TRANSFUSION MEDICINE – A BRIDGING SCIENCE

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Abstract

Transfusion medicine has come a long way and has for long been regarded a Cinderella in medicine.

Since the discovery around 1900 by Karl Landsteiner of the ABO blood groups as principle elements for compatibility, the science has been dominated by the laboratory research for immunohematology, microbiology and virology, focused on the test tube and not so much the patient.

Over the 20st century several development eras are to be recognized that contributed to the maturation of transfusion medicine as a bridging science. Twenty Nobel laureates contributed to this development.

The eras recognized are – blood group serology and immunohematology; preservation of blood and blood products; separation of blood components; transmissible diseases; community, donors and 'soft sciences'; quality management and blood safety; organization, governance and leadership. During each of these eras transfusion medicine bridged with a variety of exact, gamma and ´soft´ sciences.

Today Transfusion Medicine is maturing into a unique multidisciplinary and bridging field. The outbreak of the HIV/AIDS epidemic forced the creating of quality awareness and culture and centered the scientific attention back to the patient expressed by hemovigilance and patient blood management.

1. PRELUDIUM AND OVERTURE

1.1 Preludium

Since ancient times blood has been considered as an intriguing, life-saving and supportive body fluid. It has triggered a scientific curiosity stimulating both a mystical and a scientific thinking to unveil its capacities and potential use to serve mankind. In ancient Egypt during the reign of the Pharaos it was a royal custom to bath the wounded warriors in ox blood to allow an accelerated healing of the battle wounds. The rationale was a belief in the power of the ox that would be transferred through the blood to the wounded warier and provide its strong and healthy healing capacities to cure the injured skin and muscles. The Roman writer Ovidius describes in his 7th book of Metamorphosis an early exchange transfusion approach to rejuvenate the old king Aeson. His son Jason begged Medea to give his father back his youth. Medea granted the desperate request, took her blanc knife, cut the throat of the old man, and let the old blood out. Then refilled his old veins with a rich elixir of life. As by magic the old man regained his natural strength and splendid youth. Another Roman writer Plinius reported on the habit in old Rome of men who ran into the arena to drink the blood of dying gladiators in the expectation to acquire some of the braveness and strengths of these victims. Galen advised drinking of blood of a weasel or a dog to cure rabies. The old Vikings drunk the blood of seals and whales as a cure against epilepsy and scurvy, reflecting a primitive scientific thinking of the beneficial and healing use of human and animal blood. An old Hebrew manuscript discloses the use of blood as a fluid with special healing powers. Here it was not so much the oral consumption or external application, but an intravenous application - *´Naäm, supreme commander of the armies of Ben-Ada, king of Syria, consulted his doctors because he was suffering from leprosy*.' To kill him[1] the doctors let his blood out and refilled his veins with blood from someone else, indicating the health effects of normal blood on a diseased person. In the 13th century the Venetian magister scientist Petro de Albano describes the evil effects of drinking menstrual or leprous blood: '*He who drinks such blood will become lunatic, evil and forgetful.*', therefor attributing healthy powers to normal blood and evil powers to blood from diseased or unclean people. At the same year 1692 when Christopher Columbus discovered an entirely new world - the Americas, Pope Innocentius VIII suffering from a chronic renal disease was advised by a mystical doctor from Rome to have administered the blood from 3 young and healthy men. The available old parchment discloses that such practice would safe him from dying and give him back his youthful strength. The historiography indicates that 3 ten years old boys were selected who were remunerated a golden ducat after which the exchange transfusion would have taken place. A few days later the Pope died and the three young donors were also not able to recall the experiment. However, it is not clear whether there really has been a transfusion.[1] Probably there has been an error in translation or interpretation from the original Latin text. It is more likely that the blood was used for the preparation of a special healing potion the Pope would drink. When the Pope got notice of this he condemned the practice, and refused to drink the offered potion. The mystic doctor was punished and the Pope passed away!

[1] From the documents it is not clearly readable what was exactly meant: the killing of leprosy or of Naäm?

1.2 Overture

These blood driven practices were largely indicated by mystic and magic, albeit with a definite type of logic in the thinking over the indication and prescription. During the early Renaissance epoch the scientists Hieronymus Dardanus from Milan and Magnus Pegelius from Rostock (fig.1) 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. As early as 1615 Andreas Libavius, a philosopher, PhD in Medicine and naturalist from Halle (fig.2), 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*.' [2]

Figure 1 Magnus Pegelius

Figure 2 Andreas Libavius

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 (fig.3)in his famous monography '*Excertatio Anatomica de Modu Cordis et Sanguinis in Animalibus*.' The book solicited uncurbed speculations on the possibilities to transfuse blood and infuse medicines (fig.4).

In the same year 1628 Giovanni Colle, a philosopher and physician from Padua, 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 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 (fig.5), 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. In 1654 Folli claimed to have done successful experiments, but a continuation is not recorded since then.[4] 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 (fig.6)

Figure 3 William Harvey

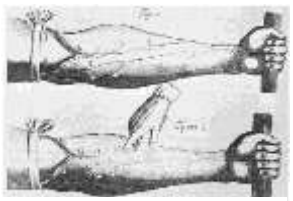


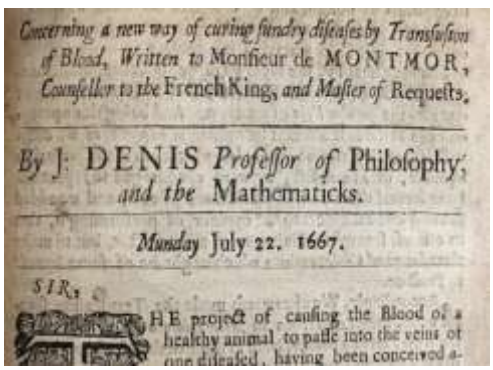
Figure 4 Harvey - drawing of veins

Figure 5 Francesco Folli

in 1665 in Oxford. 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 victim with blood from a healthy dog, causing complete recovery of the victim. 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.[6] 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 éclat 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.[7] The following patient transfused by Denis was a 34 years old man Antoine Mauroy, who suffered from a tragic love affair (fig.7). 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 dyspnoea, excreting black urine. Denis has carefully documented the event, thereby uniquely describing for the first time in medical history a classical acute haemolytic transfusion reaction (fig.8). He survived, but when a few month later his mental condition again deteriorated, Denis decide to treat Antoine Mauroy with another transfusion, which unfortunately caused his death due to acute lethal haemolysis. 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 life-saving 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 gynaecologist and obstetrician James Blundell from London (fig.9), who did his medical

Figure 6 Richard Lower

Figure 7 Denis and Emmerez - exchange transfusion



Concerning a new way of curing fundry diſeaſes by Tranſuſion of Blood, Written to Monſieur de MONTMOR, Counſellor to the French King, and Maſter of Requeſts.

By J. DENIS Profeſſor of Philoſophy, and the Mathematicks.

Munday July 22. 1667.

SIR,

HE project of cauſing the Blood of a healthy animal to paſſe into the veins of one diſeaſed, having been conceived a-

Figure 8 letter to the Royal Society, June 22, 1667

THE LANCET.

Vol. II.] LONDON, SATURDAY, JUNE 15. [1828-9.

OBSERVATIONS
ON
TRANSFUSION OF BLOOD.
By Dr. Blundell.

*With a Description of his Gravitator.**

States of the body really requiring the infusion of blood into the veins are probably rare; yet we sometimes meet with cases in which the patient must die unless such operation can be performed; and still more frequently with cases which seem to require a supply of blood, in order to prevent the ill health which usually arises from large losses of the vital fluid, even when they do not prove fatal.

In the present state of our knowledge respecting the operation, although it has not been clearly shown to have proved fatal in any one instance, yet not to mention possible, though unknown risks, inflammation of the arm has certainly been produced by it on one or two occasions; and therefore it seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins.

The object of the Gravitator is, to give help in this last extremity, by transmitting the blood in a regulated stream from one individual to another, with as little exposure as may be to air, cold, and inanimate surface; ordinary venesection being the only operation performed on the person who emits the blood; and the insertion of a small tube into the vein usually laid open in bleeding, being all the operation which it is necessary to execute on the person who receives it.

The following plate represents the whole apparatus connected for use and in action:—

* The instrument is manufactured by Messrs. Maw, 55, Aldermanbury.

Tab. 1.

No. 302.

Figure 10 The Lancet, June 13, 1828

education in Edinburgh, showed a deep interest in the potential of blood transfusion.[8] His interest was not only based on the personal experience with women in labour 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.[9] He then returned to Barbados and published nothing more. However, James Blundell, who extended Leacock's experiments and publicized 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[10] (fig.10). 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´. Despite the many opponents he continued.s From time to time he observed that the transfusion in certain women caused acute hemolysis but was unable to understand the underlying pathophysiology. Efforts were made to keep blood stored without clotting, e.g., by defribrination using a glass rod. In 1860 Neudorfer tested the effect of sodium bicarbonate added to the collected blood.[11] Braxton Hicks tried to use sodium phosphate, but without success.[12] In those days the mechanism of coagulation was not yet unraveled, hence the ignorance in understanding.

Figure 9 James Blundell

These obstacles did not work in favor of developments and the frustration about the increasing number of failures caused a temporary abandoning of the practice and adopting the use of alternatives. In particular in the USA clinicians started to use the infusion of milk with a hype between 1873 and 1880. In 1878 Brinton even prophesied that milk would completely replace human blood due to the rapid clotting of blood during transfusion. The prophecy did not hold because of the many serious side effects such as serious lung problems due to fat embolism besides the septicemias due to absence of proper sterilization technology leading to an abandoning of the use of milk transfusion in the year 1880. Scientist and reputed clinicians like Moutard-Martin and Richet, in 1879, warned that patients could be killed by milk transfusions. From then on (1884) the use of isotonic saline solutions as a blood substitute became popular.[13]

During the same period scientists like Ilya Ilyich Mechnikov at the Institute Pasteur in Paris and Paul Ehrlich at the Göttingen University Royal Institute for Experimental Therapy, discovered the existence of two lines of immune defense, the innate immunity and the adaptive immunity which explained the possible occurrence of an immune response to contacts with foreign agents. Both shared in 1908 the Nobel prize in recognition of their work on immunity.[14]

Although during the 19th century much scientific progress was made, blood transfusion as a supportive clinical intervention with a life-saving potential was still at square one. The real breakthrough came at the turn of the 19th century with the work of the Viennese physician, pathologist and scientist Karl Landsteiner (fig.11), who discovered the presence of specific antigens on the surface of red cells, genetically determined. He named them blood groups. Following the alphabet he distinguished the groups A, B and AB besides individuals who did not express A or B antigens and called those O (actually zero because of the absence of A and/or B).[15] He received in 1930 the Nobel-prize for his work that opened the gate to compatibility in blood transfusion.[14]

These scientific experiments and documented observations were the overture to the further development of the science and practice of transfusion medicine, first animal experiments and then the human trials!

Publishing and presenting the outcomes in the literature and at scientific meetings of the established Societies and peer groups stimulated an early creation of an evidence base for transfusion medicine.

Figure 11 Karl Landsteiner

2. DEVELOPMENT ERAS

The two dominant obstacles experienced during the overture epoch were incompatibility and clotting of the donor blood. The 20th century rolled out as the century of developments and progress in transfusion science and medicine. There are several eras that overlap, dominated by blood group serology, laboratory medicine, pathology, biochemistry and molecular biology.

With the breakthrough at the turn of the 19th century by Karl Landsteiner and his research group in Vienna and later in New York, the era of blood group serology and immuno-hematology had taken off and would soon be followed by others.

2.1 Blood group serology and immuno-hematology

Figure 12
Jochem J. van Loghem

The discovery of the existence of specific structures on cell surfaces – antigens, and the differences of these structures between species that are able to initiate an immune response with the creation of antibodies against a foreign or unknown antigen has been the trigger for an extended and still ongoing research for these antigens. Currently there are 30 different erythrocyte antigen or blood group systems known with 284 antigens discovered, of which fortunately a limited number are able to induce antibodies that are hemolyzing or destroying the causal target cells. However, at least 24 systems were recognized because of incompatibilities of transfusion during pregnancy.[16] Advances in analytical methods have provided insight in the molecular structures of these antigens and their connection and position on and in cell membranes. With the fresh knowledge it became possible in the early 1940s through the work of Philip Levine in Newark, NJ (1941)[17] and Birger Broman in Stockholm (1944)[18] to clarify the pathophysiology of jaundice in certain newborns, now named Hemolytic Disease of the Newborn (HDN). The disease was for long regarded an expression of syphilis, causing serious social problems. Technology, methodologies and reagents developed over the decades, starting with the work of Robert Coombs during WWII that led in 1945 to the design and introduction of a specific and sensitive antiglobulin test known as the Coombs test (direct and indirect).[19] The introduction of molecular biology in blood group serology triggered the development of highly specific monoclonal reagents. Consequence was a rapid exploring of structure and function of antigens at molecular level, and their interactions with antibodies, leading to a broader typing of both blood donors and recipients to prevent adverse reactions or events.

The intriguing scientific domain of blood group serology has for long dominated transfusion medicine, introducing and applying the science of a growing number of chemistry and physics subdisciplines e.g., analytical biochemistry and physical chemistry. Dozens of scientists largely from Britain, USA, France and the Netherlands have contributed to bridge the science, e.g., Alexander Wiener, Robert R. Race and Ruth Sanger, Marjory Stroup, George Garratty, Peter Issitt, Jochem J. van Loghem (fig.12), Paul Engelfriet. Jean-Paul Cartron, Patrick L. Mollison, David Anstee, Marion Reid, Eric Brodheim and many more.

To harmonize and standardize nomenclature the International Society of Blood Transfusion (ISBT) instituted in 1980 a working party on Terminology of Red Cell Surface Antigens, which has mapped and analyzed all existing and new blood group antigens.[20] The working party is still active.

Figure 13
Baruj Benacerraf

Besides the antigen population on the erythrocyte cell membrane, leukocytes and thrombocytes also express specific antigens to which antibodies may be produced. Of particular importance is the family of antigens that can be detected on the membrane of leukocytes and other nucleated cells. The fascinating work initiated by the scientists Baruj Benacerraf from Caracas (fig.13), Jean Dausset from Toulouse (fig.14), George Davis Snell from Bradford, MA (fig.15)(these 3 scientists shared the 1980 Nobel prize),[14] and Jon van Rood from Leiden[23] (fig.16) led to breakthrough discoveries in 1958[21,22] concerning genetically determined structures on the nucleated cell surface that regulate immunological reactions, the so called Major Histocompatibility Complex (MHC).[24] HLA is the human version of the MHC, a gene family that occurs in many species. In humans the MHC 16omplex consists of more than 200 genes located close together on chromosome 6. Genes in this complex are categorized into three basic groups: class I, class II, and class III.

Figure 14 Jean Dausset

There are three main MHC class I genes, known as HLA-A, HLA-B, and HLA-C. The proteins produced from these genes are present on the surface of almost all cells. On the cell surface, these proteins are bound to protein fragments (peptides) that have been exported from within the cell. MHC class I proteins display these peptides to the immune system. If the immune system recognizes the peptides as foreign (such as viral or bacterial peptides), it responds by triggering the infected cell to self-destruct.

Figure 15 George D. Snell

There have been recognized six main MHC class II genes in humans: HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1. MHC class II genes provide instructions for making proteins that are present almost exclusively on the surface of certain immune system cells. Like MHC class I proteins, these proteins display peptides to the immune system. The proteins produced from MHC class III genes have somewhat different functions; they are involved in inflammation and other immune system activities. The functions of some MHC genes are unknown. HLA genes have many possible variations, allowing each person's immune system to react to a wide range of foreign invaders. Some HLA genes have hundreds of identified versions (alleles), each of which is given a particular number (such as HLA-B27). Closely related alleles are categorized together; for example, at least 40 very similar alleles are subtypes of HLA-B27. More than 100 diseases have been associated with different alleles of HLA genes. For example, the HLA-B27 allele increases the risk of developing an inflammatory joint disease called ankylosing spondylitis. Many other disorders involving abnormal immune function and some forms of cancer have also been associated with specific HLA alleles. However, it is often unclear what role HLA genes play in the risk of developing these diseases.

Figure 16 John J van Rood

HLA plays a major role in patients with an impaired immune system and in need of chronic transfusions with red cells and platelets. The most frequent adverse event in multi-transfused patients is the febrile non-hemolytic transfusion reaction (FNHTR) caused by HLA

antibodies. Similarly platelet-dependent patients may become refractory as a result of HLA-antibody formation.

2.2 Preservation of blood and blood products

The second major problem was the clotting of blood extracorporeally and the need to preserve blood. The scientifically designed ailments of the late 19th century failed due to lack of knowledge. With the description of the German physician Rudolf Virchow (fig.17) of a triad of events in hemostasis[25] and the observations of Paul Morawitz from Würzburg, internist and Godfather of blood coagulation, the phenomenon of hemostasis was slowly unraveled. When one would be able to prevent the formation of the aggressive lytic enzyme thrombin, the formation of a fibrin clot would not take place. The main contribution of Morawitz was in the recognition of the role of Ca^{++} as a catalyzer for the formation of thrombin. Transfusions were given in a direct vein-to-vein technology. Either by creating arterio-venous shunts in both patients and donors or genius syringe technologies using multiple valve stopcocks as designed by Unger, Tzanck and Jouvelet. That did not solve the problem. WWI created a scenario for advanced research. The Belgian physician Albert Hustin developed in 1913 and used in 1914 the divalent cation scavenger sodium citrate solution, originally in a 1:1 ratio.[26] Richard Lewisohn experimented to find a useable ratio of citrate to blood in dogs at the Mount Sinai Hospital in New York. Richard Weil demonstrated that citrated blood could be stored safely for a couple of days outside the body in a refrigerator.[27] Based on the research of Lewisohn and Weil, Rous and Turner developed a solution containing physiological saline, isocitrate and glucose as a nutrient. The blood could be stored for 10 to even 26 days in the refrigerator. The method was published in 1916 in the Journal of Experimental Medicine under the title '*The preservation of living red cells in vitro. II. The transfusion of kept cells*'.[28] That opened the gate to modern blood preservation. The method was at a larger scale used during the battle of Cambrai in 1917 by the British army physician captain Oswald Hope Robertson (fig.18), who served at that point the US army. While serving on the Western Front in World War I he experimented with preserving human blood cells for use in blood transfusions, and became recognised as the inventor and initiator of the world's first blood bank. He used exclusively blood group O blood. The work of Oswald Robertson was overseen by the Harvard professor Roger I. Lee who insured appropriate attention to blood typing, infectious disease testing, and bacteriologic safety. Robertson designed blood collection bottles and demonstrated the safety and efficacy of 26 day red cell storage.[29,30]

Figure 17 Rudolf Virchow

Figure18
Oswald H. Robertson

The subsequent history of blood preservation and storage has been one of slow and incremental progress. Slow because of the incomplete understanding of red cell and platelet metabolisms and storage lesion, incremental because industry and regulators seem to be able to deal with one problem at a time and development cycles showed to last about a decade e.g., sterilization in the 1940s, addition of phosphate in the 1950s, introduction of plastic multiple blood bag systems in the 1960s, adenine in the 1970s, additive solutions in the 1980s and leukocyte

reduction in the 1990s.

For a period of 25 years the Rous and Turner solution became the generally applied formula for preservation of blood in glass bottles. December 1943 the British scientists J.F. Loutit, P.L. Mollison and I.M. Young published in the Quarterly Journal of Experimental Medicine the results of their research developing a small volume potent preservation solution for human blood – Acid Citrate Dextrose (ACD) to be used in a 1:4 and later 1:6 ratio.[31] Further regulatory experiments and the development of a new type of bottle were needed. April 1945 the bottles filled with the ACD solution and sterilized could then be used by the allied forces in Europe and the Pacific.

Based on the red cell metabolic studies J.G. Gibson published his studies on a new preservation formula CPD (citrate, phosphate and dextrose) in 1957[32] and a decade later adenine was added to CPD creating an even better nutritious preservative CPD-A allowing red cell preservation for over 35 days. Based on the red cell metabolic studies of John W. Harris (1963) from Cleveland and Ernest Beutler (1984) from the Scripps Research Institute at La Jolla who was the first to use mannitol as a red cell membrane stabilizer. Claus F. Högman, physician, transfusion medicine specialist and scientist from Uppsala (fig.19) developed the principle of additive solutions for an optimized red cell survival *ex vivo* – Saline, Adenine, Glucose and Mannitol (SAG-M) once collection was done in standard CPD solution.[33,34] Högman was honored for his work in 1986 by the American Association of Blood Banks (AABB) with the prestigious Karl Landsteiner award. He received in 1993 the James Blundell award of the British Blood Transfusion Society (BBTS) and in 2006 the ISBT Presidential award. Since then several variations such as AS-3 solution,[35] have been developed and are marketed globally.[36] Along the lines of red cell preservation also developments rolled out for platelets, although for these small and relatively short living cells gas permeability and biocompatibility of the storage container play an even more important role.

Figure 19
Claes F. Hogman

In the 19th century blood was collected in open receptacula, largely glass with the risk for rapid clotting and bacterial contamination. The first bottles as used by Robertson in Cambrai were closed with a flamed cotton wool stopper. The new type of bottles developed by the group of Mollison had a metal screw cap and rubber through which the needle of an administration set could be pierced together with a needle for venting to prevent vacuum.

However, the use of glass bottles with a screw cap and rubber showed quite some disadvantages such as an aggressive surface to which proteins and platelets adhere. To prevent this phenomenon the bottles were siliconized before sterilization. Other problems were the risk for microbial contamination because the system in principle is still open (screw cap and pierced rubber); the bottles were cleaned and re-sterilized with the risk of breakage and cracks; the need to vent during collection and transfusion with the risk of air embolism; and the breakability during handling, cleaning and centrifugation. Late 1940s and the 1950s, post WWII, polymer blood bag systems were developed. The initiative actually dates back to 1931 when the young student Carl Waldemar Walter (fig.20) was challenged by the neurosurgeon Harvey Cushing in Boston (Peter Bent Brigham Hospital and Harvard Medical School) to design a better workable system for blood collection and transfusion. It took Walter 16 years to finally in 1947 present his invention – a plastic collection container with a donor line and a transfusion (outlet) port.[37] His entrepreneurial neighbor T. Legare Fenn supported him financially and launched in 1949 FENWAL Laboratories. From then on,

Figure 20
Carl W. Walter

through a serendipitous contact during a flight, the science of polymer chemistry and elastometry had entered the field of transfusion medicine. As a result polymers were developed that were as bio-compatible as possible for blood cells and proteins, semi-permeable for gas, sterilisable and temperature resistant (heating and freezing), and impermeable for micro-organisms. Soon after that, late 1949, the Fenwal blood bag system was tested in the USA by the American Red Cross and a number of hospital blood banks, but it lasted another decade before the problems encountered e.g., the use of phthalates (DEHP) with the polymers, were solved and the technology registered and licensed for civil use. However, the first large scale application was during the Korean war. In 1954 the Massachusetts General hospital ordered 300,000 Fenwal multiple blood bag systems for its transfusion program.

Since then over 20 innovative improvements have taken place including the development of a multiple blood bag system for processing and separating whole blood into its components (red cells, platelets and plasma) and polyolifines with a much higher gas permeability to allow better *ex vivo* survival of platelets.[38]

Studies on preservation and storage of blood and blood components have revealed the need for slowing down metabolism (hibernation) and therefor lengthening the *ex vivo* survival provided the cells are supplied with a suitable nutrient solution and stored under appropriate physical conditions e.g., temperature, agitation for platelets. Besides the wet storage and standard cold chain conditions, blood cells may also be cryopreserved and stored at ultra-low temperatures (-80°C or lower). Knowledge of and expertise in cryobiology are essential to understand the physiology and physics of cryopreservation. The discovery by C. Polge, A.U. Smith and A.S. Parkes in 1948 that glycerol would enable fowl spermatozoa to survive freezing to -70°C, initiated a phase of dramatic developments in the application of cryobiology.[39] Although the title of the publication indicates the use of vitrification it actually describes just a classical freezing approach. In 1950 Audrey U. Smith described the use of glycerol for freezing human red cells and a year later P.L. Mollison and H.A. Sloviter reported the successful transfusion of previously frozen and deglycerolized human red cells, using a complex dialysis procedure.[40] During the 1960s extracellular additives such as polyvinylpyrrolidone and hydroxyethyl starch (HES) were used to freeze blood in special metal canisters at a controlled rate by direct immersion in liquid nitrogen (-196°C) and storage in the vapor phase of liquid nitrogen (-150°C). Before transfusion these units were washed to eliminate the toxic additives. Later polyolifine-based plastic bag systems were introduced. As researchers become more knowledgeable about basic cell biology related to viability and function of red cells, platelets and peripheral blood mononucleated cells, methods were developed to preserve specific cellular components of blood in liquid and frozen states. The toxic extracellular additives and the preservation technologies for freezing and thawing were not providing satisfactory results. So, the non-toxic intracellular additive glycerol was tested as a red cell cryoprotectant followed by post-thaw washing to remove the glycerol before transfusion. Glycerol remained the principle red cell cryoprotectant over the decades to follow. There are two approaches[41] – 1) high glycerol concentration (HGM; 45-50% w/v) enabling freezing and storage at temperatures below -65°C but preferably at -80°C; 2) low glycerol concentration (LGM; 15-20% w/v) with freezing in liquid nitrogen at -196°C and storage in the vapor phase at -150°C. The first approach has the advantage of a

higher freezing and storage temperature which can be achieved by a mechanical cabinet freezer. Frozen red cells are particularly of importance to create a bank of rare blood types.

Platelet freezing is much more difficult because these cells are more fragile and more easily damaged. Three approaches have been developed since the 1950s by E. Klein et al. (1956),[42] and A.J. Weiss and W.F. Ballinger (1958)[43] – glycerol, HES and dimethylsulphoxide (DMSO). So far the DMSO method has shown to be the most promising, with freezing and storage in the vapor phase of liquid nitrogen.[44,45] Clinical use is largely indicated for malignancies during the aplastic phase using pre-collected autologous platelets.

2.3 Separation of blood components

As early as 1914 blood separation has been practiced. Originally the work of John Abel et al. at John´s Hopkins Medical School in Baltimore, MD was focused on separation of plasma from red cells to recover hyperimmune serum.[46] The technology was based on gravity sedimentation and vacuum sucking off the supernatant plasma. Conditions were far from aseptic as containers were open until Mollison in the 1940s designed a bottle with screw cap and rubber stopper. That opened the doors to centrifugation. During WWII Edwin Cohn at Harvard University, Boston, MA introduced an adapted model E-19 de Laval cream separator for the separation of large quantities of plasma.[47] The concept of mechanical blood separation was born. Using the different specific gravities of the various blood cells, separation of whole blood could be achieved at different centrifugal forces and centrifugation times. Medical engineering brought step by step more sophistication (computer science) and refinement in separation and preparation of better blood products for clinical use. Today separation of whole blood is almost entirely automated and monitored, including the final separation following centrifugation.

Two technologies developed in parallel – the robust cooled blood bank centrifuge to separate units of whole blood, and the hemapheresis equipment to collect on line specific cells or plasma from a donor. This last technology could also be used for therapeutic purposes e.g., plasma exchange. Mechanical cell separators developed use either discontinuous flow or continuous flow. Engineering guided by J.L. Tullis and Allan Latham jr.[48] led to the development of a simplified reusable bowl mounted in a centrifuge for the discontinuous flow separation and collection of plasma and eventually to a prototype of the current bowl and an apheresis machine the Model 10 manufactured by Haemonetics in Braintree, MA introduced in the 1960s. What exactly happens in the bowl was not investigated, just a matter of trial and error until 1n 1992 a Dutch mechanical engineering graduate student Hein Smit Sibinga from the Enschede Technical University in the Netherlands designed a computer imaging program and software to unravel the physics of the separation in a spinning bowl and allowing variation of the mechanical and physical parameters to optimize the separation process.

Figure 21
Emil J. Freireich

Almost simultaneously a continuous flow centrifugation principle was developed by Robert Eisel and Emil J. Freireich at the Cancer Institute in Houston, TX (fig.21) in close co-operation with George Judson, a project engineer at International Business Machines Inc. (IBM).[49] This principle was designed primarily to collect granulocytes and resulted in the construction of the NCI-IBM continuous flow centrifugation blood cell separator, available for field trials in 1966. Since then several engineering improvements and principles were designed to

allow more pure separation of cell fractions using the physical principles of centrifugal forces.

With the same purpose in mind I. Djerassi developed a continuous flow through hollow fibre filters for apheresis of leukocytes from donors.[50] In this ingenious non-centrifugal system white cells are first entrapped by the nylon fibres and subsequently eluted for transfusion. Despite the high yield of granulocytes, adverse effects of the nylon fibres on cell morphology and function have been observed and the technique has been abandoned.

Following the successful developments in hemodialysis, plasma filtration through porous membranes, flat and hollow fibres, was devised in the late 1970s, separating in a continuous flow plasma from the cellular components. In the early 1980s both approaches were combined in a revolutionary new and admirably elegant design, enabling the harvesting of plasma and platelets from donors in a discontinuous flow system. Several refinements have been developed, largely focusing on therapeutic use of these separation principles.

2.4 Transmissible infections

It took till 1940 before the transmission of infectious diseases were recognized when transfusing blood. Syphilis was the first disease related to the transfusion of fresh blood in those days. Early investigators like T.B. Turner and T.H. Diseker from John's Hopkins hospital in Baltimore discovered that the causative bacterium *Treponema Pallidum* loses its infectivity in citrated blood when stored for 72 to 96 hours at 5°C.[51] Testing was based on the presence of reagins (VDRL or Venereal Disease Research Laboratory test). Turners observation and the routine testing for syphilis with a serologic test for syphilis or STS was the first microbiological laboratory test applied to improve safety of blood for transfusion.

A new era had begun determined by the science of microbiology and its laboratory technology. The STS or Wassermann test, despite its failures and weakness in sensitivity and specificity remained worldwide in use till the 1990s when it was replaced by a specific treponemal tests – the TPHA (Treponema Pallidum Hemagglutination Assay). Today the TPHA test can be done fully automated in a medical engineered robot. In 1984 L. Barker reviewed the social history of the introduction of donor testing for syphilis. He found it quite remarkable and completely devoid of the turmoil associated with the introduction of testing for antibodies to HIV.[52]

Figure 22
Baruch S. Blumberg

Soon after the recognition of transmissibility of the spirochete, it became known that jaundice could be the result of transfusion without hemolysis of red cells. Almost from the onset viral hepatitis was recognized as the most frequent and serious infectious outcome of blood transfusion. The remarkable study of J. Garrot Allen in the 1960s, revealed that at least 1.5% of transfused patients developed overt, acute, symptomatic hepatitis.[53] Studies that relied upon sensitive measures of liver damage were even more ominous, with frequencies of posttransfusion liver dysfunction as high as 30%! Data were clearly linked to the epidemiological background of the implicated blood donors; paid and imprisoned donors provided the greatest risk. The virology of hepatitis proved intractable. The groundbreaking work of S. Krugman did show that the so called 'serum' or 'infectious' hepatitis was caused by clearly separable infectious agents. However, in the absence of a definitive serology there was no direct means to assure that blood donors did not carry the infectious agent(s) of hepatitis. The observations

triggered two important measures: a) exclusion of donors with a history of hepatitis, assuming they still could be infected and infectious; b) exclusion of paid and imprisoned donors from blood donation which included the discard of blood collected from such donors.[54]

Also testing of donors for liver dysfunction markers such as the ALT test was introduced and is still in certain parts of the world used as a surrogate test. The breakthrough came with the essentially serendipitous discovery by Baruch Samuel Blumberg (fig.22) of 'Australia antigen' (HBsAg) and its subsequent linkage to one of the two types of transfusion associated hepatitis.[55,56] He received in 1976 the Nobel prize for his work.[14] This can be considered as the first seminal event in the development of modern blood donor screening procedures and policies. Not only was 'Australia antigen' clearly associated with what was then known as hepatitis B, some studies had established that blood positive for the antigen HBsAg clearly transmitted hepatitis B to recipients. The first test methods became available in 1969. The first generation test adopted was an Ouchterlony agar gel diffusion (AGD) using human or animal antibodies to detect the antigen in donor serum. This test was soon replaced by the second generation direct immunoprecipitation systems e.g., counterimmunoelectrophoresis or rheophoresis using the principle of an electrical potential or evaporative buffer forcing antibodies and antigens together, thus increasing speed and sensitivity. Problem was the high subjectivity of the test. L. Overby and C.M. Ling working at the Abbott Laboratories, developed a third generation tube-based solid phase radioimmunoassay (RIA) for the detection of HBsAg.[57] The sensitivity was over a five-fold of the second generation, but the disadvantage was the need for an isotope licensure to handle the test and its radioactive waste. After a relatively short time this RIA was replaced by enzyme immunoassay (EIA).

The continuation of posttransfusion hepatitis remained a serious blood safety concern, but became an enigma when R. Purcell at NIH, and 2012 ISBT Presidential award winner, identified hepatitis A virus and developed serologic tests for detection. Implementation of the test showed that residual posttransfusion hepatitis cases were neither caused by hepatitis B virus (HBV) nor hepatitis A virus (HAV) and therefore diagnosed as non-A, non-B hepatitis (NANBH).[58] In 1989 another seminal event took place with the publication of the CDC report of M. Houghton and L. Overby on the cloning of a segment of the genome of the hepatitis C virus, using the virus grown in chimpanzees. A serologic test became available in 1990 demonstrating that indeed the majority of posttransfusion NANB hepatitis cases were caused by the hepatitis C virus. With the subsequent introduction of multi-antigen tests a sharp decline in the occurrence of posttransfusion hepatitis was noticed.

Figure 23 Luc Montagnier

In 1983 the world was shaken by a new viral infection also transmissible by blood, the human immunodeficiency virus or HIV caused the deadly disease AIDS. The putative etiologic agent HIV was almost at the same time discovered by Luc Montagnier from the Institute Pasteur in Paris (fig.23) (Nobel prize in 2008)[14] and Robert C. Gallo the National Cancer Institute in Rockville, MD (fig.24). In 1985 an antibody EIA test was introduced and soon after that a combi-test sensitive to detect both HIV-antibodies and antigens was developed both for HCV and HIV.

In the meantime biochemists and medical engineers developed a nucleic acid amplification methodology and technology based on the 1983 design of the polymerase chain reaction principle, which resulted in the 1993 Nobel prize of Kary B. Mullis at Cetus Corporation, Emeryville, CA[14] (fig.25).

Figure 24 Robert C. Gallo

Additionally the biomedical industry picked up the idea to develop a method to inactivate blood-borne pathogens, viruses, bacteria and parasites. The focus has been on destruction of the genetic RNA or DNA material in these pathogens. Historically, cell-free blood products, such as human plasma, were pathogen-inactivated with a solvent-detergent (SD) technology for large plasma pools or by the addition of methylene blue (MB) for single plasma products in small-sized blood establishments. However, these methods are not transferable to cell-containing blood products as they heavily damage platelets and erythrocytes. Novel pathogen inactivation technologies (PIT), which have become increasingly available for cellular blood products e.g., INTERCEPT™ (Cerus Corporation, Concord, CA, USA), Mirasol® (Terumo BCT, Lakewood, CO, USA), and THERAFLEX® UV (Macopharma, Mouvaux, France) represent currently available technological platforms, and they are each at different stages of marketing readiness.

Figure 25 Kary B. Mullis

For the detection of bacterial contamination microbiologists and industry designed automated equipment for both aerobic and anaerobic culturing of microbes, that have been in use since the late 1980s. The most widely used machine is the BACTALERT® manufactured by bioMérieux in France.

With the outbreak in the 1990s of 'Mad Cow Disease', a spongiform encephalopathy also known as bovine spongiform encephalopathy (BSE) and its relation to sporadic Creutzfeldt-Jakob Disease (CJD) known since 1922, a variant CJD was first detected in humans and described in 1996.[59,60] Up till now the risk of transmission with human blood is still uncertain and prevention of transmission is largely based on donor interview and deferral.

This specific development era focused the transfusion medicine world on the issue of safety and prevention, and bridged transfusion medicine with biochemistry, microbiology, virology and medical engineering including computer science with information and communication technology. There are many more transmissible infectious agents recognized over the past decade and a half, and the list of emerging agents is still growing, but these do not have the bridging scientific impact as the ones described.

However, another important aspect recognized is in the science of risk perception, part of environmental psychology.

2.5 Community, donors and ´soft sciences´

For a long time little scientific attention was paid to and research done on the human source of blood as a tissue for supportive hemotherapy. Although the International

Figure 26 Richard M. Titmuss

Federation of Red Cross and Red Crescent Societies (IFRC) from the early days on propagated voluntary and non-remunerated donation of blood, the 'Gift of Life', there is still a wide spread practice to ask family, relatives and acquaintances to donate blood *ad hoc*, almost exclusively due to lack of attention and public awareness. Blood donation is an act of social solidarity based on sustained motivation and altruism. The psychology behind such behaviour has been

extensively studied and documented in 1970 by the British social researcher Richard M. Titmuss (fig.26)in his book 'The Gift Relationship'.[61] Titmuss was the founder of the academic discipline of Social Administration or Social Policy. His concerns focused especially on issues of social justice. He expressed his philosophy of altruism in social and health policy and, like much of his work, emphasized his preference for the values of public service over private or commercial forms of care. The book is influential and resulted in a study of the blood bank systems, specifically with regard to regulation on the private blood market exchange. President Richard Nixon called for a complete study of the lack of coordination within the system only months following publication of Titmuss' findings! Titmuss was the first to recognize and advocate the principle of and integral health service including the service of blood transfusion. Since then a growing number of medical sociologist and environmental psychologists entered the field of Transfusion medicine contributing to the bridging with social sciences, e.g., R.M. Oswalt,[62] J.A. Piliavin,[63,64] A.P.M. Los,[65,66] C.A.J. Vlek.[67,68] Despite the numerous reports and publications family replacement and paid blood donation continued up till today. This is largely due to serious shortcomings in the primary process operations of blood establishments, predominantly in the UNDP Low and Medium Human Development Index (HDI) part of the world. In 2004 WHO, IFRC, ISBT and the International Federation of Voluntary Blood Donor Organizations (FIODS) launched a global awareness program – World Blood Donor Day (fig.27), celebrated annually on 14th June, the day of birth of Karl Landsteiner. The goal is to achieve a 100% voluntary and non-remunerated and preferably regular blood donation all over the world.

Figure 27 WHO WBDD logo

An adequate and reliable supply of safe blood can be assured by a stable base of regular, voluntary, unpaid blood donors. These donors are also the safest group of donors as the prevalence of bloodborne infections is lowest among this group. World Health Assembly resolution WHA63.12 urges all Member States to develop national blood systems based on voluntary unpaid donations and to work towards the goal 70 of self-sufficiency.[69] In 2010 WHO and the IRC published an evidence-based guideline '*Towards 100% voluntary blood donation: a global framework for action'* designed to help in forging even stronger partnerships between health authorities and civil society in the goal to ensure the safety and availability of blood transfusion for all patients who require it as part of their treatment. This social sciences based framework for global action outlines broad goals, strategies and action points that will enable countries to move towards 100% voluntary blood donation.[70]

2.6 Quality Management and blood safety

The first review of the scientific and technical status of transfusion was published by J.R. Chadwick for the Massachusetts Medical Society in the Boston Medical and Surgical Journal in 1874.[71] Despite a thoughtful and scientific discussion of the indications for and methods of transfusion, Chadwick believed that animal to human transfusion of blood was safe. His cavalier approach to patient symptoms during and after transfusion and to basic cleanliness in blood handling date his scientific work. As safe intravenous solutions like Ringer' s lactate and Locke's solution became available at the end of the 19th century, the reputation of

safety and quality of transfusion sank very low. At the turn of the century blood transfusion was limited scientifically by a serious lack of understanding and knowledge of adverse events, and technically by the lack of reliable equipment and methods to anticoagulate collected blood. The next two to three decades showed considerable progress led by Karl Landsteiner's discovery of ABO blood group system. R. Ottenberg and D.J. Kaliski[72] then demonstrated that cross matching could improve safety and prevent major incompatibilities and Roger Lee showed the relative universality of group O donors. Citrate prevented clotting as demonstrated in the field by Roger Lee.[73] All these important though still modest improvements and advances in controlling the quality of blood transfusion had made the initial development and rapid proliferation of banking of blood possible.

Figure 28
William E. Deming

Once Mollison had introduced his closed screw cap-rubber stopper glass container for collection, processing and storage of blood, asepsis could much better be controlled, while the first preservative glucose (Rous and Turner) made a longer storage time possible.[28]

During WWII the American war industry introduced for its technical standardization of equipment and vehicles in the field the concept of Good Manufacturing Practice (GMP) which became the first comprehensive quality system in manufacturing of products. The quality Guru, electrotechnical engineer and statistician William Edwards Deming (fig.28) developed in the 1950s while in Japan the principle of the cycle of improvement consisting of four key actions – Plan, Do or implement, Check or control, and Act or improve.[74]

In 1947 following the dramatic explosion and fire in Texas City President Truman recommended that every city in the US should have a blood bank. In response the American Association of Blood Banks (AABB) was created. One of the first acts was the design, development and publication of technical recommendations. These were actually preceded by the 1941 American Red Cross Manual 784 entitled 'Methods and Techniques of Blood Procurement as Prescribed by the National Research Council for the Use in the Red Cross Blood Procurement Centers' which was revised in 1943 called 'Methods and Techniques in Red Cross Blood Donor Centers'.[75] The first manual was largely based on theory where the 1943 revision was based on practical experience. In 1944 a first manual on actual blood typing, cross matching and transfusion titled 'The Operation of a Hospital Transfusion Service' was prepared and published by Elmer L. DeGowin][76] (fig.29).

Figure 29
Elmer L. DeGowin

DeGowin, like many of the pioneers of blood banking and transfusion medicine, entered the discipline because of scientific curiosity and a desire to provide efficacious and safe allogeneic transfusions to patients. The first AABB manual was published in 1953 which contained both Standards (on 'what to do') and Procedures (on 'how to do'), followed by the first edition of the Standards for Accreditation of a Blood Transfusion Service. These separate Standards were the result of the initiative of E.B. Jennings who advocated for an AABB program of Inspection and Accreditation. He then wrote the first draft of the 1957 Standards.[75] Over the same time mathematicians developed statistical methods to be applied in data collection and processing in Transfusion Medicine - statistical process control (SPS).[77] Consequently Quality

Management in Transfusion Medicine was born strengthening the link with the sciences of mathematics and statistics to support monitoring and evaluation of 'what has been done'.

However, it needed the outbreak of the HIV/AIDS epidemic in the early 1980s to awaken quality awareness among those involved in Transfusion Medicine, the development of quality as a culture, a journey not a destination. France, shaken by the dramatic Hemophilia HIV infection disaster took the lead instituting in 1994 a mandatory hemovigilance system,[78] which was soon followed by the British Serious Hazards of Transfusion (SHOT) confidential 1996 voluntary reporting system[79] and the 2002EU[80] and 2005 EC[81] Hemovigilance alert system mandatory for all 27 Member States. The US surprisingly has shown to be a slow follower with the introduction of hemovigilance in 2007.[82]

With these developments that have pretty far advanced in the more developed part of the world unfortunately the existing gap in development with the less advanced Low and Medium HDI part of the world has widened and deepened. It has become obvious that one needs a chicken to lay an egg. The paucity of a solid organization, infrastructure, legal framework and quality management system are paramount for an operational quality system in Transfusion Medicine as a science and related practice.

In 2013 WHO reported in its Global Database on Blood Safety that 68% of reporting countries, or 122 out of 179, had a national blood policy. Overall, 58% of reporting countries, or 105 out of 181, have specific legislation covering the safety and quality of blood transfusion, including 79% of high-income countries, 64% of middle-income countries and 41 % of low-income countries.[83] Hence a significant discrepancy!

2.7 Organization, governance and leadership

The first ´comprehensive´ blood bank was established by Oswald Hope Robertson during WWI in France,[84] followed soon by Moscow, Chigaco Cook County, Rotterdam and Barcelona.

However, most of the facilities that mushroomed before WWII were small and accommodating just the need of one hospital – hospital based blood banks, active in collection and procurement of blood as well as supporting patient care through compatibility testing. None of the officials and practitioners realized that they had created a legal conflict of interest. Procuring blood and blood products holds 'product liability' where patient care brings along 'consumer rights protection'. These two legal opponents cannot be united under one final responsibility and need clear separation in their organization, operations and responsibilities. A variety of organizational and governance structures were created at the National, regional and local level, public and private, ministerial and NGO, each serving their own kingdom. It was not until the early years post-WWII that France endorsed in 1956 a specific legal framework to regulate blood transfusion in the country, followed in 1961 by the Netherlands. However, these frameworks were not complete and did allow mediocre governance and practices. The breakthrough came with the outbreak of the HIV/AIDS epidemic which created a tsunami of liability issues all over the world and disclosed the paucities and weaknesses in organization, leadership, governance, management and quality awareness. The management of quality is based on five key elements[85] –

1. Organization, (infra-)structure, governance and leadership;
2. Standards and references;

3. Documentation and traceability;
4. Education: teaching and training, and competency;
5. Assessment through monitoring and evaluation, including hemovigilance.

Any organization is in principle managed and operated through a series of processes, starting at the top with the steering processes, followed by the su pportive or secondary processes that allow a smooth and harmonized functioning of the primary or operational processes. These fundamental principles are captured in 'Management Science' to which Transfusion Medicine bridges to allow optimization of the governance, management and operations of the vein-to-vein blood transfusion chain.[86] Management Science is the broad interdisciplinary study of problem solving and decision making in human organizations, with strong links to management, economics, business, engineering, management consulting, and other sciences. It uses various scientific research-based principles, strategies, and analytical methods including mathematical modelling, statistics and numerical algorithms to improve an organization's ability to enact rational and accurate management decisions by arriving at optimal or near optimal solutions to complex decision problems. In short, management sciences help businesses to achieve goals using various scientific methods e.g., SPC, Six Sigma, ISO, and lean Six Sigma.

This science field was initially an outgrowth of applied mathematics, where early challenges were problems relating to the optimization of systems which could be modelled linearly, i.e., determining the optima (maximum value of outcome, procurement performance, quality of products and services, bandwidth and economy of scale, etc. or minimum of loss, risk, costs, etc.) of some objective function. Today, management science encompasses any organizational activity for which the problem can be structured as a functional governance system so as to obtain a solution set with identifiable characteristics.

To be able to understand and practice this supportive science in the governance of a blood establishment competent leadership is needed at top (steering processes) and middle management (supportive processes) level.

3. EDUCATION

Education consists of teaching (acquiring knowledge and understanding) and training (acquiring skills needed to implement knowledge in practice). The teaching provides the theoretical backgrounds and awareness on which the training should be based. Following the trail of development of Transfusion Medicine over the last century and a half, education was dominated by training without adequate teaching. As a consequence a knowledge gap started to grow in different parts of the world, clearly demonstrable in the Low and Medium HDI countries. Albeit partial, this is also noticeable in the higher HDI countries.

Figure 30
Jean C. Emmanuel

Teaching and training have for long been dominated by the laboratory aspects of Transfusion Medicine, targeting the work and middle management force employed in the primary and supportive processes parts of Transfusion Medicine. The numerous post-WWII initiatives at country level and internationally illustrate this developmental course in education, e.g., the Council of Europe courses, the Distance Learning Materials (DLM) of WHO, the ISBT supported workshops, the AABB seminars and webinars, and the residential

courses of the European School of Transfusion Medicine (ESTM, initiated in 1992 by Umberto Rossi from Legnano, Italy). At the turn of the century WHO realized that despite all the efforts to provide useful educational materials, no attention had been given to the necessary education of leadership. Dr. Jean C. Emmanuel, Director of the WHO headquarter Department of Blood Safety and Clinical Technology in Geneva (fig.30), launched the eminent idea to create an academic course on management in transfusion medicine focused on potential top managerial leadership in Transfusion Medicine and requested the University of Groningen to establish an Academic Institute for International Development of Transfusion Medicine that would host a post-academic education and applied science program on Management of Transfusion Medicine (MTM)[87]; the institute was created in 2001. An e-learning based intense course was designed, both theoretical (9 modules in two clusters) and a 6 months real time exposure to management of a large regional blood establishment and its clinical interface. The theoretical part included several scientific fields such as economy and econometry, information and communication, law, human resource and time management, social sciences and risk management, etc.. Fellows needed to do a research project to be published as a graduation thesis, thereby stimulating the acquisition of research skills and attitude. Currently the MTM course has been incorporated in the Graduate School of Medical Sciences, responsible for all Research Master and PhD education and training programs within the University Medical Center Groningen (UMCG).[88]
Today several Universities in different countries have established education programs and curricula for Transfusion Medicine, but not all are sufficiently comprehensive to cover the broad field of Transfusion Medicine. Many courses, workshops and seminars provide a passive curriculum which does not allow students to practice the knowledge and acquire the needed skills. Additionally the learning environment usually differs quite strikingly from the home environment, especially for developing country students, obstructing adequate implementation of what was learned. At last but by far not least diplomas and certificates have not been standardized and reflect a different level of knowledge and skills.

4. SCIENCE

Transfusion Medicine as a science has been recognized since long, but so far has been overshadowed by a number of other sciences such as immunology, immunohematology, microbiology, virology and molecular biology. The science overarches both applied research as well as more fundamental and basic research. Although the core business is in supplying hospitals and patients with safe and efficacious blood products, the way to safety and efficacy needs continuous research to improve on not only the procurement aspects, but more importantly on the long term effects of transfusion on recipients, irrespective of age and underlying pathology. The translation of the day to day routine data collected into applied scientific data is growing but still not fully matured. Every data tells a story of scientific interest that needs a fundamental curiosity to unveil these stories and document them for future and existing generations of scientists and practitioners. Only then will Transfusion Medicine as a science base its policies, strategies and practice on evidence.
There is no reason to hide away from reality and the tangible existence of Transfusion Medicine and its science because of the old Cinderella position experienced. Participating in and initiating multidisciplinary research across borders of the bio-medical field will only enrich and strengthen the field. Bridging with both soft sciences (alpha) and exact sciences

(beta) will definitely contribute to further improvements in safety and availability, efficacy and rational use. There are already examples of countries in the less developed part of the world where developments are well on their way and leadership visionary uses the generated data for scientific work and digestion, e.g., Cameroon, India, Iran, Namibia, Nepal, Pakistan and South Africa. The advantageous spin off of a growing network in the international scientific and professional community should not be underestimated.
The 1976 timely and visionary initiative developed by the Red Cross Blood Bank Groningen-Drenthe in the Netherland to organize annually an international scientific thematic symposium on blood transfusion, created a wealth of proceedings over a period of 28 years. These scientific meetings were of high quality, both scientific as well as educational and contributed to an excellent library of well documented books.

Over the past decades Transfusion Medicine in the more advanced world has embraced the science and practice of cellular engineering and editing for cellular therapies and incorporated this part integrally in the discipline. AABB has changed its expression to the outside world with the device ´*Advancing Transfusion and Cellular Therapies Worldwide*´.[90]

5. EXPLORED AND UNEXPLORED FIELDS

Transfusion Medicine started with the exploration of transfusion technology, how to transfer blood from one individual (animal or human) into another. The adverse and often dramatic outcomes initiated the exploring of the phenomena of immunology, immunohematology and blood group serology, the physiology of blood coagulation, cell metabolism and preservation of blood and blood cells *ex vivo*. Low temperature biology and cryobiology were added, as were pharmacology, biocompatibility and polymerchemistry. Microbiology, parasitology and virology have been explored for many a decade. These fields have resulted in a global implementation of basic operational principles; glass bottles have almost disappeared and the use of metabolically justified and optimized preservation solutions are common practice, albeit at different scales. The practical development of cold chain procedures and equipment is another field that has been explored for quite some time, but faces the threat of the need for a guaranteed and uninterrupted infrastructure, in particular power supply and hygiene. An increasing interest is growing for epidemiology including the indicatory benefit of an early detection of threatening developments in communities and probabilities for new strategies and directions for explorative research. Molecular biology is extending increasingly to support a better understanding of cell membrane architecture and related aspects of physiology and pathophysiology as well as more detailed insight in cell metabolism and the role preservation environments play in optimal functional survival of blood cells *ex vivo*. Medical engineering has taken a high flight over the last quarter of the 20st and first decade and a half of the 21st century. Equipment became more and more automated and sophisticated, which unfortunately also brought along vulnerability and considerable investment and maintenance costs. The operational functioning of such equipment depends almost exclusively on a stable and well advanced physical infrastructure including maintenance and servicing, and environment e.g., facilities and climate, limiting its use to advanced centers of excellence in the developed world fully compliant with current good manufacturing practice (cGMP) principles.

In a more slow pace ´soft sciences´ were introduced and started to develop and grow, but are still lacking behind – public awareness and public relations paramount for a

sustained and reliable motivation and retention of potential blood donors, clinical awareness and communication essential for a well-functioning of the clinical interface leading to rational clinical transfusion practices. The epidemiology of clinical transfusion medicine is still in its infancy as is the application of logistics and operations research to optimize the balance between demand and supply. Astonishing amounts of blood are collected during major campaigns (e.g., World Blood Donor Day) and immediately after disasters (e.g., New York 9/11) that cannot be used within the allowable shelf life period and therefore have to be wasted. Surprisingly this happens more often in the low and medium HDI countries than in the more advanced world.

Since the launch in 2000 of the UN Millennium Development Goals[91] and the continuation of this global initiative in 2016 under the title Sustainable Development Goals, [92] more attention has been created for the basic governance and leadership development as well as the key foundation of an adequate legal framework. All UN Member States have agreed to work towards achieving Universal Health Coverage (UHC) by 2030. This includes financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all. This WHO initiative to introduce the Universal Health Coverage principle has awakened an interest in a scientific approach on how to integrate Transfusion Medicine in public health and the overall health care system.[93] With that the need for research on how to structure the essential steering and supportive processes has also started to become visible. A recent survey among the 22 Member States of the WHO Eastern Mediterranean Region on existence and quality of blood safety legislation unveiled an extreme paucity. Only 9 countries responded having some legislation in place, but none of these laws and regulations comply with the WHO advocated principles and leave wide gaps in the mases of the legislative net.[94] As a consequence mal- and uncontrolled practices continue to flourish opposing and obstructing the efforts to create and achieve nationwide safety and availability of blood and blood products within the scope of universal health coverage. Here a bridge to the science of Law should be developed to create a growing evidence for the need of fundamental protection of communities from poor and maleficent transfusion practices. Another scarcely explored field is in pharmaco-economics to be used to calculate the justification of introducing fashion-tinted interventions and methodologies that do not essentially contribute to an improvement of safety, efficacy and lengthening of quality adjusted life years (QALY) in Transfusion Medicine. Researchers such as Brian Custer[95], Maarten Postma[96] and René van Hulst[97,98] can be marked as pioneers in this still largely unexplored field. WHO included blood and blood products in their growing list of Essential Medicines (EML).[99] Despite the guidance developed by WHO to adequately manage blood and blood products as essential medicines, a scientific response of observable size has not yet been developed. Similarly, Management Science needs exploration to streamline the development of well-organized and governed blood establishments with sufficient economy of scale, away from the fragmented small blood shops on the corners of the health care streets, and operating under the umbrella of a competent and adequate legal framework with a meaningful and protective licensing structure.

6. NOBEL LAUREATES AND TRANSFUSION MEDICINE[14]

Transfusion Medicine as a bridging science has so far seen 20 Nobel laureates who contributed over the second half of the 19th and the 20th century to its scientific and operational development and maturation. That will certainly not be the end.
The discipline stems from the mother clinical specialty Internal Medicine with a close relation to Hematology, Immunology, Transplantation Immunology and Genetics.

1908 – **Ilya Ilyich Mechnikov** and **Paul Ehrlich** in recognition of their work on immunity with two lines of defence, the innate immunity and the adaptive immunity. Their field was immunology.
Mechnikov's lecture was titled: 'On the present state of the question of immunity in infectious diseases'.
Ehrlich presented a lecture titled: 'Partial cell functions'.

1926 – Theodor Svedberg for his work on disperse systems. His field was colloidal and physical chemistry.
Svedberg's lecture was titled: **'**The Ultracentrifuge'.

1930 – Karl Landsteiner for his discovery of human blood groups. He worked in the field of fysiology and medicine and presented a lecture titled: 'On individual differences in human blood'.

1948 – Arne Wilhelm Kaurin Tiselius for his research on electrophoresis and adsorption analysis, especially for his discoveries concerning the complex nature of the serum proteins.
His field was analytical biochemistry, physical chemistry and he presented a lecture titled: **'**Electrophoresis and adsorption analysis as aids in Investigations of large molecular weight substances and their breakdown products'.

1976 – Baruch Samuel Blumberg and **D. Carleton Gajdusek** for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases. Both worked in the field of disease transmission, epidemiology. Blumberg discovered HBsAg and Gajdusek unravelled the root cause of Kuru disease.
Blumberg presented his lecture on 'Australia antigen and the biology of hepatitis B'.
The title of Gajdusek's presentation was 'Unconventional viruses and the origin and disappearance of Kuru'.

1980 – **Baruj Benacerraf, Jean Dausset** and **George D. Snell** for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions. These three laureates worked in the field of immunology.
Banecerraf presented his lecture on ´The Role of MHC gene products in immune regulation and its relevance to alloreactivity´.
Dausset gave his lecture on ´ The Major Histocompatibility Complex in man -- Past, Present, and Future concepts´.
Snell presented his lecture on ´ Studies in Histocompatibility´.

1984 – Niels K. Jerne, Georges J.F. Köhler and **César Milstein** for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies. Their field was immunology.
Jerne presented his lecture on 'The generative grammar of the Immune System´.
Köhler lectured on ´Derivation and diversification of Monoclonal Antibodies´.
The lecture presented by Milstein was titled ´From the structure of antibodies to the diversification of the immune response´.

1993 – Kary B. Mullis for his invention of the polymerase chain reaction (PCR) method. He worked in the field of Biochemistry and presented a lecture on 'The Polymerase Chain Reaction'.

1997 – Stanley B. Prusiner for his discovery of Prions - a new biological principle of infection. His field is disease transmission and he gave his lecture on **'**Prions'

2003 – Peter Agre and **Roderick MacKinnon** for discoveries concerning channels in cell membranes and for structural and mechanistic studies of ion channels. Their field is biochemistry, structural chemistry.
Agre lectured on 'Aquasporin channels'.
MacKinnon presented his lecture on 'Potassium channels and the atomic basis of selective ion conduction'.

2008 – Françoise Barré-Sinoussi and **Luc Montagnier** for their discovery of human immunodeficiency virus. These scientists worked in the field of disease transmission, immunology and virology.
Françoise Barré-Sinoussi presented her lecture on 'HIV: a Discovery Opening the Road to Novel Scientific Achievements and Global Health Improvement'.
The title of the lecture of Montagnier was '25 Years after HIV Discovery: Prospects for Cure and Vaccine'.

2011 – Ralph M Steinman for his discovery of the dendritic cell and its role in adaptive immunity. He worked in the field of immunology and died 30 September 2011 two months before the Nobel ceremony.
His lecture on 'Ralph Steinman and the Discovery of Dendritic Cells' was presented by Michel C. Nussenzweig.

These 20 Nobel laureates illustrate the bridging of science with Transfusion Medicine, which would not have developed and matured to its current extend without the research, publication and communication of the scientific work done. The evidence is documented, but unfortunately not that easily accessible to many of the scientists in the developing part of the world. However, WHO Headquarters[100] as well as the Offices of the WHO Eastern Mediterranean Region,[101] South-East Asia Region[102] and Western Pacific Region[103] took the initiative to institute a library with an advanced Index Medicus with abstracts of peer reviewed publications that can be consulted on request.

7. CONCLUSION

Transfusion Medicine has come a .long way, largely in the shadow of other fields of science and medical practice. Its comprehensiveness provides a unique scenery and environment to

bridge with the many supportive sciences. Most of these are exact sciences, but over the past decades increasingly 'soft sciences' and the group of applied exact sciences (gamma sciences) have been discovered and bridged

For long the field has been dominated by laboratory sciences and practice with a prime interest in the test tube and not so much the patient. Although the early work was triggered by clinical observations that showed at numerous occasions the power of failure, it deviated into a laboratory defined science, where the connection with the clinical practice was regarded as a 'milk man's shop' business, rather than a truly supportive facilitator of clinical transfusion medicine. The outbreak of the HIV/AIDS epidemic forced the creating of quality awareness and culture and centered the scientific attention back to the patient expressed by hemovigilance and patient blood management. So far in the international world of peer reviewed scientific journals there is only one journal that focuses exclusively on clinical transfusion practice – the International Journal of Clinical Transfusion Medicine,[104] bringing blood transfusion back to where it belongs: the bedside in the hospital with the prime and leading adage – *'primum est non nocere'*.

8. REFERENCES

1. Lindeboom GA. The story of blood transfusion to a Pope. J Hist Med 1954;9:455
2. Brown HM. The beginnings of intravenous medications. Ann Med Hist 1917;1:177
3. Makuf MFR. History of blood transfusion. J Hist Med 1954;8:59
4. Marinozzi S, Gazzaniga V, Ioro S. The eartliest blood transfusions in 17th-century in Italy (1667-1668). Transfus Med Rev 2018:32:1-8
5. Lower R. Philos Trans R Soc London. 1666;1:353
6. Hoff HE, Guillemin R. The first experiments on transfusion in France. J Hist Med Allied Sci 1963;18:103-24
7. Denis J. Concerning a new way of curing sundry diseases by transfusion of blood. Phil Trans R Soc London 1667; 3:489-504
8. Young JH. James Blundell (1790-1878): Experimental physiologist and obstetrician. Med Hist 1964;8:159
9. Leacock JH. On the transfusion of blood in extreme cases of haemorrhage. Med Chir J & Rev 1816;3:276
10. Blundell J. Observations on transfusion of blood. The Lancet 1828;2:321-24
11. Neudorfer J. Uber Transfusionen bei Anaemischen. Osterr Ztschr Prakt Heild 1860;6:124
12. Braxton-Hicks J. On transfusion and new mode of management. Br Med J 1868;3:151
13. Oberman HA. Early history of blood substitutes. Transfusion of milk. Transfusion 1969;9:74-77
14. Nobel Prize Laureates, accessible through https://www.nobelprize.org/
15. Landsteiner K. Uber Agglutinationserscheinungen normalem menschlichen Blutes. Wiener Klein Wochenschr 1901;14:1132-34
16. The discovery and significance of the blood groups. Reid M and Shine I, eds. SBB Books, Cambridge, MA. 2012
17. Levine P, Vogel P, Katzin FM, Burnham L. Pathonogenesis of erythroblastosis fetalis; statistical evidence. Science 1941;94:371-72
18. Broman B. The blood factor Rh in man. A clinic-serological investigation with special regard to morbus Hemolyticus Neonatorum (erythroblastosis foetalis). Acta Paedr. 1944;31 Suppl. II.
19. Coombs RRA, Mourant AE, Race RR. A new test for the detection of weak and "incomplete" Rh agglutinins. Br J exp Pathol 1945;26:255-266
20. Lewis M, Anstee DJ, Bird GWG, et al. Blood group terminology. ISBT Working Party on Terminology for Red Cell Surface Antigens. Vox Sang 1990; 58:152-69
21. Dausset J. Leuco-agglutinins. IV. Leuco-agglutinins and blood transfusion. Volx Sang 1954;4:190-98
22. Dausset J. Iso-leuco-agglutinins anticorps. Acta haemat 1958;20 :158-66
23. Van Rood JJ. Leucocyte grouping. Academic thesis University of Leiden, NL. 1962
24. Dausset J. The major histocompatibility complex in man. Past, present and future concepts. Science 1981;1466-74
25. Virchow, R. Thrombose und Embolie. Gefässentzündung und septische Infektion. In: Gesammelte Abhandlungen zur wissenschaftlichen Medicin. Von Meidinger & Sohn. Frankfurt am Main 1856:219–732.
26. Hustin A. Note sur une nouvelle méthode de transfusion. Communication préliminaire. Annales et Bulletin de la Société Royale des Sciences Médicales, 1914;72:104-11
27. Lewisohn R. A new and greatly simplified method of blood transfusion. Med Rec 1917;87:141-42

28. Rous P, Turner JW. The preservation of living red cells in vitro. J Exp Med 1916;23:219-37
29. Stanbury LG, Hess JR. Blood transfusion in WWI. The roles of Lawrence Bruce Robertson and Oswald Hope Robertson in the most important medical advance of the war. Transfus Med Rev 2009; 23:232-36
30. Robertson OH. Transfusion with preserved red cells. Br J Med 1918;1:691-95
31. Loutit JF, Mollison PL. Advantages of a disodium-citrate-glucose mixture as a blood preservative. Br Med J 1943;2:744-75
32. Gibson JG, Rees SB, McMannus TGJ, Scheitkin WA II. A citrate phosphate dextrose solution for the preservation of human blood. Am J Clin Pathol 1957;28: 569-78
33. Högman CF, Hedlund K, Zetterstrom H. Clinical usefulness of red cells preserved in protein-poor media. N Engl J Med 1978;299:1377-82
34. Högman CF, Hedlund K, Sahlestrom Y. Red cell preservation in protein-poor media. III. Protection against in vitro hemolysis. Vox Sang 1981;41:274-81.
35. D'Amici GM, Mirasole C, D'Alessandro A, Yoshida T, Dumont LJ, Zolla L. Red blood cell storage in SAGM and AS3 : a comparison through the membrane two-dimensional electrophoresis proteome. Blood Transfus 2012;10 Suppl 2:46-54
36. Hess JR. An update on solutions for red cell storage. Vox Sang 2006;13-19
37. Walter CW. Invention and development of the blood bag. Vox Sang 1984 ;47:318-24
38. Prowse CV, de Korte D, Hess JR, van der Meer PF for the Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Commercially available blood storage containers. Vox Sang; 106:1-13
39. Polge C, Smith AU, Parkes AS. Revival of spermatozoa after vitrification and dehydration at low temperatures. Nature 1949;164:666
40. Mollison PL, Sloviter HA, Chaplin HJr. Survival of transfused red cells previously stored for long periods in the frozen state. The Lancet 1952;ii:501-5
41. Lelkens CCM. Frozen red cells for military and civil purposes. Relevance, experiences and developments. Academic thesis University of Amsterdam, Netherlands. 2017
42. Klein E, Toch R, Farber S, Fiorentino R. Hemostasis in thrombocytioenic bleeding following infusion of stored, frozen platelets. Blood 1956;11:693-96
43. Weiss AJ, Ballinger WF. The feasibility of storage of intact platelets with apparent preservation and function. Ann Surg 1958;148:360-64
44. Arnaud F. Etude de cryopreservation de plaquettes sanguines ettdes cellules medullaires hematopoietiques. Applications en therapeutique humaine. PhD thesis Université Scientifique et Médicale de Grenoble, France. 1983.
45. Beaujean F, Leforestier Ch, Mannmoni P,. Cliniucal and functional studies of platelets frozen in 5% dimethyul-sulfoxide. Cryo-Letters 1979;1:98-103
46. Abel JJ, Rowntree LG, Turner BB. Plasma removal with return of corpuscules. J Pharmacol Exp Ther 1914;5:625-
47. Smit Sibinga CTh. Machine options for apheresis. In: Cash JD, ed. Progress in Transfusion Medicine. Vol. 3. Churchill Livingstone, Edinburgh/London/Melbourne/New York 1988:5-86
48. Tullis JL, Surgenor DM, Tinch RJ, et al. New principles of closed system centrifugation. Science 1956;124:792-97
49. Freireich EJ, Judson G, Levin RH. Separation and collection of leucocytes. Cancer Res 1965;25:1516-20

50. Djerassi I, Kim JS, Mittakul C, Suvansri U, Ciesielka W. Filtration leukapheresis for separation and concentration of transfusable amounts of normal human leukocytes. J Med 1970;1:358-64
51. Turner TB, Diseker GTH. Duration of infectivity of *Treponema Pallidum* in citrated blood stored under conditions obtained in blood banks. Bull Hopkins Hosp 1941;68:26
52. Barker LF. Introduction. In: Dodd RY, Barker LF, eds. Infection, Immunity and Blood Transfusion. Alan R. Liss, New York 1985:xix-xxv
53. Allen JG. The epidemiology of posttransfusion hepatitis. Basic blood and plasma tabulations. Commonwealth Fund, Stanford. 1972:1-135
54. Gocke DJ, Greenberg HB, Kavey NB. Correlation of Australia antigen with posttransfusion hepatitis. JAMA 1970;212:877-79
55. Blumberg BS, Alter HJ, Visnich A. A 'new' antigen in leukemia sera. JAMA 1965;191:541-46
56. Blumberg BS, Gerstley BJS, Hungerford DA, London WT, Sutnick AI. A serum antigen (Australia antigen) in Down's syndrome, leukemia and hepatitis. Ann Intern Med 1967;66:924
57. Ling CM, Overby LR. Prevalence of hepatitis B virus antigen as revealed by direct radioimmunoassay with 125-I-antibody. J Immunol 1972; 109:834-41
58. Feinstone SM, Kapikian AZ, Purcell RH, Alter HJ, Holland PV. Transfusion-associated hepatitis not due to viral hepatitis type A or B. N Engl J Med 1975;292:767-70
59. Turner ML. Prion diseases and blood transfusion. In: Smit sibinga CT, Das PC, Dodd RY, eds. Transmissible diseases and Blood Transfusion. Kluwer Academic Publ. Dordrecht/]Boston/ London 2002:51-56
60. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996;347:921-25
61. Titmuss RM. The Gift Relationship. Allen and Unwin, UK. 1970
62. Oswalt RM. A review of blood donor motivation and retention. Transfusion 1977;17:123-35
63. Piliavin JA. Why do they give the gift of life? A review of the research on blood donors since 1977. Transfusion 1990;30:444-59
64. Piliavin JA, Calledro PI. Giving blood. The development of an altruistic identity. Johns Hopkins University Press, Baltimore, MD. 1991
65. Los APM, Smit Sibinga CTh. Donor management information system: An investment in the future. Transfusion Today Quarterly Newsletter of the ISBT. 1998;18:4-6
66. Los APM, Smit Sibinga CTh. Community involvement: The development – the past, the present and the future of blood donation as a form of community involvement. In: Smit Sibinga CTh, Das PC, Cash JD. Transfusion Medicine: Quo Vadis? What has been achieved, what is to be expected. Kluwer Academic Publ. Dordrecht/]Boston/London 2001:21-29
67. Vlek CAJ, Haasnoot GW. Improving blood donor acquisition and retention: A multivariate model understanding 'Helping Behaviour'. In: Smit Sibinga CTh, Das PC, Alter HJ. Risk management in blood transfusion: The virtue of reality. Kluwer Academic Publ. Dordrecht/]Boston/London 1990:3-22
68. Vlek CAJ. Facts, fears and formulas about blood transfusions: On the assessment, acceptance and control of risks. In: Smit Sibinga CTh, Das PC, Snijder EL, eds. Trigger Factors in Transfusion Medicine. Kluwer Academic Publ. Dordrecht/]Boston/London 1996: 113-31

69. WHA63.12 Availability, safety and quality of blood and blood products. World Health Assembly Resolutions Geneva, CH 2010 accessible at http://www.who.int/mediacentre/events/governance/wha/en/
70. Towards 100% voluntary blood donation: a global framework for action. Dhingra N, Carolan P, eds. World Health Organization and International Federation of Red Cross and Red Crescent Societies, Geneva, CH. 2010
71. Chadwick JR. Transfusion. Boston Med Surg J 1874;41:25-32
72. Ottenberg R, Kaliski DJ. Accidents in transfusion: their prevention by preliminary blood examination based on an experience with one hundred twenty-eight transfusions. J Amer Med Assoc. 1913; 61:2138
73. Lee RI, Vincent B. The coagulation of normal human blood: an experimental study. Arch Int Med 1914;13:398-425
74. Deming WE. The new economics for industry, government and education. Massachusetts Institute of Technology Center for Advanced Engineering Study. Cambridge, MA. 1993
75. Schmidt PJ. Blood bank standards and procedure manuals. In: Smit Sibinga CTh, Das PC, Taswell HF, eds. Quality Assurance in Blood Banking and its Clinical Impact. Martinus Nijhoff Publ. Boston/The Hague/Dordrecht/Lancaster 1984:43-53
76. DeGowin EL, Hardin RC, Alsever JB. Blood transfusion. WB Saunders. 1949
77. Shewhart WA. Statistical method from the viewpoint of quality control. New York: Dover Press. 1986 ISBN 0486652327. OCLC 13822053 . Reprint. Originally published: Washington, DC: Graduate School of the Department of Agriculture, 1939.
78. Andreu G, Morel P, Forestier F, Debeir J, Rebibo D, Janvier G, et al. Hemovigilance network in France: organization and analysis of immediate transfusion incident reports from 1994 to 1998. Transfusion 2002;42:1356-64
79. Serious hazards of transfusion. Annual report 1996-1997. Machester, UK. SHOT office 1998
80. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. *Official Journal of the European Union*, L91, 30/03/2004, p25-39
81. Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/ EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events. Official Journal of the European Union, L256, 1/10/2005, p.32-40.
82. AuBuchon JP, Whitaker BI. America finds hemovigilance! Transfusion 2007; 47:1937-42
83. Global Data Base on Blood Safety (GDBS) accessible at http://www.who.int/bloodsafety/global_database/GDBS_Summary_Report_2011.pdf?ua=1
84. Hess JR, Schmidt PJ. The first blood banker: Oswald Hope Robertson. Transfusion 2000;40:110-13
85. Jansen van Galen JP, Smit Sibinga CTh. Process management in the vein-to-vein chain. In: Smit Sibinga CTh, ed. Quality Management in Transfusion Medicine. Nova Science Publ. Inc, New York. 2013:131-85

86. Beer S. Management Science: The Business Use of Operations Research. Aldus Books, London, Doubleday, New York. 1967
87. Smit Sibinga CTh. Filling a gap in Transfusion Medicine education and research. Transfus Med Rev 2009;23:284-91
88. Academic Institute IDTM accessible through http://idtm-mtm.org/
89. Graduate School of Medical Science accessible through https://www.rug.nl/research/gradschool-medical-sciences/
90. AABB accessible through http://www.aabb.org/Pages/default.aspx
91. UN Millennium Development Goals accessible through http://www.un.org/millenniumgoals/
92. UN Sustainable Development Goals accessible through http://www.un.org/sustainabledevelopment/sustainable-development-goals/
93. WHO Universal Health Coverage, accessible through http://www.who.int/universal_health_coverage/en/
94. Smit Sibinga CTh. Existing and recommended legislative framework for a National blood transfusion policy. Glob J Transfus Med 2017;2:89-96
95. Custer B. Economic analyses of blood safety and transfusion medicine interventions: a systematic review. Transfus Med Rev 2004;18:127-43
96. Postma MJ, Los APM, Ruitenberg EJ, Smit Sibinga CTh. Cost effectiveness of HIV NAT screening for Dutch donors. In: Smit Sibinga CTh, Das PC, Cash JD. Transfusion Medicine: Quo Vadis? What has been achieved, what is to be expected. Kluwer Academic Publ. Dordrecht/Boston/London 2001:45-51
97. Van Hulst M, Postma MJ. Cost-effectiveness of alternatives to allogeneic blood transfusion; reviewing the available evidence. In: Smit Sibinga CTh, Das PC, Dodd RY, eds. Transmissible Diseases and Blood Transfusion. Kluwer Academic Publ. Dordrecht/Boston/London 2002:131-42
98. Van Hulst M. Health Economics of Blood Transfusion Safety. Academic PhD thesis, University of Groningen, Groningen, NL. 2008
99. WHO Essential Medicines List, accessible through http://www.who.int/mediacentre/news/releases/2017/essential-medicines-list/en/
100. Global Index Medicus (GIM), accessible through www.who.int/entity/library/about/The_Global_Index_Medicus/en/
101. Index Medicus for the WHO Eastern Mediterranean Region (IMEMR), accessible through www.applications.emro.who.int/library/imjournals/
102. Index Medicus for the WHO South-East Asia Region (IMSEAR), accessible through www.searo.who.int/publications/library_resources/en/
103. Index Medicus for the Western Pacific Region (IMWPR) accessible through www.wpro.who.int/entity/apame/publications/en/
104. International Journal of Clinical Transfusion Medicine. Dove Press, New Zealand. https://www.dovepress.com/international-journal-of-clinical-transfusion-medicine-journal