CHAPTER 1

History of blood transfusion and patient blood management

Shannon L. Farmer[1], James Isbister[2], and Michael F. Leahy[3]

[1]School of Surgery, Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Perth, Western Australia;
Centre for Population Health Research, Curtin Health Innovation Research Institute, Curtin University, Perth, Western Australia
[2]University of Sydney, Sydney, Australia;
University of Technology, Sydney, Australia;
Monash University, Melbourne, Australia;
University of New South Wales, Sydney, Australia;
Haematology & Transfusion Medicine, Royal North Shore Hospital, Sydney, Australia
[3]Department of Haematology, Fremantle Hospital and Health Service, Fremantle, Western Australia;
School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia

Introduction

For more than two decades authorities have been calling for a major change in transfusion practice [1]. This is now even more urgent as new challenges continue to emerge. These include supply difficulties due to a diminishing donor pool and an increasing aging and consuming population, spiraling costs of blood and ongoing safety issues. Knowledge of transfusion limitations continues to grow, while a burgeoning literature demonstrates a strong dose-dependent relationship between transfusion and adverse patient outcomes [2, 3]. These factors combine to now make change vital [4].

Historically, changing long-standing medical practice has been challenging – perhaps even more so in transfusion. Despite professional guidelines and educational initiatives, wide variations in transfusion practice exist between countries, institutions and even between individual clinicians within the same institution [5–8]. This suggests that much

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practice may be based on misconceptions, belief and habit rather than evidence.

It is not the first time strongly entrenched belief has been an impediment to scientific progress. Edwin Hubble's description of an expanding universe in 1929 has been hailed as one of the great intellectual revolutions of the twentieth century. However, it has been suggested that, because of knowledge of Newton's law of gravity, an expanding universe could have been predicted over two hundred years earlier [9]. What slowed scientific progress? The widely held belief in a static universe prevailed. The belief was so strong at the time that in 1915 Einstein even modified his theory of relativity to accommodate it [9].

A brief review of the history of transfusion provides some insights as to how a behavior-based practice developed in transfusion and therefore how change may be effected by a more patient-focused approach (Figure 1.1).

Blood: early beliefs and practice

Blood has always been viewed with awe and mysticism. It has been used in rituals, to seal treaties, as nourishment, a curative and poison – all based on the belief that blood had special power [10]. It appears that transfusion of blood was first conceived in Greek mythology where the sorceress Medea shows her ability to transfuse blood to give life to the dead and dying [11]. Athena, the goddess of wisdom, gave some of the blood of the slain Gorgon leader to Asclepius, the god of medicine. Hart notes,

> "This gift of blood became 'the gift of life' and empowered him to revive the dead" [12].

There are reports as early as the seventh century BC of physicians prescribing blood to be drunk to treat a variety of diseases. An ancient Assyrian physician wrote to the king and assured him that his son was "*doing better*" after giving him blood to drink [10]. First-century Greek physician Aretaeus of Cappadocia, describing treatments for epilepsy, wrote "*I have seen persons holding a cup below the wound of a man recently slaughtered, and drinking a draught of the blood!*" [13]. Historian Reay Tannahill reported that in 1483 dying Louis XI of France hoped to recover by swallowing blood from children [14].

Bloodletting was fundamental to the medical care of patients for over 2000 years [15]. It was one of the longest lasting medical practices in history. Yet its acceptance was based on a belief – that disease was caused by an imbalance of blood and other "*humors*" in the body. Bleeding was thought to restore balance. One seventeenth-century proponent of the

	DARK AGES Before 1900	ENLIGHTENMENT 1900–1920s	ALTRUISM 1920s–1960s	MODERNISM 1960s–1980	POST-MODERNISM 1980–1990s	BLOOD SUPPLY MANAGEMENT 1990s	RE-ENLIGHTENMENT 2001–2010	PATIENT BLOOD MANAGEMENT 2011 -
EVENTS	Trial and error in attempts to give transfusions in some cases with success and others ending in disaster	Discovery of ABO blood groups leading to the scientific basis for compatible red cell transfusions.	Commitment of clinicians and donors with anticoagulation and preservation of whole blood to develop blood banks	Improvements in the storage of whole blood, development of blood fractionation and involvement of industry in the blood sector	Increasing concern about transfusion-transmitted infections, hepatitis and ultimately the AIDS catastrophe	Increasing application of precautionary principle on safety of the blood supply resulting in exponential increases in costs	Recognition that transfusion of labile blood components did not have a good evidence base and transfusion *per se* is an independent risk factor for adverse clinical outcomes	Return to a patient focus with shared clinician/patient decision making with meaningful informed consent
FOCUS	**Patient focus** Treatment of mental disorders! attempts to help patients dying from hemorrhage	**Clinician patient/donor focus.** Direct vein-to-vein blood transfusion made possible	**Clinician patient/donor focus** Transfusions for bleeding or profound anemia	**Supply focus** Whole blood and blood products	**Product focus** Viral safety and sufficiency of the blood supply	**Bureaucratic & political economic focus** Blood supply	**Evidence-based medicine focus** Return to a focus on a patient's problem and clinical decision making	**Patient focus** Problem-oriented approach to management of hemopoietic deficiencies
CONCERNS	Why are some blood transfusions potentially lethal?	Saving lives of critically bleeding or anemic patients	Community awareness of the requirement for blood donors	Blood preservation and sufficiency of the blood supply	Blood sector, bureaucracy, politicians, clinicians and patients develop "conflicting" perspectives and agendas as to the quality and safety of blood supply	Product safety and increasing expenditure on the blood supply assuming all transfusions are appropriate	Questioning many long-held assumptions and dogmas about the efficacy and safety of blood transfusion	Ensuring that a patient's own blood is managed appropriately and allogeneic transfusion is only used with patient consent and when there are no other feasible options

Figure 1.1 Transfusion history timeline.

practice, Guy Patin, Dean of the Faculty of Medicine in Paris, wrote: "*There is no remedy in the world which works as many miracles as bleeding*" [16]. It was recommended in various medical texts to treat over 100 diverse ailments including pain, plague, fever, epilepsy, melancholy, liver disease, stroke, even broken bones and hemorrhage [15, 17]. It remained one of the most trusted procedures for treatment of sickness and maintenance of health until the mid-nineteenth century [15].

An example of its "life-saving" therapeutic reputation was reported in 1825 [18]. A French sergeant, who during combat sustained a stab wound through the chest, fainted from blood loss. He was taken to a local hospital where physicians immediately began bleeding him to prevent inflammation. Over the first 24 hours they bled over half his blood volume. Over subsequent days surgeons performed more bloodletting as well as applying leeches to the wound. The patient recovered and was discharged almost 3 months later. The sergeant's physician wrote,

> "by the large quantity of blood lost, amounting to 170 ounces [*almost eleven pints*], besides that drawn by the application of leeches, the life of the patient was preserved."

In this and other cases, physicians saw improvements in the patients' symptoms, reinforcing their belief in the practice. Of interest, Starr notes that bloodletting empowered physicians in the face of diseases they did not understand – finding comfort in the fact that they were doing something for the patient [16]. This practice reinforcement was echoed in the twentieth century by Dunphy in relation to the modern practice of transfusing blood *into* patients. He wrote,

> "Transfusion certainly makes the surgeon feel better, but it may not make the patient feel better. Perhaps we all have a tendency to transfuse to make ourselves more comfortable" [19].

Blood transfusion

The practice of transfusing blood was pioneered during a period of fierce competition between England and France for world ascendency in literature, arts, science and medicine. The quest to perform the first blood transfusion was part of this, and long-held beliefs about blood's qualities were its practice foundation. It was still held that disease was a result of imbalance of humors and that bleeding might "*draw out corruption*." It was also believed that blood carried characteristics and temperament. Thus the first transfusions into humans were performed to treat psychiatric illness,

believing that the blood of a calm animal such as a lamb or calf would calm the "*phrensied*" person [10, 16, 20].

Transfusion with animal blood

Technical advances such as the description of the circulation by William Harvey in 1628 and the development of the "syringe" using a sharpened goose quill by Francis Potter in 1652 and Sir Christopher Wren in 1658 made injection of fluids into vessels possible. Members of the British Royal Society began experiments with injecting a variety of fluids including wine, beer, dye, opium and milk. Experiments with transfusing blood began between 1665 and 1668, with physicians believing it to be the most compatible fluid. The first were animal-to-animal transfusions, followed by animal-to-human transfusions [16, 21].

The English are credited with performing the first blood transfusion experiments. Beginning in 1665 scientist John Wilkins, surgeon Richard Lower and others made numerous attempts at transfusing blood from one dog to another [21]. The first successful animal-to-animal transfusion by Lower was reported in 1666. Speculation developed amongst colleagues as to what behavioral and physical changes transfusion might bring about in the recipient [16, 21]. In France physician Jean Baptiste Denis and colleagues claimed to have conceived the idea of transfusing humans almost 10 years earlier at a meeting in Paris, but only began their experiments in animal transfusions in 1667. They transfused dog blood into dogs, and then calf blood into dogs. They also reported that the transfusion of blood from a young dog into an elderly dog rejuvenated its vigor [21, 22].

These experiments led to the first human transfusion. The first is credited to Denis in June 1667 in which he transfused the blood of a lamb into a 16-year-old described as suffering a "*contumacious and violent fever*," extreme lethargy and being possessed of an "*incredible stupidity*" [21, 23]. Denis' choice of "*mild*" animal blood for transfusion was based partly on his feeling that animal blood was more pure because "*debauchedness, envy, anger, melancholy and passions corrupted human blood*" [23]. He also reasoned that transfusion achieved the same effect as bleeding, without weakening the patient. They would draw out a quantity of blood and replace it with "*new and pure*" blood. Denis reported that physicians had for the past two months been obliged to bleed this patient 20 times "*to make for saving his life*." Denis first withdrew a further 3 ounces of the patient's blood and then transfused him with 9 ounces of the lamb's blood. The patient experienced a transfusion reaction described as "*heat along his arm*", chills and "*soot black*" urine [24]. Yet Denis believed the lamb's

blood worked as the patient's symptoms resolved after the treatment, he being described as "*cheerful*," livelier and "*possessing a clear and smiling countenance*." Denis wrote,

> "that all these admirable effects undoubtedly proceed from that little Arterial blood of the Lamb, which having been mixt with the mass of his thick blood, was like a ferment to it, to rarifie and attenuate it more than ordinary."

The British, smarting at being beaten by the French, quickly followed this first animal-to-human transfusion with their own. Richard Lower and his colleague Edmund King paid one Arthur Coga 20 shillings to transfuse him with sheep's blood. He had been described as being *"a little frantic."* There appeared to be little adverse effects from the transfusion and a second was performed a week later because he still appeared to be "*a little cracked in the head*" [21, 25].

Rivalry intensified between the competitors, as did opposition from opponents of the practice [11, 21, 22]. The apparent good effects of the transfusion on some patients' symptoms fitted with its proponent's belief about blood and its character. This encouraged them to continue the practice despite its opponents and the yet-to-be-understood acute adverse effects of the transfusion they were observing. Denis continued his experiments with one patient dying and another with paralysis being viewed as cured. His most famous transfusion was in 1667 when he transfused calf's blood into Antoine Mauroy to treat his mania. The 34-year-old "*madman*" suffered "*phrensies*" during which he would swear and beat his wife, strip and run naked through the streets, setting fire to houses on the way. Denis and his assistants transfused Mauroy with "*mild*" calf blood in the hope of allaying "*the heat and ebullition*" of the patient's blood. The transfusion was stopped when Mauroy experienced a severe hemolytic reaction. The patient survived, and the next morning he appeared to be a much calmer man. Emboldened perhaps by the apparent success of the treatment, Denis performed a second and greater blood volume transfusion. After sixteen ounces of calf's blood was transfused the patient experienced an even more severe hemolytic reaction and the transfusion was stopped. The next morning he "*made a great glass full of urine, of a colour as black, as if it had been mixed with the soot of chimneys*." He survived, however, and it appeared he had been cured by the treatment. He was later calm, in great presence of mind and polite. Denis announced broadly the success of his treatment [11, 16, 20, 21].

Almost two months later Mauroy's mania returned and Denis was asked by the man's wife to carry out a third transfusion. The patient died the day after Denis' unsuccessful attempt to administer it. The death resulted

in a charge of murder being brought against Denis, from which he was later acquitted with the court finding that Mauroy's wife had poisoned him. Recent reports suggest there may be greater intrigue surrounding this case [11].

The Faculty of Medicine in Paris subsequently proclaimed transfusion dangerous and scientifically unsound. In 1670, the French parliament banned the practice. After two more deaths from transfusions in Rome, the Pope banned transfusion in most parts of Europe, and England quietly discontinued the practice [21].

First human blood transfusion

The practice of transfusions remained almost dormant until the early 1800s. By this time advances had been made in understanding anatomy, physiology, blood and the dangers of hemorrhage. English obstetrician James Blundell, concerned about the high mortality associated with postpartum hemorrhage, saw blood transfusion as a means of replacing lost blood. After animal experiments he concluded that only human blood should be transfused into humans and only to treat blood loss, not madness. He performed the first human blood transfusion in 1818 to treat a man suffering internal hemorrhage. The patient did not survive. After three more failures he transfused a woman with postpartum hemorrhage who survived. Over 10 years Blundell performed 10 transfusions with 5 patients surviving [16, 26].

Although they gained popularity, transfusions remained problematic throughout the rest of the nineteenth century. With no knowledge of anticoagulation and storage, transfusions were performed direct from donor to recipient and blood clotting in the apparatus was common. Additionally, physicians had no understanding of blood types. Alfred Higginson, a surgeon from Liverpool, performed seven transfusions from 1847–1856. Although five of the seven patients died, Higginson concluded, "*transfusion may fairly be said to be of use*" [27]. Statistics compiled in 1873 found that mortality from transfusion was 56 per cent [16]. Starr reports that the pioneer of modern surgery, Theodor Billroth, and others "*denounced transfusion as a showpiece that brought attention to the clinic at the expense of the patient*" [16].

Karl Landsteiner to the twenty-first century

By the end of the nineteenth century progress had all but ceased and it seemed there was no way forward for transfusion as a medical therapy. Many clinicians probably questioned how blood transfusion could be

"miraculously" life-saving in some cases, but lethal in others. The answer came at the dawn of the twentieth century with allogeneic blood transfusion moving out of the dark ages. In 1900 Karl Landsteiner outlined the background of his rediscovery of Mendelian genetics [28, 29]. To quote from the 1930 Nobel Prize award ceremony speech, "*Thirty years ago, in 1900, in the course of his serological studies Landsteiner observed that when, under normal physiological conditions, blood serum of a human was added to normal blood of another human the red corpuscles in some cases coalesced into larger or smaller clusters. This observation of Landsteiner was the starting-point of his discovery of the human blood groups*" [30].

A year later Landsteiner expanded on his observations, describing what is now recognized as the discovery of the ABO blood group system. It was some years before his landmark discovery resulted in the reinvigoration of interest in blood transfusion and its establishment as a therapy. To follow was the development of methods for the collection, anticoagulation, preservation and fractionation of allogeneic blood.

The history of modern transfusion had its origins at the bedside. In its early days the procedure centered on a patient and their clinical problem. The clinician responsible for diagnosing and managing the patient took the initiative in identifying the need for transfusion, for seeking out a blood donor, organizing the blood collection and performing the transfusion. This was usually by direct vein-to-vein transfer. In some respects there was, in today's terminology, a "conflict of interest," in that the clinician was responsible for both the donor and the recipient. There was thus a direct link between the donor and the recipient and overseen by the clinician.

Although citrate had been used as an *in vitro* anticoagulant in the late nineteenth century and in animal blood transfusions, it was not until 1914 that citrated blood transfusions in humans were first documented [31, 32]. It was during WWI that transfusion of citrated blood established its role in clinical practice and it was another Nobel prize winner of penicillin fame, Alexander Fleming, who published a large series of citrated blood transfusions for treating war casualties [33]. There was some debate at this time as to the best method for maintaining fluidity of donor blood following collection, and although a case was made for defibrination, citration became the accepted method. Logistically, defibrination was more difficult, but in retrospect it probably had the advantages of leucodepletion and better *in vitro* preservation [34].

With the development of effective methods for the anticoagulation, preservation and transport of blood, particularly during the Spanish civil war and WWII, the donor became separated from the recipient in time

and place [35]. Vein-to-vein transfusions had been a lucrative procedure for surgeons of the day and they initially were reluctant to relinquish their control and vested interests in the supply side of blood transfusion [16]. However, the inevitable consequence was the evolution of large, centralized blood banks, involved in the mass collection and fractionation of blood. In many circumstances these developments resulted in the centralizing of blood transfusion expertise into blood banks geographically isolated from the clinical workface. Accordingly, most transfusion policy development has been determined by the central blood bankers, where the predominant concern was the recruitment of donors and the processing and distribution of blood. At first this was considered to be of little consequence, especially as the safety and interests of the donors were ensured. However, over the years a knowledge gap developed as expertise in blood transfusion was increasingly donor-related. Marshall McLuhan's aphorism "*the medium is the message*" found an analogy in modern blood transfusion. The initial emphasis on the why and when recipient-focus of blood transfusion was eclipsed by a what, how and how much donor-focus. Clinicians no longer had responsibilities in obtaining donor blood and were constantly assured by suppliers that transfusions were safe and effective.

For over two decades there have been references in the lay press alluding to the excessive focus on blood supply to the detriment of a patient focus as illustrated by the following: "*Blood services are a product of their past. They were born in crisis in the 1940's to help victims of war and conflict and depend on the altruism of donors to give blood for the benefit of others. It is the others, the patients, who may be forgotten by centralised services. It is time for blood transfusion services to focus on the people who receive blood as much as – if not more than – those who donate it*." Glennys Bell "Vein Glory" The Bulletin July 1991.

It was during the 1970s with the development of *in vivo* cell separators for the collection of blood components that bedside clinicians, generally clinical hematologists, again became interested and involved in transfusion medicine [36]. Additionally, there has been a rekindling of interest in the use of fresh whole blood as the impact of the storage lesion is increasingly being questioned, especially in the massive hemorrhage/transfusion setting [37, 38].

New transfusion issues emerge

Transfusion-transmitted hepatitis B had a devastating impact on US servicemen during WWII [39]. During the 1970s hepatitis C infected over

20% of multi-transfused patients in the United States [40]. However, the real shock did not occur until the 1980s when it was realized that acquired immunodeficiency syndrome (AIDS) was not restricted to gay men, drug addicts and Haitians, but that hemophiliacs were contracting it from their factor VIII therapy [41]. Although allogeneic blood transfusion has always been associated with recognized immunological, infective and other hazards, it was the appearance of AIDS that became the tipping point, stimulating a wide and in-depth analysis of the risk–benefit equation for blood transfusion.

The initial presumption that an infectious agent, for which there was no *in vitro* test, was responsible for AIDS meant the only possible strategies to minimize transfusion transmission were to avoid transfusion, exclude high risk donors or adopt available autologous blood transfusion techniques. With this, the concept of "alternatives" to blood transfusion began and has persisted. Although an understandable term the reality is that most "alternatives" are actually optimal medical management. However, at the time, an evidence base for many of the strategies was lacking, so action was predominantly taken on the basis of the precautionary principle.

There were assurances that, despite concerns, all was being done to make donor blood as "safe as it has always been" perpetuating complacency by clinicians, bureaucrats, and to a degree, patients.

> "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" [42].

A November 1983 article in the Wisconsin Medical Journal "*Is our blood supply safe?*" gave no hint of the AIDS tragedy that was to come [43].

> "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."

Most clinicians insisted they had a good understanding and evidence-base for the indications and benefits of transfusions and were prepared to accept this "minute" risk and believed that any other risks were minimal. However, as one of the author's mentors used to say, "*it may well be a rare*

disease, but is very common for the person who has it." Unfortunately, it was the patients accepting the risks and clinicians were, to a significant extent, confidently practicing in an "evidence-free zone." It was a tragedy that many patients in whom there was no valid and evidence-based indication for the transfusion contracted and died from transfusion-transmitted human immunodeficiency virus (HIV) infection.

Blood transfusion had grandfathered its way into medical therapeutics and become culturally imbedded into clinical practice, with benefit being assumed and risks regarded as minimal. However, there were repeated warnings as early as 1920 and during the 1940s from doyens of blood banking and transfusion medicine to the clinical community that transfusion remained and always will remain a potentially hazardous procedure for which the risks and benefits in terms of patient outcome need to be judiciously evaluated on an individual patient basis.

To quote from the archives:

> "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."
>
> *(Keynes 1922) [44]*

> "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."
>
> *(Weiner 1949) [45]*

> "Clinicians would be less confident in the safety of blood, and therefore more eclectic in its use, if they kept in mind the many possibly weak links in the chain of its production. It has to be remembered that all reactions, and they are not as uncommon as they should be, increase the burden borne by the patient. 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. It is not just a problem of minor surgery. 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."
>
> *(Milner 1949) [46]*

It is only in recent years that there has been a concerted effort to establish a more sound evidence base for the benefits and hazards of transfusion in the wide range of clinical settings in which it is, may be, or is not, appropriate therapy. There has been a gradual awakening over the last 25 years throughout the blood sector, clinical practice, bureaucracies, governments, the community and the legal profession that, as Bob Dylan would have expressed, "the times they are a changin." There have been several drivers for change. The reassessment of the safety of transfusion in the context of questionable efficacy in improving clinical outcomes has been high on the agenda. Governments have become more focused on the blood sector leading to numerous national reviews, economic evaluations and, in some circumstances, criminal proceedings against individuals [47, 48]. The concerns about transfusion safety generally focus around transfusion-transmitted infections with increasing expenditure on ensuring infectious safety of the blood supply chain. Admirable as this may seem, the downside is the escalating costs, diversion of attention from the overall hazards of transfusion and the lack of an evidence base for improving clinical outcomes in many clinical settings [49].

There is no questioning the valuable and evidence-based role for fractionated plasma products in the management of many specific diseases, e.g. hemophilia, hypogammaglobulinemia, prevention of hemolytic disease of the newborn and others. However, the same cannot be said for the use of the labile blood components, i.e. red cells, platelets and plasma. Indeed the overwhelming accumulation of observational data implicates labile blood components as an independent risk factor for adverse clinical outcomes in hemodynamically stable patients [3].

It is rather ironic that, 100 years after the discovery of blood groups, the dawn of the twenty-first century saw the beginning of a re-analysis of why many patients were receiving transfusions that are exposing them to significant risk without evidence for meaningful clinical benefit. More and more expenditure is directed at the supply side to make products safer from infection transmission when on the demand side questions are being asked about transfusion efficacy [49]. There is unconvincing logic in making a therapeutic product safer and safer at great expense when evidence for efficacy is lacking. Few would doubt the role of transfusion in the management of hemorrhagic shock, critical life-threatening anemia, the development of major surgery procedures, the provision of blood-component therapy for specific cellular or plasma deficiencies and the development of hematological supportive care for the management of hematological malignancies. However, as the insatiable demand for allogeneic blood has continued, the usual response has been: "We need

more donors, and more blood should be fractionated." The question, "Where is all the blood going, and are all the transfusions really necessary?" is less commonly addressed. Benchmarking studies in various patient populations have revealed major differences in red cell transfusion practices for comparable patient groups [5, 8, 50]. It is difficult to explain the significant variations in transfusion rates within individual countries and internationally.

When demand appears to be outstripping supply and cost-effectiveness is being questioned, concern has been expressed with regard to:

- excessive perioperative transfusion of blood during uncomplicated elective surgery with accumulating evidence that red cell transfusion adversely impacts on clinical outcome
- unnecessary compatibility testing of blood for elective surgery
- inappropriate use of blood components without a clear identification of the patient's hematological problem, and failure to consider more appropriate therapy, e.g. treating iron deficiency
- the lack of awareness of the numerous hazards of allogeneic blood transfusion, a therapy having the widest range of potential adverse consequences
- wastage of costly donated blood due to inappropriate transfusion and expiry.

When making decisions in transfusion there has been a tendency to ask the wrong question. Clinical practice guidelines, especially for blood component therapy, have been falling into the common trap of starting with an answer before the question has been clearly considered. This is a similar error to that which is commonly made in marketing when a business does not clearly identify the sector in which it is operating, known as marketing myopia. The point is emphasized and illustrated in the classic Harvard Business Review article by Levitt in 1960. In the early history of railroads the tycoons considered they were in the business of making railroads, when in fact they were in the transport business [51]. As a result they were not able to adapt appropriately when other means of transport became available. By analogy, transfusion medicine is in the business of improving clinical outcomes, not primarily blood banking to transfuse patients. Clinical outcomes are improved by evidence-based diagnosis and therapy of diseases in which blood component therapy may have a role to play and the risks are acceptable.

In this context, the primary responsibility of clinicians is to manage a patient's own blood as a precious and unique human resource that should not be wasted, and consider donor-sourced allogeneic blood components when there is no other option. This more recent concept of patient blood

management is increasingly focusing on the patient and their clinical problems, as well as giving them a greater role and responsibility in their own clinical management. This shift towards a patient blood management philosophy in clinical practice is in contrast to behavior-based transfusion management as the main focus. Parallel to this paradigm shift is greater emphasis on clinical decision making based on sound scientific evidence and empowering of patients to be part of the process. Experiences with Jehovah's Witness patients in the early days of cardiac surgery sent a sobering message, challenging the dogma that it was impossible to operate without the use of blood transfusion. Most surgeons refused to take on such "high-risk" patients. It took the courage of Dr Denton Cooley, one of the fathers of cardiac surgery, to convince the medical community that major surgery could be undertaken on such patients if there was meticulous attention to preoperative, intraoperative and postoperative management of the patient's own blood [52]. His work, which became known as "bloodless surgery" or "transfusion-free surgery," was the foundation of patient blood management. Subsequently, there have been further observational studies on cardiac surgery in Jehovah's Witness patients confirming that, not only is surgery successful, but clinical outcomes in terms of adverse events may be better [53–55].

The history of blood transfusion is dotted with resistance to the implementation of new therapies and changes in clinical practices despite their being based on sound evidence. In many cases it is not new evidence that should have changed practice, but rather a reconsideration of the basic sciences and soundly based clinical decision making. Transfusion medicine has numerous examples of ironies, contradictions and resistance to change (Table 1.1).

The new paradigm

The "new" paradigm is a rebirth of the original. Evidence-based medicine and patient blood management should view a patient's own blood as a valuable and unique natural resource that should be conserved and managed appropriately. Altruistically donated blood is given in trust and is a valuable community resource. However, it is a costly resource with significant potential for harm. It should only be used as therapy with patient consent and when there is evidence for potential benefit, potential harm will be minimized, and there are no other feasible management options.

Paradigms shift suddenly or slowly depending on the "push-pull" factors which, as we have described in the case of blood, are numerous and complex. However, it is difficult to deny that the mission statement

Table 1.1 Ironies and contradictions in transfusion.

increasing expenditure on improving the safety of a therapeutic product when efficacy in many clinical settings has not been established; indeed in many of these circumstances the transfusion is an independent risk factor for adverse outcomes
labile blood products are the most widely used, yet have the highest potential for harm and a poor evidence base for their indication
Jehovah's Witness patients, who will not accept blood transfusion, have demonstrated that most major surgical procedures can be performed without the use of allogeneic blood transfusion
mechanistic evidence for adverse clinical outcomes from allogeneic transfusion not being acted upon until statistics-based research establishes level I evidence from randomized controlled trials (RCTs)
extreme application of the "precautionary principle" on blood supply side not based on any acceptable cost-benefit analysis, in contrast to application of the "assimilatory principle" on the demand side where cost-effectiveness can be justified
demands for "use by dates" for allogeneic blood for intravenous administration being established by *in vivo* human RCTs, in contrast to food for oral consumption being determined using *in vitro* mechanistic evidence, not RCTs
regarding minimizing bleeding and correction of treatable anemias as "alternatives" to allogeneic blood transfusion
perception that PBM is "an intervention" when in reality it is soundly based "good clinical medicine" in which a patient is diagnosed, treated, monitored and followed up appropriately
the concept that PBM is "appropriate transfusion practice" and "hemovigilance," perpetuating the paradigm that transfusion medicine is donor/product-centric and not patient-centric
recruiting blood donors by marketing rather than behaviour-based research approaches
deterministic causation establishing the serious hazards of blood transfusion with product safety interventions rarely based on levels of evidence from statistic based research, as required by evidence-based medicine

of modern medicine is to make sick people better and keep well people well. Whenever there are conflicting paradigms, as with any debate, middle ground can be difficult to find and the language can be hijacked by either side using words and terminology to mean what they want them to mean. Transfusion alternatives, blood management, precautionary principle, blood conservation and appropriate transfusions are examples for which the meaning may be different from the blood supply and demand perspectives.

The introduction of the term "blood management" and the formation of the Society for the Advancement of Blood Management (www.sabm.org) were driven from the demand/patient perspective, but blood bankers have regarded blood management as managing the supply. At a Board Meeting of the Medical Society for Blood Management (www.bloodmanagement.org) convened in Prague 2005, a Board member

and one of the authors (JI) advocated strongly that the problems of the language needed to be addressed to ensure that the direction for the new paradigm was towards the *patient*. From this time it was proposed that the terminology should be "Patient Blood Management." Consideration of other aspects of confusion with the language ensued, questioning the use of several of the above examples that implied a primary donor/supply focus for the blood sector rather than a patient focus.

Patient Blood Management is ***not*** an "intervention" per se. It is goal-oriented patient care based on sound evidence and cooperative inclusion and empowerment of patients when possible, with the aim of improving clinical outcomes [56, 57]. This book outlines how this concept can be effectively and safely incorporated into clinical practice.

References

1 Isbister JP. The paradigm shift in blood transfusion. Med J Aust. 1988 Mar 21; 148(6):306–8.
2 Hofmann A, Farmer S, Shander A. Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management. The Oncologist. 2011;16 Suppl 3:3–11.
3 Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. Transfus Med Rev. 2011 Apr;25(2):89–101.
4 Leahy MF, Muhktar S. From blood transfusion to patient blood management: a new paradigm for patient care and cost assessment of blood transfusion practice. Intern Med J. 2012 Mar;42(3):332–8.
5 Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB, Jr., Peterson ED, Gammie JS, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. JAMA. 2010 Oct 13;304(14):1568–75.
6 Hofmann A, Farmer S, Towler SC. Strategies to preempt and reduce the use of blood products: an Australian perspective. Current Opinion in Anaesthesiology. 2012 Feb;25(1):66–73.
7 Gombotz H, Rehak PH, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. Transfusion. 2007 Aug;47(8):1468–80.
8 Rao SV, Chiswell K, Sun JL, Granger CB, Newby LK, Van de Werf F, et al. International variation in the use of blood transfusion in patients with non-ST-segment elevation acute coronary syndromes. Am J Cardiol. 2008 Jan 1;101(1):25–9.
9 Hawking SW. The illustrated A brief history of time. Updated and expanded ed. New York: Bantam Books; 1996.
10 Farmer S, Webb D. Your Body, Your Choice. Singapore: Media Masters; 2000.
11 Tucker H. Blood work : a tale of medicine and murder in the scientific revolution. 1st ed. New York: W.W. Norton; 2011.
12 Hart GD. Descriptions of blood and blood disorders before the advent of laboratory studies. British Journal of Haematology. [Historical Article Portraits]. 2001 Dec;115(4):719–28.

13 Aretaeus, AF. The extant works of Aretæus, The Cappadocian. London, 1856.
14 Tannahill R. Flesh and blood : a history of the cannibal complex. London: Hamilton; 1975.
15 Kuriyama S. Interpreting the history of bloodletting. J Hist Med Allied Sci. [Biography Historical Article]. 1995 Jan;50(1):11–46.
16 Starr DP. Blood: an epic history of medicine and commerce. 1st ed. New York: Alfred A. Knopf; 1998.
17 Blood-letting. British Medical Journal. 1871;a(533):283–91.
18 Delpech M. Case of a wound of the right carotid artery. Lancet. 1825;6:210–13.
19 Dunphy JE. Ethics in surgery: Going beyond good science. Bull Am Coll Surg. 1978;63(6):8–12.
20 Farr AD. The first human blood transfusion. Med Hist. [Biography Historical Article]. 1980 Apr;24(2):143–62.
21 Myhre BA. The first recorded blood transfusions: 1656 to 1668. Transfusion. 1990 May;30(4):358–62.
22 Walton MT. The first blood transfusion: French or English? Med Hist. [Historical Article]. 1974 Oct;18(4):360–4.
23 Denis J. A letter concerning a new way of curing sundry deseases by transfusion of blood, Written to Monsieur de Montmor, Counsellor to the French King and Master of Requests. Philos Trans R Sc Lond. 1667;2(27A):489–504.
24 Denis J. Report of transfusion. Le Journal des Scavans. 1667;1:272–84.
25 Samuel Pepys diary and correspondence. London: Beckers; 1876–1879.
26 Spiess BD, Spence R, Shander A, editors. Perioperative Transfusion Medicine. Philadelphia: Lippincott Williams & Wilkins; 2006.
27 Higginson A. Report of Seven Cases of Transfusion of Blood, with a Description of the Instrument by the Author. Liverpool Med Chir Journ. 1857;1:102–10.
28 Landsteiner K. Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe. Zentbl. Bakt Orig. 1900;27:357–62.
29 Landsteiner K. Ueber Agglutinationserscheinungen normalen menschlichen Blutes. Wien Klin Wochenschr. 1901;14:1132–4.
30 Hedrén G. Award Ceremony Speech for Karl Landsteiner. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1930/press.html. Accessed 29 Nov 2013.
31 Hustin A. Note sur une nouvelle meÂthode de transfusion. Annales et Bulletin des SeÂances: SocieÂteÂ des Sciences MeÂdicales et Naturelles de Bruxelles. 1914(72e AnneÂe):104–11.
32 Agote L. Nuevo procedimiento para la transfusion del sangre. Anales Del Instituto Modelo de Clinica MeÂdica. 1915;1:24–31.
33 Fleming AF, Porteus AB. Blood transfusion by the citrated method. Lancet. 1919 June 7:973–5.
34 Platt R. Blood Transfusion: A plea for the defibrination method. Lancet. 1926 Jan 23:173–5.
35 D'Alessandro A, Liumbruno G, Grazzini G, Zolla L. Red blood cell storage: the story so far. Blood Transfus. 2010 Apr;8(2):82–8.
36 Isbister JP. Cytapheresis: the first 25 years. Ther Apher. 1997 Feb;1(1):17–21.
37 Kaufman R. A fresh take on whole blood. Transfusion. 2011 Feb;51(2):230–3.

38 Wang D, Sun J, Solomon SB, Klein HG, Natanson C. Transfusion of older stored blood and risk of death: a meta-analysis. Transfusion. 2012 Jun;52(6):1184–95.
39 Seeff LB. Transfusion-associated hepatitis B: past and present. Transfus Med Rev. 1988 Dec;2(4):204–14.
40 Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. Blood. [Historical Article Review]. 2008 Oct 1;112(7):2617–26.
41 Evatt BL. The tragic history of AIDS in the hemophilia population, 1982–1984. Journal of Thrombosis and Haemostasis: JTH. [Historical Article Review]. 2006 Nov;4(11):2295–301.
42 Bove JR. Transfusion-associated AIDS–a cause for concern. N Engl J Med. 1984 Jan 12;310(2):115–6.
43 Fritz RD, Menitove JE. Is our blood supply safe? Wisconsin Medical Journal. 1983 Nov;82(11):26–7.
44 Keynes G. Blood Transfusion: Dangers of Blood Transfusion. Oxford Medical Publications. 1922;Chapter 4:67.
45 Weiner AJ. Foolproof Blood Transfusions. The Lancet. 1949 June 18; 253(6564):1073–4.
46 Milner IH. Foolproof blood transfusions. The Lancet. 1949 July 30; 254(6570):217.
47 Wilson K. The Krever Commission–10 years later. CMAJ. 2007 Nov 20;177(11): 1387–9.
48 Simons M. Courtroom anguish as France tries 4 over tainted blood. The New York Times. [News Newspaper Article]. 1992 Jul 31:A1, A6.
49 Shander A, Fink A, Javidroozi M, Erhard J, Farmer SL, Corwin H, et al. Appropriateness of allogeneic red blood cell transfusion: the international consensus conference on transfusion outcomes. Transfus Med Rev. 2011 Jul;25(3):232–46 e53.
50 Gombotz H, Rehak P, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. Transfusion. 2007;47(8):1468–80.
51 Levitt T. Marketing Myopia. Harvard Business Review. 1960(July–August):45–56.
52 Ott DA, Cooley DA. Cardiovascular surgery in Jehovah's Witnesses. Report of 542 operations without blood transfusion. Jama. 1977 Sep 19;238(12):1256–8.
53 Emmert MY, Salzberg SP, Theusinger OM, Felix C, Plass A, Hoerstrup SP, et al. How good patient blood management leads to excellent outcomes in Jehovah's witness patients undergoing cardiac surgery. Interact Cardiovasc Thorac Surg. 2011 Feb;12(2):183–8.
54 Reyes G, Nuche JM, Sarraj A, Cobiella J, Orts M, Martin G, et al. Bloodless cardiac surgery in Jehovah's witnesses: outcomes compared with a control group. Rev Esp Cardiol. 2007 Jul;60(7):727–31.
55 Pattakos G, Koch CG, Brizzio ME, et al. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. Archives of internal medicine 2012;172:1154–60.
56 Bardes CL. Defining "patient-centered medicine". N Engl J Med. 2012 Mar; 366(9):782–3.
57 Barry MJ, Edgman-Levitan S. Shared decision making–pinnacle of patient-centered care. N Engl J Med. 2012 Mar;366(9):780–1.