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FORUM

HIV and hemophilia

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An attempt to rewrite history

Almost 25 years after the first hemophilia patient developed clinical manifestations of HIV, a paper has been written vilifying treaters, theblood-manufacturing industry and the blood-banking industry [1]. At a time when patients with hemophilia are beginning to move forward on this terrible issue, this self-serving, inaccurate paper demands documentation and/or its correction.

Cryoprecipitate allowed surgical intervention and was used to initiate self-infusion. Its discovery made concentrate manufacture possible. Screening of all donors (no matter the source) was uniform and, at the time, followed optimal international and Food and Drug Administration regulations.

The availability of concentrate to all the USA hemophilia patients by 1972 made possible home infusions and surgeries, which emancipated patients and families [2].

The initial meeting in July 1982 called by Health and Human Services (HHS) was to determine the common thread amongst the 4H groups (homosexuals, hemophiliacs, Haitians, heroin addicts) who had developed this new syndrome. These groups were all exposed to multiple donors, had markers for hepatitis B, elevated globulins, and abnormal liver function.

The name 'A.I.D.S.' was given to this new syndrome at that HHS meeting. From that time forward, the blood-banking community, the National Hemophilia Foundation (NHF), and the National Institute of Health developed advisory groups to maintain a continued surveillance over this new syndrome, to understand its epidemiology, potential etiology, and to determine what, in particular, to tell recipients of blood transfusions. The Centers for Disease Control (CDC) was consulted and hopefully provided input to all those groups.

The advisory committee of the NHF, the Medical and Scientific Advisory Council (MASAC), met regularly to develop recommendations and provide education as this disease unfolded. The author of this paper [1] was charged with reviewing all ongoing NHF recommendations and could offer alterations at any time. This paper fails to document any advice he offered that was ignored by hemophilia treaters.

The evaluation of surrogate markers to define AIDS carriers by the blood-banking community was unsuccessful. Self-deferral was chosen, before HIV testing was available, and it was highly successful in removing infected donors when no tests were available. The CDC offered no advice that was not followed in an attempt to eliminate infected donors.

Heat treating of factor VIII was recognized to destroy HIV [3]. The first US heat-treated product was introduced in 1983 (before HIV and HIV-inactivation were recognized). There were data that showed that its intent to remove hepatitis non-A non-B by heating was inadequate [4]. These data, coupled with concerns that heating these proteins might alter them and make them more immunogenic, led the vast majority of treaters to refuse to treat their patients with this product. At no time did the CDC recommend that this product would be safer for recipients and that MASAC should recommend its adoption. The author's suggestion that there were no 'data' to support the fear of inhibitors if heated concentrates were used is unsupported by anything in the author's paper.

Treaters of hemophilia, with their patients, were challenged with available and evolving data to make therapeutic choices. Cessation of treatment, postponing elective surgery, initiating or changing to cryoprecipitate were all considered and discussed with patients, and the CDC was constantly apprised of the decisions being recommended by MASAC. All agencies and people involved did the best they could with the information at hand.

No one could have predicted that patients and treaters and the CDC would have so miscalculated the benefit/risk of this incredible treatment, which had markedly changed the lives of hemophiliacs at that time. It is unfortunate that it has taken 25 years for the author to put in writing his convictions and recommendations as to treatment alternatives (never put forward at the time) that he now asserts were not acted upon; the CDC, as an organization, never made such recommendations.

One can never argue about the virtue of revisiting history, but this is a prime example of rewriting history. Now is the time of healing, not finger-pointing. Retrospection is fine, but it needs to be accurate.

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The author states that he has no conflict of interest.

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The author graciously accepts Aledort's expression [1] of his personal thoughts on 'the tragic history of AIDs in the hemophilia population, 1982–1984' as an opportunity to re-emphasize important issues concerning the history of this era [2].

First, the historical facts and concepts that Aledort implies were grievous omissions by the author are in fact Aledort's redaction of facts and/or concepts clearly presented and well referenced in the article [2]. The reader is urged to refer to the article and its references if additional clarity is needed.

Secondly, the author specifically avoided designating 'good' or 'bad' to any proposal or decision. Instead, the author presented the documented chronology of events and the iterated basis of decisions made at the time. Subsequent events determined the soundness of those decisions.

Thirdly, rather than 'vilifying' treaters, the author carefully explained that individual hemophilia treaters held a wide spectrum of opinions concerning AIDS and hemophilia, but reached decisions about guidelines as a group (as do members of most organizations). Most of the individual treaters and the National Hemophilia Foundation (NHF) played an extremely important role in assisting the investigation and ending the epidemic. Where strong disagreements existed within the group, the author presented those positions that affected policy. The author purposely avoided naming the opposing protagonists.

Fourthly, the roles of the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), and the NHF were clearly defined and constrained by governmental policy as well as events. The role of the CDC (and that of the author) was to investigate the epidemic and, if possible, to identify a method of control. Critical to this effort was the identification of early cases (often before the attending physicians suspected AIDS) by means of requests for pentamindine distributed by the author's division at the CDC for pneumocystis infection [2]. As official policy, the CDC does not have regulatory authority of blood banks and the blood industry, nor does it make any recommendations concerning patient management of conditions such as hemophilia. Instead, it provided the results of its ongoing investigations of the epidemic to the NHF, the FDA, the National Institutes of Health and other health organizations. The role of the NHF was to assess the evolving information, issue recommendations concerning patient management, and inform their constituency; the role of the FDA was to function similarly on blood policy and regulation. The author's personal opinions were irrelevant to these processes; however, the author did describe the bases when the actions of the author and other individuals at the CDC could affect critical policy change.

Fifthly, the Medical and Scientific Advisory Council (MASAC) of the NHF made a crucial decision in October 1984 to recommend heat-treated factor; this was based solely on data developed in our laboratory in spring 1984 and in collaboration with Cutter Pharmaceuticals during the late summer 1984 [2,3]. The CDC's preliminary data on the effect of heat treatment on LAV (HIV) and the recommendations of the MASAC were published in the *MMWR Morbidity and Mortality Weekly Report* in October 1984 and widely distributed by the NHF in the US [3,4]. Also, the author provided detailed methods and results of the CDC's experiments to anyone who requested this information (nationally and internationally) in November–December 1984 and early 1985. Both the CDC's article (inexplicably rejected by another journal in early 1985) and Jay Levy's article (referenced by Aledort) on heat inactivation of HIV were published, respectively, in August and September 1985, at a time when new infections had already ceased for US patients with hemophilia [2,5–7]. In early 1985, with knowledge of the NHF's recommendations and the CDC's preliminary data, continuing to prescribe non-heated product *if heated product were available*, imposed unnecessary risks on patients.

Finally, the AIDS epidemic will not be the last human plague. Group dynamics observed during this epidemic

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replicate how experts, faced with little or incomplete scientific data, often adhere to existing paradigms rather than embrace new unproven ideas to make critical decisions. Similar responses occurred in many other major epidemics, for example, yellow fever in Cuba and the US, cholera in London, smallpox in the United Kingdom, and puerperal (postpartum) fever in Austria in the 1800s. The NHF's early recognition of risks hastened the integration of new treatment approaches that were critical to ending the hemophilia AIDS epidemic. Hopefully, faced with future plagues, decision-makers will consider new hypotheses more readily.

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AIDS tragedy: lessons learned

Evatt's historical sketch, 'The tragic history of AIDS in the hemophilia population, 1982–1984', [1] provides an excellent documentation of events as seen from his vantage point at that time as Director, Division of Host Factors, at the Centers for Disease Control (CDC).

In writing this commentary, we originally envisioned our purpose to be twofold: (i) to add some of our unique perspectives on the happenings of this period; (ii) to note an important lesson, namely, the importance of integrating public health epidemiology and clinical outcome data for improved decision-making. However, instead we decided to focus primarily on (ii).

With the introduction of clotting factor concentrates (CFCs) in the late 1960s and the nationwide development of hemophilia treatment centers (HTCs; a nationwide network of hemophilia treatment centers established in the mid to late 1970s with partial funding support from the Office of Maternal and Child Health, Health Resources and Services Administration, DHHS) offering comprehensive care in the mid to late 1970s, the treatment of hemophilia was dynamic. This network provided a vehicle through which data were collected, clinical trials were conducted and information was disseminated in relation to Acquired Immune Deficiency Syndrome (AIDS)/HIV and hemophilia. Patients with severe hemophilia, for the first time in history, were educated by HTC physicians, nurses, and other healthcare professionals to aggressively manage (at home) the 30–50 bleeding episodes they experienced every year. Bleeding-related mortality decreased substantially. People with this bleeding disorder were now able to live a nearly normal lifespan and lifestyles that allowed full and productive lives. This was the 'golden age' of hemophilia.

In contrast, in the early 1980s, the treatment of hemophilia was relatively static. Also, at this time, new public health data were rapidly emerging regarding the epidemic of AIDS in the hemophilia population. The remarkable health and lifestyle outcomes of the 1970s [2] were being challenged by a new iatrogenic disease, which, at that time, was almost always terminal (usually in less than a year).

Hemophilia patient care was driven by clinical outcome data based on new advances in medical management, which emphasized aggressive treatment of bleeding episodes (primarily with CFCs, 85–90%) and comprehensive care at HTCs. Emerging public health data, however, were driven by epidemiologic

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studies. Clinical outcome data and public health data were not fully integrated into clinical management decision-making among most opinion leaders in the medical community.

Between 1982 and 1984, it became clear that AIDS was being transmitted by a blood-borne agent, most likely a retrovirus. Although definitive scientific data (using Koch's postulates) [3] were lacking, the growing body of evidence was clear that AIDS would infect a vast majority of people with severe hemophilia in the United States. Without 'definitive' clinical data, it was important that prudent courses of action be taken based on the growing body of epidemiologic evidence.

There were therapeutic options to consider, such as:

- Continue to treat at home with CFCs (pooled source, up to 20 000 donors per treatment).
- Convert to hospital-based treatment with cryoprecipitate (single source, 10–15 bags of cryoprecipitate per episode; thus exposure to 10–15 donors per episodes and an estimated 300–500 donors per year).
- Do not treat bleeding episodes unless most severe or life-threatening.

The answers to the above options, or the risk/benefit ratios, were not readily apparent because bleeding-related mortality was greater (although rapidly losing ground) to mortality associated with AIDS (and new emerging data putting liver disease, also blood-borne, as the second leading cause of death) [4]. The enormous clinical successes in the treatment of hemophilia with CFCs and HTCs over the previous decade (the 1970s) masked the compelling importance of the rapidly growing incidence of AIDS in the hemophilia population. As a result, many physicians resisted addressing the options above. Equally important, many did not discuss these therapeutic options with their patients or their parents.

This was compounded by the vastly different interpretations and messages being given (often concurrently), by Evatt at the CDC, the Bureau of Biologics of the Food and Drug Administration (FDA), and representatives of the blood banking community (e.g. the American Association of Blood Banks, the American Red Cross, etc.).

In some instances, physicians did discuss options with their patients, and a few physicians urged patients to convert from CFCs to cryoprecipitate. Overwhelmingly, the most informed patients would not convert from CFCs to cryoprecipitate. Converting to 'cryo' was viewed as reverting to the 'bad old days', which represented two to five emergency room visits per month, crippling joint damage, missing semesters in school and not being able to hold down a job. Many patients had experienced the 'normal life' and were not willing to give that up, even in the face of life-threatening consequences.

There was seemingly little recognition that integrating public health and clinical data for decision-making has profound consequences in the following areas:

- Therapeutic options (discussed above).
- Education of patients/families.
- Regulation (e.g. donor screening, hepatitis B core antibody testing).
- Research (e.g. viral inactivation).
- Public policy (e.g. safety of blood supply).

With this as a backdrop, Evatt's paper chronicles the beginning of the tragic history of AIDS in the hemophilia population.

Fortunately, by late 1984, the blood-borne agent, LAV/HIV was identified [4–6], and was shown to be heat labile [7]. In late 1984 and early 1985, the majority of physicians treating persons with hemophilia switched their patients to heat-treated products. The last few patients with hemophilia in North America were infected in 1986. What, during the early 1980s, seemed like an enormously long time had come to an end.

What did we learn from this terrible time? We must sharpen the focus on the importance of integrating clinical and public health epidemiologic data for improved and more timely clinical and public policy decision-making, as well as communication to patients/families, the medical community and the public.

We also learned that too many lives were lost while various influential groups bickered over interpretations of emerging epidemiologic data. National agencies must cooperate for the good of mankind rather than grandstanding to maintain their turf.

Evatt eventually was able to take a leadership role, resulting in a partnership of the CDC, the National Hemophilia Foundation and its chapters, physicians treating persons with hemophilia, and the HTCs, which brought an end to this tragic epidemic.

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