INTRODUCTORY NOTES

The book 'Blood Groups and Transfusion' by Alexander S. Wiener was originally published by the Hafner Publishing Company, New York. Chapter IV of the third edition reprint of this book, published in 1962, is titled 'History of Blood Transfusion' (pages 50-59 inclusive).

As well as descriptions of some of the early attempts of blood transfusion by Denis, this document provides information about blood group incompatibility related to transfusion and the historical development of the different techniques of transfusion, especially the details of the direct (artery-to-vein) transfusion techniques that were pioneered in the USA in the early part of the 20th century.

BLOOD GROUPS AND TRANSFUSION

Alexander S. Wiener

CHAPTER IV
HISTORY OF BLOOD TRANSFUSION

From early historical times the use of blood as a therapeutic measure was advocated, some people believing that the blood not only carried the vital force of the body, but was also the seat of the soul. Thus, Pliny and Celsus describe the custom of the people who rushed into the arena to drink the blood of dying gladiators. During the middle ages, the drinking of blood was much recommended for rejuvenation and the treatment of various diseases, and the often cited "transfusion" of the blood of three youths into Pope Innocent VIII in 1492 was probably of this nature.

Hieronymus Cardanus (1505-1576) and Magnus Pegelius suggested the possibility of transferring blood directly from the blood vessels of one individual into those of another, and Andreas Libavius (1615) was the first definitely to advocate blood transfusion, describing a technic similar to that used until quite recently. Libavius wrote in 1615: "Let there be a young man, robust, full of spirituous blood, and also an old man, thin, emaciated, his strength exhausted, hardly able to retain his soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the young man, and put it into one of the tubes, fastening it in. Let him immediately after open the artery of the old man, and put the female tube into it, and then the two tubes being joined together, the hot and spirituous blood of the young man will pour into the old one as it were from a fountain of life, and all of his weakness will be dispelled." It is doubtful whether or not Libavius ever actually carried out the experiment that he proposed (Scheel).

The actual beginning of the history of blood transfusion should be dated from the discovery of the circulation of the blood by Harvey in 1616, and the publication in 1628 of his immortal monograph, "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus." This was followed in 1658 by the experiments of Christopher Wren, astronomer and architect, who injected medicaments into the veins of dogs by means of slender quills fastened to bladders. These experiments were continued by Robert Boyle and others, and the following year the first infusion of solutions of drugs into human beings was performed in London on a convicted malefactor.

FIG. 16. CONTEMPORARY ILLUSTRATION OF EARLY LAMB BLOOD TRANSFUSION. LAMSWEERDE, 1684

The first authentic blood transfusion was performed in England by Richard Lower in 1665. In this experiment, dogs which had been exsanguinated were kept alive by transfusion of blood from other dogs. Lower accomplished this by connecting the carotid artery of one dog (the donor) with the jugular vein of the other dog (the recipient) by means of quills. It is of interest to note that the technic used by Lower does not differ in any fundamental respect from one of the methods used more than 250 years later for transfusions in human beings.

The first transfusion in human beings[1] was performed in 1667, when Denys and Emmerez transfused nine ounces of blood from the carotid artery of a lamb into the vein of a young man. This transfusion was successful, and encouraged by his success, Denys performed other similar operations. In his writings he referred to the fact that the patient passed urine as black as soot following the transfusion. In the meanwhile, Lower and King performed a successful transfusion in England, in which nine ounces of the arterial blood of a sheep was transferred to the veins of a man.

These experiments terminated when the fourth patient transfused by Denys in France died from the effects of the procedure. The symptoms exhibited by the patient who received the fatal transfusion are of interest in light of our present knowledge. The patient, a luetic, had been transfused with some alleviation of his mania, it was claimed, twice before, the first transfusion being symptomless, but following the second transfusion "his arm became hot, the pulse rose, sweat burst out of his forehead, he complained of pain in the kidneys and was sick at the stomach. The next day the urine was very dark, in fact black." It is clear that the hemolytic reaction following the second transfusion was due to the immunization of the patient against sheep blood, and the third transfusion resulted in a fatal shock. A charge made by the patient's wife that her husband had been poisoned by Denys, led to a long legal battle which ended with the exoneration of Denys, but the court decreed that further transfusions were to be prohibited, except with the sanction of the Faculty of Medicine of Paris.[2] Ten years later (1678) an edict of Parliament specifically prohibited the operation, thereby closing this chapter in the history of blood transfusion.

For a period of 150 years, no further progress was made and very little interest was shown in blood transfusion. In 1818, inspired by a desire to do something for the many distressing cases of death from hemorrhage occurring especially in midwifery, James Blundell attempted to revive the operation of blood transfusion. He devised a rather crude apparatus consisting of a large receptacle for the blood connected to a syringe by which the blood was injected through a tube into the patient. From the modern point of view his technic would be less satisfactory than that used by Lower, but Blundell's researches on blood transfusion, as well as on the properties of the blood and the effects of its withdrawal, served to revive the interest of the profession in blood transfusion.

Through the efforts of many workers, too numerous to mention, the operation of blood transfusion was gradually perfected until today it is a safe and invaluable therapeutic procedure when performed by properly trained physicians. Before the present state of perfection could be attained, however, two main difficulties had to be overcome: (1) Unfavorable reactions to transfusion caused by "incompatibility" of the bloods of the donor and recipient had to be recognized. (2) Difficulties caused by coagulation of the blood had to be prevented by perfection of the transfusion apparatus and technic.

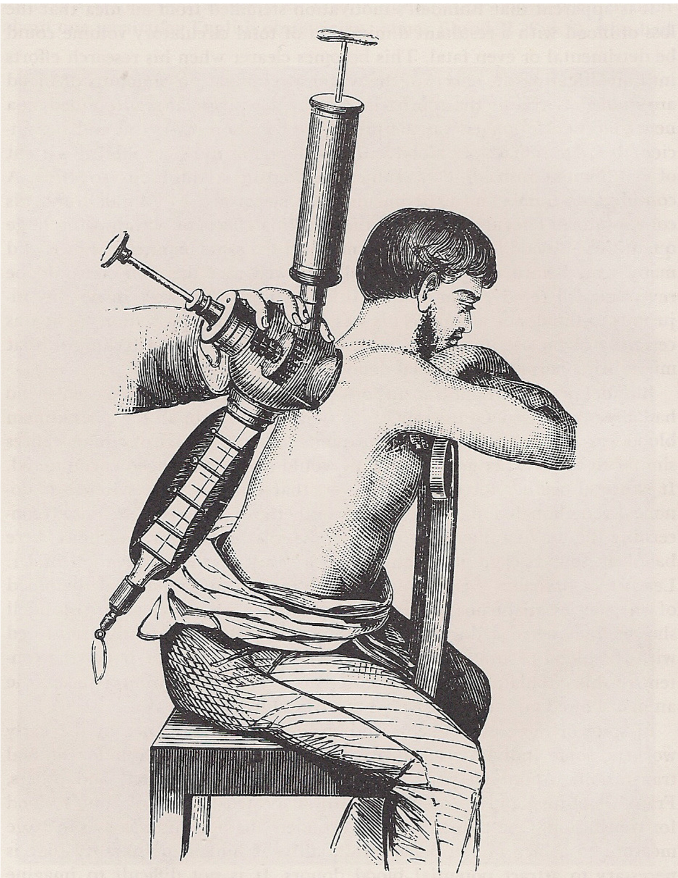

Fig. 17. APPARATUS FOR CAPILLARY BLOOD TRANSFUSION DEVISED BY GESELLIUS

INCOMPATABILITY OF BLOOD IN RELATION TO BLOOD TRANSFUSION

Although it was noted that the transfusion of blood of domestic animals into man was often followed by hemoglobinuria (black urine), lever, or even death, animal blood was still used during the nineteenth century. In the latter half of the nineteenth century, Panum and Landois, in a series of experiments showed that while an animal which had been depleted could be saved by transfusion of the blood of another animal of the same species (as in the famous experiment of Lower), it would die if the blood of an animal of a different species was used. Landois showed that if human blood was mixed *in vitro* with the blood of other animals, the human red blood cells would become hemolyzed, and the white blood cells would cease their ameboid motion and die. Similarly, Ponfick found that transfusions between animals of the same species were safe, whereas if donor and recipient of different species were used, anuria or hematuria, coma, and even death might often follow.[3]

This work, however, did not explain why transfusions with human blood should be followed by dangerous or fatal reactions, a fact which was the cause that blood transfusion was almost completely abandoned as a therapeutic measure. These reactions were finally explained by Landsteiner in 1900, when he showed that the serum of one normal human being can agglutinate or hemolyze the bloods of certain other individuals. This is undoubtedly the most important single discovery relating to blood transfusion, and Landsteiner himself,[5] fully realizing the practical significance of his findings, pointed out the importance of the blood groups for blood transfusion in his original paper on blood groups. In 1907, Hektoen[6] repeated the suggestion that the blood groups be made the basis of the selection of donors for blood transfusion. Ottenberg[7] and Schultz[8] were probably the first to apply Landsteiner's discovery for the determination of compatibility in an actual transfusion.

An experimental confirmation of the importance of blood grouping in transfusion was offered by the work of Ottenberg and his collaborators on transfusions in dogs and cats.[9] In 1913, Ottenberg and Kaliski[10] reported their observations on 128 human blood transfusions. In three of these cases it was shown by agglutination tests that the patient's serum reacted with the donor's cells. One of the three patients developed anuria and died eight hours after transfusion, and a second died within 48 hours. In each case blood smears made during and after the transfusions showed phagocytosis of the red blood cells. On the other hand, when the bloods of donors and recipient were compatible, none of these reactions occurred. Hemolytic reactions reported by other authors at about this time were also shown to be due to incompatibility.

These observations, and especially the experience acquired during the first World War led to the universal adoption of blood grouping as a basis for the selection of blood donors. This has proved so satisfactory that at present there exist Blood Donor Agencies which have lists of donors of each group, so that the proper donor can be obtained on short notice.

In more recent years, with the increasing popularity of blood transfusion as a therapeutic procedure, occasional instances were encountered of hemolytic reactions following the use of blood of the same group as the patient. These have been attributed to the presence of irregular isoantibodies in the patient's serum, but not in all cases were such antibodies demonstrable by cross-matching tests. New information on this point was obtained in 1940 when Landsteiner and Wiener[11] detected a new factor in human blood (Rh) unrelated to the agglutinogens A and B, and shortly thereafter Wiener and Peters[12] observed three instances of hemolytic reactions, one fatal, in which isoantibodies for this factor were present in the patient's sera. These were patients who had received previous transfusions, the anti-Rh isoantibodies being most likely the result of isoimmunization. Furthermore, it was found that transfusion accidents can occur at an initial transfusion due to isoimmunization in pregnancy, the fetus *in utero* supplying the foreign antigen (Levine and Stetson,[13] Wiener and Peters,[12] Levine, Katzin and Burnham[14]). Some of these accidents had previously not been recognized as related to the transfusion, but were believed to be merely pregnancy complications. Apparently the great majority of the reactions in repeated transfusions and in pregnancy cases are due to the Rh factor.

DEVELOPMENT OF THE TECHNIC OF TRANSFUSION

One of the main difficulties encountered by the early workers in blood transfusion was the readiness of blood to coagulate when in contact with the apparatus or air. The coagulated blood would either clog up the apparatus, thus interfering with the continuation of the transfusion, or if introduced into the recipient's circulation might cause fatal embolism. This difficulty was combated in two ways: (A) by increasing the speed of the operation or by lining the apparatus with substances which did not favor coagulation, (B) by modifying the donor's blood so as to prevent its coagulation. The former constitutes the transfusion of unmodified blood, and the latter the transfusion of blood modified by defibrination or the addition of certain anticoagulants.

A. *Transfusion of Unmodified Blood.*

The possible methods of transfusing unmodified blood may be grouped under three headings: (1) the direct method, in which a blood vessel of the donor was sutured to a blood vessel of the recipient; (2) the semi-direct method, in which the blood was allowed to flow or was pumped through tubes from the donor to the recipient or was transferred with the aid of syringes; and (3) the indirect method, in which the donors' blood was collected in a receptacle, and then administered to the recipient by the intravenous route.

(1) It is a curious circumstance that the most difficult of the three methods of transfusion was the earliest to be perfected. Inspired by Carrel's work on end-to-end anastomosis of blood vessels, Crile[15] devised a method for the direct transfusion of blood in 1907. In order to maintain the flow of blood an artery of the donor was connected to a vein of the recipient. In Crile's method a small cannula was used (cf. fig. 18) through which the vein of the recipient was drawn and cuffed back over the cannula. The artery of the donor was then drawn over the vein, thus forming a continuous lining of intima without any rough areas to favor coagulation. Crile's technic would of course have been impossible without the development of aseptic surgery at the end of the nineteenth century.

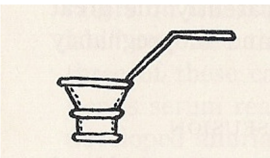

Fig. 18. CRILE'S CANNULA

The direct method of transfusion has been abandoned, however, because of the following difficulties: considerable surgical skill was necessary; the amount of blood transfused could not be accurately measured; an artery of the donor had to be sacrificed; the same donor could only be used once or twice; there was danger of transferring disease from recipient to donor; and a slight motion of either donor or recipient might sever the anastomosis, a very distressing complication.

(2) By connecting the artery of the donor with the vein of the recipient by means of tubes, the surgical technic can be considerably simplified. This semidirect method of transfusion had been used by Lower in his experiments, already quoted, in which he connected the carotid artery of one dog to the jugular vein of a second dog by means of quills. During the nineteenth century tubes made of metal, caoutchouc, pieces of artery of animals, etc. were used. Most of the attempted transfusions were unsuccessful or only partly successful, however, since the blood would coagulate inside the tubes, and the transfusion would have to be interrupted. In 1915, Bernheim[16] used this method successfully by using paraffin-lined tubes to connect the blood vessels of donor and recipient (cf. fig. 19). Since an artery of the donor must be severed, this method is open to most of the objections that have been raised against the direct method of transfusion, and it has therefore also been abandoned.

For the reasons just mentioned attempts were made to transfuse blood from a vein of the donor to a vein of the recipient. In this semidirect method of transfusion of blood, since there is little or no difference in pressure between the circulations of donor and recipient, external force must be used to propel the blood. Blundell's apparatus was of this nature, but it was so complicated that the blood soon coagulated and only small transfusions could be given. During the nineteenth century attempts were made to devise an apparatus which would speedily transfuse the blood from donor to recipient, but they were all too complicated to succeed.

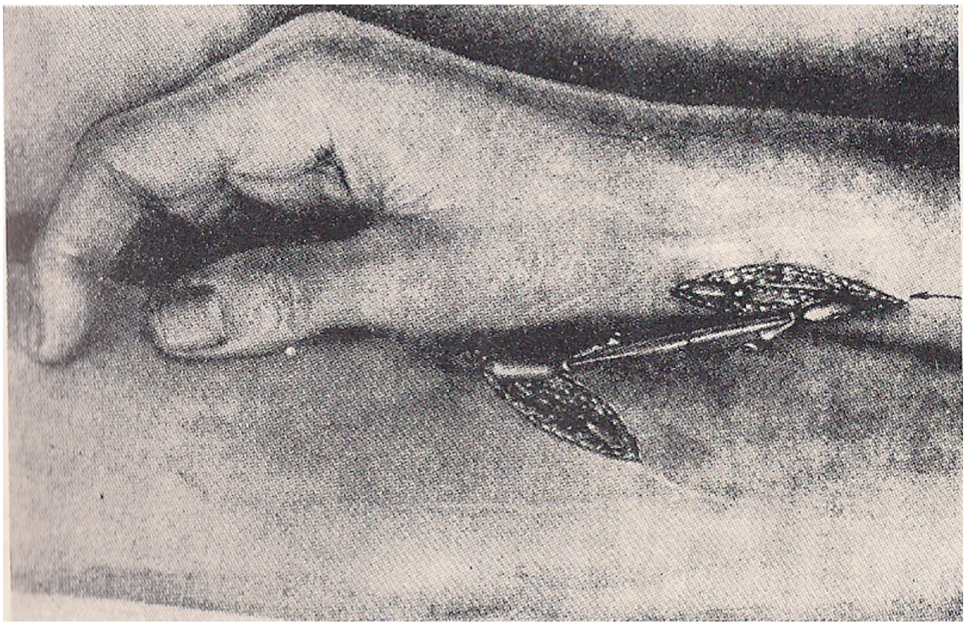

FIG. 19. ARTERIOVENOUS TRANSFUSION, BERNHEIM

The present popular methods of semidirect transfusion were made possible by the use of the syringe and intravenous needle. In 1892, von Ziemssen[17] successfully performed a blood transfusion by drawing 20 c.c. of blood at a time into a syringe from the donor's vein and injecting it into that of the recipient. In 1913, Lindeman[18] improved this technic by using a large number of syringes that were kept constantly clean by an assistant who washed them with saline solution. This method was not very popular because a team of trained assistants was necessary, and the danger of coagulation was ever present. Finally, in 1915, by making use of a syringe with a four-way stop-cock, Unger[19] devised an apparatus that made possible transfusions of large, measured amounts of blood, without placing undue hardships on either the donor or the recipient. The same year Miller[20] described a simple apparatus which employed a similar principle; and numerous satisfactory syringe-valve apparatus with different mechanisms have since been devised.

(3) The indirect transfusion of unmodified blood was made possible by the discovery that if the receptacle in which the blood is collected is evenly lined with paraffin, coagulation of the blood is delayed. A special cylinder invented by Kimpton and Brown[21] in 1913 was used for transfusing measured amounts of unmodified blood by this method. Although the method has certain disadvantages, the original Kimpton-Brown tube, or modifications of the tube were still being used for blood transfusions in certain institutions as late as 1937 both in this country and abroad.

B. *Transfusion of Modified Blood*

Discouraged by his unsuccessful attempts to transfuse unmodified blood, Bischoff[22] suggested defibrination of the donor's blood. For this purpose various types of apparatus were devised whereby the donor's blood could be whipped until all the fibrin had been removed. The blood was filtered through gauze to remove any small clots that may have formed and then injected into the recipient. Recently, the method has been revived, particularly by Filatov,[23] who claims satisfactory results from the transfusion of conserved defibrinated blood.

The addition of phosphate of soda to the donor's blood was suggested and used by Braxton-Hicks[24] as an anticoagulant, but this method was found to be dangerous on account of the harmful effect of the phosphate. Hirudin was tried at the suggestion of Landois (1892), but was discarded on account of its toxicity. Citrated blood was used for the first time by Hustin[25] in 1914 but his method consisted in infusing highly diluted blood mixed with sodium citrate and dextrose. At the beginning of 1915 Agote[26] and Lewisohn[27] simultaneously described the transfusion of citrated whole blood, but Lewisohn worked out the technic in detail, especially the amount of citrate to be used as an anticoagulant. Because of its simplicity, the method was used extensively during the first World War.

Recent Developments. During the two decades following the first World War a controversy existed as to the relative merits of citrated blood and unmodified blood for transfusion. The proponents of unmodified blood transfusions pointed to the supposed toxic action of the citrate ion and the physiologic advantages of injecting blood in as natural a state as possible. The proponents of the citrate method, on the other hand, pointed out its simplicity, and that sodium citrate in the doses required for transfusion was harmless, while the rapidity with which transfusions of unmodified blood must be carried out to avoid coagulation can be dangerous to patients with weak myocardia. Salant and Wise[28] showed that while the citrate ion is stable in blood stored in vitro, it is rapidly oxidized by the tissues in vivo, so that the body can tolerate fairly large amounts of citrate provided it is administered slowly. Utilizing this principle for carrying out massive transfusions by the drop method, Marriott and Kekwick[29] found that relatively enormous doses of citrate could be given without harm to the patient. When it was found, moreover, that the incidence of chills and fever was no higher following transfusions of fresh citrated than for fresh unmodified blood,[30] the pendulum began to swing more definitely in favor of the citrate method. In more recent years the safety of the use of stored citrated blood and plasma for transfusions has been established, and the transfusion of unmodified blood has lost much of its favor, though there is still a small group of cases in which ii remains the method of choice.

REFERENCES / NOTES

1 The claim that the first blood transfusion from man to man was made by Franz Folli is contradicted by Mayrhofer [*Med. Welt.* 12: 473 (1938)].

2 For fuller information concerning the early history of blood transfusion, *see:* Scheel, *Die Transfusion des Blutes, Copenhagen* (1802); Landois, *Die Transfusion des Blutes,* Leipzig (1875); Oré, *Transfusion du sang,* Paris (1876); Jennings, *Transfusion,* London (1883); Roussel, *Transfusion of Human Blood (*trans. from the French and German by Guiness), London (1877). For the more recent history of blood transfusion *see:* Zimmerman and Howell, *Ann, Med. Hist.* 4: 415 (1932) [cf. Correspondence, *Jour. Amer. Med. Asso.* 100 208 (193)] Feinblatt *Transfusion of* Blood, New York (1926); Beck*, Erg. inn. Med. u. Kinderheilk.* 30: 150 (1926); Snyder *Blood Grouping in Relation to Legal and Clinical* Medicine, Baltimore (1929); Ottenberg, *Jour. Mt. Sinai* Hosp. 4: 264 (1937), etc.

3 One would expect that these results would lay, forever, the ghost of animal blood transfusion, yet according to Zimmerman and Howell, as recently as 1928, a monograph appeared in France again advocating the transfusion of animal blood into man.

4 *Cenrtralbl. f. Bakteriol.* 28: 357 (1900).

5 *Wein. klin. Woch.* 14: 1132 (1901), also *see:* Wiener, *Jour. Amer. Med. Assoc.* 100: 208 (1933).

6 *Jour. Amer. Med. Assoc.* 48: 1739 (1907).

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8 *Berlin klin. Woch.* 47: 1407, 1437 (1910).

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10 *Jour, Amer, Med. Assoc.* 61: 2138 (1913).

11 *Proc. Soc, Exp. Biol. And Med.* 43: 223 (1940).

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22 *Arch. f. Anat., Physiol., u. wiss. Med.*, p. 347 (1805).

23 *Beitr. z. Klin. Chir.* 164: 9 (1936). Also *see:* Bagdassarov, *Le Sang*, 11: 466 (1937).

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26 *Ann. de Inst. mod. de clin. med.* Buenos Aires, Jan. (1915).

27 *Med. Rec.* 87: 141 (1915); *Surg. Gyn. and Obst.* 21: 37 (1915).

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29 *Lancet* 1: 977 (1935).

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For a rather complete bibliography on the history of blood transfusion, see *Bull. N. Y. Acad. Med.* 15: 622 (1939). Also see Kilduffe and DeBakey's "The Blood Bank and the Technique and Therapeutics of Transfusions." Chapter I. C.V. Mosby Co., St. Louis (1942).