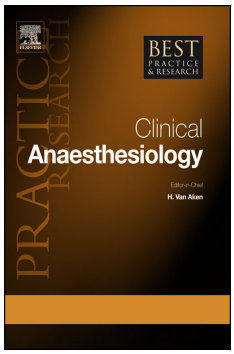

Roads travelled: the Journey to Patient Blood Management at 35 Years

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TITLE PAGE

Roads travelled: the Journey to Patient Blood Management at 35 Years

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Abstract

Patient Blood Management evolved in recent years focusing on the haematopoietic system as relevant to all disciplines of medicine. The allogeneic blood supply chain travels from donation, to fractionation, preservation, and storage, to a therapeutic, established treatments or prophylactics for a wide range of medical conditions. This supply chain ‘connects’ altruistic blood donors to patients in need, symbolising a 'gift relationship', emphasising the empathetic bond between donor and recipient.

In 1988 the author proposed a paradigm shift in blood transfusion and in 2005 introduced the term Patient Blood Management (PBM). PBM's origins are traceable to the late 19th century when blood transfusion wasn't feasible for managing exsanguinating haemorrhage or critical anaemia. Landsteiner's discovery of the ABO blood groups firmly established blood component therapy into medical therapeutics. This article recounts the journey from a pre-blood transfusion era patient centred approach, through the 20th century's blood product focus and thenceforth back to the patient with the advent of PBM.

Keywords: Blood Transfusion; Hematopoietic System; Anemia; Patient Blood Management

Introduction

During the acquired immunodeficiency syndrome (AIDS) pandemic of the 1980s, blood banks and the broader blood sector faced immense pressure when it became evident that the Human Immonodeficiency Virus (HIV) could be transmitted through blood transfusion. Not only did AIDS wreak havoc as a global pandemic, but the early cases of transfusion-transmitted AIDS were the harbinger for countless personal and familial tragedies. AIDS created a perfect storm for the blood sector, healthcare systems, and governments.

As a clinical haematologist specialising in critical care medicine, bone marrow transplantation and haematological supportive therapy, the author found himself at the frontlines of this crisis. While blood bank professionals and the wider blood sector dedicated their efforts to addressing the infectious safety of blood components, the author's expertise centred on the broader aspects of transfusion medicine practice at the clinical workface.

This historical review, of what is now termed Patient Blood Management (PBM), is PBM redux.

Setting the scene

William Harvey (1578–1657) was remarkably prescient in his understanding of the relationship between the blood and the circulation. The close physical, molecular and rheological relationships between the blood and endothelial cells is focus of ongoing physiological and pathophysiological research. In his treatise: Exercitationes de generatione animalium (1651), Harvey predicted the pivotal 'infrastructure' role of the blood, stating:

"For the blood is rather the author of the viscera than they of it, because blood is in being before the viscera, nor does it come from the mother into the egg, indeed not one drop. The soul is in the blood. Innate heat is the author of life and where it most abounds there it exists principally and primarily."

"And likewise of the blood, why before all things, and how it has in it the beginning of life and of the creature. why it requires to be moved and driven up and down; and then for what cause the heart seems to have been made."

The advances in medicine during the late nineteenth century featured the integration of clinical pathology laboratories into hospital practice for understanding pathophysiology, diagnosis, and management of diseases.[1] Among these methods, blood examination emerged as a crucial tool. It was recognised that study of a patient's blood provided insights into a wide range of physiological functions and pathophysiological perturbations observed in many disease states. Blood analysis provided accessibility to valuable information in the diagnosis and management of various diseases.

In 1899 there was a notable surge of articles emphasising the importance of examination of patients' blood.[1-6] In America, much of this integration of clinical medicine with clinical pathology occurred at Johns Hopkins Hospital. In 1889 on the foundation of this institution, William Osler (the first Physician-in-Chief) was instrumental in the creation of the Johns Hopkins School of Medicine in 1893 and is generally regarded as the father of modern clinical medicine. The Johns Hopkins model established a blueprint for medical education in America following the landmark 1910 Flexner report.[7 8]

The establishment of the new medical school had a transformative impact on medicine and medical education in America and Canada. The impact on what is now PBM is apparent in a 'sleeping beauty' article by Hamilton Fish. Fish received his postgraduate training at Johns Hopkins. He subsequently practiced in a Colorado gold mining town and in 1899 published what is probably the first article on PBM in the medical literature specifically addressing the importance the blood in the perioperative setting.[9] It is astonishing what Fish achieved in his clinical practice, research, innovation and writing in a short few years before dying at the young age of 31, and can perhaps be nominated as the father of PBM and perioperative medicine.

Box 1.

The 20th Century Evolution of Transfusion Medicine

The origins of modern blood transfusion are traceable back to the 19th and early 20th century. The focus of blood transfusion was on the patient, the clinician identifying the need for transfusion, managing the logistics, and being responsible for care of the donor. Blood was transferred directly from the donor's artery to the patient's vein making it a true blood 'transfusion'.

Karl Landsteiner's discovery of the ABO blood groups took several years to impact transfusion with testing of patient and donor compatibility becoming a routine procedure.[10 11] Transfusion was increasingly undertaken leading up to and during the Great War. There were many doyens of early blood transfusion who served on the battlefields on the Western Front, including surgeons from the United States, Canada, France, and Great Britain.

It wasn't until 1914 that citrated blood transfusions in humans were first documented, allowing the donor and recipient to be physically separated. Advancements in anticoagulation, preservation, and transportation of donor blood allowed separation of donor and recipient in time and space. This progressed to the emergence of large, centralised blood banks and eventually commercial involvement in plasma processing of individual fractionated blood products.

These developments had the unintended consequence of concentrating blood transfusion knowledge and expertise, with transfusion policies determined by central blood banks. At first, this seemed inconsequential, as donor safety and interests were protected. At the clinical workface the risk-benefit equation for blood transfusion was generally front and centre as opinion leaders in the early evolution of blood transfusion were practicing clinicians.

In 1963 the United States National Academy of Sciences National Research Council prepared a landmark publication titled The General Principles of Blood. At this time there remained a relatively seamless knowledge and expertise link, manifest in the professional lives of the authors of this publication, between the patients in need and altruistic donors. This is a publication worth revisiting,[12] with one particular quote remaining relevant today: *"Transfusions should never be administered to treat the 'diagnosis' of anemia, per se. Definition of the mechanism of the anemia needs to be made in order to correct the cause, if possible."* [12] The section on transfusion for anaemia, makes no mention of haemoglobin 'triggers', stating instead that: *"Transfusion requirements differ depending upon the age and clinical circumstances of the patient".*

The evolution of the separation between donor blood supply and the patient

The late 1960s marked a pivotal point in blood transfusion practices during which the supply of blood components starting to take precedence to the disadvantage of a patient-centred approach. This shift gradually resulted in a knowledge gap, with the bulk of expertise in blood transfusion accumulating at the donor blood supply side. Clinicians, no longer responsible for procuring donor blood, were reassured by blood banks that allogeneic blood transfusions were safe and effective, with blood banks considering themselves the authority on blood transfusion indications and practices.

Throughout the 1960's and into the 1970's there were advances in treatment of haematological malignancies, with some becoming curable. Most treatment regimens were combinations of marrow suppressive chemotherapy. As a result, requirements for blood component therapy increased and became more complex, with regular blood banks struggling to respond to these specialised needs. This resulted in the development of *in vivo* blood cell separators for

harvesting blood components. Clinical haematologists became involved in allogeneic blood transfusion and blood component therapy from the patient and donor perspectives.[13] This strengthened the scientific and social bonds that link patients with their blood and organ donors

A consequence of the advances in treatment of haematological malignancies was declining interest and research in the non-malignant haematological conditions, especially the 'nutritional' and secondary anaemias. This may have been an inflection point in the history of haematology as a clinical specialty as attention was deflected from the development of PBM towards curing haematological malignancies. Thrombosis and haemostasis continued to receive interest as they were relevant to pathophysiology and therapy of many common diseases, especially cardiovascular disease.

More emerging hazards of blood transfusion with re-evaluation of risk and benefits

The hazards of infection transmission through allogeneic blood transfusions have been acknowledged widely. During WWII, passive serum vaccination for yellow fever and the use of dried plasma transmitting Hepatitis B had a devastating impact on US servicemen.[14] During the 1970s there was a high rate of transfusion transmitted Hepatitis C in multi-transfused patients, especially in the United States.[15]

In the 1970s, the American scientist Paul Terasaki, a pioneer in kidney transplantation technology, observed that transplant patients who had undergone multiple blood transfusions were less prone to transplanted kidney rejection.[16] This 'blood transfusion effect' sparked research into the phenomenon of Transfusion-Related Immunomodulation (TRIM).[17] Despite this finding being a reminder that allogenic blood transfusion is a tissue transplant, little interest was aroused outside nephrology. This complacency should have changed in 1982 when an article appeared in *The Lancet* titled, "Effect of blood transfusions on colonic malignancy

recurrent rate". [18] This observation went under the radar and was widely disregarded by cancer specialists.

The rather belated epiphany that allogeneic blood transfusion is effectively an organ transplant occurred at same time that TRIM was attracting attention was the devastating, and usually fatal post-transfusion graft versus host disease (TAGVHD). In retrospect, several cases of fatal postoperative erythroderma reported in 1955 were almost certainly this entity. [19 20]

It was not only colorectal surgeons who regarded the incorporation of blood transfusion as an integral component of the standard care for surgery. Indeed, it was widely accepted that transfusion was an essential component of many medical and surgical clinical pathways, and that informed consent for blood transfusion was implied. If specific consent was sought it was commonly a 'tick-a-box' in small print. At the time, having been consulted on adverse allogeneic transfusion events, the author repeatedly observed that there was no clear indication for transfusion or evidence for benefit. Blood transfusion had become embedded as part of many clinical practices with risk outweighing questionable benefit.

In the same year TRIM created broader interest, AIDS appeared, creating extraordinary challenges for both medicine and society at large. For the blood industry, it was a major crisis and reputational threat, questioning the reliability and safety of a service that was previously held in high regard and valued for its altruistic contribution to community health and patient care.[21] At first, there was some resistance, even a degree of denial, predicated on the belief that the risks were outweighed by the benefits of blood transfusions.

An article titled "Is our blood supply safe?" in November 1983 provided no foreshadowing of the impending AIDS transfusion crisis, with the authors stating: *"The risk of developing AIDS from receiving a blood transfusion is minute. The health risk posed by a frantic, uninformed reaction to the AIDS mystery is great. Your informed cooperation is urgently requested".*[22]

This somewhat condescending perspective was the beginning of a reality check for the blood industry as they prepared to navigate an entirely new regulatory environment.[23] Government enquiries ensued, probing into the structure and functioning of organizations providing blood components to the health sector.[24-27] Blood bank directors initially considered it unreasonable to impose strict regulatory requirements on their 'not-for-profit' organisations.[28 29]

Although allogeneic blood transfusion has always been associated with recognised immunological and infective hazards, it was AIDS that was the tipping point, prompting a thorough and in-depth analysis of the risk-benefit equation for allogeneic blood transfusion.[30] The initial presumption that an infectious agent, for which initially there was no *in vitro* test, was responsible for AIDS meant the only possible strategies to minimise transfusion transmission were to (1) avoid transfusion; and (2) exclude high risk donors. The concept of 'alternatives' to allogeneic blood transfusion evolved and was a driver for the formation of the Network for the Advancement of Transfusion Alternatives (NATA), now the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis.[31 32]

While it seemed rational and reassuring to discuss alternatives to allogeneic blood transfusion, many of these alternatives should have already been a standard of care. During this period, the evidence-base for most labile blood component therapy was questionable. Understandably, measures were implemented based on the precautionary principle. The blood industry asserted that, despite genuine and valid worries, all measures were being taken to maintain the safety of donor blood, and transfusion remained 'safe as it has always been'.[33] The concept and definition of safety and risk were overstated and misrepresented to clinicians and the community, as illustrated by this statement in a 1984 editorial in a leading medical journal: *"Although the risk is extremely low the concern is great, and physicians can expect potential recipients to be anxious. Patients should be reassured that blood banks are taking all possible*

steps to provide for safe blood transfusion. In turn, physicians should use these products when, and only when, they are unquestionably indicated".[34]

This quote implied there was an evidence-base for the use of allogeneic blood components. However, the evidence base for efficacy of transfusion had always been shaky, the clinical benefits had been assumed, hazards regarded as minimal and blood a free resource. From a stewardship of altruistically donated blood perspective, it was again assumed that clinicians were appropriately prescribing blood transfusion for patients with the known risks outweighed by assumed benefits. Blood transfusion had become a default decision in the context of clinical uncertainty. This attitude is perhaps traceable back to the earlier days of blood transfusion in such statements as that by Bertram Bernheim in 1917, a pioneer of vascular surgery who stated that: "….*in the chronic bleedings and the anemias it is the hemoglobin; but one must never lose sight of the fact that at times all signs fail, and there remains naught for guidance but experience and judgment. Under these circumstances my advice is, When in doubt, transfuse!"*[35]

Lionel Whitby in 1941 had a contrary opinion, stating that: "*Blood Transfusion should always be performed with a definite object. It is necessary to have this object clearly in mind and to know whether the various derivatives of blood will fulfil the requirements. The convenience of blood derivatives must not lead to improper use."*[36]

In regard to anaemia, specifically perioperative anaemia, a dogma had evolved that blood transfusion was indicated for haemoglobin levels less than 10 g/dL.[37] This 'standard of care' was devoid of scientific evidence and seemingly had its origins back to a 1942 opinion article by Adams and Lundy.[38]

Most clinicians believed they were well-informed about the indications for blood component therapy and accepting what they regarded as minimal risks. This perspective ignored that blood

transfusions exposed patients to a broader range of potential serious and possible lethal hazards, more than other medical intervention.[39 40]

Drivers for change and the paradigm begins to shift

There were several drivers for change **(Figure 1)**: governments were concerned about the blood sector and established national reviews, there were increasing medicolegal transfusion-related negligence claims, and altruistic blood donors could reasonably expect that their blood would be used to benefit the greatest number of patients with minimal chances of adverse impacts.

Despite the emergence of these drivers, there was continuing resistance to accept evidence questioning the efficacy and safety of RBC transfusions.[33] This should have been the case for elective surgery and in hemodynamically stable anaemic patients who were receiving RBC transfusions, in most cases prophylactic and discretionary.

By the 1990's the paradigm was shifting back to the patient with clinicians refocusing on managing a patient's own blood. It was in 1988 that the author penned an opinion article, *"*The paradigm shift in blood transfusion".[41] It was the purpose of this article: *"to analyse the current philosophies of blood-transfusion therapy, to assess the effects of the acquired immunodeficiency syndrome (AIDS) on transfusion policies and practices and to suggest that we are undergoing a major paradigm shift in clinical blood transfusion therapy"*.

The subspecialty of transfusion medicine developed with the aim of addressing the 'gap' in the blood supply chain and to improve communication and liaison between the clinical workface and blood banks.[42 43] This was fertile soil for two new journals specifically devoted to transfusion medicine.[42] Addressing AIDS was an early focus in the first issue of *Transfusion Medicine* and reference to the indications for transfusion included a quote from a summary of 'Indication for Blood Transfusion in Uganda', which read: *"Blood transfusion may have major*

consequences for good or bad in patient care. Indications and contraindications are different from those in developed countries and are not available in textbooks".[44]

Throughout the 1990s, extensive epidemiological observational data identified the probability that transfused allogeneic blood was an independent risk factor for negative clinical outcomes.[45] This was not surprising as transfusion of allogeneic blood has potential immunological consequences beyond stimulation of alloantibodies. There was also a better understanding of TRIM and the probable contribution to adverse clinical outcomes.[46] The storage lesion was also being studied on a mechanistic basis and clinical evidence as a contributor to adverse clinical consequences was accumulating.[47-50]

A cardiac anaesthesiologist in an article titled; "Blood Transfusion: The Silent Epidemic", opined that *"Physicians today are still driven by the widely held belief that transfusion is lifesaving. The literature does not provide support that transfusion is lifesaving in all cases, and evidence-based medicine would dictate a very conservative use of blood products".*[51]

It is informative to reflect on the widely varying messages in blood transfusion review articles at the time. Review articles in major journals from the 1970's to the 1990's rarely made meaningful or evidence supported reference to the indications for transfusion of the labile blood components; indeed, most reviews were devoted to collection, processing, administration and hazards.[52-54] This was about to change as illustrated in an extensive a two-part review of blood transfusion in 1999 in which the majority of the review is devoted to the hazards and alternatives to transfusion, with only minimal mention of the clinical indications.[55 56] The first of these articles appeared in the same issue of the *New England Journal of Medicine* in which a landmark restrictive versus liberal RBC transfusion RCT was published.[57]

The introduction and registration of any new medical therapeutic naturally commences with the focus on efficacy and safety. All aspects of the technology, pharmaceutical formulations,

and administration protocols involved must be thoroughly scrutinised, comprehensively validated, and concisely articulated. Clinical indications for a new therapy may not always be explicitly definable due to variations in disease presentations and patient conditions. It is incumbent upon the clinician to make a risk-benefit decision for each specific patient. With the assistance of clinical practice guidelines, this decision implies a careful and thoughtful translation of evidence from population statistical data to individual patient circumstances.

At a broader health system level, considerations of cost-effectiveness come into play along with impact of reimbursement policies.[58] Navigating these waters is recognised as a complex, costly, and potentially risky endeavour, demanding a level of scrutiny previously foreign to the blood sector. If allogeneic blood and blood components were to be re-submitted for regulatory approval, registration, and reimbursement, in the current regulatory environment, they may encounter significant challenges due to strict evidence for efficacy and safety.[59]

The safety emphasis on blood components was primarily concentrated on the risk of infection transmission, overlooking, or underemphasising the many other known hazards. This narrow focus fostered a sense of complacency among clinicians, administrators, and, to some extent, patients. Numerous pioneers in the field of blood transfusion had consistently cautioned about the dangers and stressed the importance of careful risk-benefit analysis when prescribing blood transfusions. It was a tragedy that so many patients for whom there was no defensible indication for a transfusion contracted and died from AIDS. This was case for women with mild anaemia resulting from minor or moderate post-partum haemorrhage. Top up RBC transfusions were prescribed to relieve their ‘fatigue’ and ‘help them cope better at home’ or ‘support breastfeeding’,[33] despite a century of warnings from influential clinicians that allogeneic blood transfusion has always been a hazardous therapy and should only be embarked on if there are no alternatives. **(Box 2)**

The growing body of observational evidence indicating an overuse of RBC transfusions for anaemia, particularly in haemodynamically stable patients, generated the equipoise for RCTs. Two landmark trials were initiated comparing liberal versus restrictive RBC transfusion policies. The most cited of these trials is Hebert's 1999 study conducted in the critical care setting.[57] Concurrently, there was a single centre trial addressing haemoglobin thresholds for RBC transfusion in coronary artery bypass procedures. The latter trial was a bold venture conducted at the Texas Heart Institute with Denton Cooley, a pioneer of bloodless medicine.[60] Both trials confirmed that limiting RBC transfusion to a specified haemoglobin level did not impact on clinical outcomes. Over the course of the subsequent two decades these findings were validated across a wide variety of clinical contexts.[61]

Prior to and concurrent with these trials there were several inquiries probing into the structures, regulation, and failures of the blood sector during the AIDS tragedy. ‘L’affaire du sang contaminé’ that reported the events in France during the 1980s and 1990s was the earliest enquiry and one of the most significant, exposing a distressing event in the nation's public health history. The scandal revolved around the distribution of blood products, particularly those used for haemophiliacs, that were tainted with HIV and Hepatitis C.[62]

The 1997 Krever Royal Commission into the blood system in Canada is generally regarded as a landmark document.[25] Justice Krever made 50 recommendations informing changes to the system, with two being of central importance, namely: (1) the precautionary principle; and (2) the restructuring of the governance system that placed a priority on safety. In 2001 there was an Australian review of blood banking and plasma product sector by Sir Ninian Stephen. Stephen’s incisive review and report gave confidence that the patient and donor voices were heard and his report is a landmark document for PBM in Australia.[27]

Governments, regulatory authorities, blood services and safety and quality organisations now have systems monitoring and regulate the blood supply sector, transfusion medicine and PBM.

It is only in recent years that there has been a concerted effort to establish a sounder evidence base for the benefits and hazards of allogeneic blood transfusion in the wide range of clinical settings in which it is, may be, or is not, appropriate therapy.[63] There is good evidence from trials for efficacy for specific plasma deficiencies, prevention of RhD immunisation and haematological support in oncology.[64-68]

Re-enter Patient Blood Management

Regardless of medical specialisation, healthcare professionals have a duty of care to manage patients' blood as a precious and unique biological resource. This includes limiting wastage and only using allogeneic blood components when absolutely indicated. There is an evolving trend in medicine and PBM which places greater emphasis on an individual patient-centred approach and collaborative decision-making.[69]

Jehovah's Witness patients in the pioneering years of cardiac surgery challenged the prevailing belief that cardiac surgery was impossible without blood transfusion. Most surgeons balked at accepting such presumed high-risk patients. It took Denton Cooley, cardiac surgery pioneer, to prove that major surgeries could be successfully 'bloodless' with meticulous preoperative, intraoperative, and postoperative care of the patient's own blood.[70] This approach known as bloodless medicine and surgery laid the groundwork for PBM.[71 72] Ron Lapin was another, albeit rather flamboyant and controversial surgeon who practiced bloodless medicine from the 1970's and who contributed to some of early trials of fluorocarbons.[73-76]

Later retrospective observational studies on elective cardiac surgery in Jehovah's Witness patients supported the feasibility of these procedures in elective surgery and suggested that the avoidance of transfusion may be associated with improvements in clinical outcomes.[77] The 'new' PBM paradigm is a return to Hamilton Fish's 1899 focus on the patient's blood that should regarded and protected as their own valuable and unique natural resource to be

conserved and managed appropriately. It's remarkable to note that the 7.0 g/dL haemoglobin threshold for Hébert's RCT aligns closely with that suggested by Fish a century earlier in 1899 of a 50% haemoglobin, by the visual comparison method used before colorimeters had been invented.[9 57]

The return to a patient-focused blood management from a blood product focus

While 1899 was a significant year for PBM, the same can be said of 1999.[56 78] Perceptions of blood transfusion had changed significantly during and following the AIDS tragedy, but there remained different perspectives depending on one's position within the blood donor supply to patient chain. The patient regards blood transfusion as special and beneficial but have a low appetite for risk over which they have no control. The donor has an understanding that their contribution is a gift to the community through which they have unique physical connection with another human being in need. They assume that quality, safety, and stewardship of their gift will be respected and maintained throughout the blood supply chain and that it will be used appropriately.

The blood sector often focusses on supply and demand. The provision of donated allogeneic blood and blood components are clinical services, but they may also be considered commodities.[79] In certain countries, payment for blood donation does commodify blood components, thus diminishing or negating stewardship and ethical implications.[80 81] A European blood service questionably promoted donor blood as the 'safest pharmaceutical' implying commodification of an altruistically donated human resource with minimal interest or concern as to how it was used by clinicians.[82] Some governments tended to regard donated blood as a commodity and blood transfusion as an expensive therapy that should be regulated and controlled by the market principles.[33 83]

The definition of Patient Blood Management

The introduction of the term "blood management" and the formation of the Society for the Advancement of Blood Management (SABM) were driven from the patient perspective, at odds with the blood bank interpretation of the term, which is the management of the supply chain.[84] At a Board Meeting of what is now the International Foundation for Patient Blood Management (IFPBM) convened in Prague in 2005, the author advocated that the problems of the language needed addressing to ensure that the direction for any paradigm shift was back to the patient and broader community health.[85] It was proposed that the terminology should be Patient Blood Management and Donor Blood Management. The term PBM first appeared in the title of an article in 2008.[86]

PBM is not an 'intervention' *per se*. It is goal-oriented patient care based on core foundations of modern medicine based in a sound understanding of physiology and pathophysiology and evidence for efficacy of therapeutic interventions. PBM includes multidisciplinary collaboration and shared clinical decision-making with patients or their advocates whenever possible. PBM is accepted globally and by the WHO as a standard of clinical care.[87-89] There is general agreement as to what PBM involves in clinical practice with a clear definition developed in 2022,[90] specifically:

Patient blood management is a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient's own blood, while promoting patient safety and empowerment.

A corollary of PBM is minimising inappropriate blood transfusion, ensuring appropriate use and availability of altruistically donated blood, and respecting what donors expect when they donate blood. In some countries there have been concerns from some areas of the blood sector that may be related to the impact of PBM on commercial interests.[91]

Conclusions and where to now?

It is not the purpose of this historical review to delve into the clinical practice of PBM. There is now an extensive literature on PBM, including various resources, guidelines and several textbooks.[84 85 92 93]

Despite the growing body of literature on the subject, assessing the beneficial impacts of PBM programs is challenging. For patients due to undergo elective surgery, the PBM preparation period should, when possible, commence well before the scheduled operation. This allows adequate time for thorough screening and management of anaemia and other risk factors, and this process may continue well into the postoperative recovery period. Despite the self-evident benefits of such clinical pathways, it is all too common for this not be routine standard of care.[94]

A pivotal event in the global PBM landscape occurred in May 2010, when the 63rd WHO World Health Assembly adopted resolution WHA63.12 concerning the availability, safety, and quality of blood products, thus giving endorsement to PBM. This resolution was followed by the WHO Global Forum for Blood Safety which was orchestrated with the express intent of improving quality and safety in patient care and public health. The conference's attendees also aimed to evaluate the prevailing barriers in implementing PBM programs and pinpoint strategies to enhance the impact of such initiatives.

The next important progress on the global stage was in 2021 with the development of the WHO Policy Brief on PBM, which states that “patient education and empowerment, informed consent, and shared decision-making” are key principles of PBM.[95] A PBM implementation guidance document is now in development.

If PBM focuses on the three E’s of evidence based medicine, evidence, ethics, and economics, there will also be optimal allogeneic blood use and stewardship.[96] **(Figure 2)** PBM is no different than the management of any other organ or body system, normal or dysfunctional. A

sound understanding of physiology and pathophysiology is a *sine qua non* in providing optimal patient care and ensuring the best clinical outcomes.

(Figure 3)

Practice Points

There is an ongoing need for a paradigm shift away from blood supply and safety of allogeneic blood components to PBM.

This paradigm shift is PBM Redux as advocated in 1899.

A patient's hematopoietic system is the starting point and ongoing anchor for PBM.

Research agenda

Large-scale quality improvement initiatives need to be developed using the Donabedian triad (structure, process, outcome) to ensure effective PBM implementation and monitoring.

A criticism of PBM has been a degree of neglect of core physiological and pathological principles with over metrification of blood parameters guiding treatment irrespective of the underlying causation of the abnormal metric. Further research is needed into alternative therapeutic triggers for transfusion of blood products, rather than absolute laboratory thresholds.

The broader public health benefits of PBM need to be further investigated. These include health economics, quality and safety, and blood transfusion need-supply services.

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Box 1: Hamilton Fish's 1899 perioperative "Patient Blood Management" recommendations

Hamilton Fish's 1899 Perioperative "Patient Blood Management" recommendations
• *A solution of the problem of safety in anaesthesia can be attained only in the laboratory, and it is a subject well worthy of the attention of our scientific investigators.*
• *We would see our cases in the earlier stages before the ravages of disease had undermined the general health. The shrunken and debilitated form, the pain-'racked body, the anguished mind of the "last resort," now so familiar a sight, would become but "ghosts and shadows of the past."*
• *The time now required for the performance of many operations would be shortened. Our mortality tables, resulting from surgical. procedures, would be lessened. Instead of the procrastination now so much in evidence, the less severe operations, the shorter time required for their performance, · the smaller amount of anaesthetic vapor inhaled, with a proportionate decrease in the pathological disturbances created, would all tend to place operative surgery upon a pinnacle of safety to which the afflicted would come early for relief. In the blood we have a gauge, the readings of which give us a fairly accurate insight into our patient's general condition.*
• *It is as much the duty of the surgeon to prepare his patient for an operation as it is to exercise the greatest skill at his command in its performance. With the exception of those emergency cases that require immediate surgical intervention to save life, the condition rarely presents itself when sufficient time cannot be given to the thorough understanding of our patient's health in general.*
• *Many deaths-from surgical operations and anaesthetics are believed to be the result of our neglect in employing the means at our command for knowing thoroughly our patient's condition beforehand, and of a non-correction, as far as is possible, of pathological conditions before attempting operative procedures or the production of general anaesthesia.*
• *Neurasthenics, anaemics, chlorotics, leukaemics, and those of a so-called lymphatic temperament, withstand general anaesthetizations and operations poorly, and in all of these the blood shows marked changes from the normal, which is believed to account for the difficulties and dangers attendant upon operative procedures in these individuals.*
• *It is imperative that a routine practice of blood-examinations should be instituted by surgeons and by internes of surgical hospitals in conjunction with the methods established, giving us thereby absolute indications for palliative or radical treatment.*
• *No surgeon's armamentarium is complete and no surgical hospital perfect in detail without the instruments necessary for thorough blood examinations.*
• *These examinations should be conducted with as much care as would be exercised in the methods of an aseptic technique or in a dissection among vital parts during the performance of an operation. The ultimate result depends as much upon the correction, as far as is possible, of the abnormalities found at the preliminary examination as upon those obtained by a rigid aseptic technique and the exercise of the greatest operative skill.*
• *A safe rule to follow is, never produce a general anaesthetization in an individual whose blood shows a haemoglobin percentage of less than 50 per cent. I have demonstrated that safe anaesthesia is dependent upon, first, the percentage of haemoglobin in the blood before, during, and after anaesthetization; and, second, a normal or increased number of the polynuclear neutrophiles. Oligochromaemia, from whatever cause, should invariably be considered as a contraindication for the administration of a general anaesthetic for diagnostic or operative purposes. As this condition is usually dependent upon pathological changes, or is an accompaniment of them, in the formed elements of the blood, the morphology of these must not be overlooked.*
• *A mild leucocytosis of the polynuclear neutrophiles before, during, and after anaesthesia and operation is desirable, as they combat anaesthetic shock, and facilitate wound-regeneration.*

Box 2: Some of warnings from influential clinicians that allogeneic blood transfusion has always been a potentially a hazardous therapy and should only be embarked on if there were no alternatives.

A century of warnings on the safety of blood transfusion and its judicious use	Clinician
Judiciously employed, transfusion will surely prove a valuable, often life-saving, resource; injudiciously employed, it will surely become discredited.	1909 G.W. Crile
At the beginning of the twentieth century, with the discovery of 'blood groups,' it was thought that all danger had been eliminated. At the present time the pendulum is swinging back again, and the problem of the complete elimination of danger is proving more complex than it was thought to be a few years ago."	1922 G.L. Keynes
The transfusion of blood may be a life-saving procedure under certain circumstances, it may be a necessary supportive measure under others, but it is too often undertaken when the doctor can think of nothing else to do after all other therapy has failed. My objective today is to discuss briefly the common surgical and medical conditions for which transfusion of blood is indicated, in which we can expect good physiological results, and to point out those conditions in which it is little more than a gesture, done, as it were, to satisfy the urge to do something.	1936 A.V. Bock
Blood transfusion is ordinarily considered a simple and safe procedure .... but has caused the death of patients with relatively benign ailments from which they could have recovered if only left alone."	1949 A.S. Weiner
Blood transfusion has in recent years developed into a mass-produced remedy which daily presents fresh problems. In the hands of experts it is virtually safe, and very valuable; but there is little doubt that today, in this country as elsewhere, many deaths supposed to have occurred 'in spite of transfusion' have really been caused by it. Administration of fluids is not a duty that should be 'relegated' to inexperienced juniors. In fact, there are few risks in transfusion when the doctor fails to insert a needle or cannula into a vein; they begin to mount once he succeeds.	1949 I.H. Milner
I am unrepentant in condemning the giving of blood during straightforward operations. ....smooth operation should lead to smooth convalescence without biochemical assistance.	1949 W.H. Ogilvie
Thoughtless prescription of blood transfusion is playing Russian roulette with bottles of blood instead of a revolver. While the odds are in the physician's favor that nothing will go wrong, the patient takes the risk.	1953 W.H. Crosby
Blood is an extremely valuable and lifesaving fluid, but it is a potentially lethal fluid. Thought as to whether blood is really needed may remove the hazard altogether.	1968 M.C. Crocker
The ready availability of stored blood, the lack of awareness of its hazards, and the apparent, logical reasons for transfusion have prevented a scientific analysis of the indications for transfusion. No clinical trials have ever been performed to establish the indications for the transfusion of red cells. Anaemia is considered by many to be an anomaly which should always be corrected.	1985 J.P. Isbister

Box 3: Challenges to transfusion practices and drivers for change.

Challenges to blood transfusion practices and drivers for change

- Why is anaemia so often overlooked as a significant, diagnosable, and manageable clinical problem?
- How is it possible that more than 20% of patients awaiting elective hip and knee arthroplasty arrive with undiagnosed and untreated iron deficiency and subsequently receive red blood cell transfusions?
- Why is there such a significant discrepancy in red blood cell transfusion rates for similar standard-risk procedures across different medical institutions and countries?
- Why is there a continuous call for randomised controlled trials comparing restrictive versus liberal strategies to establish the safety of allogeneic red blood cell transfusion, when there is scarcely any evidence proving that red cell transfusions enhance clinical outcomes for anaemic patients who are haemodynamically stable?
- Why do most surrogate endpoints for transfusion efficacy (eg Haemoglobin rise) poorly correlate with improved clinical outcomes?
- Why does the complex interplay of supply, demand, and clinical need present challenges in the field of blood banking and transfusion medicine?
- Why does the precautionary principle dictate decisions on the supply side of allogeneic blood and the opposite has applied, the assimilatory principle on the patient need side?
- Why are there calls for randomized controlled trials to validate the efficacy of PBM, when PBM is essentially a fundamental Oslerian medical practice of diagnosing and treating patients in any clinical scenario?
- Why isn't the haematopoietic system viewed and managed in the same way as other body systems?

Box 4: Echoes of wisdom emanating from the past

William Harvey (1578-1657) Father of Physiology

Blood acts above all the powers of the elements and is endowed with such notable virtues and is also the instrument of the Omnipotent Creator, no man can sufficiently extol its admirable and divine faculties. The heart is the mere organ for its circulation, and it clearly appears that the blood is the generative part, the foundation of life, the first to live, the last to die and the primary seat of the soul.

William Hewson (1739-1774) Father of Haematology

An Inquiry into the Properties of the Blood, it is presumed, will be thought, in a particular manner, interesting, since there is no part of the human body upon which more physiological reasoning is founded, nor any from which more inferences are drawn for the cure of diseases. And, as the Inquiry is made by Experiments upon the Blood as near as possible to the state in which it circulates in the vessels, it is hoped that the conclusions made from them will stand the test of a candid examination, and lead to further observations and improvements.

Elie Metchnikoff (1845-1916) Father of Innate Immunity and Gerontology

Whatever concerns health is of real public interest.

An extensive series of experiments carried out in the last few years has proved that the essence of immunity lies in the living elements of the body, and that it is the phagocytes which deliver, us from our enemies.

Karl Landsteiner (1868-1943) Father of Blood Transfusion

Accordingly, my experiment consisted of causing the blood serum and erythrocytes of different human subjects to react with one another. It became established that both agglutinogens A and B are dominant hereditary characteristics and that transmission of these characteristics follows Mendel's laws.

The first blood transfusion in which the agglutinin reaction was taken into account was carried out by Ottenberg, but it was only during the emergencies of the Great War that the method of transfusion with serological selection of donor was widely adopted - a method which has since remained the normal practice.

American surgeons also recommend the treatment before major operations where the patient is in a weakened condition. The number of transfusions given is surprisingly large, and it may well be that use of this technique has been taken too far.

Denton Cooley (1920-2016) - Father of bloodless Medicine.

"Patient blood management is a compelling concept to pre-empt anemia, correct bleeding disorders, and minimize blood loss. This evidence-based, multidisciplinary approach does not only lead to reductions in the use of blood and blood products, and therefore to considerable cost savings, but-more importantly-it also improves patient outcomes and patient safety. Patient Blood Management has evolved into a widely accepted holistic treatment concept that is a must-have for all modern health care systems."

Figure 1: Drivers for change back to Patient Blood Management.

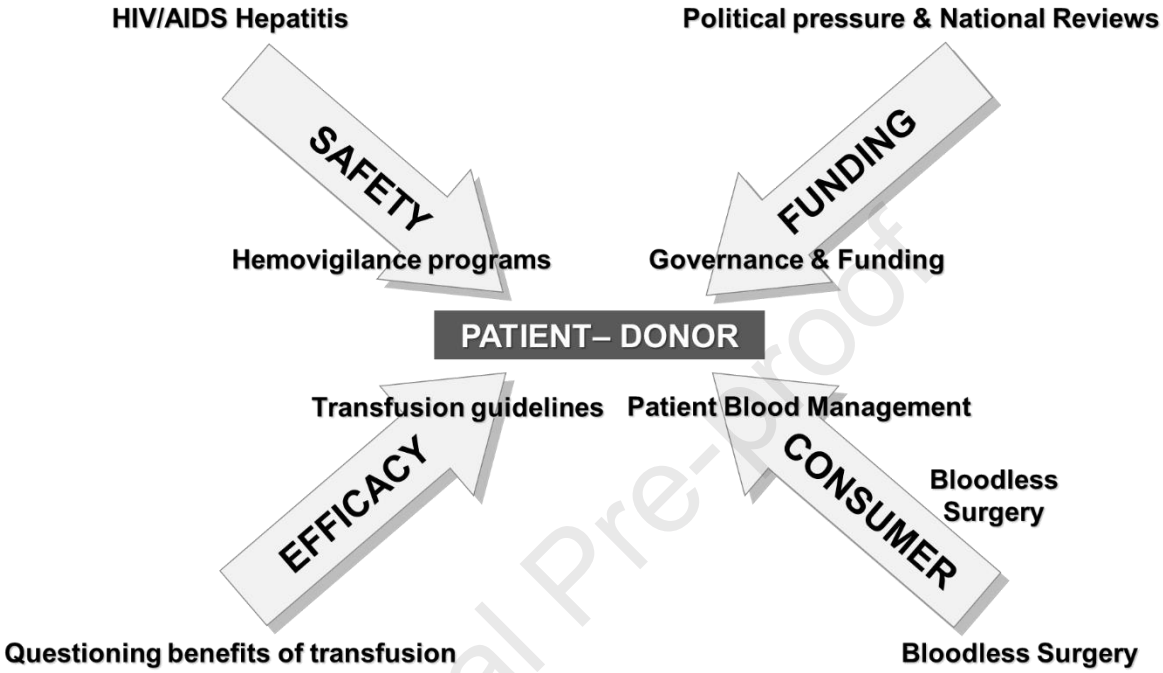
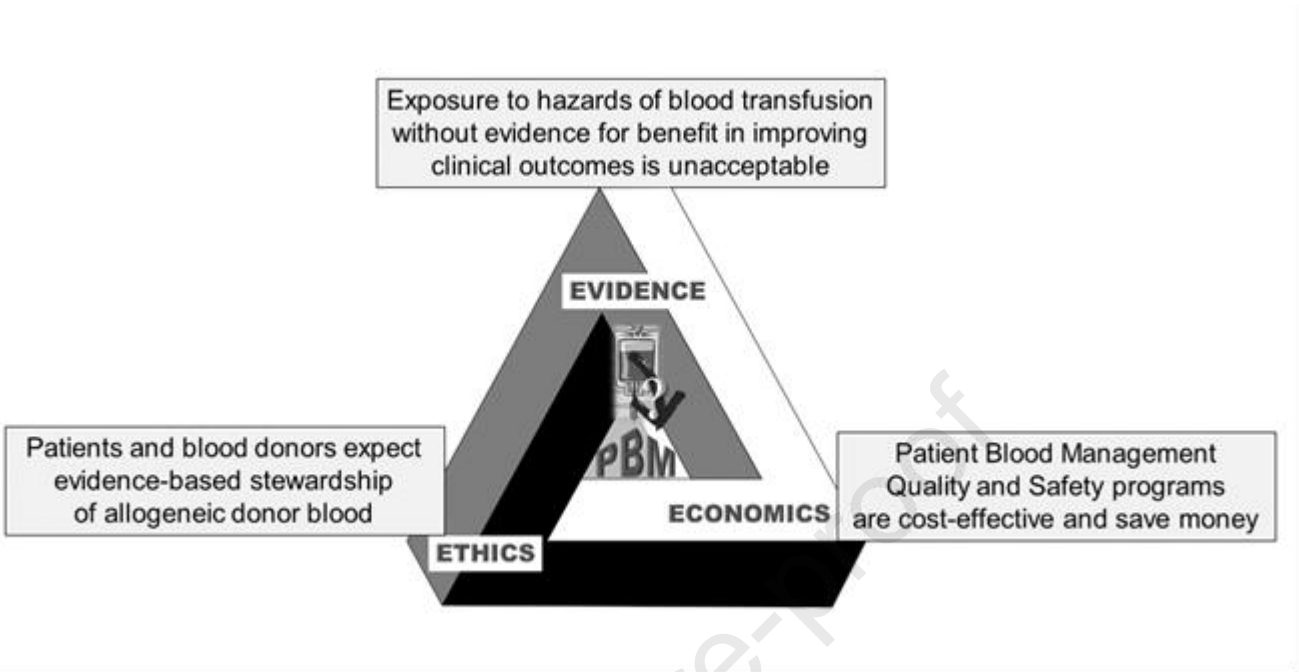


Figure 2: The Three E's of Patient Blood Management



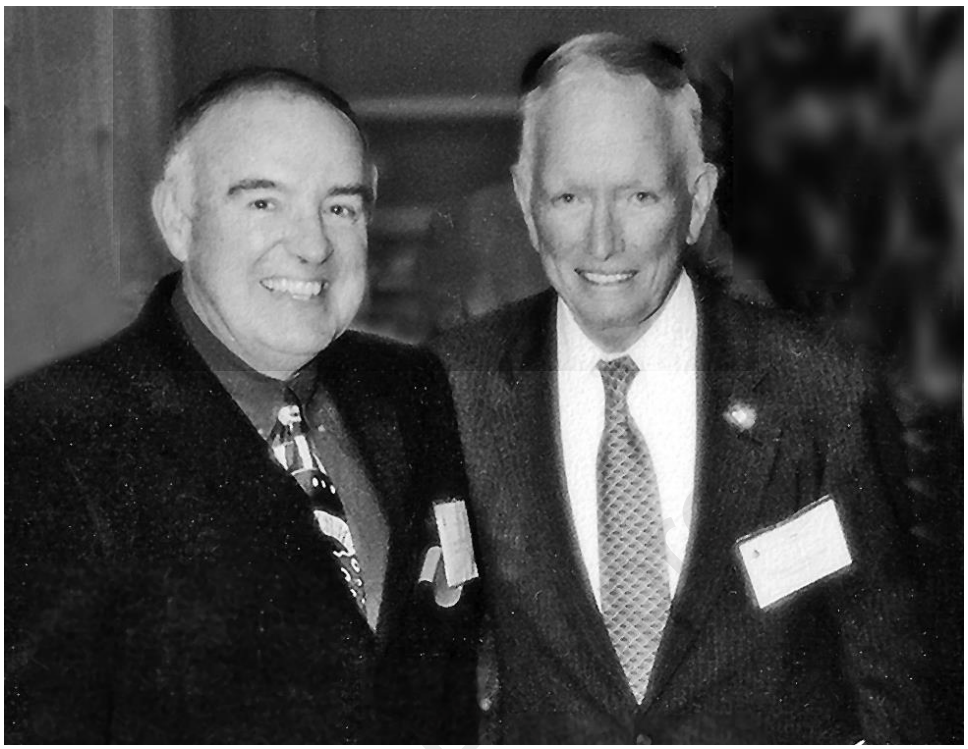


Figure 3

The Author with Denton Cooley in 2005. Cooley, “the father of bloodless medicine” was awarded the 2005 Society for the Advancement of Blood Management president’s award for his contributions to Patient Blood Management.

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4 July 2023

Prof H Van Aken
Editor-in-Chief
Best Practice & Research Clinical Anaesthesiology

Roads travelled: the Journey to Patient Blood Management at 35 Years

NO CONFLICTS OF INTEREST

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