THE HISTORY OF BLOOD TRANSFUSION PRIOR TO THE 20th CENTURY - PART 2

ABSTRACT / SUMMARY

Although there are a number of descriptions of 'blood infusion' in antiquity, it was the publication of the discovery of the circulation of blood in 1628 by William Harvey and the work of Christopher Wren and Robert Boyle in 1663 on the infusion of different materials into dogs that paved the way to the possible practical attempts at actual blood transfusion. Although these early experiments, principally by Richard Lower in England and Jean Denis in France provided valuable information regarding inter-species incompatibility and the problems of blood coagulation, it was not until the work of James Blundell in the early part of the 19th Century that blood transfusion was used as a means of blood replacement. However, blood transfusion was not to become an accepted therapeutic possibility until the discovery of practical anticoagulation and the ABO blood groups at the start of the 20th Century.

RENEWED INTEREST

James Blundell (1790-1877) a noted physician, physiologist and one of the outstanding obstetricians of his day is credited not only with rekindling interest in blood transfusion in the second decade of the 19th Century and providing it with 'a semblance of a rational approach' (Young, 1964) but was also the first person to transfuse human blood (Myhre, 1995). Many people in fact regard Blundell as 'the father of modern blood transfusion'. Even though he was one of the pioneers of blood transfusion the *Dictionary of National Biography* makes no reference at all to his work on transfusion.

Blundell initially became interested in transfusion as a method of treating post-partum haemorrhage, being *"appalled at my own helplessness at combating fatal haemorrhage during delivery"*. His experiments began by exsanguinating dogs and then reviving them by transfusing arterial blood from other dogs (Blundell, 1818). His experiments also identified that transfusing blood from a different animal species was dangerous and he therefore turned to the use of human blood for transfusion, stating:

"*Although, however, the blood of one genus of animals may, perhaps, without fatal consequences, be sparingly mixed with large quantities of the blood of another genus, all the facts which have hitherto come to my knowledge, go to prove, that if an animal be drained of the blood in its larger vessels, and replenished with large quantities of blood derived indifferently from another genus, great danger, and in general death will ensue*."

It must however be noted that Blundell received his medical degree from the University of Edinburgh and was influenced by the work of Dr John Henry Leacock. Although Leacock's manuscript on the subject of transfusion was written after he had returned to Barbados, his experiments were performed during his time in Edinburgh where one of his contemporaries was Blundell. Utilising a six-inch length of ox ureter (as the 'tube') with crow quills attached to both ends (as the 'needles') Leacock operated on dogs, resuscitating exsanguinated animals by transfusion. Although Leacock did not perform a human transfusion, he argued against the mixing of blood from different species and his experiments quite clearly pointed to the advantages of such treatment (Schmidt & Leacock, 2002). In 1817, Leacock concluded his dissertation on transfusion as follows:

"*The consequences of haemorrhages where the functions are not dangerously affected do not of course require transfusion, since other remedies will suffice. But when the danger is imminent, and the common means are ineffectual, as when a parturient*

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women trembles on the brink of the grave from uterine haemorrhage, or when a soldier is at the point of death from loss of blood, what reason can be alleged for not having recourse to this last hope, and for not attempting the recruit the exhausted frame and turn the ebbing tide of life."

The historic date of the first documented transfusion of human blood is the 22nd December 1818. The procedure was published in 1819 under the title 'Some account of a case of obstinate vomiting in which an attempt was made to prolong life by the injection of blood into the veins' (Blundell, 1819). This case study describes how Blundell, with the help of the surgeon Henry Cline, transfused a man with *"scirrhosity of the phylorus"* (gastric carcinoma). When first seen by Blundell the patient was near to death. Approximately 14 ounces of blood was transfused by syringe in small amounts from several donors at about five minute intervals. Despite a temporary improvement in his condition the patient died two days later.

Between 1818 and 1829, Blundell and his colleagues performed a total of ten transfusions using human blood. No more than four of these can have been successful, though two patients were in fact probably already be dead when the transfusion was started (Jones & Mackmull, 1928). The first successful transfusion was of a woman who recovered from severe post-partum haemorrhage after receiving eight ounces of blood from Blundell's assistant during the course of three hours. This case was published in *The Lancet* journal (Blundell, 1829) and contains the first reference to the 'life-giving' property of a blood transfusion as follows:

"*... the patient expresses herself very strongly on the benefits resulting from the injection of the blood; her observations are equivalent to this - that she felt as if life were infused into her body*."

Blundell reported patients who *"... suffered fever, backache, headache and passed dark urine"* (presumably due to ABO incompatibility) but still argued for the use of human blood in transfusions rather than animal blood, noting (somewhat amusingly) of the impracticability of using animals as follows:

"*What is to be done in an emergency? A dog might come when you whistled, but the animal is small; a calf might have appeared fitter for the purpose, but then it had not been taught to walk properly up the stairs!*"

Blundell also identified that blood transfusion might be performed needlessly and stressed that it should be reserved for desperately ill patients only. He also actively encouraged his fellow obstetricians to use transfusion in cases of post-partum haemorrhage. Two of the most active 'transfusionists' of the time were Dr Doubleday and Dr Waller. Dr E. Doubleday described in great detail the transfusion of a woman suffering post-partum haemorrhage who was transfused with her husband's blood (Doubleday, 1825). His report noted that after six ounces had been given the woman who had previously been semi-comatose, suddenly exclaimed, *"By Jasus, I feel as strong as a bull"*.

Dr C. Waller reported an improvement in a patient with post-partum haemorrhage following the transfusion (by syringe) of only approximately 4 ounces of blood taken from her husband (Waller, 1825). Although, Blundell had previously identified from his experiments on dogs that blood replacement using a volume less than that lost was capable of sustaining life, this report was questioned from the viewpoint that the quantity of blood transfused was insufficient to effect the recovery of the patient. However Blundell argued that because no other therapy had been effective, the outcome must have been due to the transfusion. The fact remains though that many transfusions of the time were made with very small amounts of blood (i.e. 4 - 6 ounces being equivalent to 100 - 150 mL), which may in hindsight be thought of as being insufficient to produce a

recovery on their own given the apparent clinical situations of the patients concerned.

Blundell's experiments also included transfusing a dog with approximately 4 ounces of blood per day over a three week period whilst depriving the dog of food, so as to investigate the belief that blood was 'nourishing' (Blundell, 1824). At the end of this time period, the dog was found to have lost approximately one third of its body weight and reportedly died shortly after. The concept that the transfusion of blood was nourishing was a popular belief of the time, being thought of as analogous to food and as such was one of the arguments for using animal blood for transfusion (Farr, 1980). In addition, it should be noted that although Blundell showed remarkable insight into developing basic concepts related to the process of transfusion he would have been influenced by the established medical procedures of his day and commonly applied leaches to the skin of both donor and recipient reportedly in an attempt to prevent inflammation of the veins (Blundell, 1828).

During the first half of the 19th Century considerable debate continued regarding the use of transfusion, many people believing the procedure to be dangerous and to have possibly hastened the death of some patients. In addition, it was claimed that many of the patients who were stated to have benefited from a transfusion would have recovered anyway. Blundell however had argued strenuously on behalf of the use of transfusions, noting repeatedly that the dangers of haemorrhage in these patients far outweighed the possible danger from transfusion. This debate was still raging in 1849 when a report lists 48 recorded cases of transfusion of which 18 were given to patients who died, a mortality reported as being *"… rather less than that of hernia or about the same as the average amputation"* (Routh, 1849). The greatest danger of transfusion was identified to be the transmission of air, that the quantity of blood transfused should be *".... not less than 6 ounces nor more than 16 ounces"* and that the indications for transfusion included severe haemorrhage.

Blundell did however establish so many fundamental concepts that it is difficult to exaggerate the importance of his work in the history of transfusion medicine especially given the fact that at the start of his interest in the subject there was a general underlying prejudice against the procedure together with very little published experimental information to support the beliefs surrounding some of the possible effects of transfusion. Blundell for example investigated one of the ideas, which was that transfusion was capable of resuscitating people who had only recently stopped breathing, by performing a transfusion on a woman who had died only a few minutes earlier (Blundell, 1824).

However, after 1830 Blundell's interest in blood transfusion waned and he retired from medical practice in 1847 (at the age of 57) with a fortune of approximately £350,000 that is recorded to have been accumulated from his medical practice and bequests (Ellis, 2007). Although Blundell lived in comparative obscurity after his retirement he was a controversial figure, frequently at odds with the Medical Society of London and the Directors (and Treasurer) of Guy's Hospital. He died at the age of 87 on the 15th January 1878 (Editorial, 1878).

Reports of transfusions in non-European countries during the 19th Century are rare. Although George McClellan is stated to have transfused a patient in 1832 and William Hammond is said to have transfused soldiers in New Mexico in 1849 (Schmidt, 1968), transfusion was unlikely to have been practiced in the United States before 1854 when an anonymous report of a transfusion performed in New Orleans was published (Oberman, 1996). The physician Andrei Martynovich Wolff is stated to have performed the first human-to-human blood transfusion in Russia in 1832, having learned of the technique in London in 1830 from James Blundell (Huestis, 2004).

ESTABLISHING TRANSFUSION PROCEDURES

Many of the writings during the 19th Century on establishing practical transfusion procedures appear to have been mainly directed towards the development of either

increasingly refined devises and techniques used for direct transfusion or the description of rather ingenious (and in some cases bizarre) pieces of equipment for the indirect transfusion of blood.

James Blundell noted that vein-to-vein direct transfusions were impractical due to blood clotting but attaching the artery of the donor to the vein of the recipient rendered the procedure feasible. In 1824 he described a direct method of transfusing blood from the donor's '*radial, anterior tibial or preferably ulnar artery*' to the patient's vein, the connection being made by fine tubes. He also described an indirect method using a simple syringe and cannula to remove blood from the donor's vein and to then inject it immediately into the recipient's vein. He noted the necessity of removing air from the instrument before transfusion as well as describing the considerable problems of blood clotting, *"... the blood is satisfactory only if it is allowed to remain in the container for but a few seconds"* (Blundell, 1824). Blundell had previously described his syringe as able to hold two ounces of blood and to be "…*air secure, made of brass, tinned internally, not offensive with oil, of course perfectly clean*" (Blundell, 1818). A variation of this method is mentioned by Routh who allowed blood to flow from the donor vein directly into a basin from which a syringe was filled and then injected into the recipient (Routh, 1849). A modified syringe devise was also used by Samuel Lane in 1840 for the first recorded transfusion of a patient with haemophilia at St George's Hospital, London. Lane's transfusion syringe included a three-way valve and a funnel that was used to collect the blood from the open vein in the arm of the donor, who was described as being a *'… stout, healthy young woman'* (Farr, 1981).

Blundell also described an instrument called an 'Impellor' that was essentially a funnel and pump combined. The donor's blood was made to flow into a funnel that was enclosed by a double-walled jacket filled with warm water to help keep the blood fluid. The action of a pump made from two opposite-acting spring valves within the water jacket of the funnel forced the blood along a tube to a cannula that was inserted in the patient's vein. According to the illustration, the impellor was designed to be fixed to the back of a chair to give the equipment stability as well as apparently providing somewhere for the donor to sit whilst they bled into the funnel. Blundell later invented another instrument, the 'Gravitator', in which as the name implies, gravity provided the motive force for pushing the blood into the patient's vein (Blundell, 1829). The equipment consisted of a funnel at the end of a long flexible bracket, which was again attached to a chair or similar object for stability. The funnel is connected to a tube with a cannula that was buckled to the patient's arm. An illustration shows the blood donor standing by the equipment while he watches his blood flowing into the funnel. Blundell, like a number of his contemporaries, was at pains to demonstrate by experiment that the blood was not 'injured' by its passage through such an instrument.

Although indirect transfusion methods were becoming more popular during the 19th Century, one of the chief exponents of a direct method of blood transfusion was the obstetrician Dr J.H. Aveling. His apparatus was described and illustrated in an article published in 1873 and consisted of a simple tube with a central rubber bulb that provided a pumping action together with a tube (and valves) at alternative sides of the bulb (Keynes, 1949). Aveling described the apparatus as being extremely convenient, and wrote:

"*It consists of an india-rubber tube to form an anastomosis between the emittent and recipient veins and a little bulb in the middle to act as an auxiliary heart. With the exception of two silver tubes to enter the veins and two stop-cocks, this is the whole of the apparatus, and I carried it about in my pocket to every confinement I attended for eight years until at length the opportunity for using it arrived*."

Aveling was to eventually use his direct transfusion apparatus in 1872 on a 21-year-old woman *"… in extremis"* from post-partum haemorrhage. She received 60 drachms (approximately 220 mL) of blood from her coachman and apparently soon recovered,

though Aveling added in his report that:

"… *the mental improvement of the patient was not as marked and rapid as I anticipated, but this was perhaps due to the quantity of brandy she had taken*."

The blood donor is stated to have been a coachman and is described as being *"… collected and cheerful"* throughout the procedure.

Dr J. Roussel of Geneva is stated to have first employed a direct arm-to-arm transfusion method in 1865. The technique involved placing a glass vessel filled with water over the donor's arm and a lancet (operated through the top of the vessel) then punctured the donor's vein. By means of a rubber bulb within the tubing and a two-way tap the water was rejected through one cannula and the blood injected into the recipient through a second cannula inserted into a vein. Roussel subsequently reported that he used this apparatus in thirty-five transfusions (of which sixteen were successful), emphasised the importance of using only human and not animal blood for transfusion and claimed that his method was without danger either to the donor or the recipient. Roussel's 'transfuseur' apparatus is stated to have been subsequently officially adopted for use by the French Army and apparently used during the Franco-German war (Keynes, 1949).

The dangers of infection (both local and systemic) relating to safe transfusion methods did not start to be resolved until after 1865 when Louis Pasteur identified that bacterial/fungal contamination caused putrefaction. As a result, the sterilisation of instruments and antiseptic methods began to be gradually introduced. However, one of the major drawbacks to the development of safe blood transfusion practice was that no successful practical method had been found to prevent donor blood from clotting, though defibrinated blood was used to prevent coagulation, the process involved a variety of (complex and non-sterile) stirring techniques. Sir Thomas Smith used this procedure in 1873 at St Bartholomew's Hospital in the first reported case of a transfusion to an infant (who was suffering from Haemolytic Disease of the Foetus/Newborn). The defibrinating procedure is stated (Smith, 1873) to have required the following equipment:

"… *a wire egg-beater, a hair sieve, a three-ounce glass aspirator syringe, a fine blunt-ended aspiration cannula, a short piece of india-rubber tubing with a brass nozzle at either end connecting the syringe with the cannula, a tall narrow vessel standing in warm water for defibrinating the blood, and a suitable vessel floated in warm water to contain the defibrinated blood*."

Although a variety of chemicals such as sodium bicarbonate, sodium phosphate and oxalic acid were employed as anticoagulants from the mid 19th Century it was not until 1894 that the British pathologist Professor A.E. Wright identified that the soluble salts of several acids could postpone clotting indefinitely, but he doubted if non-toxic citrates could bind enough calcium *in vivo* without producing convulsions (Wright, 1894). It would in fact be 21 years after the publication of Wright's paper before a practical means of anticoagulation using sodium citrate was devised that provided the impetus for development of practical indirect transfusion methodology in the 20th Century (Lewisohn, 1915).

ONE STEP FORWARD – ONE STEP BACK

Although Blundell had shown that the blood from one species of animal was potentially fatal to another, many people in Europe continued to attempt to re-assert the use of animal blood for the transfusion of humans. In 1868, Franz Gesellius (a physician of Wilna, Poland) is stated to have initially attempted to use human 'capillary-blood' for transfusion, obtained by means of a rather gruesome piece of apparatus that

simultaneously punctured the skin at numerous sites on the donor's back. The blood was collected and then transfused into the recipient's vein. He later obtained blood directly from the donor's vein using a syringe device but also (and confusingly) supported the use of animal donor blood and tried to demonstrate by experimentation that the transfusion of human blood was more dangerous than animal donor blood (Oberman, 1996).

Oscar Hasse (a physician of Nordhausen, Germany) appears to have initially been a supporter of the use of human venous defibrinated donor blood and is stated to have performed 16 transfusions with this product. However, like Gesellius, he argued for the transfusion of lamb's blood in both acute and chronic anaemia, achieved by the use of a simple short cannula connection between the animal's carotid artery and the patient's antecubital vein (Keynes, 1949). Many of these sheep-to-human transfusions resulted in symptoms of dyspnoea, cyanosis, back pain, chills, vomiting and convulsions, however Hasse argued that some of these symptoms were a sign of "*…over-activation of the patient by the animal's fresh spirits*".

The issues regarding inter-species incompatibility were resolved by the experiments of Emile Ponfick (1844-1913), pathologist at the University of Breslau, who reported extensively on the dangers of transfusion between species. He was the first person to note that the dark urine produced after what would now be recognised as an incompatible transfusion reaction was in fact haemoglobinuria (and not haematuria as previously reported), resulting from the destruction of the donor red cells and not those of the recipient. In addition, as well as summarising and commenting on the outcomes of a large number of animal-to-human and human-to-human transfusions performed by different workers, Leonard Landois published details of the effects of his own cross-species experiments including the identification that the red cells of sheep undergo lysis in human serum *in vitro* (Maluf, 1954). This work appeared to finally put an end to the use of animal blood for transfusion to humans.

Because of the difficulties encountered with the clotting of blood used for transfusion (Pelis, 1997), a brief attempt was made in the 1870's in the United States to use milk for transfusion, even though this product had been identified as unsuitable by the injection experiments of Christopher Wren (Boyle, 1663). In 1873 Joseph Howe experimented by injecting goat's milk into dogs having first transfused three patients with goat's milk, two of which died (Howe, 1875). Even though the transfusion of milk to seven patients between 1875 and 1878 resulted in them having severe reactions involving fever, tachycardia and headache, they all recovered, which is presumably the only reason why it was concluded that there was "*…a brilliant and useful future for intravenous lacteal injections*" (Thomas, 1878). However, by 1880 the use of milk for transfusion purposes was abandoned, presumably because of the increasing numbers of adverse reactions associated with the procedure.

By the end of the 19th Century the practical use of blood transfusion can be identified to be only slightly less primitive than it had been two and a half centuries earlier. The principle accomplishment during this period was the recognition of the inappropriateness of using animal blood (or milk!) for human transfusion. However, even with the use of human donor blood the number of severe reactions (graphically described in some reports) remained a worrying problem. These effects were for a long time attributed to the introduction of air into the patient's circulation. It was however to be the introduction of sterile methodologies, the development of practical anticoagulation and the discovery of the ABO blood group system at the beginning of the 20th Century that paved the way for modern practical blood transfusion procedures. Certainly, the concept that 'empirical treatment is often adopted before a rational basis is known' is well exemplified by the history of blood transfusion prior to the 20th Century.

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