1 History

1.1 Ancient times

For centuries, blood has been considered to have mystical properties and has been associated with vitality. In ancient times, bathing in or drinking the blood of the strong was thought to invigorate the weak. For instance, among Ancient Romans it was customary to rush into the arena to drink the blood of dying gladiators [1]; among others, to drink or bathe in blood was thought to cure a variety of ailments [2]. Bleeding was practiced to let out bad blood and restore the balance of humors, thus hopefully returning the patient to health.

It is not known when and by whom the idea of transfusing blood was developed. It is said that the first transfusion was given to Pope Innocent VIII in 1492. According to this legend, the Pope was given the blood of three boys, whose lives were thus sacrificed in vain [1, 3] because the attempts did not save the Pope. In another version of the story, the blood was intended to be used in a tonic for the Pope, which he refused, thus sparing the boys’ lives [2].

1.2 The period 1500–1700

Others to whom the idea for blood transfusion is attributed include Hieronymus Cardanus (1505–1576) and Magnus Pegelius. Little is known about Cardanus, but Pegelius was a professor at Rostock, Germany, who supposedly published a book describing the idea and theory of transfusion [1]. It can be substantiated that Andreas Libavius (1546–1616) proposed blood transfusion when in 1615 he wrote:

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 enter the artery of the young man, and put into it one of the tubes, fastening it in. Let him immediately 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 this weakness will be dispelled [1].

Despite these possibilities, it also seems unlikely that the concept of transfusing blood could have developed before William Harvey’s description of the circulation in 1616. Despite Harvey’s description of the circulatory system, there is no evidence that he considered blood transfusion. However, the concept of the “circulation” may have preceded Harvey’s publication. For instance, Andrea Cesalpino (1519–1603), an Italian, used the expression “circulation” and proposed that fine vessels (capillaries) connected the arterial and venous systems [1, 4].

A number of the major developments that led to the beginning of blood transfusion occurred during the mid-1600s [1]. In 1656, Christopher Wren, assisted by Robert Boyle, developed techniques to isolate veins in dogs and carried out many studies of the effects of injecting substances into the dogs. It is not clear whether Wren ever carried out blood transfusion between animals. The first successful transfusion from one animal to another probably was done by Richard Lower [1, 5, 6]. Lower demonstrated at Oxford the bleeding of a dog until its strength was nearly gone but revitalized the previously moribund dog by exchange transfusion using blood from two other dogs, resulting in the death of the donor animals [6].

Subsequently, a controversy developed over who had first done a transfusion. In 1669, Lower contended that he had published the results of transfusion in the Philosophical Transactions of the Royal Society in December 1666. In 1667, Jean Denis of France described his experiments in animals and applied the technique to man, which Lower had accomplished only in animals. Others mentioned as possibly having carried out animal-to-animal transfusions about this time are Johann-Daniel Major of Cologne, Johann-Sigmund Elsholtz of Berlin, don Robert de Gabets (a monk) in France, Claude Tardy of Paris, and Cassini and Griffone in Italy [1].

Denis apparently was a brilliant young professor of philosophy and mathematics at Montpellier and physician to Louis XIV. In 1667, Denis carried out what is believed to be the first transfusion of animal (lamb’s) blood to a human. A 15-year-old boy with a long-standing fever, who had been bled multiple times, received about 9 ounces of blood from the carotid artery of a lamb connected to the boy’s arm vein. Following the transfusion, the boy changed from a stuporous condition to a clear and smiling countenance. During the next several months, Denis may have given transfusions to three other individuals [1]. The second patient, Antoine Mauroy, was an active 34-year-old who spent some of his time carousing in Paris. It was thought that blood from a gentle calf might dampen Mauroy’s spirits. On December 19, 1667, he received with no untoward effects 5 or 6 ounces of blood from the femoral artery of a calf. Several days later, the procedure was repeated. During the second transfusion, Mauroy experienced pain in the arm receiving the blood,
vomiting, increased pulse, a nosebleed, pressure in the chest, and pain over the kidneys; the next day he passed black urine. This is probably the first reported hemolytic transfusion reaction. Mauroy died about 2 months later without further transfusions. Reportedly, members of the Faculty of Medicine who were opposed to transfusion and hated Denis bribed Mauroy’s wife to state that he had died during the transfusion [1]. Denis was tried for manslaughter but was exonerated. It was later revealed that Mauroy’s wife had been poisoning him with arsenic and that was the actual cause of his death [7]. Also in late 1667, Lower performed a human transfusion before the Royal Society in England. The man received 9–10 ounces of blood from the artery of a sheep and was said to have “found himself very well” afterward [1]. However, the death of Mauroy was used by Denis’ enemies as an excuse to issue an edict in 1668 that banned the practice of transfusion unless the approval of the Faculty of Medicine in Paris was obtained. This series of events led to the discontinuation of transfusion experiments, but more importantly to the abandonment of the study of the physiology of circulation for approximately 150 years [1].

1.3 The 1800s

Interest in transfusion was revived during the early 1800s, primarily by James Blundell, a British obstetrician who believed it would be helpful in treating postpartum hemorrhage [8]. Blundell carried out animal experiments and avoided the error of using animal blood because of the advice of a colleague, Dr. John Leacock. Blundell reported to the Medico-Chirurgical Society of London on December 22, 1818, the first human-to-human transfusion. It is not clear whether the transfusions given by Blundell were ever successful clinically [1]. However, Blundell’s contributions were very substantial. Unfortunately, his warnings about the dangers of transfusing animal blood into humans were not generally heeded.

Dr. Andrei Wolff carried out a human-to-human transfusion in St. Petersburgh, Russia, in 1832 having learned of blood transfusion from Dr. Blundell on a previous visit to London [9]. There is no evidence of additional transfusion in Russia until the 1920s when a transfusion institute was established in Moscow.

Key work in understanding the problems of using animal blood for human transfusions was provided by Ponfick and Landois [1]. They observed residues of lysed erythrocytes in the autopsy serum of a patient who died following transfusion of animal blood. They also noted pulmonary and serosal hemorrhages, enlarged kidneys, congested hemorrhagic livers, and bloody urine due to hemoglobinuria and not hematuria when sheep’s blood was transfused to dogs, cats, or rabbits. Landois observed that human red cells would lyse when mixed in vitro with the sera of other animals. Thus, evidence mounted that interspecies transfusion was likely to cause severe problems in the recipient.
1.4 First transfusions in the United States

In the USA, transfusions were first used in the mid-1800s, but it is not clear where they were first performed. They may have been done in New Orleans in about 1854 [2]. During the Civil War, the major cause of death was hemorrhage [10]. However, at that time blood transfusion was not developed and it appears to have been used in only two to four patients [2]. Two cases are described by Kuhns [10]. One was transfused at Louisville and one at Alexandria within about 10 days of each other. There is no evidence that the procedures were jointly planned or that the physicians involved communicated about them. In both cases, the patients improved following the transfusions [10].

1.5 The discovery of blood groups

The accumulating experiences began to make it clear that transfusions should be performed only between members of the same species. However, even within species transfusions could sometimes be associated with severe complications. Because of this, and despite the experiences during the Civil War, few transfusions were carried out during the last half of the 1800s. The discovery of blood groups by Landsteiner opened a new wave of transfusion activity. It had been known that the blood of some individuals caused agglutination of the red cells of others, but the significance of this was not appreciated until Landsteiner in 1900 reported his studies of 22 individuals in his laboratory. He showed that the reactions of different combinations of cells and sera formed patterns and these patterns indicated three blood groups [11]. He named these blood groups A, B, and C (which later became group O). Apparently none of the staff of Landsteiner’s laboratory had the less common group AB, but soon this blood group was reported by the Austrian investigators Decastello and Sturli [1]. Soon thereafter, several other nomenclature systems were proposed, and the American Medical Association convened a committee of experts, who recommended a numerical nomenclature system [12] that never gained widespread use [11]. Others later demonstrated that the blood groups were inherited as independent Mendelian dominants and that the phenotypes were determined by three allelic genes. Hektoen of Chicago first advocated the use of blood grouping to select donors and recipients and to carry out transfusion [13], but it was Ottenberg who put the theory into practice [14]. These activities are the basis for the widely held belief that blood banking in the United States had its origins in Chicago.

1.6 Anticoagulation

Another factor that inhibited the use of transfusions during the late 1800s was blood clotting. Because of the inability to prevent clotting, most transfusions were given by direct methods. There were many devices for
direct donor-to-recipient transfusion that incorporated valves, syringes, and tubing to connect the veins of donor and recipient [15].

Although there were many attempts to find a suitable anticoagulant, the following remarks must be prefaced by Greenwalt’s statement that “none of them could have been satisfactory or else the history of blood transfusion would have had a fast course” [1]. Two French chemists, Prevost and Dumas, found a method to defibrinate blood and observed that such blood was effective in animal transfusions [1]. Substances tested for anticoagulation of human blood include ammonium sulfate, sodium phosphate, sodium bicarbonate, ammonium oxalate and arsphenamine, sodium iodide, and sodium sulfate [16, 17]. The delays in developing methods to anticoagulate blood for transfusion are interesting because it was known in the late 1800s that calcium was involved in blood clotting and that blood could be anticoagulated by the addition of oxalic acid. Citrates were used for laboratory experiments by physiologists and by 1915 several papers had been published describing the use of sodium citrate for anticoagulation for transfusions [1]. It is not clear who first used citrated blood for transfusion [1]. It could have been Lewisohn [18], Hustin, or Weil [19]. In 1955, Lewisohn received the Landsteiner award from the American Association of Blood Banks for his work in the anticoagulation of blood for transfusion.

### 1.7 Modern blood banking and blood banks

Major stimuli for developments in blood transfusion have come from wars. During World War I, sodium citrate was the only substance used as an anticoagulant. Dr. Oswald Robertson of the U.S. Army Medical Corps devised a blood collection bottle and administration set similar to those used several decades later [1] and transfused several patients with preserved blood [20].

Between World Wars I and II, there was increasing interest in developing methods to store blood in anticipation of rather than response to need. It has been suggested that the first “bank” where a stock of blood was maintained may have been in Leningrad in 1932 [1, 2]. A blood bank was established in Barcelona in 1936 because of the need for blood during the Spanish Civil War [21]. In the United States, credit for the establishment of the first blood bank for the storage of refrigerated blood for transfusion is usually given to Bernard Fantus at the Cook County Hospital in Chicago [22]. The blood was collected in sodium citrate and so it could be stored for only a few days.

### 1.8 Cadaver blood

Cadavers served as another source of blood during the 1930s and later. Most of this work was done by Yudin [23] in the USSR. Following death, the blood was allowed to clot, but the clots lysed by normally appearing fibrinolytic enzymes, leaving liquid defibrinated blood.
The use of cadaver blood in the Soviet Union received much publicity and was believed by many to be the major source of transfusion blood there. Actually, not many more than 40,000 200-mL units were used, and most of them at Yudin’s Institute [1]. In 1967, the procedure was quite complicated, involving the use of an operating room, a well-trained staff, and extensive laboratory studies. This was never a practical or extensive source of blood.

1.9 The Rh blood group system and prevention of Rh immunization

In 1939, Levine, Newark, and Stetson published in less than two pages in the *Journal of the American Medical Association* [24] their landmark article, a case report, describing hemolytic disease of the newborn (HDN) and the discovery of the blood group that later became known as the Rh system. A woman who delivered a stillborn infant received a transfusion of red cells from her husband because of intrapartum and postpartum hemorrhage. Following the transfusion, she had a severe reaction but did not react to subsequent transfusions from other donors. The woman’s serum reacted against her husband’s red cells but not against the cells of the other donors. Levine, Newark, and Stetson postulated that the mother had become immunized by the fetus, who had inherited a trait from the father that the mother lacked. In a later report they postulated that the antibody found in the mother and subsequently in many other patients was the same as the antibody Landsteiner and Wiener prepared by immunizing Rhesus monkeys [25]. This also began a long debate over credit for discovery of the Rh system.

During the early 1900s, immunologic studies had established that active immunization could be prevented by the presence of passive antibody. This strategy was applied to the prevention of Rh immunization in the early 1960s in New York and England at about the same time [26, 27]. Subjects were protected from Rh immunization if they were given either Rh-positive red cells coated with anti-Rh or anti-Rh followed by Rh-positive red cells. Subsequent studies established that administration of anti-Rh in the form of Rh immune globulin could prevent Rh immunization and thus almost eliminate HDN. Currently, control of HDN is a public health measure similar to ensuring proper immunization programs for susceptible persons.

1.10 Coombs and antiglobulin serum

In 1908, Moreschi [28] is said to have described the antiglobulin reaction. The potential applicability of this in the detection of human blood groups was not appreciated until 1945 when Coombs, Mourant, and Race [29] published their work on studies of the use of rabbit antibodies against human IgG to detect IgG-coated red cells. Red cells were incubated with
human sera containing antibodies against red cell antigens, washed, and
the rabbit antihuman sera used to demonstrate the presence of bound IgG
by causing agglutination of the red cells. The availability of antihuman
globulin serum made it possible to detect IgG red cell antibodies when the
antibody did not cause direct agglutination of the cells. Thus, red cells
coated with anti-IgG red cell antibodies could be easily detected, and the
era of antibody screening and crossmatching was born. This greatly
improved the safety of blood transfusion and also led to the discovery of
many red cell antigens and blood groups.

1.11 Plasma and the blood program during
World War II

Techniques for collection, storage, and transfusion of whole blood were
not well developed during the 1930s. The outbreak of World War II added
further impetus to the development of methods to store blood for periods
longer than a few days. Although the method of blood anticoagulation was
known by the mid-1920s, red blood cells hemolyzed after storage in
sodium citrate for 1 week. This limitation also slowed the development of
blood transfusion. Although it was also known that the hemolysis could be
prevented by the addition of dextrose, the practical value of this important
observation was not recognized for over a quarter of a century.
Anticoagulant preservative solutions were developed by Mollison in Great
Britain [30]. However, when the glucose–citrate mixtures were autoclaved,
the glucose caramelized, changing the color of the solution to various
shades of brown. The addition of citric acid eliminated this problem and
also extended the storage time of blood to 21 days. The advance of World
War II also brought an understanding of the value of plasma in patients
with shock [31, 32]. In the early 1940s, Edwin J. Cohn, Ph.D., a Harvard
biochemist, developed methods for the continuous flow separation of large
volumes of plasma proteins [33, 34]. This made possible during World
War II the introduction of liquid and lyophilized plasma and human
albumin as the first-line management of shock. Initial work using plasma
for transfusion was carried out by John Elliott [31, 32]. This combination
of technological and medical developments made it possible for
Charles R. Drew to develop the “Plasma for Britain” program [35].

1.12 Plastic bags and blood components

One of the next major developments in blood banking was the discovery
and patenting of the plastic blood container by Carl Walter in 1950.
This made possible the separation of whole blood and the creation of
blood component therapy. Dr. Walter’s invention was commercialized by
the Baxter Corporation. Fenwal division that later became a freestanding
company. The “-wal” of Fenwal represents Dr. Walter’s name. The impact
of the introduction of multiple connected plastic containers and the
separation of whole blood into its components also began to generate enormous amounts of recovered plasma, which made possible the development of large-scale use of coagulation factor VIII concentrates.

### 1.13 Cryoprecipitate and factor VIII

In 1965, Dr. Judith Pool reported that if fresh frozen plasma (FFP) was allowed to thaw at refrigerator temperatures, precipitate remained that contained most of the coagulation factor VIII from the original FFP [36]. This made it possible for the first time to administer large doses of factor VIII in a concentrated form to hemophiliacs and opened an era in which the bleeding diathesis could be effectively managed. A few years later, reports began to appear describing the use of a concentrated factor VIII prepared using the plasma fractionation technique developed by Edwin Cohn [33]. This further simplified the management of hemophilia because the ability to store the factor VIII concentrates in home refrigerators enabled the development of home treatment programs involving prophylactic or immediate self-administration of factor VIII.

### 1.14 Red cell preservation

The role of 2,3-diphosphoglycerate in oxygen transport by red cells was discovered in the mid-1960s [37, 38]. It had been known previously that this compound was better maintained at higher pH, while adenosine triphosphate (ATP), which appeared to be involved in red cell survival, was maintained better at a lower pH. The addition of adenine was shown to improve ATP maintenance and prolong red cell survival and storage for transfusion [39]. The next major advance in red cell preservation was the development of preservative solutions designed to be added after removal of most of the original anticoagulated plasma, thus further extending the storage period of red cells [4, 40].

### 1.15 Leukocyte antigens and antibodies

In 1926, Doan described the sera of some individuals that caused agglutination of the leukocytes from others [41]. Subsequent studies established the presence of leukocyte antibodies, the presence of these antibodies in the sera of polytransfused patients, the occurrence of white cell agglutinins in response to fetomaternal immunization, and the alloimmune and autoimmune specificities associated with these antibodies. These studies, along with studies of the murine histocompatibility system, led to the description of the major histocompatibility system (human lymphocyte antigens (HLA)) [42] in humans and the understanding that there are separate antigenic specificities limited to neutrophils as well [43]. These studies also defined the causative role of leukocytes in febrile nonhemolytic transfusion
Chapter 1: History

reactions [44]. Strategies were sought to prevent these reactions by removing the leukocytes from blood [45, 46], one of the first methods being reported by Fleming [46], the discoverer of penicillin.

1.16 Platelet collection, storage, and transfusion

The relationship between bleeding and thrombocytopenia had been known for some time, but the development of the plastic bag system for blood collection made platelets available for transfusion. Several years of work by many investigators—predominantly at the National Cancer Institute during the 1960s—developed the methods for preparing platelets and established that platelet transfusion to thrombocytopenic patients reduced mortality from hemorrhage [47]. Initially, platelets had to be transfused within a few hours after the whole blood was collected, and thus large-scale application in the general medical care setting was impractical. The seminal report by Murphy and Garner [48] showing that room temperature allowed platelets to be stored for several days revolutionized platelet transfusion therapy.

1.17 Apheresis

Plastic bags were used to remove whole blood, separate the plasma from the red cells, retain the plasma, and return the red cells, thus making it possible to obtain substantial amounts of plasma from one donor [49]. This initiated the concept of attempting to obtain only selected portions of whole blood in order to collect larger amounts of plasma or cells. The centrifuge developed by Cohn for plasma fractionation was modified by Jack Latham and became a semiautomated system for plasmapheresis [50] and subsequently was used for platelet collection as well [51, 52]. At the National Institutes of Health Clinical Center, an IBM engineer worked with hematologists to develop a centrifuge that enabled collection of platelets or granulocytes from a continuous flow of blood through the instrument [53, 54]. Later versions of these instruments have become widely used for plateletpheresis and leukopheresis.

1.18 Granulocyte transfusions

As the benefits of platelet transfusion for thrombocytopenic patients were recognized, interest developed in using the same strategy to provide granulocyte transfusion to treat infection in neutropenic patients. Initial attempts involved obtaining granulocytes from patients with chronic myelogenous leukemia (CML) [55, 56]. Transfusion of these cells had clinical benefits [57], and this led to a decade of effort to develop methods to obtain granulocytes from normal donors [58]. At best, these methods produced only modest doses of granulocytes; improvements in antibiotics and general patient care have supplanted the need for granulocyte transfusions except in very limited circumstances (see Chapter 12).
1.19 Summary

Blood banking and transfusion medicine developed slowly during the 1950s but much more rapidly between the 1960s and the 1980s. Some of the important advances mentioned here were understanding blood groups and the identification of hundreds of specific red cell antigens; the development of the plastic bag system for blood collection and separation; plasma fractionation for the production of blood derivatives, especially factor VIII; improved red cell preservation; platelet preservation and transfusion; understanding hemolytic and febrile transfusion reactions; expanded testing for transmissible diseases; and the recognition of leukocyte and platelet antigen systems. Blood collection and storage is now a complex process operated much like the manufacture of a pharmaceutical. Transfusion medicine is now the complex, sophisticated medical–technical discipline that makes possible many modern medical therapies.

References


