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INFLECTION POINTS

TRANSFUSION

A novel virus transforms blood transfusion

This is the first in a series of periodic commentaries by leaders in transfusion medicine reflecting on transformational events in their careers.

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It is a privilege to submit the first in a series of invited opinion papers describing events that transformed Transfusion Medicine. Transformative events or "inflection points" exist largely in the mind (and personal experience) of the beholder. As we confront new challenges during the evolving COVID-19 pandemic, I considered it particularly fitting to reflect on an earlier "event" that changed blood transfusion forever—the emergence of HIV-AIDS.

AIDS influenced virtually every aspect of blood transfusion, from donor screening and testing, to transfusion practice, regulation, research, and the ethics of blood transfusion. I shall describe a few examples below.

During the 1970s, blood safety focused almost exclusively on hepatitis viruses. Few transfusion experts foresaw the emergence of some totally new pathogen, let alone one that manifested itself through extreme immunosuppression.[1] No single observation or publication led to the realization that a novel agent with a long incubation period and a frightening mortality had crossed the species barrier and entered the blood supply. Whereas the emergence of AIDS cases in patients with hemophilia suggested that something new and different was happening to transfused patients, I date my personal epiphany regarding transfusion-associated AIDS to two publications. The first was a CDC report of a newborn infant who received multiple transfusions and who subsequently acquired severe cellular immunodeficiency and multiple opportunistic infections.[2] One of the blood donors turned out to be a man subsequently diagnosed with AIDS. The second publication, 2 years later and more convincing, was a summary of AIDS cases that CDC investigators associated with transfusion.[3] A year earlier, I had argued with the senior author of that paper, a friend and former fellow house officer, that the evidence failed to convince me that a transmissible agent could cause AIDS. Shortly thereafter, in a meeting in Atlanta in January 1983, CDC epidemiologists warned representatives of several blood-banking organizations that blood donations were likely infectious.[4] For me, confirmation came from a sometimes-overlooked transmission study in a non-human primate performed by investigators in my own institution.[5] The lessons—show humility when arguing with someone who has access to more data than you do and find a way to test their hypothesis. Today we are almost too sensitive to the possibility that novel or emerging exotic agents pose transfusion risks.

1 | BLOOD DONATION AND DONOR SCREENING

Prior to the AIDS epidemic, blood collectors doubted that volunteer donors would tolerate questions about sexual orientation. Initially, donors were provided an information sheet that aggregated HIV risk factors to be read and acknowledged. This proved to be a halfway measure. Eventually direct donor questioning regarding "sensitive" issues became an accepted standard. There is little evidence that this practice either offended or discouraged blood donors. This is an important lesson as blood collectors are currently considering questions involving risk practices which some consider even more sensitive and intrusive.

An additional consequence of the new screening policy was the indefinite exclusion of a class of prospective blood donors, males who have had sex with

other males (MSM) even once since 1977. This rule persisted unchanged for almost 40 years and raised a question of social justice. Only recently has this policy been revisited.[6]

2 | DONOR TESTING

Prior to the AIDS epidemic, infectious disease testing of blood donors relied on specific serologic tests and surrogate assays. In 1994, then Food and Drug Administration (FDA) Commissioner David Kessler organized a public workshop in the Masur Auditorium of the NIH Clinical Center. Kessler insisted that to ensure blood safety, direct screening tests for HIV viral nucleic acid needed to be developed and implemented. Most attendees considered this an almost impossible objective. I listened as participant after participant rose to state that the polymerase chain reaction (PCR) was too sophisticated to adapt to a screening assay, too complicated to be performed by blood centers, and too costly. I attribute the revolution in donor screening technology to the concern about AIDS and the constant pressure of the regulatory agency.

3 | TRANSFUSION PRACTICE

As information accumulated indicting transfusion as a vector for HIV, and well before the licensure of the first screening test in 1985, the public lost confidence in the safety of blood.[7] As a result, patients (and physicians) were far more circumspect about blood transfusion. Red cell use plummeted. Autologous blood collection proliferated. Patients refused blood transfusions or demanded that their blood come only from friends and relatives whom they deemed, incorrectly, as it turned out, completely safe. One unanticipated positive outcome was the initiation of studies that defined a scientific basis for the different autologous transfusion strategies.

An additional important advance was the rapid development and licensure of pathogen-reduced clotting factor concentrates Factors VIII and IX. Several manufactures had already developed promising technology, possibly years earlier, but the infection and death of 95% of patients with severe hemophilia, and the ensuing public outrage, likely spurred commercializing the processes.

4 | REGULATION AND ACCREDITATION

Arguably, the most far-reaching post-HIV changes for blood centers involved the decision by the FDA to regulate blood programs with the same rigor as it regulates pharmaceutical manufacturers. Institution site inspections conducted by a strengthened Division of Compliance became more frequent and less collegial. The FDA Commissioner emphasized the role of the agency as policeman and enforcer.[8] Blood centers experienced an increase in penalties and license suspensions, and at one point in time institutions under federal consent decree collected more than 90% of the blood in the US. The change in the regulatory environment had major consequences for blood center economics and for non-federal accrediting organizations as well as for blood safety.

5 | RESEARCH

The AIDS epidemic resulted in at least two major changes in the Transfusion Medicine research enterprise. On the one hand, instituting quality programs and regulatory compliance was expensive, and many independent community blood centers reduced or eliminated locally funded research budgets. During the 5-year period following the hiring of the first compliance officer at the Sacramento Blood Center some 24 personnel were hired for compliance and Good Manufacturing Practices activities. At 5 years, Sacramento was spending more than a million dollars a year on these activities.[9]

On the other hand, the AIDS epidemic spawned the single most important NIH-funded research initiative in blood transfusion, the Retrovirus Epidemiology Donor Study (REDS) sponsored by the National Heart, Lung, and Blood Institute (NHLBI).[10] Now more than 30 years old and in its fourth iteration, REDS multicenter programs have published seminal studies on improving blood safety and availability in the United States. REDS II included international study sites in Brazil and China. Highlights included development of mathematical modeling, large-scale donor surveys, innovative methods of repository sample storage, and establishing an infrastructure to respond to potential emerging blood safety threats. The fourth iteration includes research with newborns, children, and pregnant women.[11]

6 | PUBLIC POLICY

Numerous changes in blood policy in the US and internationally emanated from the federally-commissioned Institute of Medicine (IOM) Report.[6] Still other policies were developed in reaction to the hundreds of lawsuits in the US and the criminal proceedings in a number of countries including Canada and France. Canada reorganized

its entire blood system as a consequence of the Royal Commission of Inquiry on the Blood System in Canada (Krever Commission).[12] The Krever Commission report endorsed a precautionary approach to public health that recommended taking action rather than waiting for high-level evidence and scientific certainty. The Precautionary Principle, with its many definitions and interpretations, created a cottage industry of risk management conferences, seminars, and decision-making processes. Blood collectors have expended enormous energy and resources on rapid responses to perceived emerging threats, some like the West Nile and Zika viruses readily justified, whereas others, such as vCJD and XMRV arguably less so.

7 | LESSONS LEARNED

There are numerous lessons that Transfusion Medicine can learn from the AIDS epidemic. My personal list includes:

1. Blood donors will answer very sensitive/intimate questions if they believe that compliance will increase transfusion safety. We should investigate, not prejudge, their compliance.
2. New and unimagined infectious agents from animals or from laboratories will continue to appear. We have already experienced vCJD, SARS, MERS, and SARS-CoV-2.
3. Novel technology should not be rejected out of hand because it appears difficult or expensive to introduce.
4. Data should trump expert opinion. Follow the data.
5. Regulation, while imperfect, plays a major role in protecting the blood supply and the professionals who provide blood for transfusion.
6. Community voices are critical in developing transfusion policy.
7. Blood providers, blood donors, and transfusion recipients function ideally as partners and not as adversaries.
8. Research continues to play a critical role in any rational approach to public health and blood safety.
9. The Precautionary Principle is a double-edged sword.

Finally, circumstances change with time, experience, and research. We should not hesitate to modify or reverse practices as times change.

The opinions expressed are those of the author and do not represent the views of the National Institutes of Health, the Department of Health and Human Services, or the U.S. Federal Government.

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