

## Where now for transfusion: the evolution of a paradigm and its logical progression

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The development of transfusion over the past century and a half has been described as one of the blessings of modern medicine. But, in some ways, it is emerging as a decidedly mixed blessing, bringing epidemics as well as improved health. Given all the practice has been through, now is the right time to take a critical look at blood transfusion as it is practiced today, and whether it serves the individual patient as effectively as the interests of those who administer it.

### INTRODUCTION—REFLECTIONS ON THE EVOLUTION OF BLOOD TRANSFUSION

*From its experimental beginnings, the blood and plasma industry has grown to become a global enterprise because of three key developments: typing, fluidity and plastic bags. But those developments had ramifications: they encouraged the use of component therapy over whole blood and an over-riding concern for maintaining inventory.*

The mystique accorded to blood over the ages led to several attempts to transfer its properties through transfusion.<sup>1</sup> Despite numerous attempts throughout history (such as, the questionable practices of Denis and Blundell) transfusion could only become a mainstream practice after Landsteiner's discovery of the main blood group system and Lewisohn's development of nontoxic anticoagulants. The gradual evolution of the recognition of hypovolemia as a major contributor to shock and a cause of mortality in battlefield injury<sup>2</sup> led to the first blood banks in the First World War<sup>3</sup> and the Spanish Civil War.<sup>4</sup> Although virtually unnoticed in the West, the Soviet Union's use of cadaveric blood probably constituted the first blood bank network.<sup>5</sup> Yet even these advances led to deleterious effects. During the Second World War an over-appreciation of the role of plasma—the first “blood component”—led to an overuse of plasma in lieu of whole blood for patients with life-threatening bleeding, resulting

in unnecessary mortality until the need for whole blood transfusion as a resuscitation medium gained renewed appreciation.<sup>2</sup> This supplantation of blood by a component, with its unfortunate consequences, represents the first example of poor clinical transfusion outcomes due to mistaken or incomplete physiological principles, based on what was known at the time.

Following the Korean war, the gradual availability of plastic bag technology, with its capacity to produce sterile blood components through closed fluid paths, contributed to the wholesale adoption of blood component therapy, but it did not tip the balance by itself. Even after the switch from glass bottles to plastic bags, concentrated red blood cells (RBC) were only used for severe cases of otherwise normovolemic anemia. Until the early 1960s the majority of transfusions, whether for medical or surgical interventions, were given as whole blood.<sup>6</sup> But over the following decade two principal developments changed this situation. In 1965, Judith Pool published her method for producing concentrated antihemophilic factor VIII (cryoprecipitate) in blood banks, use of a closed double plastic bag system which permitted the use of the cryoprecipitate-poor blood or the use of plasma and RBCs.<sup>7</sup> This led to a huge demand for this product, which revolutionized the treatment of hemophilia A in the developed world. Meanwhile, developments in RBC preservation through replacement of plasma by novel additive solutions allowed RBCs storage to be extended.<sup>8</sup> This need

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to extend shelf-life was especially felt in the United States.<sup>9</sup> Titmuss argues that the system's inefficiency at this time was due, to a significant extent, on its dependence on paid donors, which affected its capacity to manage properly its inventory.<sup>10</sup> This led to a high rate of RBC expiry, spurring efforts to prolong RBC storage periods.

These developments ensured that by the end of the 1970s<sup>6</sup> the majority of blood donations were separated into RBCs and plasma, or RBCs, plasma and platelets as developments in platelet storage allowed harvesting of the latter.<sup>11</sup> In subsequent years, as blood banks introduced higher levels of manipulating donated blood, they evolved into manufacturing units, generating an inventory of stored components. The not-for-profit (NFP) status of most blood banks, using (with the exception of the United States until the early 1970s), voluntary donors, contributed to their relative insulation from the oversight of regulatory agencies. The result was the development of a dual blood-related economy<sup>12</sup>: a gift economy overseeing the procurement of a voluntarily donated raw material, and a market economy based on the provision of manufactured goods, including plasma for fractionation harvested from the donated blood and sold to commercial fractionation companies.

*These two economies battled for the soul of transfusion over the next 30 years, but the emergence of a patient centric paradigm, as we propose further on in this review, will contribute to an effective synthesis which combines the recognition of the unique nature of the donors' gift with the realities of evidence-based health care.*

## CATASTROPHE FOLLOWS COMPLACENCY

*Things seemed to be going well for the transfusion industry until the AIDS crisis intervened. Beyond exposing a general vulnerability, the epidemic revealed fault lines between epidemiologists and blood bankers, and between the interests of donors and those of recipients. So it should be no surprise that even after AIDS was dealt with the system had to deal with another painful crisis in the form of hepatitis C transmission. While lessons have been learned, a particularly important one—the precautionary principle—has only partially been applied.*

The seemingly trouble-free progression of blood transfusion to an exalted, altruistically based and safe therapy ground to a halt in the early 1980s as a result of the AIDS crisis. These events have been extensively documented by one of the authors,<sup>13</sup> and other work has commented about the fault lines in different blood systems which led to these crises.<sup>14</sup> We view these events as resulting from a convergence of diverse factors. The development of blood systems as providers of manufactured therapeutics basically without adequate oversight led, in the most instances, to a system of self-regulation, which was unprepared for the challenges of the AIDS epidemic.

The recognition that any measures taken to decrease risk, initially, had to be based on deferring whole social groups and hence would possibly curtail supply delayed the required actions.

A particular example of the various tensions in play during this period bears scrutiny. As the players involved in the issue came to grips in the United States over the crucial years 1982-83, a divergence emerged between the scientific cultures of the Centers for Disease Control (CDC) and the blood establishment, with the Food and Drug Administration (FDA) providing a weak and equivocal series of requirements. The CDC, whose epidemiologists could see the clear signs of a growing epidemic from their discipline, were unable to influence in a timely fashion the blood establishment who being unused to grappling with epidemiological issues, continued to underestimate the risk through inept interpretations of "a one in a million risk."<sup>15</sup> In addition, the blood establishment adhered strongly to the interests of blood donors, frequently articulated through donor associations, which delayed the necessary deferral and communication strategies needed to exclude the high risk groups associated with AIDS. This combination of factors led to continued obfuscation in the crucial period; as late as early 1985, the former chair of the FDA's Blood Products Advisory Committee, and himself a prominent blood banker, was expressing resistance to mandatory donor selection based on sexual history.<sup>16</sup>

The relative lack of oversight and accountability for blood systems ended with the HIV crisis and the blood scandals, although residual deficiencies were to contribute to a second wave of infections involving hepatitis C (HCV) in the 1990s.<sup>17,18</sup> These incidents greatly impacted the blood establishment and led to closer oversight of blood services, more akin to that of pharmaceuticals. The establishment and strengthening of a regulatory framework for blood<sup>19</sup> was strongly recommended by the various inquiries set up to examine the viral epidemics. The urgency of the problems did not permit prolonged reflection on how this was to be done. The agencies with the required legal mandate had little experience or expertise in this product. Any expertise was nearly all located within the industry. The inclusion of such experts within the advisory bodies of the FDA, for example, drew concern from the inquiry conducted by the Institute of Medicine which was commissioned by the US Government to investigate the transmission of HIV by blood in the United States.<sup>20</sup> The convergence of urgency and restricted expert input contributed to the regulatory agencies' adoption of, essentially, traditional frameworks for the oversight of the blood system, based on the well-established principles of pharmaceutical good manufacturing practice (GMP), which had been introduced for plasma fractionation products in previous decades. In addition, the problems of infectious disease risks ensured that, in this area at least,

the authorities and the blood systems adopted a strict interpretation of the precautionary principle already in place in European law<sup>21</sup> to guide decision making on issues underpinned by uncertainty.

We suggest that the interpretation of the principle by the blood systems and their overseers has been limited, both in scope and in application. The application of the principle to the whole range of adverse effects of blood other than infectious disease has been modest. Concurrently, little effort has been made to review and if necessary, revise or remove measures once scientific developments made them outdated, as the principle advocates.

In tandem with, and partly consequential to the establishment of these frameworks, the blood systems and guiding bodies, such as, the World Health Organization<sup>22,23</sup> continue to undervalue whole blood for transfusion when appropriate, while cementing in place the use of separated, stored, components.

In addition, blood banks morphed into manufacturing units separated—from the clinical units use of the blood—structurally, organizationally and, in many instances, geographically. This has partly happened as a result of the requirements of GMP, which favored the establishment of large, centralized centers for the collection and processing of blood units. This contributed strongly to a culture in which the maintenance of inventory is emphasized as the end, rather than a means, of the blood-banking process.

*Although these developments contributed to the detachment of transfusion from the clinical environment, they also eliminated the complacency which had reigned previously regarding the safety of blood. The introduction of a pharmaceutical paradigm has enhanced the safety of blood, albeit at a cost.*

### CONSEQUENCES OFFSHORE

*Our policies of exporting our blood bank philosophy to the developing world, may be harmful. In many of these countries other modes of procurement, such as, family donation may be more appropriate. Also, given the reduced needs of component therapy in many instances, the abolition of fresh whole blood is against patient interests.<sup>24</sup> Are we practicing neocolonialist transfusion?*

We summarize the current dominant paradigm in Table 1. Regrettably, this paradigm also forms the basis of assistance programs to burgeoning transfusion activities in emerging countries. The principles underlying the support of programs, such as, the US President’s Emergency Plan for AIDS Relief include commitments and performance metrics linked to centralization of blood services, the use of voluntary nonremunerated blood donors and conversion to blood component therapy.<sup>25</sup> The increased costs linked to centralization of blood services in an envi-

**TABLE 1. Features of the current transfusion paradigm**

Component therapy
Centralized blood establishments
Infectious disease as the main risk
Inventorism
Detachment from clinical environment

ronment supported by minimal infrastructure have been shown to triple the cost of blood.<sup>26</sup> This concern increases when the issue of sustainability of such programs is considered, following the termination of the prescribed contracts, as shown in Kenya where workers hired for the program had to be laid off at its termination, despite a continuing need to improve their blood services.<sup>27</sup> Imposing Western notions of the ethics of blood donation through mandating voluntary donation also presents risks if this results in the exclusion of the safe and culturally integrated practice of family donation.<sup>28</sup> In an era when the Western blood systems are increasingly emphasizing the appropriate use of blood products, it is important to recognize the different transfusion patterns between wealthy donors and the recipient countries. This is especially reflected in the majority of transfusions being given, appropriately, as whole blood in these recipient countries.<sup>24,29</sup> Imposing component therapy is hence unwise and counterproductive to the development of sound and modern transfusion practice.

*The introduction of Western transfusion methods in emerging countries may have untoward effects. However, an enhanced awareness of the benefits of decentralized blood systems may also benefit the donor countries.*

### THE EMERGENCE, AND ESTABLISHMENT, OF “TRANSFUSION MEDICINE”

*Meanwhile, the emergence of an academic discipline—“Transfusion Medicine”—in the past 30 years has introduced academic rigour to the sector. But it also threatens to create a body of academics invested in the status quo and resistant to change.*

As we have discussed above, the industrialization and consolidation of transfusion practice to GMP-driven centralized blood “factories” since the 1980s has contributed to a detachment from clinical medicine as, increasingly, blood systems have become passive purveyors of remotely manufactured blood products. One of the authors (Albert Farrugia) currently works in Italy after extensive experience in the Australian blood system. The Italian and Australian blood systems represent diametrically opposite poles with the Italian system’s continued embedment in the public hospital system,<sup>30</sup> contrasting with the Australian system of one blood center in each of the Australian states, dispensing blood products to remote clinical

outlets.<sup>31</sup> There are pros and cons in both systems, but there is little doubt that the Italian system is more closely integrated to the medical environment.

Somewhat ironically, the detachment of blood transfusion from clinical medicine has been accompanied by the institutionalization of the field as a new medical specialty—"Transfusion Medicine." Having emerged in the 1970s and 1980s, this discipline has assumed all the trappings of the other areas of academic medical commodification, including journals, conferences, and university departments with dedicated Chairs. The research achievements of this endeavor have been commendable and extensive. Significant work has gone into validating and extending the storage lives of donated components, developing extended algorithms for infectious disease testing, and introducing increasingly sophisticated donor questioning techniques etc. This body of work has widened the intellectual capital of the transfusion community, but much of it supports the current overemphasis on inventory and infectious issues. As these areas assume less relevance to patient-centered issues, it is possible to note encouraging examples of research efforts questioning the primacy of inventory over patient needs. These may well contribute to reforming the transfusion system. In the interim, it may be well to ponder on the probable tensions emerging from the generation of a possibly elitist, hubristic, medical specialty, with the resulting dangers of elitism and resistance to change.<sup>32</sup>

*The increasing "academification" of transfusion has brought benefits, particularly in the development of rigorous research methodology which may be usefully applied in more patient centric applications than has hitherto been the case.*

### THE DIVERGENT POSITIONS OF DIFFERENT BLOOD PRODUCTS—PLASMA DERIVATIVES VERSUS BLOOD COMPONENTS

*Even though plasma products have to pass muster as both safe and efficacious, transfused components have only had to show safety and basic recovery in the circulation. The question of their effectiveness has always been assumed, and has been "grandfathered in" for regulation and use. This contrasts with the products of fractionation.*

The industrial manufacture of plasma derivatives draws from both whole blood donations and from collections by apheresis for its raw materials. Plasma "recovered" from voluntarily given whole blood donations and sold on the open market represents an important source of income for many blood systems and hence influences the maintenance of the current paradigm. In some countries, a commitment to national self-sufficiency in blood products results in an effort to source all plasma for manufacture from domestic blood donors.

We note that an overzealous and unaccountable adherence to such a policy underpinned the events around the blood scandals in Canada and France.<sup>14</sup> The bulk of fractionated plasma globally, however, is obtained through apheresis of paid donors, mostly in the United States, through collection centers integrated into the main fractionators.

Plasma derivatives, although extracted from blood, have had a tenuous and uneasy position in the transfusion paradigm, having arisen primarily outside the transfusion systems. Although the plasma harvested for Cohn's albumin fractionation during the Second World War was primarily obtained from whole blood donors, soon after the war the fractionation industry came to rely on material from collection centers outside the mainstream blood system. The demand for albumin and, from the 1960s, for factor VIII, increased the requirements for plasma and generated a collection industry supplying the growing number of fractionators. This industry was subject to regulation earlier than the transfusion sector. Although this did not prevent the transmission of infectious disease and other problems, in the early stages of the AIDS epidemic, when behavior-based donor deferral was the only apparent risk reduction measure, the plasma industry in general took action earlier than the transfusion sector.<sup>20</sup> Due to the large number of donors contributing to industrial plasma pools, mass HIV epidemics, particularly in hemophiliacs, occurred, and transmissions continued until effective viral inactivation processes were in place, even from pools screened with the first available HIV tests.<sup>33</sup> Following the development of further inactivation steps for HCV, these patients have been free from new infections for the past 25 years,<sup>34</sup> while transmissions of HIV to transfusion recipients have continued, sporadically, over this period.<sup>35,36</sup>

Another divergence between plasma derivatives and transfusion components lies in the extent of regulation. In contrast to the plasma products industry, which has to prove therapeutic efficacy against specific claims for its products, the labile blood component sector faces no such oversight. A historical assumption that these products are inherently efficacious and the insulation of transfusion medicine from evidence based medicine (EBM) have, until recently, contributed to a lack of attention to these aspects. The only criteria formally in place specify the required recovery in the circulation of transfused RBCs and platelets. Twenty-four hours post transfusion of the RBC product 75% of the transfused RBCs need to be in the circulation,<sup>8</sup> and the recovery of platelets at the end of a requested shelf life has to be 66% of fresh platelets.<sup>37</sup> By pharmaceutical standards, these are modest criteria, but proposals by regulators to enhance them are not well received by some parts of the blood industry.<sup>38,39</sup> The possible burden of permitting the presence of up to 25% of effete RBCs has been noted.<sup>40</sup>



There are no other current requirements to assure that these measurements of recover in the circulation are predictive of patient outcomes. This would require different measurements more relevant to clinical outcomes. Unfortunately, these have not been applied so far. The physiological function of RBCs—oxygen delivery to the tissues—is influenced by the deformability of the RBC<sup>41</sup> and by the affinity of hemoglobin for oxygen,<sup>42</sup> both of which can be measured. The hemostatic function of platelet concentrates can be assessed by the platelet function analyser.<sup>43,44</sup> Use of these parameters and others requires considerable work in validation and standardization<sup>39</sup> but would provide a specification for these transfusion products that may be the basis for evaluating efficacy.

Reflecting further on the respective environments involving the production of blood components and plasma derivatives, we conclude that the requirement for GMP is clearly appropriate for plasma derivatives. It is less appropriate for hospital-based manufacture, and blood component production in general has moved away from such an environment. Hospital-based practices are subject to standards, such as, those of the International Standardization Organization, which are suited to the routine practice of hospital-based blood transfusion centers. This poses a regulatory problem in which two different sets of standards apply to the fractionation products, depending on whether the plasma was harvested at a collection center or as part of a whole-blood donation at a hospital. It is difficult to envisage two different quality standards for transfusion components and fractionation raw material. This issue is the basis of much of the problematic aspects of GMP in blood banking, and we suggest that it provides one of several drivers to focus fractionation plasma collection on apheresis collection and away from mainstream transfusion needs.

*Absorbing the efficacy component of the regulatory paradigm will enhance the evidence base for transfusion and benefit patients, if approval agencies recognize the particular features of transfusion practice which limit the applicability of mainstream drug development principles.*

## INVENTORY VERSUS PATIENT

*The preoccupation with inventory has led to a certain blind assumption about the effectiveness of transfusion. New studies are now questioning that assumption. They are finding that red cells lose their effectiveness more rapidly than previously realized, as do platelets, while the use of plasma is increasingly unjustified.*

With the rapid detachment of much of the transfusion activity from the clinical to the pharmaceutical model, many aspects of product use have been made subservient to the needs of the system rather than those of the individual patient. As discussed above, the practice of component therapy originated partly in response to the

needs of hemophilia and other fractionation activities directed toward relatively small patient populations, when compared with the main transfused population. In addition, maintaining RBC inventories led to the removal of plasma from the majority of blood donations, to allow suspension in additive solutions designed to prolong storage. As discussed, this occurred against the background of satisfying pharmacokinetic criteria detached from physiological function. As the needs of the inventory grew, the policy of first in, first out ensured the transfusion of considerable amounts of aged RBCs and the quasi extinction of fresh blood as a transfusion modality.

A number of randomized clinical trials (RCTs) have been performed to address the issue of RBC storage effects. Their results are now available and have generally found that clinical outcomes with stored RBCs are similar to those with fresh cells.<sup>45-47</sup> The results of the three large RCTs have alleviated some of the concerns regarding stored RBCs. We suggest that this may be tempered with an appreciation of Bradford Hill's criteria,<sup>48</sup> according elements to assigning causality which supplement a statistical determination. Hill proposes that such a determination, in itself, cannot answer these questions, and we concur that consideration of Hill's criteria of plausibility and coherence (mechanism) generated by the considerable body of experimental data indicating possible harm from stored RBCs should also be included. We note some similarities between this controversy and the long-standing issue of universal leucocyte reduction (ULR), which bedevilled transfusion for many years. The introduction of ULR was not supported by several RCTs designed to address the putative benefits suggested by experimental data, but its eventual introduction is widely recognized as having enhanced the quality and safety of blood transfusion. Despite a dearth of RCT-driven evidence, ULR has become a standard for transfusion. We would encourage consideration of this example, as well as recognizing the continuing uncertainty on the issue of RBC storage length.<sup>49,50</sup> It may be that any concerns based on the presumption of a change to current inventory management systems may be better addressed through more inventive approaches utilizing sophisticated information technology, capable of shortening the shelf life with minimal loss.<sup>51</sup> For example, Atkinson et al.<sup>52</sup> have shown that an allocation policy of transfusing blood with a storage threshold of 14 days, while leading to a decrease in the age of transfused blood of 10-20 days, may be introduced with minimal increases in the need to supplement the RBC inventory through importation. Similarly, one Australian transfusion service has a minimize platelet expiry through a collaborative platelet inventory concept comprised of moving Day 4 platelet blood stocks from low usage sites to high usage sites and then sharing a common multisite near expiry Day 5.<sup>53</sup>

The demand to maintain inventory affects other components in addition to RBCs. The hemostatic capacity of platelets deteriorates progressively over storage.<sup>54</sup> Platelets are stored at 22°C to minimize cytoskeletal protein alterations occurring at refrigeration temperatures, which result in sharply decreased survival.<sup>43</sup> This feature has determined the conditions of platelet storage, despite the superior hemostatic properties of cold-stored platelets,<sup>43</sup> as such a decrease in survival may increase the required transfusion frequency with all its possible sequela of adverse events and negative impact on inventory. The 5-day shelf life currently granted to platelet storage systems may be extended to 7 days if bacterial testing assures sterility,<sup>55</sup> despite the demonstrable inferiority of 7 versus 5 day platelets in both hemostatic capacity and the established kinetic parameters.<sup>56</sup>

Fresh frozen plasma (FFP) transfusion, while languishing in the dubious status of the least evidence-based of the component modalities,<sup>57</sup> has also been affected by the inventory paradigm. The perceived need to avoid discarding FFP thawed for emergency transfusion but subsequently unused has seen the emergence of “banking” thawed FFP, with the attendant features of other types of component banking. The scientific rationale has focused on the maintenance of an adequate level of coagulation factors measured in such stored, thawed plasma,<sup>58</sup> despite the finding that thawed banked plasma has less thrombin generation capacity.<sup>59</sup> Focusing simply on hemostatic also does not consider the progressive loss of other factors, such as, the maintenance of endothelial integrity in shocked patients,<sup>60</sup> which may have higher importance in FFP transfusion than the contribution of coagulation factors.

In all these aspects, we note the emphasis in the majority of the transfusion literature and in the relevant policy documents on the need to maintain inventory levels. As the emerging patient blood management (PBM) paradigm becomes more established, with its already visible effects on decreasing the use of blood, we would hope that the blood establishment feels more relaxed in ensuring that the quality of patient-relevant properties supersedes the need for fully stocked shelves of components with storage lesions.

Citing Vamvakas,<sup>61</sup> we propose these pillars of a patient-centric transfusion paradigm:

*PBM versus blood component therapy:*

Each patient's transfusion needs are met through an individualized combination of approaches aimed at avoiding as many allogeneic donor exposures as possible

*Focus on the individual patient (vs. on the component):*

Our focus is not on the quality of the component but on the quality of the medical service that we pro-

vide each patient through optimally combining PBM modalities

*Primacy of individual needs (vs. primacy of inventory):*

The overriding concern is not to avoid blood shortages but to reduce the transfusion risk for each patient to a level as low as is reasonable achievable.

This paradigm should also feature the inclusion of patients to share the decision-making process involving transfusion versus alternative approaches,<sup>62</sup> through informed consent of all the issues. Any concerns from the funding authorities regarding the costs of such a program may be alleviated through the demonstration of the decreased transfusion rates achievable with equivalent clinical outcomes<sup>63</sup>

*Augmenting the results of RCTs with a consideration of biological mechanism and plausibility will align transfusion more closely to the principles of causality assignment and support precautionary measures to minimize harm, in the current period of continued uncertainty on the effect of the red cell storage lesion. These principles will form part of a patient-centric transfusion paradigm.*

## EMPIRICISM, PRECAUTIONISM, AND THE BLOOD INDUSTRY

*While increasing the evidence for transfusion is welcome, important safety questions should give a higher importance to the precautionary principle. The statistical application of randomized trials to transfusion should not take precedence over patient safety. Patients deserve the benefit of the doubt.*

EBM arrived late in blood transfusion, but its peak instrument—the RCT—has now been used to address a number of important questions, including the evidence base of blood component dosage.<sup>64,65</sup> The RCTs regarding the fresh versus old blood issue mentioned above constitute an application of EBM, exemplifying this community's adherence to empirical data over other forms of experimental evidence. The scientific assessment of the blood storage lesion leaves little doubt on the issue,<sup>66</sup> but the RCT has spoken.

Or has it? The EBM paradigm guiding therapeutic decision making is being supplemented, if not supplanted, by the growing application of personalized medicine and patient-centered care.<sup>67</sup> Parameters involved in oxygen delivery, such as, RBC deformability show significant variability between patients in different disease states,<sup>68</sup> while inter-donor variability is evident in the mechanical fragility and autohemolysis of donated RBCs.<sup>69</sup> This suggests that a closer alignment between donor and patient features may lend itself to improved

outcomes in RBC transfusion, providing a better guiding therapeutic principle than epidemiologically driven RCTs.

In view of the tensions of the EBM construct with individual patient interests, we propose at least as vigorous a consideration of the other principle which has influenced the transfusion sector over the past 20 years, the precautionary principle. Although possibly unintentionally, this was best captured, in relation to the infectious disease risk which by then was absorbing the current paradigm, by the report of Justice Krever on the debacle of the blood system in Canada<sup>18</sup>:

“Preventive action should be taken when there is evidence that a potentially disease-causing agent is or may be blood borne, even when there is no evidence that recipients have been affected. If harm can occur, it should be assumed that it will occur. If there are no measures that will entirely prevent the harm, measures that may only partially prevent transmission should be taken.”

*Are we honestly able to say, based on all we know about the blood storage lesion, that harm “can(not) occur”? Does not the patient deserve the benefit of the doubt?*

## FINAL THOUGHTS FROM TWO BLOOD “BUFFS”

One of us (Albert Farrugia) is a transfusion scientist with 35 years of practical academic experience immersed in the field. The other author of this work (Douglas Starr) has written a widely cited account of the development of blood transfusion and the problems of the past 30 years. Both of us continue to have an interest, and affection, for this discipline. We have chronicled its history, in our different ways, in other works, and we have noted its achievements and its failures. At its best, this technology has served medicine by contributing to the development of interventions saving and improving countless lives, and has provided a great source of community and solidarity. But blood is big business representing a market of billions of dollars yearly. This rubs shoulders uneasily with the NFP dimension of the sector and the altruistic motive of many donors. We are encouraged that the movement for PBM and rational blood use is, among other things, stimulating developments in the rational reintroduction of fresh whole blood and other patient-centric interventions described in other parts of this supplement. We hope that this and other drivers will shift the current paradigm away from the excesses of “Transfusion Medicine,” and toward a more patient-oriented approach.

## CONFLICT OF INTEREST

Albert Farrugia provides compensated services to providers of therapies manufactured from blood. Douglas Starr declares no conflict of interest.

## REFERENCES

- Greenwalt TJ. A short history of transfusion medicine. *Transfusion (Paris)* 1997;37:550-63.
- Hardaway RM. Wound shock: a history of its study and treatment by military surgeons. *Mil Med* 2004;169:265-9.
- Hess JR, Schmidt PJ. The first blood banker: Oswald Hope Robertson. *Transfusion (Paris)* 2000;40:110-3.
- Coni N. Medicine and the Spanish Civil War. *J R Soc Med* 2002;95:147-50.
- Yudin SS. Transfusion of cadaver blood. *J Am Med Assoc* 1936;106:997-9.
- Greenwalt TJ. An autobiographical perspective of blood banking, 1946 to 1988. *Transfusion (Paris)* 1989;29:248-58.
- Pool JG, Shannon AE. Production of high-potency concentrates of antihemophilic globulin in a closed-bag system. *N Engl J Med* 1965;273:1443-7.
- Hess JR. An update on solutions for red cell storage. *Vox Sang* 2006;91:13-9.
- Stansbury LG, Hess JR. Tibor Jack Greenwalt: Father of Transfusion Medicine. *Transfus Med Rev* 2010;24:325-8.
- Titmuss R. *The Gift Relationship - from human blood to social policy*. The New Press 1970;360p.
- Gulliksson H. Platelet storage media. *Vox Sang* 2014;107:205-12.
- Chaveau S. The contaminated blood affair in France - a turning point in blood donation. In: Charbonneau J, Smith A (eds). *Giving blood: the institutional making of altruism*. London: Routledge 2015; p. 79-93.
- Starr D. *Blood: an epic history of medicine and commerce*. London: Little, Brown and Company; 1998. 430 p.
- Feldman E, Bayer R. *Blood feuds: AIDS, blood, and the politics of medical disaster*. New Edition. New York: Oxford University Press; 1999. 400 p.
- Bove JR. Subcommittee of the Committee on Government Operations, House of Representatives, 98th Congress, First Session; 1983.
- Bove JR. The response to AIDS. *Transfusion (Paris)* 1985;25:1-2.
- Commonwealth of Australia C. Hepatitis C and the blood supply in Australia [Internet]. 2004 [cited 2015 Sep 28]. Commonwealth of Australia. Available from: [http://www.aph.gov.au/Parliamentary\\_Business/Committees/Senate/Community\\_Affairs/Completed\\_inquiries/2002-04/hepc/report/index](http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Completed_inquiries/2002-04/hepc/report/index)
- Finlay T. Report of the tribunal of inquiry into the blood transfusion service board [Internet]. 1997. Government of Ireland. Available from: [www.lenus.ie/hse/bitstream/10147/45442/1/7843.pdf](http://www.lenus.ie/hse/bitstream/10147/45442/1/7843.pdf)

19. Farrugia A. The regulatory pendulum in transfusion medicine. *Transfus Med Rev* 2002;16:273-82.
20. Lauren B Leveton, Harold C Sox Jr, Michael A. Stoto. HIV and the blood supply: an analysis of crisis decisionmaking [Internet]; 1995 [cited 2015 Aug 25]. Available from: [http://www.nap.edu/openbook.php?record\\_id=4989](http://www.nap.edu/openbook.php?record_id=4989)
21. European Commission. The precautionary principle [Internet]; 2015 [cited 2015 Sep 21]. Available from: <http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=URISERV:l32042&from=EN>
22. World Health Organization. WHO | Processing of donated blood [Internet]; 2015 [cited 2015 Nov 27]. Available from: <http://www.who.int/bloodsafety/processing/en/>
23. World Health Assembly. Availability, safety and quality of blood products [Internet]; 2010 [cited 2015 Nov 27]. Available from: [http://apps.who.int/gb/ebwha/pdf\\_files/WHA63/A63\\_R12-en.pdf?ua=1](http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R12-en.pdf?ua=1)
24. Spinella PC, Stranden G, Rein EB, et al. Symposium on fresh whole blood for severe hemorrhagic shock: from in-hospital to far forward resuscitations. *Transfus Apher Sci* 2012;46:113-7.
25. Ala F, Allain J-P, Bates I, et al. External financial aid to blood transfusion services in sub-Saharan Africa: a need for reflection. *PLoS Med* 2012;9:e1001309.
26. Lara AM, Kandulu J, Chisuwu L, et al. Laboratory costs of a hospital-based blood transfusion service in Malawi. *J Clin Pathol* 2007;60:1117-20.
27. Matata L. Kenya: Health Ministry denies firing 140 National Blood Transfusion workers. *The Star (Nairobi)* [Internet]. By Lydia Matata; 2015 [cited 2015 Oct 4]. Available from: <http://allafrica.com/stories/201504091277.html>
28. Allain J-P. Moving on from voluntary non-remunerated donors: who is the best blood donor? *Br J Haematol* 2011; 154:763-9.
29. World Health Organization. Blood safety: key global fact and figures in 2011 [Internet]; 2015 [cited 2015 Oct 4]. Available from: [http://www.who.int/worldblooddonorday/media/who\\_blood\\_safety\\_factsheet\\_2011.pdf](http://www.who.int/worldblooddonorday/media/who_blood_safety_factsheet_2011.pdf)
30. Verlicchi F, Facco G, Macrì M, et al. Blood transfusion practice: a nationwide survey in Italy. *Blood Transfus* 2011;9: 430-5.
31. Farrugia A. The Australian government's review of the plasma fractionation arrangements in Australia. *Pharm Policy Law* 2007;383-402.
32. Hunter DJ. From tribalism to corporatism - the managerial challenge to medical dominance. In: Purdy M, Banks D (eds). *The sociology and politics of health*. London: Routledge; 2001. p. 272.
33. Farrugia A. Safety issues of plasma-derived products for treatment of inherited bleeding disorders. *Semin Thromb Hemost*. In press 2016.
34. Soucie JM, Richardson LC, Evatt BL, et al. Risk factors for infection with HBV and HCV in a large cohort of hemophilic males. *Transfusion (Paris)* 2001;41:338-43.
35. Phelps R, Robbins K, Liberti T, et al. Window-period human immunodeficiency virus transmission to two recipients by an adolescent blood donor. *Transfusion* 2004;44:929-33. (Paris).
36. Nübling CM, Heiden M, Chudy M, et al. Experience of mandatory nucleic acid test (NAT) screening across all blood organizations in Germany: NAT yield versus breakthrough transmissions. *Transfusion (Paris)* 2009;49:1850-8.
37. Vostal JG. Efficacy evaluation of current and future platelet transfusion products. *J Trauma* 2006;60(6Suppl): S78-82.
38. Dumont LJ, AuBuchon JP. Evaluation of proposed FDA criteria for the evaluation of radiolabeled red cell recovery trials. *Transfusion (Paris)* 2008;48:1053-60.
39. Hess JR, Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Scientific problems in the regulation of red blood cell products. *Transfusion (Paris)* 2012;52:1827-35.
40. Hess JR. Conventional blood banking and blood component storage regulation: opportunities for improvement. *Blood Transfus* 2010;8(Suppl 3):s9-15.
41. Connes P, Triplette J, Mukisi-Mukaza M, et al. Relationships between hemodynamic, hemorheological and metabolic responses during exercise. *Biorheology* 2009;46:133-43.
42. Valeri CR, Yarnoz M, Vecchione JJ, et al. Improved oxygen delivery to the myocardium during hypothermia by perfusion with 2,3 DPG-enriched red blood cells. *Ann Thorac Surg* 1980;30:527-35.
43. Becker GA, Tuccelli M, Kunicki T, et al. Studies of platelet concentrates stored at 22 C and 4 C. *Transfusion (Paris)* 1973;13:61-8.
44. Borzini P, Lazzaro A, Mazzucco L. Evaluation of the hemostatic function of stored platelet concentrates using the platelet function analyzer (PFA-100). *Haematologica* 1999;84: 1104-9.
45. Lacroix J, Hébert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. *N Engl J Med* 2015;372:1410-8.
46. Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med* 2015;372:1419-29.
47. Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA* 2012;308:1443-51.
48. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295-300.
49. Ng MS, Ng AS, Chan J, et al. Effects of packed red blood cell storage duration on post-transfusion clinical outcomes: a meta-analysis and systematic review. *Intensive Care Med* 2015;41:2087-97.
50. Pereira A. Will clinical studies elucidate the connection between the length of storage of transfused red blood cells and clinical outcomes? An analysis based on the simulation of randomized controlled trials. *Transfusion* 2013;53:34-40. (Paris).



51. Fontaine MJ, Chung YT, Erhun F, et al. Age of blood as a limitation for transfusion: potential impact on blood inventory and availability. *Transfusion (Paris)* 2010;50:2233-9.
52. Atkinson MP, Fontaine MJ, Goodnough LT, et al. A novel allocation strategy for blood transfusions: investigating the tradeoff between the age and availability of transfused blood. *Transfusion (Paris)* 2012;52:108-17.
53. South Australia Red Cross Blood Service. BloodMove Platelets - a successful system to significantly reduce platelet wastage | National Blood Authority [Internet]. 2015 [cited 2015 Dec 2]. Available from: <http://www.blood.gov.au/blood-move-platelets>
54. Shrivastava M. The platelet storage lesion. *Transfus Apher Sci* 2009;41:105-13.
55. Food and Drug Administration. Bacterial detection testing by blood collection establishments and transfusion services to enhance the safety and availability of platelets for transfusion - draft guidance for industry [Internet]. 2014 [cited 2015 Sep 26]. Available from: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf>
56. Dumont LJ, AuBuchon JP, Whitley P, et al. Seven-day storage of single-donor platelets: recovery and survival in an autologous transfusion study. *Transfusion (Paris)* 2002;42:847-54.
57. Stanworth SJ, Hyde CJ, Murphy MF. Evidence for indications of fresh frozen plasma. *Transfus Clin Biol J Société Fr Transfus Sang* 2007;14:551-6.
58. Tholpady A, Monson J, Radovancevic R, et al. Analysis of prolonged storage on coagulation Factor (F)V, FVII, and FVIII in thawed plasma: is it time to extend the expiration date beyond 5 days? *Transfusion (Paris)* 2013;53:645-50.
59. Spinella PC, Frazier E, Pidcoke HF, et al. All plasma products are not created equal: characterizing differences between plasma products. *J Trauma Acute Care Surg* 2015; 78(6Suppl1):S18-25.
60. Pati S, Matijevic N, Doursout M-F, et al. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. *J Trauma* 2010;69:S55-63.
61. Vamvakas E. Reasons for moving toward a patient centric paradigm of clinical transfusion medicine practice [Internet]. *Swisstransfusion 2012 Congress of the Swiss Association for Transfusion Medicine*; 2012 Sep 7 [cited 2015 Nov 27]; Basel, Switzerland. Available from: [http://www.swisstransfusion.ch/\\_pdf/Vamvakas\\_Reasons\\_for\\_moving\\_toward\\_a\\_patient\\_centric\\_paradigm\\_of\\_clinical\\_transfusion\\_medicine\\_practice.pdf](http://www.swisstransfusion.ch/_pdf/Vamvakas_Reasons_for_moving_toward_a_patient_centric_paradigm_of_clinical_transfusion_medicine_practice.pdf)
62. Friedman M, Bizargity P, Gilmore S, et al. Patient inclusion in transfusion medicine: current perspectives. *Int J Clin Transfus Med* 2015;2015:7-16.
63. King R, Michelman M, Curran V, et al. Patient-centered approach to ensuring appropriateness of care through blood management. *South Med J* 2013;106:362-8.
64. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med* 1999;340:409-17.
65. Slichter SJ, Kaufman RM, Assmann SE, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010;362:600-13.
66. Tsai AG, Hofmann A, Cabrales P, et al. Perfusion vs. oxygen delivery in transfusion with "fresh" and "old" red blood cells: the experimental evidence. *Transfus Apher Sci* 2010;43:69-78.
67. Personalized Medicine Coalition. *PMC.com: the case for personalized medicine* [Internet]. 4th ed. 2014 [cited 2015 Sep 25]. 66 p. Available from: [http://www.personalizedmedicine-coalition.org/Resources/The\\_Case\\_for\\_Personalized\\_Medicine](http://www.personalizedmedicine-coalition.org/Resources/The_Case_for_Personalized_Medicine)
68. Dobbe JG, Hardeman MR, Streekstra GJ, et al. Analyzing red blood cell-deformability distributions. *Blood Cells Mol Dis* 2002;28:373-84.
69. Tarasev M, Alfano K, Chakraborty S, et al. Similar donors-similar blood? *Transfusion (Paris)* 2014;54:933-41. 