CLOSING THE CIRCLE

A Thirty-Year Retrospective on the AIDS/Blood Epidemic

By

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The HIV/AIDS contamination of the American blood supply that first came to our attention approximately 30 years ago is a dark chapter in our nation's history. It represents one of the worst medical disasters in United States history. In hindsight, this preventable disaster was in part the result of bad decisions, leading to dangerous policies, and the subsequent widespread transmission of HIV/AIDS to America's hemophilia community. Over 50 percent of the US hemophilia community was infected with HIV/AIDS during the 1980s. For those with severe hemophilia, the infection rate was over 90 percent. There were also another roughly 12,000 HIV/AIDS transmissions associated with blood component transfusions (1).

The AIDS/Blood epidemic devastated four generations of families with hemophilia. But the real story predates HIV/AIDS by four decades. Pharmaceutical companies are required by law to manufacture prescription drugs and biologics that are safe and free from unreasonably dangerous defects. Despite this requirement, the blood community, from the commercial producers of blood products to the blood banks and blood centers, remained indifferent to the presence of hepatitis viruses in the American blood supply. That indifference first led to escalating transmission of hepatitis B virus (HBV) and non-A, non-B hepatitis (hepatitis C virus [HCV]) through blood and blood products, and later it set the stage for the HIV/AIDS catastrophe.

It was as if a "collective denial" spread throughout the blood community and the relevant medical establishments. It was business as usual across the blood system. The warning signals were there and yet the system continued to allow questionable, if not outright dangerous, blood collection practices such as collection of plasma from prison donors and importation of plasma from less developed countries. In fact, the collection of plasma from prisons for the manufacturing of blood products did not end until 1993 when the Food and Drug Administration (FDA) put an end to this dangerous practice. It had been allowed to flourish for over three decades.

In the hemophilia world the warning signals were growing well before the HIV/AIDS epidemic emerged. Most notably, by the mid-1970s hepatitis joined intracranial bleeding as the leading killer of persons with hemophilia. In fact, in a 1977 editorial in the Annals of Internal Medicine, two prominent hepatitis experts noted the "unequivocal evidence for the existence of chronic hepatitis in patients with hemophilia" (2). As the years progressed, the dangerous infectious disease consequences of factor usage were indisputable as HCV-associated liver disease and failure escalated in the hemophilia community.

Yet, this important warning signal did not lead to the alarms that one would have expected in hindsight. It was different from other fast moving "epidemics". This epidemic was slow-moving and plasma product manufacturers, hemophilia doctors and their factor-deficient patients alike tended to deny the risk. Instead, they continued to operate under the assumption that the "potential" transmission of hepatitis viruses was an acceptable risk given the remarkable benefits of factor concentrates in the lives of persons with hemophilia. Even the growing issue of HCV infection and liver disease in hemophilia did not result in significant changes – neither in therapeutic choices nor in what was being communicated to persons with hemophilia. The long-term risks of hepatitis-associated liver disease were hardly mentioned. Informed consent procedures largely ignored the risk of hepatitis transmission through the blood supply.

A clear understanding of the risk posed by the presence of hepatitis was not part of the process – neither for those needing an occasional transfusion during surgery nor those such as persons with hemophilia who depended on the blood supply for their survival. All involved continued to operate as if the nine hundred pound gorilla in the room, infectious hepatitis, did not warrant a more intensive assessment of the true risk it posed (3).

In hemophilia, factor concentrates were considered the "Golden Goose" that revolutionized the treatment of bleeding episodes. Concentrates brought a level of independence from the hospital and a convenience of treatment never before attained. However, given the risk of infectious diseases, the risk-benefit equation became flawed. The denial of the risk of hepatitis was deeply rooted throughout the blood community. The escalating rates of hepatitis due to HCV in hemophilia clearly indicated that something was certainly going awry in the era of factor concentrates, yet no alarms were sounded.

But, as more and more cases of serious liver disease began to surface, the risks of transmitting dangerous hepatitis viruses through blood products became well known. Unfortunately, within the walls of the commercial suppliers of factor VIII and IX, mechanisms to decrease that risk, either through selection of safer donors or post-collection treatments, were largely ignored. For example, early attempts to address the transmission of hepatitis viruses were made by Dr. Ed Shanbrom at Hyland Laboratories. Dr. Shanbrom, the first person to commercially fractionate plasma, responded to two early warning signals. One was the transmission of hepatitis to workers handling the product (4). The other was the burgeoning problem of the transmission of hepatitis to persons with hemophilia. Shanbrom spent the rest of his days working to create safer and more efficacious plasma derivatives. Unfortunately, the manufacturers of blood products chose to ignore the important early warning signals and did not adopt an aggressive approach to viral inactivation. This set the stage for the twin epidemics of HIV/AIDS and HCV in hemophilia.

Shanbrom addressed the issues at a 1996 conference of the hemophilia community in Japan where he went on to apologize to those present, "I would like to officially and openly apologize for the pain and suffering to all the hemophiliacs and their

families", adding that, "While we attempted to do good we also did harm. For this I apologize." (5).

Factor concentrate sales became a large and profitable business. In the early 1980s, just as the HIV/AIDS contamination of the blood supply was unfolding, the industry had roughly $800 million of product in the pipeline. The historical record in this industry is clear. The decisions within the companies regarding the balance of product safety and product profit can only be viewed as erring on the side of the industry's bottom line and not their customers' health.

The failure occurred at many levels. Different parts of the blood system – both regulatory and commercial - contributed to the overall failure through both their lack of timely response, and their choice of responses when they were taken. The level of caution in the choices taken by government regulators and the blood community/industry was contrary to what was warranted. Given the level of risk for those whose dependence on the safety of the blood supply was absolute, far more aggressive actions were required. Instead, cautious responses lacking the necessary urgency emerged. In retrospect, these should have served as the canaries in the mineshaft. If they had, HIV/AIDS would have never been a threat to recipient of blood and blood products.

Widespread denial blinded the entire blood system in this country - from manufacturers, to regulators, to the doctors treating hemophilia, to those living with the disease. All had lost the independence of perspective in the hype and reality of factor concentrates and their impact in the hemophilia world. All were together reinforcing the climate of business as usual. The Centers for Disease Control (CDC) warned the community. But even in the face of mounting evidence that something with grave consequences in its worst-case scenario was before the community, inertia prevailed. The community must never forget that the worst-case scenario, one of the worst medical disasters in US history, followed.

In July 1982, after the initial 3 cases of AIDS were reported in persons with hemophilia and 3 others were under investigation (6), a meeting was held in Washington, DC. Attendees included the blood and plasma collecting institutions, people from both the gay and hemophilia communities and government organizations (CDC, FDA and the National Institutes of Health [NIH]). The CDC team brought the issue of the day to the floor – the occurrence of AIDS in blood product recipients. The hope from the CDC was that logical preventive actions would be taken by the FDA and plasma and blood industries. These would include the exclusion of gay men, Haitians and drug users from donating blood or plasma, as well as possible use of surrogate tests and enhanced inactivation procedures of fractionated intermediates (7).

For a variety of reasons, little action followed. There was reluctance in the hemophilia community to be linked to this new "gay" disease and potentially lose access to factor VIII and IX concentrates that had substantially improved their quality of life. There was reluctance of the gay community to be deferred from donating blood as concerns were expressed regarding their civil rights. This occurred while the FDA staff

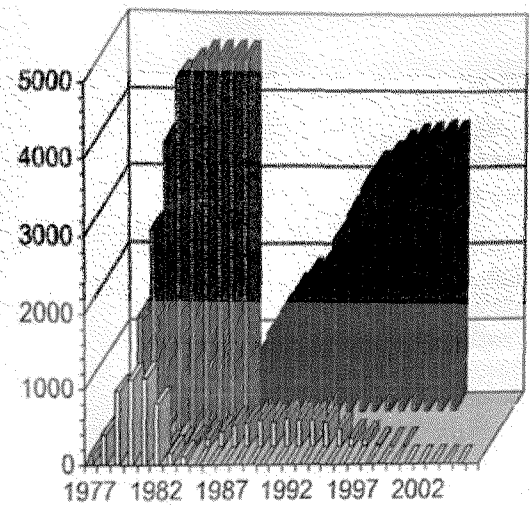
was both uninformed about the situation and overly concerned with CDC's apparent incursion into their regulatory turf (8).

At that time, the regulations required the exclusion from donating if a donor had a history of viral hepatitis or intravenous drug use. This was the case, with the exception of the production of immunoglobulin (gamma globulin), which requires donors to have a high prevalence of anti-hepatitis virus antibodies for the product to be useful. Logic and regulation required that only the immunoglobulin fraction be used from this "high risk" plasma. But the commercial fractionators were reluctant to discard the remaining fractions that could be used to make other products, most notably factor VIII and IX. This is where the pooling of source plasma to reach economies of scale for the production of multiple plasma derivatives became a much riskier proposition. In the end, it led to HIV/AIDS disaster.

In essence the most desirable donors for the production of immune-globulins (those who had been infected with multiple infectious diseases) represented a serious risk if their plasma was added to the plasma pools used to make factor concentrates. These pools contained plasma from thousands to hundreds of thousands of donors (9). The riskier donors, important for the production of immunoglobulin, were now pooled with the rest thus significantly escalating the risk of infectious diseases for those who received resulting derivatives. It was well known at the time that the new disease, AIDS, occurred in the same people at risk for HBV. Thus, adding their plasma to the pools used to produce factor concentrates substantially increased the risk of AIDS in recipients of that material. This use of high-risk donor plasma in the pools destined to produce factor concentrate is the piece of the puzzle that it took the hemophilia community years to uncover. It clarified why factor concentrate use was such a high risk for HIV infection. It answered the question of "Why" this disaster happened. It was simply the industry choosing economy of scale and profits over product safety.

By the time this was rectified, it was too late for a majority of the nation's hemophilia population (See Figure 1 below: Occurrence of AIDS in People with Hemophilia - CDC). They had already been infected. They and their family's lives became dominated by attending the escalating numbers of funerals and wakes of their comrades. The epidemic descended upon them and it was difficult to get basic information about what was occurring in the climate of fear and stigma that surrounded the HIV/AIDS epidemic in the 1980s. It felt as though their world had been turned upside down yet they were left alone as individuals and as a community to face this unfathomable nightmare.

Figure 1: Occurrence of AIDS in People with Hemophilia-Centers For Disease Control and Prevention



AIDS and Hemophilia 1977–2002. The graphs show national numbers for yearly and cumulative infection with HIV-1 and death in hemophilia. Front row bars, number of individuals infected by year; second row bars, number of deaths due to AIDS by year; third row bars, cumulative infections by year; last row bars, cumulative deaths by year. There were 3915 deaths in hemophilia nationwide at the time of this analysis; 135 hemophiliacs died of AIDS at the UNC Center. The names in the background were the 135 patients who died at the UNC Center, but have been changed to John Doe to comply with HIPAA regulations. (copyright G. C. White, II).

While the manufacturers/fractionators controlled the process of source plasma donor collection and plasma-derivative production, it was the blood banking side of the blood system that set the tone and the parameters for the screening and testing of whole blood and platelet donors. For instance, the joint American Association of Blood Banks (AABB) and NIH Transfusion Transmitted Diseases Committee consistently responded with caution regarding the adoption of HIV surrogate testing of all donors as suggested by the CDC.

From the early 1980s forward, some profound irony played out. The initial deferral of gay donors and fear in the hemophilia community of the stigma associated with AIDS left these two communities at odds during those early years. Yet, with time, the two groups came together. Indeed, it was the gay community that provided education and support for the infected hemophilia community members during the 1980s when so little was available to this devastated community.

By 1992, just as another wave of deaths came forth, the hemophilia community started to come together in a more organized manner. A stronger and more powerful community voice emerged in this period as the Committee of Ten Thousand (COTT) and others such as the California based Hemophilia HIV Peer Association, continued to educate and advocate for the community. From the beginning of 1993, community efforts were centered on providing support structures for those infected and affected,

while in Washington D.C. hemophilia community activists focused on Congress and the federal regulatory structure for the blood supply, led by the FDA.

The community's initial efforts with the regulatory structure were, at first, met with hostility or indifference to the community's plight or a little of both. This only served to intensify and clarify community initiatives and slowly there appeared what the was viewed as, "cracks in the establishment wall" that opened a space for dialogue between the hemophilia's infected and affected, and the regulatory structure which led to positive, although turbulent outcomes.

By 1993 COTT and others had raised the visibility of the AIDS/Blood epidemic and the people impacted by the crisis. Through confronting the government and the manufacturers directly, the community became agents of change rather than the victims of this disaster. As a result, the infected and affected hemophilia community built strong, grass-roots, community voice within the regulatory structure for the nation's blood supply. Through the efforts of COTT and others, Senator Edward Kennedy from Massachusetts, and then Department of Health and Human Services (DHHS) Secretary Donna Shalala, tasked the National Academy of Sciences, Institute of Medicine (IOM) to empanel a blue ribbon committee with the goal of producing an analysis of how the system failed and why so many people were infected with HIV/AIDS as a result.

Meanwhile in 1995, then FDA Commissioner David Kessler appointed a member of COTT's leadership (Corey Dubin) to the FDA Blood Products Advisory Committee. While this appointment was widely opposed by the blood community, it was another of the seeds of cooperation planted during the height of the so-called blood wars. An important step in raising the level of the interaction between those harmed by the disaster, the blood community and those tasked with regulating the nation's blood supply.

The 1995 publication of the IOM Report, "HIV and the Blood Supply: An Analysis of Crisis Decision Making" (10), was a watershed moment in the struggle of ensure a safe and available national blood supply. It provided a blueprint for improving the nation's blood system and focused on key areas where serious breakdowns had occurred. The IOM recommended where changes were necessary and warranted if the country was to greatly reduce the risk of a disaster of this magnitude occurring again. Rather than focusing on individual responsibility, the IOM looked at the failure of the different structural components of the nation's blood system and what contributed to this tragic medical disaster.

The Report stated that "The Committee concluded that when confronted with a range of options for using donor screening and deferral to reduce the probability of spreading HIV through the blood supply, blood bank officials and federal authorities consistently chose the least aggressive option that was justifiable" (11). From the community's perspective this level of caution permeated the response or lack thereof throughout this nation's entire blood system. The Report also cited the serious lack of coordination between federal agencies and a serious lack of leadership that permeated the government's response to the HIV/AIDS contamination of the blood supply.

The process of engaging the regulatory structure directly contributed to some of the most important policy discussions, including changes in technology such as nucleic acid amplification testing (NAT) and the impact this new technology could have not only on reducing risk from window period infections but also on our ability to track pathogens and other emerging threats to the safety of the blood supply. We also moved to the "Precautionary Principle" as the root guidance to the safety of the blood supply. The IOM Report stated in recommendation VI that, " While uncertainty or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm" (12)

This and other important discussions and policy directives were rooted in the IOM Report and the investigations and reports of the House Government Reform and Oversight Committee then chaired by Representative Christopher Shays from Vermont. The IOM Report and the two reports issued by the House Government Reform and Oversight Committee became critical policy building blocks for the evolving precautionary principle (13). These were important steps that served multiple ends. First and foremost, an overall improved safety landscape, especially for plasma derivatives, and secondarily, to the development of more educated and informed policies.

However, hindsight is again an important tool for understanding the past and the future and the question remains, "at what cost'? The human cost is staggering for both the infected and the affected: destroyed lives and broken families certainly represented the highest psychosocial cost. At the same time when calculating the cost of improved safety, the human cost is usually not part of the calculation. Certainly when one considers the societal costs of treating those infected and affected by a medical disaster of this magnitude, screening and testing appear to be far more cost effective as do other measures designed to reduce known and unknown threats to the blood supply.

The infected and affected hemophilia community played an important role in the IOM Report and the two Government Reform and Oversight Committee Report as well. While at times a contentious and challenging process, it served to begin the process of rebuilding trust between those impacted, the government regulatory structure and the Congress. The IOM Report also led to the creation of the DHHS Advisory Committee on Blood Safety and Availability (ACBSA) (14). For the recipient/end user community, this represented one of the most important steps that had been missing through the 1970s and 1980s, an interagency committee reporting to the Secretary of Health. While we had high hopes for the ACBSA, its history has been that of a mixed bag. At times the Committee has functioned well, producing positive outcomes. The men having sex with men deferral review in 2010 was particularly effective. There have also been periods where the Committee has floundered, appearing out of touch with the blood provider and recipient communities, as well as its client, the DHHS Secretary.

It was the hemophilia community's sincerity, hard work and commitment that eventually won the respect of federal regulators and the blood community. It was during this period that the users of the pharmaceutical products began to rebuild relationships with the key manufacturers. In addition, hemophilia community members ("consumers")

were being appointed to the relevant federal advisory committees and, thus, became full stakeholders in the process.

But those in the community who survived this ordeal would be remiss if they did not take a strong and critical eye to their own role in the unfolding events of the 1970s and 1980s. First and foremost, the community as a whole was not vigilant and not inclined to respond to things happening around it. Clearly, when CDC experts tried to sound the alarm, the community denied the risk to itself. The hemophilia community assumed that others in the system were looking out for its safety. In the end, it abdicated its responsibility to itself. Certainly there were those who asked tough questions and never really got straight risk-assessment answers. Clearly "the golden goose" of new factor concentrates did change the way the community related to its disease and the way people could live their lives. Because of these very positive changes, there followed a profound denial and resistance to change when a serious, yet mysterious, disease was put before the community. With the greatly improved clinical outcomes associated with Factor VIII and Factor IX therapy, who wanted to see the downside? Bleeding episodes had become significantly more manageable and controllable with this more targeted treatment. Think how far therapy had come since the days of whole plasma and its inefficient ability to control bleeding episodes. While limited and certainly not what the activist hemophilia community sought, it quickly became clear that with the IOM Report in hand, we now had "official" support for our demands that significant change occur.

It was in this period when the seeds of cooperation and future collaboration were sown between the organized and activist hemophilia community and segments of the nation's blood system. Although at times painfully slow, community activists were beginning to bridge the gap that existed between the hemophilia community and the components of the blood community. First and foremost, community efforts were based on COTT's conclusion that the community needed to build a more substantive and active relationship with the FDA. It is the FDA, which, through the Centers for Biologics, Evaluation and Research (CBER), possessed regulatory authority over the nation's blood supply and system. COTT has always sought a stronger and more independent FDA as a fundamental goal.

For the remaining survivors of the AIDS/Blood epidemic in hemophilia, ensuring a safe and available national blood supply continues to be rooted in understanding the colossal medical failure that devastated America's hemophilia community. Through understanding the past, the community can ensure better outcomes in the future. It can also guarantee that the federal regulatory structure is part of a larger interagency system of communication that will allow for that critical, coordinated federal response in the face of a serious and/or lethal threat to our nation's blood supply, the very coordination that was totally lacking in 1980 and was central to allowing the HIV/AIDS Blood epidemic to get away from us. Strong and coordinated public health initiatives could have and, history tells us, would have, significantly reduced the blood borne transmission of HIV/AIDS through the nation's blood supply.

For those who continue to possess, "an arm in the game", and whose dependence on the blood supply is absolute, significant progress has occurred in a

number of areas since the dark days of the AIDS/Blood epidemic. Since the 1990s the manufacturers of plasma derivatives have worked consistently to improve their collection, testing, and manufacturing of human plasma derivatives and developed recombinant clotting factors. In fact, recombinant Factor VIII and IX, introduced in the first half of the 1990s, are now enjoying widespread usage in the hemophilia community.

As we survey the American blood system in 2013, 30 years after the blood borne transmission of HIV/AIDS was confirmed at the University of California, San Francisco, Medical Center and Irwin Memorial Blood Bank, we must not become complacent due to the significant regulatory policy and scientific gains attained in that period. We must resist the influence of conflict of interest while rejecting the scientific and medical arrogance that contributed to the AIDS/Blood epidemic.

We must never forget the human cost of one of the worst medical disasters in US history. The voices of those lives lost and sacrificed must always retain their cautionary influence over our nation's regulatory perspective and policies. The advances made in both regulatory policy and science has certainly altered the blood system and its oversight. Yet, if there is a constant here it is that we must give Mother Nature her due, always preparing ourselves for the unexpected and the unforeseen. We must do this while always remaining rooted in good public health theory and practice. For, it is from here that we will construct tomorrow's roadmap for appropriate responses to emergent threats to the blood, organ and tissue supply of our nation.

The hemophilia community is committed to "closing the circle", and is eager to work together with FDA and blood and plasma communities to remain vigilant to evolving risks and assure willingness and capacity to respond quickly. A strong and independent regulatory system for the nation's blood, tissue and organ supply, coupled with responsible leadership in the larger blood community, can ensure the highest level of safety attainable and commensurate with the threats it is designed to contain. Yet safety will never be an absolute; it is only as good as the human beings on the frontline and the guidance under which the system is regulated.