in homosexual patients with lymphadenopathy associated syndrome. Above all, the blood bank organizations remained unconvinced that the CDC had shown the condition to be a blood-borne disease and some FDA officials remained unconvinced that AIDS was actually a distinct disease. Dr Koplan proposed a set of consensus recommendations at the end of the day and all were soundly defeated [12].

The blood banking organizations were clearly displeased with what, in truth, was the CDC's intrusion into areas considered FDA's responsibility. The attitude was reflected in a memo from a senior ARC official that stated, 'It has long been noted that CDC increasingly needs a major epidemic to justify its existence... In short, we can not depend on the CDC to provide scientific, objective, unbias[ed] leadership...' [25]. Two days after the January meeting in Atlanta, the blood banking organizations, the AABBs, the ARC and the Council for Community Blood Banks, met in Washington, DC, to form a Task Force against AIDS and on 13 January issued a joint statement restating their opposition to donor screening using questions regarding sexual preference [26].

The NHF, shaken by the data presented at the CDC meeting on 4 January, quickly met with the blood industry on 14 January 1983 to pressure for tough donor screening of 'at risk donors'. Alpha Therapeutics had begun to screen donors in December 1982, and the other US companies soon followed; however, more than 20% of the plasma used for factor concentrates was obtained from blood banks that refused to screen on the basis of sexual preference. The NHF pressed hard for surrogate test screening without success, but did issue a number of important recommendations designed to reduce the use of clotting factor, including postponing elective surgery and using cryoprecipitate in newborns and patients without previous clotting factor exposure. Yet some vocal members of the NHF's MASAC were still unconvinced that AIDS was a blood-borne disease (or at most a very rare complication) and forced a compromise recommendation that other hemophilic patients should continue to use clotting factor concentrates unless advised otherwise by their personal physician [27].

Many of us at the CDC were dismayed by the outcome of the meeting on 4 January. No recommendations would be forthcoming from the Assistant Secretary's Advisory Committee and actions of groups present at the meeting (with the exception of the NHF) suggested that they would be happy if we were not involved in the blood transmission investigation. We decided, however, to raise the visibility of the theory of blood transmission by suggesting the US Public Health Service (PHS) issue a number of official AIDS-related recommendations on blood donations. We drafted a set of guidelines to be considered by the Assistant Secretary of Health and the other public health service agencies, thereby bypassing FDA regulatory authority. This action was clearly a breach of protocol in that the responsibility for such guidelines lay with the FDA, but we reasoned it was worth the risk of severe criticism in order to move the issue from its dead-end position. This draft included exclusion of high-risk donor groups and surrogate testing of screen donors. This draft was promptly rejected by the other agencies, but after appropriate amendments, the FDA, CDC and NIH agreed on a set of guidelines that was published by the PHS on 4 March 1983, although it was clearly short of what we, as individuals, at the CDC wanted. By this time 12 patients with hemophilia and six possible transfusion cases had been identified. The publication of these guidelines marked the beginning of a slow change in public policy on transfusion-associated AIDS.

Also in March 1983, Hyland Therapeutics of Baxter Healthcare licensed a form of clotting FVIII that had been heated in lyophilized form and marketed as a product (at a substantial increase in cost) with reduced risk for hepatitis B

[12]. Unfortunately, clinical studies soon demonstrated that the hepatitis risk was not eliminated and patients and physicians considered the process ineffective. Physicians also worried that heating FVIII would induce antigenic modifications to the FVIII molecule and increase the incidence of inhibitors, although no data supported this fear. Because of the high cost and feared risk, the product did not achieve widespread use. Soon, the other three US manufacturers of clotting factor concentrates, Cutter Biological, Armour Pharmaceutical and Alpha Therapeutics, licensed similar products as the number of hemophilia AIDS cases continued to rise [12]. By summer, AIDS appeared in FIX-deficient patients, even as doubt that AIDS was a blood-borne infection still existed in some segments of the hemophilia community, blood banking industry, physicians and FDA staff members [28,29]. At the end of August 1983, 26 patients with hemophilia and 26 transfusion recipients had been diagnosed with AIDS [12].

The epidemic ends abruptly for hemophilic patients

During mid-1983, the scientists at Institute Pasteur in Paris isolated a virus from patients with lymphadenopathy associated syndrome [30]. In February 1984, the Pasteur Institute, using CDC samples acquired from Dr Don Francis, presented data at the CDC that clearly demonstrated that their virus, LAV, was found in AIDS patients but not in the controls [31]. Dr Jean-Claude Chermann of the Institute gave the CDC samples of the LAV virus in February 1984.

Dr Steve McDougal in my division at the CDC's immunology laboratory developed an assay for quantifying the virus in various samples in spring 1984 [32]. The author discussed with Dr McDougal the urgent need to determine whether the virus was heat sensitive. If the virus was inactivated, the means was at hand to immediately stop the hemophilia epidemic. Key proprietary methodology concerning the heating process was requested from manufacturers. Behringwerke AG, a European company that used pasteurization to heat clotting factor, refused because of the proprietary nature of their information, but the details of their process were obtained from the US patent office. Dr Peter Levine, Medical Director, NHF, obtained details of the processes used by the US companies for CDC. The virus was grown in our laboratory, mixed with reconstituted concentrate, then the samples were either heated for various times and temperatures in the liquid state (Behringwerke method) or lyophilized and heated (US methods) and quantities for residual virus determined. The LAV virus was readily destroyed by short periods of heat exposure.

Three weeks later, the author presented the results of these experiments during a Hemophilia AIDS Update at the August 1984 World Federation of Hemophilia Congress in Rio De Janeiro, Brazil. Instead of immediately recommending heat-treated clotting factor, the physicians and scientists were still more concerned about the risk of inhibitor formation and wanted to see data obtained by the actual manufacturing processes. Mr Brownstein arranged a luncheon meeting during the Rio Congress with the author,

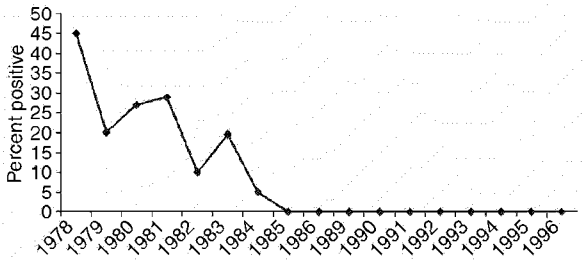

Fig. 1. Frequency of human immunodeficiency virus (HIV) infection in US hemophilia birth cohorts. Proportions of persons in each birth cohort, for whom the results of laboratory testing for HIV were available in medical records and who tested positive among 2772 males with hemophilia in six US states. Modified from Ref. [36].

representatives of the four US manufacturers, and himself. Two of the manufacturers, Cutter Biological and Alpha Therapeutics, agreed to work with the CDC to do the definitive experiments.

The author again enlisted Dr McDougal's laboratory. During September 1984, concentrate was sent to the CDC from Cutter (and later Alpha), mixed with large quantities of virus, and then the contaminated material returned to the manufacturer for lyophilization and heating (controls were lyophilized but not heated). The finished material and controls were then returned to the CDC for quantification of virus. No virus was detected in the heated samples [33–34].

Immediately on the completion of these experiments, an emergency meeting of key members of the MASAC was called to review and draft guidelines for consideration at a MASAC meeting in October 1984. At the MASAC meeting, a small but vocal minority still strongly opposed the recommendation, on the basis of high cost and the absence of clinical trials proving safety from AIDS. These voices were overruled, but the wording of the recommendation to use heat-treated factor was diluted to accommodate the minority [35]. The stronger parts of the recommendation and heating experiment results were published in the MMWR in October 1984 [33]. The world's hemophilia community quickly adopted the MASAC recommendation, so that by the beginning of 1985 little non-heated clotting FVIII was used anywhere. The AIDS epidemic in the hemophilic patients thus suddenly ceased. Subsequent studies of birth cohorts demonstrated that no hemophilic patients, born in the USA in 1985 and later, were infected with LAV, later to be renamed HIV (Fig. 1) [36]. Tragically, during the period 1981 to 1984, more than 50% of the population of hemophilic patients in the USA had already become infected and these individuals would continue to present clinical symptoms of AIDS during the next decade and many would die [37,38].

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Disclaimer

The observations expressed in this manuscript are solely those of the author, based on his personal experiences. They may or may not reflect the official opinions and policies of the Federal Agencies of the United States Government identified in the manuscript.

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