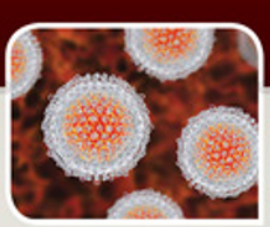
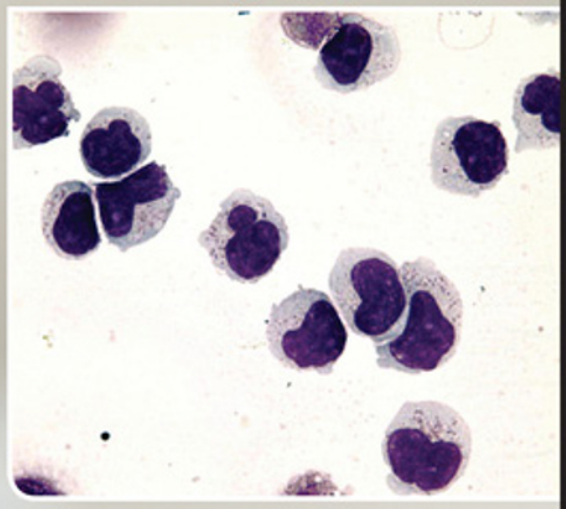
JEFFREY McCULLOUGH

TRANSFUSION MEDICINE

FIFTH EDITION





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Transfusion Medicine

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FIFTH EDITION

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Preface

In the first four editions, I wrote the entire book except for the HLA chapter, which was done by my good friend and former fellow, Yoon Choo. For this fifth edition, it seemed appropriate to begin to involve others but I wanted to keep this as a Minnesota book. Thus, I invited some former fellows to assist with this edition. These authors represent quite a range of stages of the fellowship program. David Stroncek dates back to the 1980s and the early days of unrelated marrow transplants to more recent fellows Tom Gniadeck and Stephanie Kinney who has provided a new chapter on pediatric transfusion medicine. Two authors are from countries other than the United States: Vincent Laroche from Canada and Ulrike Konigbauer from Germany, whose husband Josef was a wonderful musical and scientific mentor to one of my sons. One of the authors (Ram Reddy) retired after preparing his chapter and sadly another author (Randy Coven) died unexpectedly during the preparation of this book. Another former fellow and good friend, Phyllis Warkentin has not authored any chapter in the book but is acknowledged in the chapter on cellular engineering for her work in establishing our first bone marrow-processing laboratory, which ultimately led to the current sophisticated comprehensive facility at University of Minnesota, which provided the initial venue for doctors McKenna and Stroncek, who have co-authored the above-mentioned chapter in this book.

Tom Watkins deals with the blood donor situation which continues to be a challenge; Gary Bachowski the complex evaluation of donors and blood collection, and Alecia Kaplan component production and the wide variety of resulting components and Nancy Van Buren the complex laboratory testing of donated blood. Sarah Ilstrup brings us up to date with blood groups and ulrke Konigbauer the extensive process of getting the right blood components to right patients at the right time and safely. Vincent Laroche educates us about clinical uses of blood components and Jim Stubbs elaborates on some special clinical situations. Scott Koepsell summarizes current perspectives on transfusion complications. Dave Mckenna and Dave Stroncek provide a wonderful chapter on exciting novel blood related cellular products.

Preparing the preface for this fifth edition provides a nice opportunity to reflect on the evolution of the content of these five editions. There are still challenges in recruiting adequate number of donors to maintain a regular supply of blood, given the demographic evolution underway and its impact on potential donor availability. This has led to discussions on paying donors, which would have been unthinkable at the time of the first edition. Blood centers evolved from multifaceted community hubs into manufacturing sites almost entirely focused on blood collection, having shed most of the exciting diverse activities they carried out during a couple of decades.

The organizations that provide the supply have gone through mergers and are now operated almost like a commodity business with substantial competition. While this might have been inevitable, I find it unfortunate.

Collection and production of traditional blood components has changed very little and still involves putting complex multiple bag systems into a centrifuge and then separating the plasma from red cells, much as was envisioned by Carl Walter in the 1950s, but now with far more complexity.

Collection of blood products by apheresis has continued to thrive and essentially all platelets in the United States are now produced by apheresis. Unimagined in the first edition is collection of a modest portion of red cells by apheresis. Therapeutic apheresis has evolved for the most part away from blood banks and transfusion medicine but is widely used to treat a variety of conditions.

A major development in transfusion medicine during these five additions relates to blood safety and transfusion-transmitted infections. Blood safety has continued to improve with current rates of test positive units of less than one in a million. Infectious agents have come and some have gone. Our good fortune is that respiratory viruses such as influenza and, more recently, SARS Co-V are not transmitted by blood transfusion. We have arrived at the point where bacterial contamination of platelets is now the major transmissible infection risk.

Pathogen reduction, a paradigm shift in approach to blood safety, has progressed much more slowly than I imagined. It is disappointing that more than 20 years after some of these initial efforts, there is only one technology approved in the United States and that is for platelets and plasma but we still have no approved PR technology for whole load or red cells. While these PR technologies are not particularly scientifically complex, applying them to the world's blood supply has been difficult and expensive, resulting in disappointingly slow progress. This is probably due to multiple factors: the cost of developing and implementing the technology, unrealistic and unreasonable expectations of how the technology will perform, failure of leadership of transfusion medicine and blood banking to enthusiastically support and assist in the development of this technology, and failure of regulatory agencies to be open-minded and recognize that these are first-generation technologies. Clearly, this is the future of blood safety; we just need to get the right technologies and get them implemented.

The use of plasma derivatives, particularly IVIG, has grown enormously, leading to the establishment of many centers for collecting plasma from paid donors in the United States. In fact, these US paid plasma donors form the basis for a large portion of the world's plasma derivative products.

The molecular basis of blood groups has now been determined and some molecular testing is making its way into practice. Little of this was known at the time of the first edition.

Granulocytes for transfusion continue to be a fringe product and it is surprising that after almost 50 years, their clinical value has never been established. The trial (RING) that probably would have settled this was unfortunately halted prematurely due to ending of NIH funding for this work.

Quality systems was an appendix to the first edition because i had written the book before deciding to include the topic. This expertise has been introduced into blood banking and is now an integral part of our regular operations in the collection and production of blood products as nicely described by Kristen Mascotti, whose career has evolved along this pathway. These concepts have extended into clinical care as evidenced by patient blood management.

At the writing of the first edition, I expected that by now, we would have a red cell substitute oxygen carrier but this has not happened despite considerable investment by several companies. Nor are there "synthetic" platelet products, although exciting developments are underway. While producing blood components such as red cells and platelets from stem cells in a laboratory is scientifically exciting, this is unlikely in the near future.

In the first four editions, there was a separate chapter on hematopoietic growth factors, but these have settled into their place in transfusion medicine and are now included in other chapters.

There are some interesting cycles in our field of transfusion medicine. Whole blood has evolved from efforts to convert clinicians to the use of packed red cells but now is making a comeback in the management of acute blood loss and trauma. Dr. Stubbs has been a leader in these therapies and provides a nice summary of that in his chapter. Another interesting cycle is platelet storage. In the 1970s, this was done in the refrigerator until the seminal report by Murphy and Gardner, which led to room temperature storage. Cold stored platelets are making a comeback, partly driven by the desire to extend the shelf life and to cope with possible bacterial contamination of the platelet product. Ironically, it appears that cold stored platelets might have special therapeutic advantages. Another interesting cycle is paying donors. When I was a resident, we paid donors at the University of Minnesota hospitals donor center, but this practice was discontinued and considered inappropriate for many years. Now, a plan to pay donors has resurfaced and the first of these high-quality paid platelet donor centers has been established just about a mile from my house.

Many of us in the United States have been able to develop a global perspective because of the variety of interactions and friendships that developed during the era reflected by these five for additions. This was also partly facilitated by the President's Emergency Plan for AIDS Relief (PEPFAR), which provided support for blood banking and transfusion medicine work in many countries and, for instance, made it possible for me to work in Afghanistan along with several other countries in sub-Saharan Africa.

Over the years, it has been a pleasure to work with the staff at Wiley, the publisher who has done all additions after the second. They have done a great job of producing, marketing, and distributing these multiple editions of the book.

Well now it has come to this. It has been a pleasure to write and produce this book for you and an honor that you found it valuable enough to obtain it. I hope this most recent edition will continue to meet your needs and help guide you in your career. I do not know whether there will be a sixth edition and if so whether I will be part of it. So I wish you a successful career and I hope this book might help you along the way.

My great admiration, affection, and respect for all those who passed through our fellowship program and those of you who have been kind enough to be a colleague and to include me in your life.

First you were of me and now I am of you.

1 History

Jeffrey McCullough MD

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]. Ironically, the concept of transfusion blood from younger donors to revitalize older individuals has reappeared recently, although without any scientific background or basis.

1.2 The period 1500–1700

Others to whom the idea for blood transfusion is attributed include Hieronymus Cardanus (1501–1576) 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 in 1615 when 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

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> 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 [6] demonstrated at Oxford the bleeding of a dog until its strength was nearly gone, but then revitalized the previously moribund dog by exchange transfusion using blood from two other dogs, resulting in the death of the donor animals.

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 human, 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-Sigismund 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's 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 [8], a British obstetrician who believed it would be helpful in treating postpartum hemorrhage. 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 [8] 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 caused by 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 United States, 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 had not been 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 [11] 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 [11] 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 [13] of Chicago first advocated the use of blood grouping to select donors and recipients and to carry out transfusion, but it was Ottenberg [14] who put the theory into practice. 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, Prévost 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. Early in the war, transfusions were vein to vein, but in 1917, 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, some estimate hundreds of 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. In England, blood donations were begun within days of the outbreak of WWII in 1939. The British established a Home Depot for collecting blood and shipped blood to Europe even during the Dunkirk campaign.

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 [24] published in less than two pages in the *Journal of the American Medical Association* 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 and washed, and the rabbit anti-human sera were used to demonstrate the presence of bound IgG by causing agglutination of the red cells. The availability of anti-human 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 more than a quarter of a century. Anticoagulant preservative solutions were developed by Mollison [30] in Great Britain. 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, PhD, 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. The Fenwal division 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 was allowed to thaw at refrigerator temperatures, precipitate remained that contained most of the coagulation factor VIII from the original fresh frozen plasma [36]. This made it possible for the first time to administer large doses of factor VIII in a concentrated form to patients with hemophilia 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, whereas adenosine triphosphate, which appeared to be involved in red cell survival, was maintained better at a lower pH. The addition of adenine was shown to improve adenosine triphosphate 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 [40].

1.15 Leukocyte antigens and antibodies

In 1926, Doan [41] described the sera of some individuals that caused agglutination of the leukocytes from others. 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) [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], who discovered 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 patients with thrombocytopenia 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 Gardner [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 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 leukophoresis.

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 patients with neutropenia. Initial attempts involved obtaining granulocytes from patients with chronic myelogenous leukemia [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 Chapters 10 and 11).

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 in this chapter 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 manufacturing of a pharmaceutical. Transfusion medicine is now the complex, sophisticated medical–technical discipline that makes possible many modern medical therapies.

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2 The Blood Supply

Jeffrey McCullough MD

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 1,215,000 units of blood are collected annually worldwide [1]. The amount of blood collected in relation to the population ranges from 50 donations per 1,000 population in industrialized countries to 0.3 donation per 1,000 in the least developed countries [1]. Thus, there is a concentration of blood transfusions in industrialized countries, with 15% of the world's population receiving approximately 48% of the world blood supply [1]. 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]. It is important that the government makes 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 hundred to thousands per year, and there may be extensive or 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 the World Health Organization (WHO) [2–5], and is beginning in other parts of the world [6–13]. 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. Donors may be friends or relatives of patients, voluntary nonremunerated volunteers (VNRDs), or paid donors.

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

Government commitment
A national blood policy
Formation or designation with responsibility to operate the program
Appointment of a suitable director
Appointment of qualified staff
Development of partnerships with appropriate nongovernment organizations
National guidelines for the clinical use of blood
Identification of low-risk donor populations and development of strategies to promote blood donation
Education programs for physicians, nurses, and other appropriate staff regarding transfusion therapy
Systems for donor notification and counseling
Blood transfusion safety: voluntary blood donation, national blood transfusion services, and safe and appropriate use; World Health Organization website programs and projects.

Although the WHO urges the use of VNRD, this source is inadequate in many countries, and VNRD rates range from 0% to 100%, with a median of 45% [1]. In low-resource countries, more than almost half of blood is donated by friends or relatives of patients who are transfusion recipients (Table 2.2) [13–16]. 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 for transfusion-transmitted infection from first-time [2, 15, 17] and paid donors is much higher than from volunteers [18] (see Chapter 3). These risks are further accentuated by the lack of comprehensive testing of donor blood for transfusion-transmissible diseases that sometimes occurs in developing and least developed countries (Table 2.2). In many countries, blood donations are not tested routinely for the combination of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus, and syphilis [1]. This is because of a shortage of trained staff, unavailability of 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, 21]. 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 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 [3, 5, 7–12]. "Many factors influence the global implementation of self-sufficiency" [23, 24], and a consensus statement from WHO experts is available defining the rationale [24].

In much of the world, components are not used routinely. The whole blood is converted into components ranging from <25% in low-resource countries to 97% in high-income countries, and use of whole blood ranges from 0% to 100% [1].

US blood supply

In contrast with the worldwide supply, the US 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 in this chapter as the US blood supply system, although they are not really a unified system.

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

	Donor testing for						
	HIV	HBV	Syphilis	All volunteer donors	Some replacement donors	Some paid donors	% Repeat donors
Developed	100	100	94	85	20	5	88
Developing	66	72	71	15	80	25	47
Least developed	46	35	48	7	93	25	20

HBC, hepatitis B virus; HIV, human immunodeficiency virus.
Source: Data are summarized from Gibbs WN, Corcoran P. Blood safety in developing countries. *Vox Sang* 1994; 67:377–381.

The US 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; therefore, currently about 90% of the US blood supply is collected by blood centers [25, 26].

Traditionally, blood centers were freestanding organizations, almost all of which were nonprofit. These centers were 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 was determined by historical factors and was not developed according to any overall plan. Rather, local interests dictated whether, how, and what kind of community blood program was developed. There is a total of approximately 66 accredited blood centers in the United States [25, 26], although these are combining and it appears that soon there may be only a few blood collection organizations in the United States. As a result of the HIV epidemic [27], the regulatory environment changed [28], and the blood collection system in the United States underwent substantial revisions [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 [28, 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 21). This structure is now undergoing extensive change. Blood centers are merging, forming large national organizations that have less local focus. These organizations collect blood in the most efficient manner and sell that blood where it is more advantageous.

Most hospitals in the United States do not collect any blood but rather 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 of 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

Periodically the CDC surveys blood collection organizations and hospitals to determine the blood supply and utilization [26]. The most recent report is from 2017, when data were obtained from 88% of blood suppliers and 80% of hospitals. In 2017, 10,397,000 units of allogeneic whole blood and 10,000 units of autologous blood were collected [26]. An additional 1,794,000 units of red cells (15%) was collected by apheresis, giving a total of 12,201,000 units. Laboratory testing led to discard of 78,000 (0.6%), and an additional 590,000 units was not suitable for use, leaving a total of 11,533,000 units available for transfusion [26].

There have been several trends in the nation's blood supply since the 1970s, partly influenced by the AIDS epidemic. From 1980 to 1988, there was an increase in the amount of allogeneic blood collected [25] (Figure 2.1). Between 1988 and 1998, there

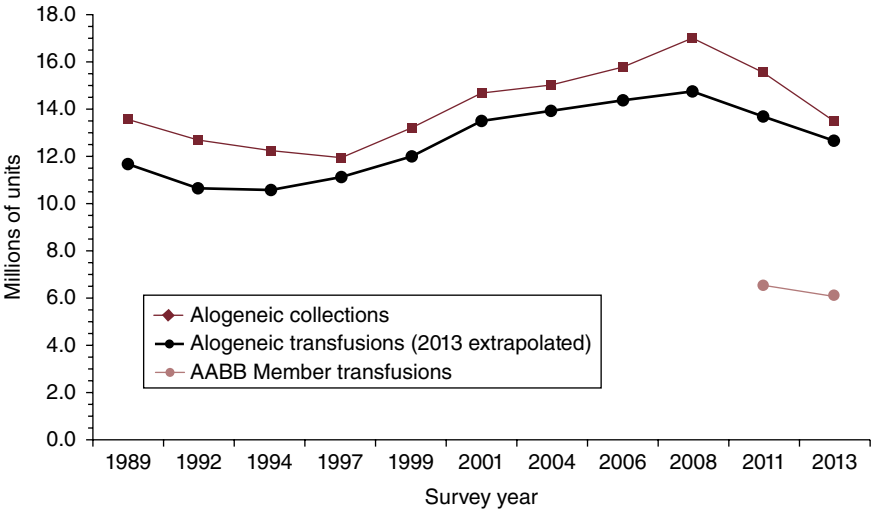

Figure 2.1 US allogeneic white blood/red blood cell collections and transfusions, 1989–2013. (*Source:* Whitaker BI, Rajbhandary S, Harris A. The 2013 AABB blood collection, utilization, and patient blood management survey report. Bethesda, MD: American Association of Blood Banks, October 21, 2015. Reproduced with permission of AABB.)

was a substantial increase followed by an increase and then plateau from 1997 to 2008. However, a substantial decrease has occurred since then, with a 3% decrease from 2015 to 2017 [26]. The decrease in collections reflects a decreased use of 6.8% from 2015 to 2017 [26]. Autologous donations showed a surprising increase of 35%, although the number of units was very small (27,000) [26]. Collection of red cells by apheresis was essentially unchanged from 2015, but this represents a valuable portion of the red cell supply of about 15% in 2017 and is particularly helpful in collecting blood from type O donors [26]. Almost all blood is converted into components; however, in 2017, 5,776 units of whole blood were distributed [26]. Of whole blood and red blood cells collected, 5% were not used.

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 plateletpheresis, although a few are prepared from whole blood. In 2017, 2.259,000 units of platelets were provided. The number of plateletpheresis procedures was smaller because a median of 1.9 products were obtained from most procedures [26]. This is a 4.6% increase from 2015. Most (93.4%) platelets are prepared and stored in plasma and the remainder in platelet additive solutions [26]. Although most platelets are prepared by plateletpheresis, 221,000 units, or 9% of the supply were prepared, from whole blood (see Chapter 5). Apheresis platelets are used primarily, but as many as 19% were not used in 2017 [26].

Plasma production for transfusion

Most plasma for transfusion is a by-product of whole blood. Depending on how it is prepared, this may become fresh frozen plasma, plasma frozen within 24 hours, or cryoprecipitate-reduced plasma (see Chapter 5). In 2017, 3,210,000 units of all plasma

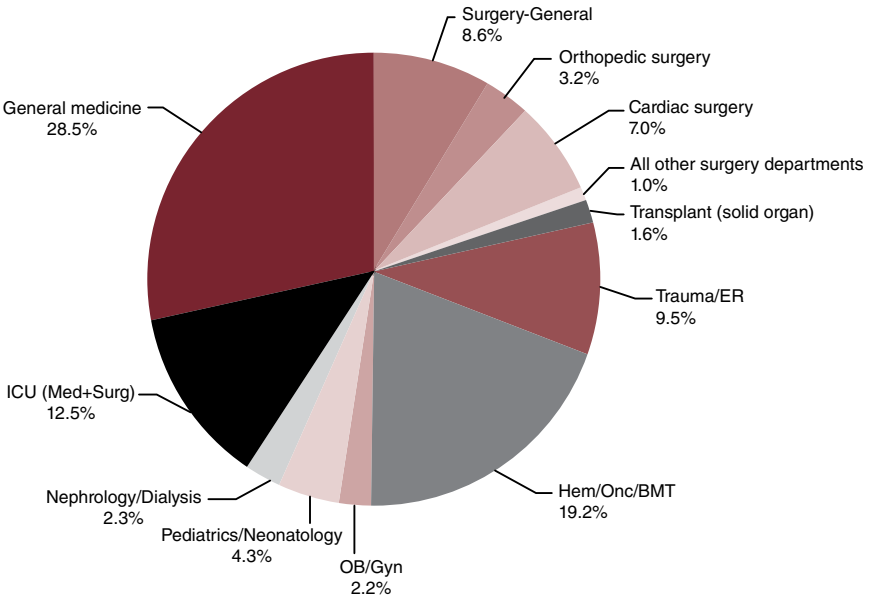

Figure 2.2 Red blood cell use by hospital service in 2013. BMT, bone marrow transplantation; ER, emergency department; Hem, hematology; ICU, intensive care unit; OB/Gyn, obstetrics and gynecology; Onc, oncology. (*Source*: Whitaker BI, Rajbhandary S, Harris A. The 2013 AABB blood collection, utilization, and patient blood management survey report. Bethesda, MD: American Association of Blood Banks, October 21, 2015. Reproduced with permission of AABB.)

products were produced, and 2,318,000 (72%) were used [26]. This represents a 13.6% decrease in products and a 15% decrease in use. Cryoprecipitate production increased 16% to 2,156,000 units, but use decreased 8.5% to 1,068,000 from 2015.

Plasma increases might be because of production of AB plasma, which now represents a substantial portion of plasma for transfusion, probably because of changes in the management of trauma and acute blood loss (see Chapter 11).

2.3 Management of the blood supply

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. As the nature of blood supply organizations has changed (see earlier US Blood Supply section), local and regional relationships have weakened, and each organization manages to collect and distribute their products in the most cost-efficient and revenue-generating way possible.

This process of moving blood considerable distances is increasing as hospitals contract with blood suppliers based on cost and availability, breaking long-time regional or local relationships. This has converted most blood supply organizations into a national perspective.

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 suppliers have