ISSN: 2753-7919
British Journal of Healthcare and Medical Research; Vol. 13 No. 01 (2026) (322-328)
https://doi.org/10.14738/bjhr.1301.19916

Where does the Vein-To-Vein Transfusion Chain Start?

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Abstract: Blood transfusion has been subject of scientific thinking within health care since the 16th century based on disease expressions and therapeutic and supportive innovative ideas on how and what to transfuse from one individual to another. While exploring quite a number of mysteries were found which needed to be unraveled. History learns the difficulties to overcome and the development of the science and technology needed to safely treat and support patients in need. There is a demand for and a use of blood and blood components or products which create a need. As the transfusion of blood or blood components is a transplant practice, immunology and compatibility, cells and proteins but also materials (surface phenomena) need to be looked for and into. In the 1970s the 'vein-to-vein transfusion chain' came to life, interpreted and practiced starting with the source (blood donors) followed by the processing of the donated blood and ending with the patient to transfuse. Asking the question: Where does the vein-to-vein transfusion chain start?, needs a change in scientific thinking, operations and education. This despite the fact that the right quality treatment and support (pharmaceutical or other interventions) play an important role (need or requirement).

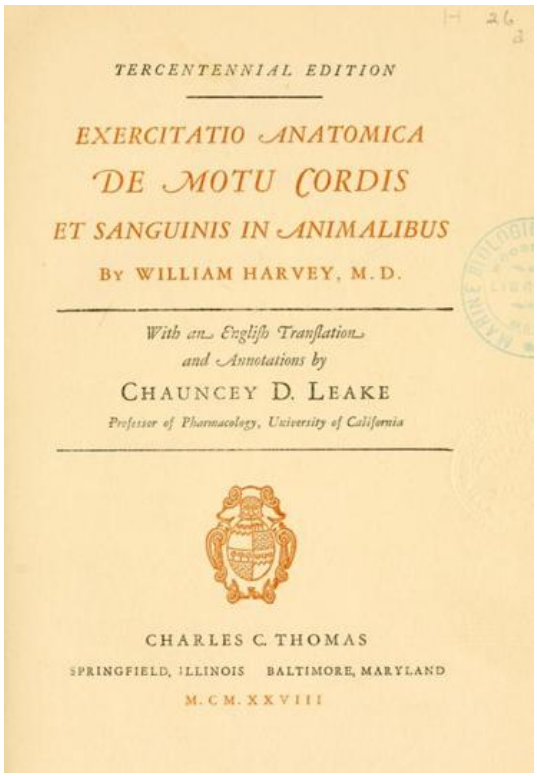
Keywords: blood transfusion, history, vein-to-vein transfusion chain, patient care, use, demand, Need.

INTRODUCTION

Transfusion of human and animal blood has been in the mind of physicians since the 16th Century. These blood driven practices were largely indicated by mystic and magic, albeit with a definite type of logic in the medical scientific thinking over the indication and prescription. During the early Renaissance epoch, the scientists Hieronymus Dardanus from Milan, Italy and Magnus Pegelius from Rostock, Germany suggested with a certain vision that transfusion of blood from one individual to another should be feasible. However, during the following period of the 16th century no further documents could be retrieved indicating further research and progress to evidence their hypothesis. In 1615, early in the 17th Century, Andreas Libavius, a philosopher, PhD in Medicine and naturalist from Halle, Germany, debuted his strong plea for the transfusion of blood and described in detail a method for such transfusion using a silver catheter for an arterio-arterial shunt from donor to recipient. He was remarkably much concerned with the health of the donor – *"Let the young man (donor) not suffer from weakness, provide him good care and food."* [1]

An early though important milestone in the history of transfusion medicine has been the academic experimental study and discovery in 1613, and ultimate description in 1628 of the blood circulation by the advanced English court physician and naturalist William Harvey in his famous monography 'Excertatio Anatomica de Modu Cordis et Sanguinis in Animalibus.'

(Figure 1) The book solicited uncurbed speculations on the possibilities to transfuse blood and infuse medicines intravenously [2].


TERCENTENNIAL EDITION

EXERCITATIO ANATOMICA
DE MOTU CORDIS
ET SANGUINIS IN ANIMALIBUS

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Fig. 1: William Harvey's Publication

HOW DID BLOOD TRANSFUSION START?

In the same year 1628 Giovanni Colle, a philosopher and physician from Padua, Italy suggested the idea that transfusion of blood might prolong human life [3]. During the 17th century several scientists contested for the honor to be the first to transfuse a patient with blood. Probably the eccentric painter and experimentalist Francis Potter, Fellow of the Royal Society in London, was the first to develop a practical method for the transfusion of blood in humans. The idea was based on the myth of Medea in Ovidius' Metamorphosis, using goose quill-feather and a system of tubes. His animal experiments, however, were not really successful. In 1680 Francesco Folli, physician and scientist from Florence, Italy published his Stadera Medica in which he describes his brilliant technology to transfuse blood; he designed a silver pipe which was inserted in the vein of a recipient and an artery of an animal [4]. In 1654 Folli claimed to have done successful experiments, but a continuation is not recorded since then. However, in 1658 at a scientific meeting in Paris, the Benedict friar Robert des Gabets published a new method to transfuse blood, based on an invention of the mendicant friar Pichot consisting of 2 silver cannulas connected through a small leather bag. Most likely the first public demonstration was given by the English physician and anatomist Richard Lower in 1665 in Oxford, England. This experiment was done connecting the venae jugularis of two dogs. Unfortunately, the blood clotted in the cannula. The observation led to a change in the methodology, connecting the coronary artery of the donor dog with the jugular vein of the recipient dog – the blood did not clot! He was then

invited in 1665 by the Royal Society in London to demonstrate his design, which was published in the Philosophical Transactions of the Royal Society, December 1666 [5]. Richard Lower was also the first scientist who demonstrated that blood transfusion could be life-saving. In the experiment he first almost exsanguinated a dog and then transfused the dog with blood from a healthy dog, causing complete recovery of the animal. A year later, 23 November 1667, Lower presented a first human experiment in which Authur Coga was hired by the College for the sum of 20 Shillings to undergo within a month two intravenous transfusions with lambs blood, of which the latter did not provide a very cheerful outcome. At the same time in France at the court of Louis XIV the young court physician and "most able Cartesian philosopher" Jean Baptiste Denis from Montpellier together with the surgeon Paul Emmerez did quite some dog-to-dog transfusion experiments. When he was presented a severely ill 15 years old boy with fever and weakness due to the many blood lettings, he decided to transfuse the boy with lambs blood, which resulted in a miraculous curing effect! Shortly after this success a second 45 years old healthy male was successfully transfused, followed by the son of the Minister of Foreign Affairs of the king of Sweden who fell seriously ill while in Paris. Denis decided to treat him with two subsequent transfusions, and with good success. The report was published in the Philosophical Transactions of the Royal Society of July 1667 [6]. The following patient transfused by Denis was a 34 years old man Antoine Mauroy, who suffered from a tragic love affair. He received over a period of a couple of months several calf blood transfusions, but started after the second transfusion to react with fever, pain in the lumps, increased pulse rate, sweating, and dyspnea, excreting black urine. Denis has carefully documented the transfusion event, thereby uniquely describing for the first time in medical history a classical acute hemolytic transfusion event. He survived, but when a few month later his mental condition again deteriorated, Denis decided to treat his patient Antoine Mauroy with another transfusion, which unfortunately caused his death due to acute lethal hemolysis. Denis was accused of murder but during the Châtelet trial in Paris plead not guilty. However, the conservative Paris University Sorbonne forbid further blood transfusion experiments. Also, in England further experiments were forbidden, followed by the anathema of the Pope. Almost a century later the French scientist Cantwell from Paris raises his voice for a plea to revive the experiments as he stated that blood transfusion could very well be lifesaving in case of severe trauma and calamities. Unfortunately, he was not well received and it lasted again more than half a century until in England the progressive gynecologist and obstetrician James Blundell from London, England who did his medical education in Edinburgh, showed a deep scientific interest in the potential of blood transfusion. His interest was not only based on the personal experience with women in labor who postpartum bled to death, but also by the scientific experiments of John Leacock from Barbados. In 1816 John Henry Leacock reported systematic experiments in Edinburgh on dogs and cats that established that donor and recipient must be of the same species, and recommended inter-human transfusion [7]. He then returned to Barbados and published nothing more. However, James Blundell, who extended Leacock's experiments and published the results widely, is credited by many with introducing transfusion into clinical use, but he always gave credit to Leacock for his initial work. In fact, they were the founders of modern immunology and the principle of compatibility presenting scientific evidence for species specificity. The scientific and clinical value of these observations became much later understood and practiced. Blundell decided based on his animal experiments to apply the lessons learned in human pathology. A 35 year old man with a terminal stomach cancer was successfully transfused directly. Most

of his work was published in The Lancet [8]. In an editorial of the 1825 Philadelphia Journal of Medicine, Physics and Science Blundell´s premiere has been debated in a footnote arguing that Dr. Philip Syng Physick did the same already in 1885. However, that practice was never published nor presented publicly. Blundell continued his work and managed to save the lives of dozens of women in labor and was frequently consulted about blood transfusion. He was indeed the first clinical specialist who deserved the classification of ´Transfusion Medicine Specialist´. Several attempts have been done based on a scientific thinking initiated through a patient story.

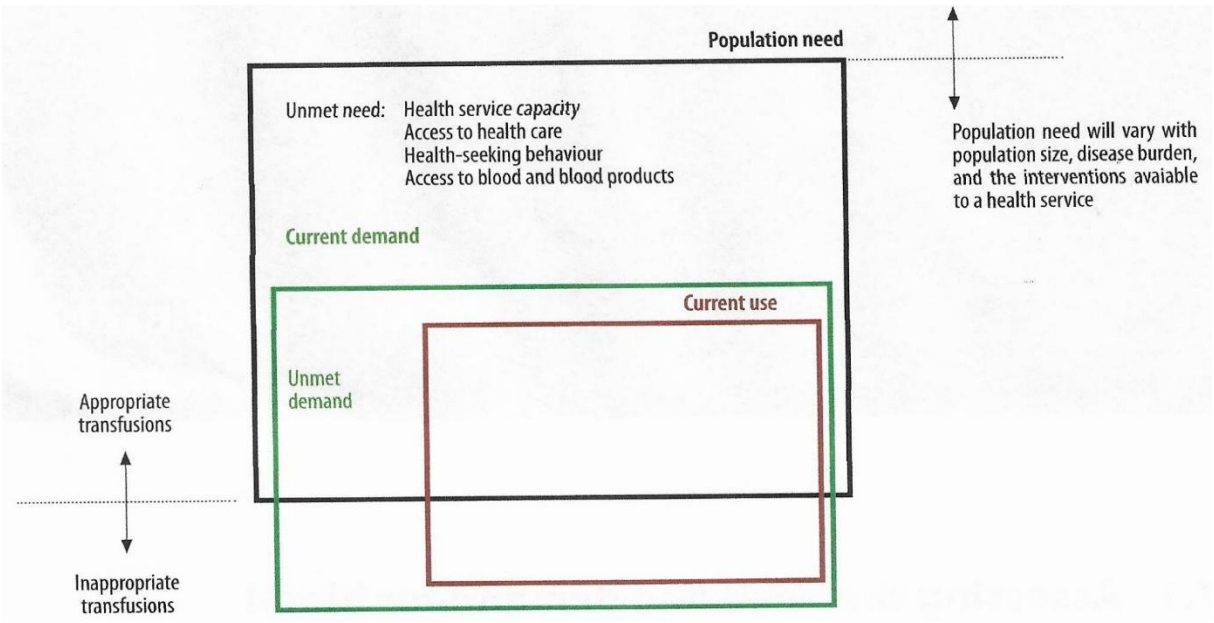

Fig. 2: Paradigm of '*use of*, *demand for*, *and need for blood*'. Blacxk box = population need; green box = current demand; brown box = current clinical useu(source WHO)

WHAT IS MORE IMPORTANT?

WHO has developed the definitions to evaluate the differences between the demand for, use of , and need for blood:

- Use: The actual amount of blood currently transfused; use may be appropriate or inappropriate.
- Demand: The amount of blood that would be transfused if all prescriptions for blood were met. Demand may reflect appropriate or inappropriate indications and practices.
- Need: An estimation of the amount of blood needed to meet the transfusion requirements of the patient population according to current policies, clinical guidelines and best practices.

These definitions and figure 2 summarize current concepts on trying to measure the use of, demand for, and need for blood.

As with all other treatment modalities, a manifold of factors influence the requirements for blood to meet the health care needs of a given population. These include income levels, current status and rate of development of the health care system, and accessibility of health care facilities to the public. The use of, demand for, and need for blood in a country could be affected by geography and climate, population migration, and epidemiology of diseases for which blood might be needed. All blood transfusion services and operators, to varying degrees, invest considerable time and resources in predicting use of and demand for blood, and adjusting clinical prescription practice and donation schedules of blood. Shortages of blood, whether real or potential, have impacted all countries at differing times, including more recently during the COVID-19 pandemic. In the early stages of the pandemic there were major concerns about lack of availability of potential blood donors and blood for transfusion. The pandemic demonstrated clearly that the clinical use depends on the patient's demand, determining the need. Appropriate clinical use is not an endpoint in the vein-to-vein transfusion chain, but the beginning of the chain and is highly dependent on education and continuing knowledge economy.

Blood establishments in developed countries may apply different approaches to assessing changes in demand for blood, including use of detailed historical blood supply data to predict incremental increases in demand (time series analysis). A further approach to estimating current demand is to use real-time hospital blood bank data on blood requests. A potential disadvantage of this approach is that the number of blood transfusion requests received by hospital blood banks and the amount of blood requested may not be an accurate reflection of true demand or use and need. This is more likely to be the case where the blood supply has actually been, or has been perceived to be, insufficient [9].

However, there is no simple formula to provide reliable or useful estimates of the demand and need for blood in a national health system. A national assessment of blood requirements would usually be necessary for short-term or long-term national blood program planning. Using a survey of a representative sample of hospitals, Drammeh et al. [10] estimated that approximately 6.2 blood donations per 1000 population are needed in the United Republic of Tanzania. This number is only slightly more than half of the 10 per 1000 population value that is used as a rough estimation for developing countries. Mammen et al. [11] estimated that, based on the population, 26.2 million units (95% CI 17.9–38.0) of whole blood collection would need to be collected annually. This is equivalent to a donation rate of approximately 19.4 donations per 1000 population. A different epidemiological approach was used for the study, which included the determination of diseases and conditions requiring transfusion, estimation of the population at risk through a comprehensive literature review, and estimation of the percentage of people with diseases and conditions requiring transfusion and transfusion needed through the Delphi method. The study also identified a gap between demand an need (estimated at 13 million units), and highlighted the importance of addressing the multifactorial causes that lead to the existence of the gap [11]. Demographic change is likely to be one of the main drivers of long-term increases in blood requirements in developed countries [12, 13]. It can be modelled by describing current blood use by age, and by applying the results to predictions of future population size and structure [14]. The development of new medical interventions may also impact future blood requirements in developing countries, but these are harder to predict given the current foreign aid cuts and may in fact serve to reduce the need for blood transfusion as well as potentially increase it. Data reported to WHO indicate significant differences in the age

distribution of patients transfused (use). In high-income countries, the most frequently transfused patient group is aged > 60 years (mostly cardiovascular and cancer), which accounts for up to 76 % of all transfusions. In low-income countries, up to 54% of all transfusions are for children aged < 5 years (malaria and helminths), usually followed by females aged between 15 and 45 years (obstetrics). There is evidence of significant differences in patterns of clinical blood demand and use between high-, middle-, and low-income countries. In high-income countries, transfusion is most commonly used for supportive care in cardiovascular and transplant surgery, massive trauma, and therapy for solid and hematological malignancies. In low- and middle-income countries, on the other hand, it is more often used to treat pregnancy-related complications and severe childhood anemia [15]. These data show the importance of patient care as the number one to be followed by a system to create the availability of treatment and support.

CONCLUSION

In the 1970 the concept of the vein-to-vein transfusion chain was introduced and WHO started in 1975 to map the world for blood transfusion with a strong focus on blood donation and the manufacturing of blood products. Raising the question: Where does the vein-to-vein transfusion chain start? With the blood donor or the patient? However, history learns a focus on the patient (demand) and shows a protracting struggle how to successfully transfuse blood from one individual to another (use). Immunology and compatibility were for long a mystery as were preservation, surface interactions and blood coagulation. Due to these mysteries it took centuries to develop the science needed to solve these problems, while patients remained suffering (morbidity) and died (mortality. Health care has always been focused on patients and not on the treatment and support modalities per se, despite the fact that the right quality treatment and support (pharmaceutical or other interventions) play an important role (need or requirement).

It is clear that the chain of blood transfusion starts with the patient, driven by use and demand, and ends with the source of the need – human blood. That needs a change in our professional thinking, operations and professional education.

Conflicts of Interest: The author has nothing to declare

Funding: No financial support was received

Acknowledgement: None

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