INTRODUCTORY NOTES

The first chapter of the third edition of the book 'Immunohematology' by Chester M. Zmijewski, published by Appleton-Century-Crofts, New York, in 1978, is titled 'The History of Blood Transfusion'.

Appleton-Century-Crofts publishing company no-longer exists and I have been unsuccessful in my attempts to try to identify who now holds the copyright for this publication, or if it is now in the public domain. Professor Zmijewski died in 2016. As such, this transcript is presented in this format for personal study only and must not be downloaded, copied, modified or reproduced further – it is provided here as an additional source of information relating to the history of blood transfusion.

This illustrated chapter contains a comprehensive account of the 'transfusion' of Pope Innocent VIII as well as interestingly, the publications of the German chemist and physician Andreas Libavius and the English vicar Francis Potter. The involvement of Christopher Wren, Robert Boyle and Richard Lower in England and Jean Denis in France in the early development of blood transfusion is included together with pioneering work of James Blundell. The chapter also includes comments on the development of effective anticoagulation, though some other key developments of the 20th century related to the history of transfusion are only sparingly covered towards the end of the chapter prior to mentioning the development of cell separation techniques of blood donation.

IMMUNOHEMATOLOGY

Professor Chester M. Zmijewski

Chapter 1
THE HISTORY OF BLOOD TRANSFUSION

Man's centuries-long desire to perform blood transfusion as a therapeutic procedure forms the cornerstone of the modern science of immunohematology. At the present time, the use of whole blood is a well-accepted and commonly employed measure, without which many modem surgical procedures could not be carried out. One who is thoroughly familiar with this now routine technique and studies its historic development cannot help but wonder why so many of the difficulties encountered, with seemingly simple solutions, were not resolved more quickly. It is only by transposing ourselves into a world that had no knowledge of immunology, genetics, modern biochemistry, statistics, and many other basic disciplines that we can truly appreciate the efforts of the pioneers to whom we owe our heritage.

Blood has held a mysterious fascination for man since the dawn of time. We can imagine the awe of the cave men as they watched this peculiar red fluid oozing from the wounds of one of their fellows. If the wound was severe enough to allow a great deal of the vital humor to escape, the man would grow cold and die; less serious wounds would leave him weak and almost lifeless. It is no wonder that traditionally blood was thought of as being the living force of the body and the seat of the soul.

Historians tell us that the ancient Egyptians, cognizant of the beneficial and life-giving properties of blood, used it for baths to resuscitate the sick and rejuvenate the old and incapacitated. As early as 76 to 100 A.D. Pliny the Elder and Celsus, two scholarly Roman authors, described the custom of spectators rushing into the arena to drink the blood of dying gladiators. The people felt that such blood was especially beneficial since the athletes were strong and brave, qualities that certainly were seated in and transmissible by their blood.

In the middle ages, the drinking of blood was advocated as a tonic for rejuvenation and for the treatment of various diseases. In the summer of 1492 the blood of three youthful and robust boys was given to the ailing Giovanni Battista Cardinal Cibo who was then Pope Innocent VIII (Fig. 1). Apparently the procedure was not successful, since it is recorded that the Pope died on July 25, 1492. Interestingly enough, this particular therapeutic regimen was even more devastating, since the three youths also died as a result of their donation.[16]

According to Keynes[11] a similar series of events is related in Malory's *Mortre d'Arthur*. Although these procedures involved the transfer of blood from one individual to another, they cannot be considered transfusions in the same sense as we regard modern transfusions, since the intravenous route was probably not used. This is not surprising in view of the fact that widespread knowledge of the circulation of the blood and the vascular system did not occur until after 1628. In that year, Harvey published his immortal monograph, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus,* which described the theory of blood circulation. Nevertheless, as early as 1505 and 1576, individuals with the foresight of Hieronymus Cordanus and Magnus Pegelius suggested the possibility of transfusing blood from one individual to another.

FIG. 1: Pope Innocent VIII, a recipient of a blood draught. (From Brusher: *Popes Through the Ages.* Courtesy of Borden Publishing Company)

Traditionally it is accepted that Andreas Libavius was the first to advocate a blood transfusion in 1615.[13] The method he described was essentially a direct transfusion, but most historians seriously doubt that he actually attempted his experimental procedure. Libavius wrote, "Let there be a young man, robust, full of spirited blood; and also an old man, thin, emaciated, his strength exhausted, hardly capable of retaining his soul. Let the master of the art have two silver tubes fitting one into the other. Let him open the artery of the robust young man and into it insert one of the tubes, fastening it in; immediately after, let him open the artery of the old man and put the female tube into it. And then when the two tubes are joined together, the hot and spirited blood of the young man will pour into the old one as if it were from a fountain of life, and all of his weakness will be dispelled." This is truly a monument to man's daring ingenuity, and reaffirms the idea that thoughts of the scientific community in those days regarding the value of blood revolved about the central theme of it being a tonic. The concept that blood had a certain critical volume within the body, below which life could rot be sustained, was not yet realized.

There is no question that Harvey's treatise added impetus to the investigation of intravenous therapy. Even as today, we often encounter minor skirmishes regarding the priority of a great discovery, so also many scientists of the seventeenth century claimed to be the originators of the idea of blood transfusion. One of these, Francesco Folli,[5] published a pamphlet in 1680 stating that he invented the procedure 26 years before and demonstrated it to Ferdinand II, Grand Duke of Tuscany. Later on, however, he casually confessed that he had never perfected the experiment and that he had stated his views merely to teach, inspire, and spare others expense in their own investigative efforts.

An interesting account of attempted transfusions between chickens by a certain Vicar of Kilmanton, Francis Potter, in 1652, has been cited by Keynes.[11] It should serve as an inspiration to all students of the fine art of phlebotomy, who experience failure at their first few attempts. The Vicar wrote, "I am as yet frustrated, *in ipso limine,* but it is only by my owne inexpertness, who never attempted any such thing upon any creature before; for I cannot, although I have tried divers times, strike the veine so as to make him bleed in any considerable quantity." Some historians[17] interpret this passage as meaning that there existed an overwhelming fear of venesection especially on the part of the operator.

FIG. 2: Sir Christopher Wren. (Courtesy of Trent Collection, Duke University Medical Center Library)

Regardless of the numerous claims published, actual credit for the introduction of intravenous therapy must go to Sir Christopher Wren (Fig. 2). As early as 1657, this

English astronomer, architect, and physician injected various medications and other sometimes noxious potions into the veins of dogs. He used an apparatus which consisted of a needle fashioned from a slender quill to which was affixed a bladder. This formed an instrument much like the medicine dropper of modern times, but with a sharp point capable of penetrating the skin. Apparently the animals reacted to these injections by vomiting, being purged, intoxicated, killed, or revived according to the medication administered. Similar experiments were performed by the famed Robert Boyle (Fig. 3), and, as far as these authors can ascertain, he was the first to infuse soluble drugs into humans. His experimental subjects consisted of incarcerated volunteers in a London prison.

FIG. 3: Robert Boyle (Courtesy of Trent Collection, Duke University Medical Center Library)

One of the pioneers of the authentic practice of transfusion was Richard Lower (Fig. 4), an English physician, who performed his experiments on dogs in 1665. His account of the procedure is the first description of a direct transfusion from artery to vein. According to Lower,[15] a small dog was exsanguinated from the jugular vein until he was almost dead. Then a quill was connected to the cervical artery of a large donor dog, and the blood allowed to flow until the recipient was "overfilled and burdened by the amount of the inflowing blood." The procedure was repeated several times, after which the recipient dog's condition returned to normal. In subsequent experiments Lower substituted specially designed silver tubes for the quills originally employed as a means of anastamosing the circulation of the two animals (Fig. 5). During the next several years similar studies were being repeated in England and in France. The investigators, however, began to vary their techniques somewhat; they attempted exchanges of small amounts of blood between animals of different species. Eventually, of course, their thoughts turned to man.

In 1667, Jean Denis (Fig. 6), physician to Louis XIV, transfused 9 ounces of blood from a lamb into the vein of a young man suffering from luetic madness. The technique was successful, and he wrote that following the transfusion, the patient passed urine as black as soot, but apparently there was little effect in either disturbing his good physical state or mending his poor mental one. A short time later, Lower and King transfused sheep blood into man. The manner in which these experiments were performed was often diagrammed in textbooks of the day. One such illustration from Scultetus, 1693[19] (Fig. 7), shows a man being transfused with the blood of a dog. A puncture had been made in the subject's arm from which the blood rushed geiser-like into a basin, no doubt to make room for the blood flowing in from the dog. This concept was in keeping with the original method used by Lower when transfusing dogs.

FIG. 4: Richard Lower. (Courtesy of Trent Collection, Duke University Medical Center Library)

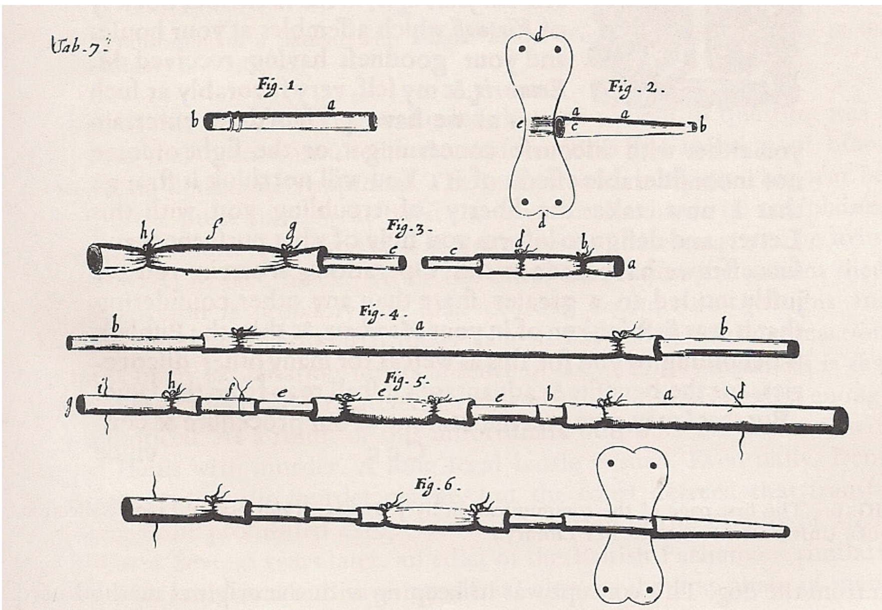
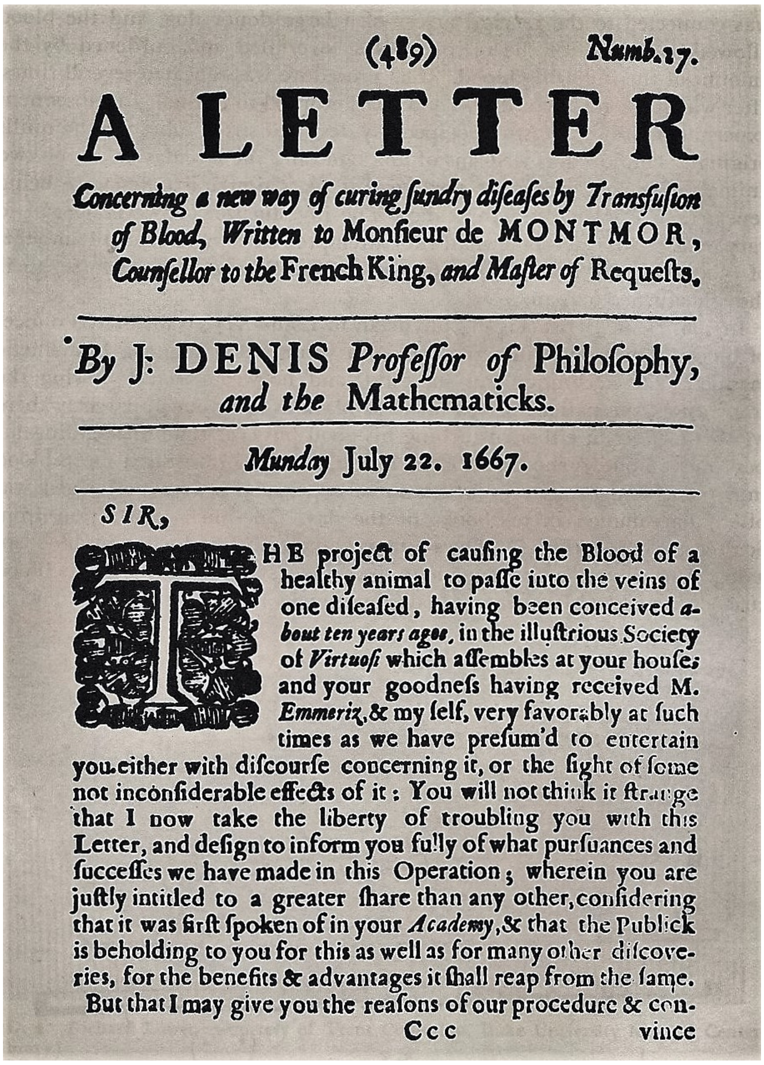


FIG. 5: Cannulae designed by Lower for performing direct blood transfusions. (Courtesy of Trent Collection, Duke University Medical Center Library)



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A LETTER

Concerning a new way of curing ſundry diſeaſes by Transfuſion 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,

THE project of cauſing the Blood of a healthy animal to paſſe into the veins of one diſeaſed, having been conceived *about ten years agoe*, in the illuſtrious Society of *Virtuoſi* which aſſembles at your houſe; and your goodneſs having received M. *Emmeriz*, & my ſelf, very favorably at ſuch times as we have preſum'd to entertain you either with diſcourſe concerning it, or the ſight of ſome not inconſiderable effects of it: You will not think it ſtrange that I now take the liberty of troubling you with this Letter, and deſign to inform you fully of what purſuances and ſucceſſes we have made in this Operation; wherein you are juſtly intitled to a greater ſhare than any other, conſidering that it was firſt ſpoken of in your *Academy*, & that the Publick is beholding to you for this as well as for many other diſcoveries, for the benefits & advantages it ſhall reap from the ſame.

But that I may give you the reaſons of our procedure & con-

Ccc vince

FIG. 6: The first page of the communication by J. Denis. (Courtesy of Trent Collection, Duke University Medical Center Library)

After his initial success, Denis continued his experiments on two other patients. Unfortunately, the fourth patient in his series died. Denis' description of this particular case indicated that the patient in question was a luetic who had been transfused twice before. The first infusion of blood produced no detectable symptoms. The second time, however, "his arm became hot, the pulse rose, sweat burst out over his forehead, he complained of pain in the kidneys and was sick at the bottom of his stomach. The urine was very dark, in fact, black." After the third transfusion the patient died. This description is probably the first recorded account of the signs and symptoms of what is recognized today as a hemolytic transfusion reaction. The most likely explanation for its absence in the previous instances is that the volumes of blood were relatively small and the symptoms benign enough to go unnoticed. As a result of this unfortunate outcome, the patient's wife charged Denis with murder. A long legal battle ensued. Eventually, Denis was exonerated of the murder charge, but the court decreed that transfusions were to be prohibited except with the sanction of the Faculty of Medicine of Paris. Several years later, an edict of the British Parliament similarly prohibited transfusions and drew an official close to the first phase of man's desire to replace the vital force of the body.

The actual practice of transfusion lay dormant for nearly 150 years, although the basic idea did not escape the minds of the scientific community. As medical knowledge advanced, physicians began to understand the real importance of blood, not merely as a mysterious tonic or rejuvenating potion, but as an essential material with a physiologic function that made it a requirement for life.

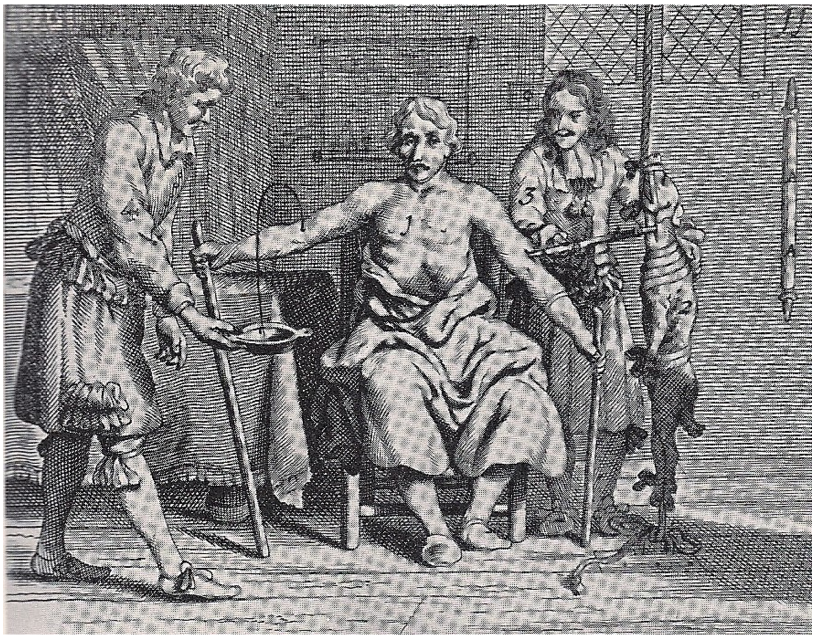


FIG. 7: Transfusion of a patient with animal blood. (From Scultetus. Courtesy of the National Library of Medicine)

Although some claim that a Dr. Philip Syng Physic of Philadelphia performed a transfusion as early as 1795,[18] many stories have been written about one particular English obstetrician, James Blundell (Fig. 8), who had a great deal of compassion for his patients. It has been said that he was appalled at his own helplessness at combating fatal hemorrhage during delivery. Therefore, in 1818, he revived the procedure of blood transfusion. His contributions were great enough to earn him the title of father of modern blood transfusion.

It is apparent that Blundell's motivation stemmed from an idea that the loss of blood with a resultant diminution of total circulatory volume could be detrimental or even fatal. This becomes clearer when his research efforts into investigating the effects of the withdrawal of various amounts of blood are studied. Certainly the approach taken by this physician was founded on a new concept. No longer was the procedure based on mysticism and the ancient desire to replace old blood with new blood or to rid a suffering patient of evil humors. Instead, it was subjected to astute scientific investigation. A considerable number of experiments were performed by Blundell and his collaborators. They demonstrated the shocking effects of withdrawing large quantities of blood from an animal, much in the same manner as Lower did many years before. However, they also showed that these effects could be reversed with relatively small quantities of blood that were in no way injurious to the donor animal. This was an important observation for it was certainly of no use to proceed with the development of a technique that might bring harm to a potential donor of blood.

Blundell performed ten transfusions,[1-3] two of which were on patients who had already expired. Of the total, four were successful. In all the cases human blood was used. This was indeed fortunate, otherwise a set of circumstances similar to those experienced by Denis would surely have been encountered. It is not altogether fortuitous, however, that humans were selected as donors. Even though numerous purely aesthetic objections were raised concerning the use of animals for this purpose, the reasons for the choice were based on sound scientific judgment. As a result of the observation of Dr. Leacock of Barbados[11] experiments which seemed to foretell that the blood of one species might not be suitable for another were performed. Blundell showed that when a dog was exsanguinated and subsequently transfused with the blood of another dog he survived. If on the other hand, the contents of his circulatory system were replaced with blood from a sheep, the animal showed an initial recovery but invariably died.

FIG. 8: James Blundell – father of modern blood transfusion therapy. (Courtesy of Trent Collection, Duke University Medical Center Library)

In spite of these experiments and the previous experience of the early workers, some individuals had an almost fanatic enthusiasm for animal transfusions. About 60 years after the successes of Blundell and others, Franz Gesellius[6] and Oscar Hasse[7] still advocated the use of lamb's blood for transfusion. One cannot help but wonder whether this was due in large measure to a lack of the particular quality of human personality that is necessary to attract potential blood donors. It is not difficult to imagine that blood procurement was considerably impaired when knowledge of the apparatus used for collecting the blood was passed on to the layman by formerly willing donors. One such piece of armamentarium designed by Gesellius to obtain capillary blood is shown in Figure 9. It is indeed a most formidable piece of apparatus.

Although this practice of animal transfusion has lain in abandonment for many years[21] a case was described in the relatively recent literature. The investigators transfused a patient with 50 cc of a 50 percent suspension of bovine erythrocytes because her serum contained a potent cold agglutinin that reacted with the red cells of almost all human donors, thus prompting the performance of this biologic test. The symptoms of the ensuing reaction, although not fatal, were severe enough to discourage any further attempts at transfusing animal blood.

As with most fields of endeavor, however, necessity becomes the mother of invention, and blood transfusion was rapidly advanced because of the Franco-German war. The technique of direct transfusion with human donors was used with a moderate degree of success under field conditions, adding proof that it was a valuable therapeutic measure.

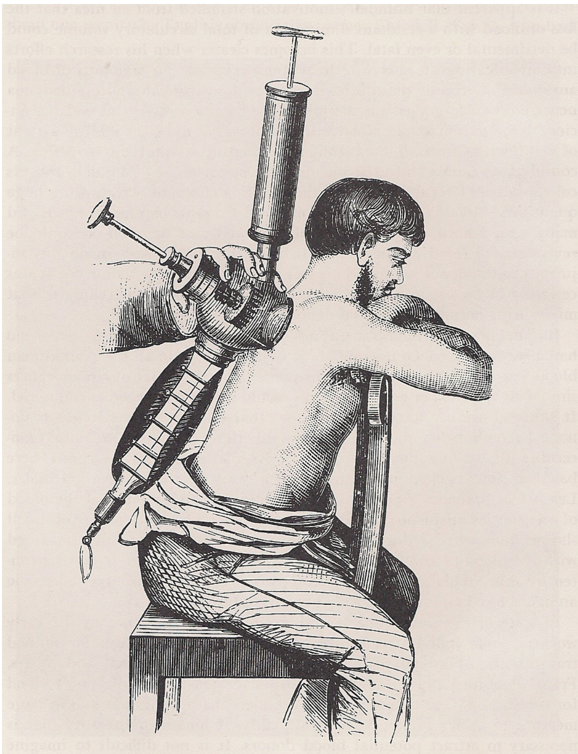


FIG. 9: Instrument designed by Gesellius for obtaining capillary blood from donors. (Courtesy of Trent Collection, Duke University Medical Center Library)

Two major problems still remained unsolved. One of these was the property of blood to clot when withdrawn from a vein. Clotting was quite an annoyance in that it obstructed the passages of the various complex instruments that were used for infusion, such as the Waller syringe shown in Figure 10. As a result, direct transfusions were most often employed. Even so, very ingenious devices were used to speed up the flow in order to prevent clotting.

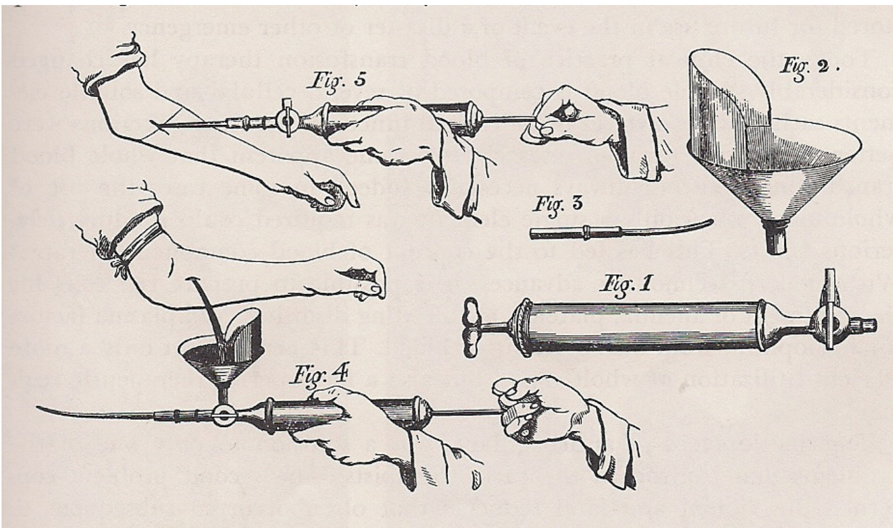


FIG. 10: Syringe designed by Waller to expedite direct transfusions. (Courtesy of Trent Collection, Duke University Medical Center Library)

Initial attempts at circumventing this difficulty ranged from defibrinating the blood with a wire paddle, resembling an egg beater, to the use of certain chemicals, the first of which was sodium bicarbonate[12] and later sodium phosphate. The latter compound did indeed prevent coagulation but unfortunately was toxic and may have caused the death of four patients treated by Hicks in 1869.[8] For the next several years various other compounds were tried, including citrate solutions. These seemed to be the most promising but, unfortunately, they were also toxic in the concentrations employed. In 1914 and 1915, the problem was solved when it was noted by Hustin, Agote, Lewisohn, and Weil and other investigators that small non-toxic quantities of citrate were capable of preventing the coagulation of blood. In 1916, Rous and Turner[17] discovered that the addition of small amounts of dextrose added greatly to the preservation of the qualities of blood undergoing storage. The ultimate anticoagulant and preservative that is in widespread use today was not described until 1943, by Loutit and Mollison.[14] The solution ACD (acid-citrate-dextrose) is capable of maintaining blood in a transfusable condition for 21 days. A newer solution, CPD (citrate-phosphate-dextrose), has been developed which will permit a shelf life of up to 30 days.

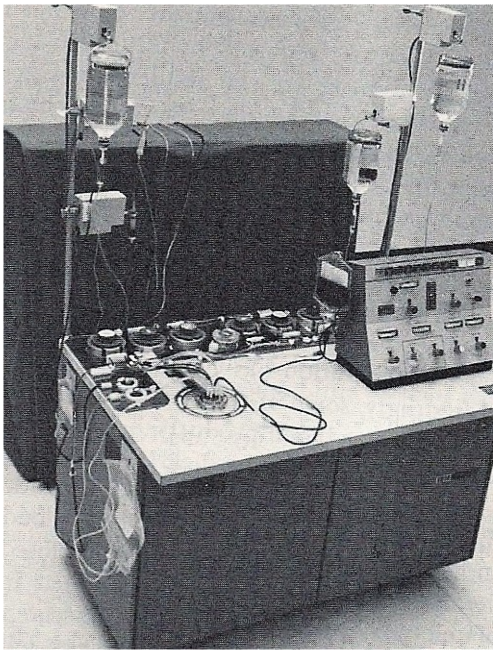
Another novel approach to transfusion was introduced by Shamov[20] and by Yudin,[22] who pioneered the use of cadaver blood for transfusion. This technique offers certain advantages in that anticoagulants are not required due to natural fibrinolysis, and large transfusions can be given from a single donor. There are numerous disadvantages as well, however, including an adequate supply of suitable cadavers, i.e. individuals who have died from causes other than septicemia, malignancy, or metabolic disease affecting the blood. Even though this method is very popular in Russia, it has never reached widespread use in this country.

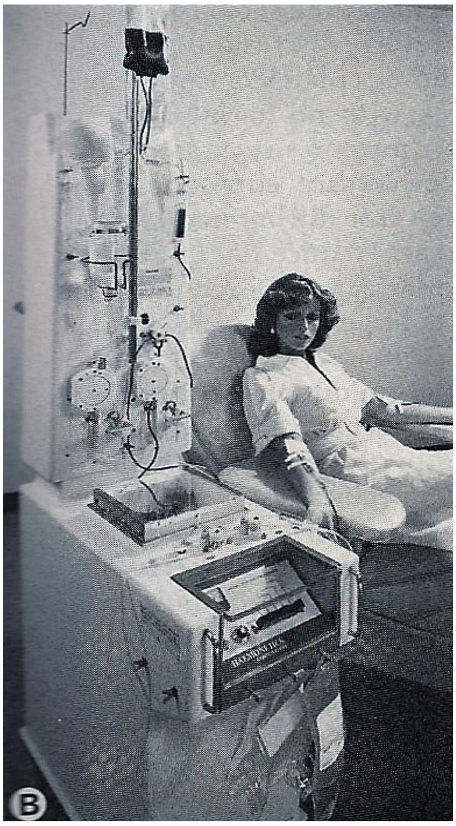
The field of blood storage and preservation has been the subject of intensive investigation in recent years. Whereas at one time it was necessary to bring an animal or human donor into the bed chamber, it is now possible to collect blood at leisure, ship it across great distances, and even store it in the frozen state with the aid of certain solutions. In this manner large quantities of rare blood and even ordinary blood can be stockpiled and stored for future use in the event of a disaster or other emergency.

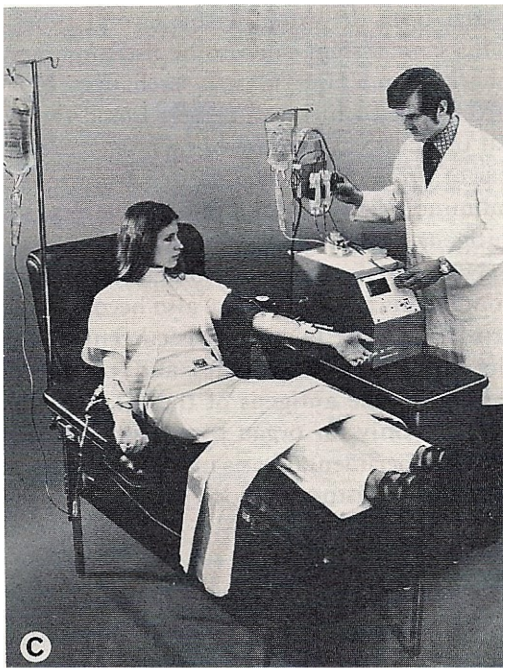
Today the clinical practice of blood transfusion therapy has changed considerably. Whole blood is composed of several cellular and soluble elements each with its own set of individual functions. As these functions were better understood through research, it became apparent that whole blood transfusions were not always necessary. Indeed in some cases the use of whole blood when only a single element was required could produce deleterious effects. This has led to the concept of blood component therapy.[9] With modern technologic advances, it is possible to prepare red cells for the treatment of anemia, platelets for bleeding disorders, and plasma factors for hemophilia from a single unit of blood. This permits not only a more efficient utilization of whole blood but also a far superior therapeutic regimen.

The development of anticoagulants was a solution to only one of the problems that confronted the early therapists. The second problem concerned the violent and fatal sequelae that often occurred subsequent to blood transfusion. The first account of such a reaction was described earlier in this chapter. That particular reaction was due principally to the fact that animal blood was used for transfusion. Similar events, however, undoubtedly occurred even when human blood was used, and these account for the limited successes reported by Blundell and others. We know today that these phenomena are the result of red cell destruction by immunologic mechanisms that take place because of the individual differences of human blood. This problem was not solved until after 1900 and was the precise reason for generating interest in an area that was to become the field of immunohematology and the bulk of the subject matter of this book.

Fig. 11: Instruments used for the continuous-flow processing of blood components. A: I.B.M., B: Haemonetics, and C. Fenwal blood processors are connected in-line with the donor's blood flow. The blood is drawn into the machine, the components separated and collected, and the unwanted components returned to the donor (Photos courtesy: I.B.M., Princeton, N.J.; Haemonetics Corp., Natick, Mass.; Fenwal Labs, Morton-Grove, Ill.).







Almost to the delight of the experimentalist, however, transfusion therapy still offers many fascinating and perplexing riddles for solution, which have arisen along with the advent of the component mode of therapy mentioned earlier. The need for the development of newer methods of component preparation has created an avenue for new ideas in engineering.[10] Interestingly, some of the instruments devised for the collection and preparation of these blood products, because of their size and complexity, take on the aura of apparatus used early in transfusion history (Fig. 11).

The achievements possible with these devices, however, are most remarkable in that one can separate whole blood into red cells, platelets, plasma, and even white cells in a continuous closed system; permitting reinfusion of the donor with the unwanted product. In this manner, large numbers of platelets or leukocytes can be collected repeatedly from the same individual on numerous occasions. Since the red cells are returned to the donor, the total circulating red cell mass is not depleted and e.g., platelets can be prepared from the same person several times a week with no harmful effects. This same system can also be used for therapeutic purposes such as plasmapheresis and even plasma exchange. Finally, devices are currently being investigated which can recycle blood that has been lost during major surgical procedures. The use of such devices would greatly reduce the total number of units of red cells needed from separate donors, thereby reducing the immunologic risks inherent in the exposure to a large number of foreign antigens.

New and fascinating problems dealing with the immunologic aspects of component transfusion are also becoming apparent. As an example, the modern blood bank laboratory is currently beginning to give serious thought to the antigens of leukocytes and platelets. Most specifically, this involves typing for the antigens of the HLA system, a task formerly believed to be of value only for organ transplantation or immunogenetics and performed on an experimental basis in research laboratories. This is indeed an exciting time in the history of blood transfusion.

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