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Preface to the Fourth Edition

It is an honor to prepare this fourth edition of *Transfusion Medicine* because it indicates a level of interest sufficient to warrant publication. When beginning this edition, I thought that developments and innovations in *Transfusion Medicine* had slowed the last few years, but that is not the case. Funding for research has become more difficult to obtain. Due to cost constraints, there is little appetite for adoption of innovations. Despite this, there have been exciting advances in transfusion medicine. There is expanded implementation of the conservative red cell transfusion trigger and the age of red cell issue has been resolved at least for cardiovascular surgery. The red cell storage lesion is better understood thanks to funding from the NIH. A lower dose of platelets is clinically effective but this has not been widely adopted. A well conducted clinical trial established that prophylactic platelets are clinically valuable at least for some patients and cold stored platelets may return for the treatment of bleeding patients. Molecular typing for red cell antigens is now readily available but adoption has largely involved prenatal typing for Rh and typing for donor recipient matching for chronically transfused patient such as those with sickle cell disease. Novel cellular therapies and products continue to evolve and increase but slowly. There has been progress in immune therapies for some malignancies. Production and use of T regulatory cells and mesenchymal stromal cells has exciting potential as yet unrealized in practice. Umbilical cord blood transplants have plateaued and blood stem cells and marrow continue as the mainstays of unrelated transplants. Therapeutic apheresis has increased, mainly due to plasma exchange for solid organ transplants and the use of photopheresis for GVHD.

One of the most dramatic and fundamental changes involves the management of acute blood loss and massive transfusion. The traditional priority of replacing lost blood volume with saline or albumin has been discredited because when coagulopathy develops it cannot be overcome. Instead, the contemporary approach is immediate replacement with plasma, platelets, and red cells to prevent coagulopathy. This has evolved from the military into the civilian setting in the form of massive transfusion protocols. Replacement of all three major components together has led to renewed interest in whole blood for use in massive bleeding.

The expansion of risk areas for infectious diseases has had a huge impact on transfusion medicine. An unprecedented response to West Nile virus limited the number of transfusion transmitted cases and testing for WNV is now routine. Babesia is recognized as an important transfusion
transmitted infection. A babesia test is now available but the testing strategy is still being developed. Other emerging infectious agents for which there are no mitigating strategies are chikungunya, dengue fever virus, and most recently the Zika virus. A donor screening test for Zika is becoming available but donor screening tests are not anticipated for chikungunya or dengue. Malaria continues to be an important disease world-wide and can be transmitted by transfusion. Testing in endemic areas is not feasible and many otherwise suitable donors are excluded in the USA. The alternate approach for improving blood safety is pathogen inactivation. After more than 20 years of development, pathogen inactivated plasma and platelets are now available in the USA and other countries and pathogen inactivated whole blood is approved in Europe. We appear to be on the cusp of broad implementation of pathogen inactivation, which will be a paradigm shift in blood safety.

Another topic, although not covered extensively in this book, is the difficult economic situation among blood supply organizations. This is due in part to decreases in blood utilization as a result of more conservative transfusion practices and also due to price competition among blood suppliers. As a result, US blood supply organizations are undergoing substantial change.

The book is intended to be comprehensive and extensively referenced, yet easy to read. It should be helpful to those with a first exposure to transfusion medicine such as residents and fellows, but also valuable for those doing transfusion medicine full-time or supervising hospital blood bank laboratories on a part-time basis. I hope it is especially valuable for physicians such as hematologists, surgeons, and anesthesiologists who use blood in their practice.

While this is a single author book, it cannot be prepared alone. Physicians, technologists and nurses at the University of Minnesota, North Central Region of the American Red Cross, and Innovative Blood Resources have contributed more than they know by my involvement in that wonderful group and from what I have learned from those interactions. My friend and former fellow, Yoon Choo, prepared the exceptional chapter on HLA (Chapter 16). Colleagues from throughout the USA and the world have enriched my understanding, which thus contributes to this book. Then there is the hard work of organizing, word processing, and reference searching that has been provided by my long-time assistant, Penny Milne. This book would not be possible without all of these people and I am indebted to them for their friendship, support, and assistance.

By the time this book is available, I will have left my home base for about 40 years at the University of Minnesota. However, my professional life continues with involvement in several projects, clinical trials, and advisory groups and thus does not include retirement. I look forward to seeing you and meeting new friends.

I hope you enjoy this book.
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. Petersburg, 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
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5

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
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

2 The Blood Supply

2.1 Worldwide blood supply

Blood transfusion occurs in all parts of the world, but the availability, quality, and safety of the blood depends on the general status of medical care in that area. Approximately, 92 million units of blood are collected annually worldwide [1]. The amount of blood collected in relation to the population ranges from 40 donations per 1,000 population in industrialized countries to 10 donations per 1,000 in developing countries and 3 donations per 1,000 in the least developed countries [2]. Thus, there is a concentration of blood transfusion in industrialized countries, with 15% of the world's population receiving approximately 48% of the world blood supply [2]. Ten countries account for 65% of global blood collection [2]. Lack of blood is a major problem in many parts of the world.

Blood services are best provided if there is a national, or at least regional, organization [2, 3]. It is important that the government make a commitment to the nation's blood supply (Table 2.1). Blood may be collected by individual hospitals, private blood banks, the Red Cross, Ministries of Health, or some other part of the national government. The number of units of blood collected at individual centers can range from a few hundreds to thousands per year and there may be extensive or very little coordination and standardization. The adoption of a national blood policy is recommended along with establishing a national organization [2]. This has been achieved in the developed world where virtually all countries operate a national blood supply system as part of their public health structure as recommended by World Health Organization (WHO) [2–5] and is beginning in other parts of the world [6–12]. The United States is essentially the only developed country without a single unified national blood supply organization.

Although great progress has been made in establishing national or centralized blood transfusion services, some blood is still collected without national control or organization. In many parts of the world, there is little or no organized donor recruitment system and so the blood supply fluctuates. In 40 countries, more than 75% of blood is donated by friends.
or relatives of patients who are transfusion recipients (Table 2.2) [13–15]. Although these donors are considered to be volunteers, they may be donating under family pressure or they may be individuals unknown to the family who have been paid to donate blood. This is unfortunate because the risk of transfusion-transmitted infection from first-time [3, 16, 17] and paid [18] donors is much higher than from volunteers [7] (Chapter 3). These risks are further accentuated by the lack of testing of donor blood for transfusion-transmissible diseases that sometimes occurs in developing and least developed countries (Table 2.2). In 39 countries blood donations are not tested routinely for TTD [2]. This is because of a shortage of trained staff, unavailability or poor quality of test kits, or infrastructure breakdowns. Sometimes transmissible disease testing is not done because the need is so urgent that the blood must be transfused immediately after it is collected. Rapid tests may be useful [19]. The cost of transmissible disease testing is also problematic because it may approach the annual per capita expenditure for all of health care in some countries [20]. This, combined with the use of replacement or paid donors and the low rates of repeat blood donors with their lower rate of positive tests for

### Table 2.1 Key elements of a nationally coordinated blood transfusion service.

<table>
<thead>
<tr>
<th>Element</th>
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<tbody>
<tr>
<td>Government commitment</td>
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<tr>
<td>A national blood policy</td>
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<tr>
<td>Formation or designation with responsibility to operate the program</td>
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<tr>
<td>Appointment of a suitable director</td>
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<tr>
<td>Appointment of qualified staff</td>
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<tr>
<td>Development of partnerships with appropriate NGOs</td>
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<td>National guidelines for the clinical use of blood</td>
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<tr>
<td>Identification of low risk donor populations and development of strategies to promote blood donation</td>
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<td>Education programs for physicians, nurses, and other appropriate staff regarding transfusion therapy</td>
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<tr>
<td>Systems for donor notification and counseling</td>
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</tbody>
</table>

*Blood transfusion safety: voluntary blood donation, national blood transfusion services, and safe and appropriate use; WHO web site programs and projects.

### Table 2.2 Activities related to blood availability and safety in different countries.

<table>
<thead>
<tr>
<th>Donor testing for</th>
<th>HIV</th>
<th>HBV</th>
<th>Syphilis</th>
<th>All volunteer donors</th>
<th>Some replacement donors</th>
<th>Some paid donors</th>
<th>% Repeat donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed</td>
<td>100</td>
<td>100</td>
<td>94</td>
<td>85</td>
<td>20</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>Developing</td>
<td>66</td>
<td>72</td>
<td>71</td>
<td>15</td>
<td>80</td>
<td>25</td>
<td>47</td>
</tr>
<tr>
<td>Least developed</td>
<td>46</td>
<td>35</td>
<td>48</td>
<td>7</td>
<td>93</td>
<td>25</td>
<td>20</td>
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transfusion-transmissible diseases, leads to a major concern about blood safety in developing and least developed countries [21, 22]. Impressive progress has been made in establishing testing systems, increasing blood collections, standardizing operations, and increasing the availability of safe blood [4, 5, 7–16, 18–23]. “Many factors influence the global implementation of self-sufficiency” [24] and a consensus statement from WHO experts is available defining the rationale [24].

**United States blood supply**

In contrast, the United States blood supply is provided by many different organizations with different organizational structures and philosophies. These organizations function rather effectively to meet the nation’s blood needs and thus are referred to here as the United States blood supply system, although they are not really a unified system.

The United States blood collection system is heterogeneous because blood centers developed for a variety of reasons mostly during the 1940s and 1950s. Some were continuations of blood collection activities initiated during World War II; others were civic or philanthropic activities, and some were formed by groups of hospitals to collect blood for their own needs. However, most hospitals have stopped collecting blood so that currently about 90% of the United States blood supply is collected by blood centers [25].

Blood centers are freestanding organizations, almost all of which are nonprofit. These centers are governed by a board of local volunteers; their sole or major function is to provide the community’s blood supply. Each blood center collects blood in a reasonably contiguous area. The blood center may supply hospitals in its area but may supply hospitals in other areas as well. The area covered by each center is determined by historical factors and is not developed according to any overall plan. Rather, local interests dictate whether, how, and what kind of community blood program is developed. There are a total of approximately 79 accredited blood centers in the United States [25]. As a result of the HIV epidemic [26, 27], the regulatory environment changed [28] and the blood collection system in the United States underwent substantial change [26–28]. The organizations have adopted philosophies and organizational structures resembling those found in the pharmaceutical industry rather than the previous hospital laboratory and medical model. Modern quality assurance systems and good manufacturing practices [27–29] like those used in the pharmaceutical industry have been introduced. New computer systems now provide greater control over the manufacturing process [29] and changed management structures deal with the new kinds of activities and philosophy. Blood centers and supply organizations are now operated using a very structured business and manufacturing philosophy, organization, and culture (see Chapter 20).

Most hospitals in the United States do not collect any blood but acquire all of the blood they use from a community center. Blood banks that are part of hospitals usually collect blood only for use in that hospital and do
not supply other hospitals. However, few, if any, hospitals collect enough blood to meet all their needs. They purchase some blood from a local or distant community blood center. Of those that do collect blood, there are no good data available to define the proportion of their needs that they collect. This can be presumed to be quite variable and involve primarily plateletpheresis.

### 2.2 Amount of blood collected

In 2013, 11,679,000 units of allogeneic whole blood and 55,000 units of autologous blood were collected [25]. An additional 1,856,000 units of red cells (14%) were collected by apheresis giving a total of 13,590,000 units. Laboratory testing led to discard of 90,000 (0.7%) and an additional 629,000 were not suitable for use leaving a total of 12,871,000 units available for transfusion [25]. Approximately 14 million individuals presented as potential donors, a 21% decrease from 2011, and 6.8 million actually donated, a 24.9% decrease from 2011 [25].

There have been several trends in the nation's blood supply since the 1970s, undoubtedly influenced by the AIDS epidemic. From 1980–1988, there was an increase in the amount of allogeneic blood collected [25]. Between 1988 and 1998 there was a substantial decrease (Figure 2.1) followed by an increase then plateau from 1997 to 2008. However, a substantial decrease has occurred since then with a 12% decrease from 2011 to 2013 [25]. The decrease in collections reflects a decrease use of 7.3% from 2011 to 2013 [25]. Autologous donations continued a multi-year decline, decreasing to 55,000 or a decrease of 47% between 2011 and 2013 [25].

![Figure 2.1](image-url) **Figure 2.1** US allogeneic WB/RBC collections and transfusions, 1989–2013. Source: Whitaker et al. 2013 [25]. Reproduced with permission of AABB.
Collection of red cells by apheresis decreased 5.5% between 2011 and 2013 [25], but this represents an increasing portion of the red cell supply reaching 18.8% in 2013 [25]. Almost all blood is converted into components; however, in 2013, 6418 units of whole blood were distributed [25]. Of whole blood and red blood cells collected, 3.4% was outdated and an additional 5.6% was wasted [25] although the meaning of this is not clear.

General medicine, surgery, and hematology-oncology transplant patients are the largest users of red blood cells (Figure 2.2). In times of inventory shortage, conserving or postponing elective transfusions to medical patients conserves a larger proportion of the red cell supply than canceling major elective surgery [30].

**Platelet production**

In the United States, most platelets are produced by platelethpheresis, although a few are prepared from whole blood. In 2013, 1,241,000 platelethpheresis procedures were done. These on average produced 1.8 platelet units because of the large number of platelets in each collection. Thus, 2,200,000 units of platelets were available for transfusion [25]. This is a 2.5% decrease from 2011 [25]. Most (98.3%) platelets are prepared and stored in plasma and the remainder in platelet additive solutions [25]. Platelets are used primarily by the hematology-oncology transplant service [25]. Platelets were transfused at an average storage time of 3.2 days and 10.7% were outdated plus an additional 16,000 units discarded for non-test results reasons [25].
Plasma production for transfusion
Most plasma for transfusion is a byproduct of whole blood. Since 2011 plasma decreased 26% to 4,300,000 units [25]. Depending on how it is prepared, this may become fresh frozen plasma, plasma frozen within 24 hours (PF24), or cryoprecipitate-reduced plasma (see Chapter 5). Plasma collected by apheresis increased 21.2% from 2011 primarily due to production of AB plasma which now represents 9.7% of plasma for transfusion, probably due to changes in the management of trauma and acute blood loss (see Chapter 12).

2.3 Blood supply sharing
Certain areas of the United States are chronically unable to collect enough blood to meet their local transfusion needs. This occurs mostly in metropolitan areas that serve large trauma, tertiary, and transplantation centers. This can cause several difficulties, including possible unavailability of blood or components when needed, complex inventory management, technical disparities, emergency appeal-type donor recruitment, higher costs, decreased independence, and higher risk management costs. Blood sharing may also be used for financial reasons. Some blood centers import blood because they can obtain this blood less expensively than their own costs of production. Other blood centers export blood because the increased volume of collection helps to reduce their own average costs.

This process of sharing blood among blood centers is decreasing as more blood centers contact directly with distant hospitals. Thus, hospitals contract with blood supplier’s based on cost and availability breaking long time regional or local relationships.

Despite the fact that there is not a unified blood banking system or a single national inventory or blood resource sharing system in the United States, blood centers have made major efforts to utilize blood from areas where it is available in excess. Since 1953, the AABB has operated the National Blood Exchange that coordinates the distribution of about 185,000 units of blood and components annually.

One of the major issues in blood resource sharing is the attitude of blood donors. In the only study focused on donors’ attitudes about being asked to donate more blood than is needed by their local community [31], donors to several ARC blood centers indicated a willingness to donate for patients in other areas of the United States as long as their local blood needs were being met.

2.4 Other activities of community blood centers
In the past, blood centers carried out a variety of activities that provided services in addition to the blood components. These include continuing education for physicians, technologists and/or nurses, human leukocyte antigen (HLA) typing, therapeutic apheresis, red cell reference laboratory
testing, outpatient transfusions, and medical consultation for transfusion medicine. These services were often provided to hospitals and the medical technical nursing community at little or no extra charge because the activities were subsidized by the income generated from the charges for the blood components. However, as blood centers have attempted to stabilize or reduce their prices to hospitals, it has become necessary for these additional services to become self-supporting financially. In most situations, hospitals have been unwilling to pay for the services and, as a result, blood centers have reduced or eliminated these activities. Blood centers are now more narrowly focused on collecting and distributing blood.

### 2.5 The plasma collection system

A method was developed at the beginning of World War II to process large volumes of plasma so that some of the proteins could be isolated, concentrated, and used for medical purposes [32]. This plasma “fractionation” process is the basis for a large industry that provides many medically valuable products generally referred to as plasma “derivatives” [33–35]. There are many FDA-licensable plasma derivatives (see Chapter 5). The production of these plasma derivatives is a complex manufacturing process taking 7–9 months and usually involving batches up to 10,000 liters of plasma or plasma from as many as 50,000 donors.

**Plasma definitions**

The FDA uses two terms for plasma that may serve as the starting material for the manufacture of derivatives: plasma and source plasma. Plasma is “the fluid portion of one unit of human blood intended for intravenous use” [36]. This plasma, which is a byproduct of whole blood collected by community blood banks or hospitals, is sold to commercial companies in the plasma fractionation industry, who in turn manufacture the plasma derivatives and sell them in the pharmaceutical market. The blood banks’ sale of their plasma to the commercial fractionator (manufacturer) may, but usually does not, involve an agreement to provide some of the manufactured derivatives back to the blood bank.

The amount of plasma obtained from whole blood is not adequate to meet the needs for raw material to produce plasma derivatives. An additional 32 million liters are collected annually by plasmapheresis in about 450 collection centers in North America and Europe [37]. This is called source plasma, which is “the fluid portion of human blood collected by plasmapheresis and intended as the source material for further manufacturing use [36].” Automated instruments are usually used to obtain 650–750 mL of plasma up to twice weekly from healthy adult donors. An individual can donate up to about 100 L of plasma annually in the United States, if the plasma protein levels and other laboratory tests and physical findings remain normal.
Federally licensed plasma collection and manufacturing organizations

Organizations and facilities need FDA licenses for either plasma collection or the manufacture of derivatives from plasma, or both, depending on the activities they conduct. In the last decade, this system has undergone considerable change, consolidating from ten to four companies operating in 40 states [35].

Countries other than the United States have nonrenumerated plasma donor programs; however, few, if any, of these provide all the plasma needs. The United States’ system of paid plasma donors produces about 80% of the United States and 60% of the world plasma supply [37]. Thus, the United States is a major exporter of plasma or finished product derivatives.

Plasma collection activity

Data regarding the plasma derivative industry is proprietary and thus is not readily available. It is estimated that the United States plasma and plasma products industry employs over 10,000 people nationwide and produces approximately 14 million liters of plasma annually in the United States [37]. Individuals who donate plasma to support the plasma derivative industry receive between $15 and $20 per donation and it is estimated that donors receive compensation of more than $244 million from plasma collection facilities annually. This is in contrast to whole blood donors, who donate voluntarily and do not receive compensation. Much of the plasma obtained from whole blood collected by blood banks is also used for derivative production. The volume of this plasma can be very roughly estimated as follows: approximately 13 million units of whole blood, suitable for use, are collected annually. If approximately 2 million units are used for fresh frozen plasma and cryoprecipitate, the remaining 11 million units could produce about 2–2.5 million liters of plasma.

2.6 Nongovernmental blood bank organizations

Some organizations such as the American Medical Association, the College of American Pathologists, the American College of Surgeons, or the American Society of Anesthesiologists may from time to time take positions on blood bank and transfusion medicine related issues and maintain blood bank or transfusion medicine committees. The American Society of Hematology includes transfusion medicine in its scientific programs and a section of its journal Blood. Several nongovernmental or professional organizations are devoted exclusively to blood banking and transfusion medicine.

American Association of Blood Banks (AABB)

The AABB is a professional, nonprofit, scientific, and administrative association for individuals and institutions engaged in the many facets of blood transfusion and cellular therapies. AABB member facilities collect virtually all of the nation’s blood supply and transfuse more than 80%.