Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Chapter 3

Blood: Vital but Potentially Dangerous

The life of the flesh is in the blood.

Leviticus 17:11

Blood has a powerful mystique, eliciting respect but instilling fear. People admire a full-blooded animal but cringe at the sight of blood. Since ancient times, blood has been equated with life. The Bible enjoins one to refrain from "eating" blood because "I have given it to you upon the altar to make atonement for your souls; for it is the blood that maketh atonement by reason of the life" [1]. Blood has always been a substance both revered and reviled. One speaks of "life blood" or "precious drops of blood" when describing its life-sustaining qualities, but uses the term "bloody" as a curse word. Blood is used as an adjective in describing people, objects, and activities: "blood brother," "blood money," and "blood sport," but it is also used to connote something more ominous, as in "blood bath," "blood feud," and "blood-thirsty." Blood may also be "bad" when relationships have soured (bad blood) or "cold" when referring to someone lacking compassion or acting without remorse: "a cold-blooded murderer" or "slain in cold blood." Aristocrats are said to have "blue" or "royal" blood; however, in Shakespeare's time, Macbeth says of the King's corpse: "Here lay Duncan, /His silver skin laced with his golden blood" [2]. However, Lady Macbeth is consumed with guilt and cannot wash this blood from her hands: "Out, damned spot! Out, I say!" But the blood stain resists removal: "What, will these hands ne'er be clean?" [3]. Thus, blood is often given mystic powers, and the many terms used to describe it reflect our special relationship with this life-sustaining liquid that plays such an important role in our daily existence.

Blood has figured prominently in religious ceremonies. For example, in Roman times, a priest would sacrifice a bull and shower the blood on a citizen seeking spiritual rebirth. The blood was considered to have rejuvenating power [4]. Christians receiving the Eucharist or Holy Communion remember

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the instruction of Jesus at the Last Supper, when He gave his disciples bread, saying "This is my body," and wine, saying "This is my blood." During the festive dinner (Seder) on Passover, Jews recall the plagues that God inflicted on the Egyptians. Those attending the ceremony recite aloud the name of each of the 10 plagues, spilling a drop of wine as each is intoned. The first plague was "blood" ("dam" in Hebrew). These rituals demonstrate that blood has great symbolic significance; in addition, it can arouse strong emotions. For example, some people develop a pathologic fear of blood; the mere sight or even the thought of seeing blood induces fainting. The main protagonist in the contemporary British television comedy series, "Doc Martin," has to relinquish his career as a surgeon because of a violent reaction (vomiting) at the sight of blood.

Blood is not a homogeneous liquid; it contains various cellular elements. These were initially described by Antonj van Leeuwenhoek in 1674 [5]. He wrote: "The Blood is composed of exceeding small particles, named globules, which, in most animals are of a red color, swimming in a liquor, called by physicians, the serum…" [5]. Today, we know that the average person weighing 150 pounds has approximately 5 quarts of blood containing approximately 2 quarts of cells comprising 10^{13} (more than 20 trillion) individual cells. This cellular compartment contains red cells, white cells, and platelets; all are progeny of parent or stem cells that reside in the bone marrow. The red cells provide the tissues with oxygen and remove carbon dioxide, the white cells fight infection, and the platelets assist in blood coagulation. Individual red cells circulate for 120 days and platelets circulate for 10 days, but most white cells have a lifespan of only a few hours.

During febrile illnesses, a thick green layer of white cells and proteins appears on the surface of blood allowed to clot in a test tube. This was called phlegm by ancient philosophers and was thought to cause disease; removing the blood was seen as a way of ridding the body of this noxious material [6]. Blood-letting became the preferred treatment for many disorders well into the 19th century. The practice was accompanied by purging with emetics; there is no doubt that the major loss of bodily fluids from these "treatments" resulted in a decrease in blood pressure (shock) and the death of many sufferers. Most remarkably, blood-letting was even applied to control hemorrhages in persons with hemophilia! [7]. In his 1872 *Treatise on Haemophilia*, the English physician, Wickham Legg, warned that "the terrible danger attending its use (blood-letting) must deter every careful practitioner from such an idea." He stated further that "death has very frequently followed its employment, and the danger of this more than counterbalances any probable good" [8]. He and others advocated purging; this practice probably induced dehydration and decreased blood pressure, possibly benefiting a bleeding person by slowing the rate of blood loss.

Anemia was one of the first clinical disorders directly linked to blood. For hundreds of years, a condition called chlorosis had been recognized in young women, and it often had a fatal outcome. These women usually had a history of heavy menstrual periods and/or multiple pregnancies, and their skin was a

sickly green color. They were probably very anemic; a study by Gabriel Andral in 1845 reported that their red blood cells were remarkably small [9]. A decrease in the size of the red cells is characteristic of iron deficiency anemia. Iron is essential for red cell production, and most of the body's iron resides in the red blood cells. This iron is lost when there is excessive menstrual bleeding or blood loss at the time of childbirth. During the 19th century, physicians confirmed that chlorotic blood contained less than the normal amount of iron, and they found that iron preparations were an effective treatment [10]. A method for dying red cells so that the small cells of iron deficiency could be differentiated from the large cells found in vitamin B_{12} deficiency (the cause of pernicious anemia) was subsequently developed by the Nobel Prize–winning physician and scientist, Paul Ehrlich (1854–1915) [11].

Although iron salts are effective in treating anemia due to chronic blood loss, acute bleeding requires a more rapid method for restoring blood volume. This is accomplished by blood transfusion, which was first attempted in dogs as early as 1666 [12]. The success of transfusion in animals was followed by the infusion of animal blood into humans, with often fatal outcomes, and led to a moratorium on further transfusions. However, in 1818, Blundell reported successful transfusions in four women with postpartum hemorrhages by using blood from their husbands [13]. However, subsequent experiences with transfusion were dismal and the practice was abandoned until the 20th century.

In 1901, Karl Landsteiner, a Viennese physician, discovered the existence of blood groups [14]. He separated serum (the liquid appearing after blood has clotted) from the red cells and showed that sera from some individuals would cause clumping (agglutination) of other persons' red cells, and vice versa. The first group was said to have group A cells and the second group was said to have group B cells. In addition, there were instances in which the cells would not be agglutinated by sera from either group A or group B, and he called these group C (now called group O) cells. Subsequently, a fourth group, AB, was delineated in which the cells are agglutinated by sera from groups A and B. These were enormously important discoveries, and Landsteiner was awarded the Nobel Prize. Since that time, many other blood groups (Rh, Duffy, Kell) were identified and characterized.

The red cell agglutination that Landsteiner described occurs whenever there is a mismatch between the cells of the donor and those of the recipient. It is due to the formation of antibodies by the recipient that recognize that the donor red cells are nonself or foreign. The antibodies in the serum attach to the red cells and cause them to agglutinate. This is an example of an immune response that has evolved to protect individuals from potentially dangerous nonself organisms such as viruses and bacteria. Humans are immersed in a world of microbes that are trying to survive by feasting on the body's cells and tissues, and to defend against this persistent attack a sophisticated system has evolved to recognize and destroy these invaders. This system comprises two components, the innate and adaptive immune systems.

The innate immune system consists of a set of genetically determined cell surface components capable of recognizing the chemical signatures of a variety of disease-causing microbes. These protective components are designed for the immediate engagement and killing of foreign organisms [15] and include several types of cells and their secreted products. On detection of an invader, white blood cells release antimicrobial agents that can kill bacteria directly or trigger other cells to ingest the organisms and degrade them. One type of white blood cell, the neutrophil, defends against infection by extruding fibers that enmesh and immobilize bacteria. These neutrophil extracellular traps have only recently been discovered and are an important component of the immune defense repertoire [16].

The other component of immunity is the adaptive immune system. Various species of scavenger cells—dendritic cells, macrophages, monocytes—patrol our bodies looking for microbial threats [17]. When these cells encounter a foreign protein, they attach this protein to a region on their surface called the major histocompatibility complex (MHC). They then travel to the lymphoid tissues, where they present the microbial protein to thymus-derived lymphocytes called T cells. T cells have CD4 molecules on their surface that can bind the MHC–microbial product complexes; this event signals for a series of changes in the T cells. They multiply, release molecules that assist in the killing of bacteria, and attach to another type of lymphocyte called the B cell. B cells produce antibodies directed against the specific invader; they also retain a memory of the encounter so that they can rapidly mount a defense if there are future exposures to this agent. CD4-bearing lymphocytes are the target of human immunodeficiency virus (HIV), and their destruction by the virus wreaks havoc on the immune system (described in later chapters).

This brief review of the immune system provides a foundation for understanding the responses people have to transfusions of blood and blood products. Blood banks attempt to closely match the red cells of the donor and recipient. However, recipients who have had multiple previous transfusions often have developed a variety of antibodies, and locating compatible donor red cells for them can be problematic. If mismatched red cells are transfused, they will be quickly destroyed and the recipient might experience chills, fever, and kidney damage. Deleterious reactions can occur not only to the red blood cells, but also to the proteins derived from the blood, such as the clotting factors used to treat hemophilia. A basic premise of the immune response is that foreign proteins are recognized as being different from the person's own proteins [18]. This response can be harmful to people with bleeding disorders, because the coagulation proteins that they receive might be identified as nonself, and the immune responses that are provoked can result in the loss of the beneficial clotting activity. In addition, the burden of these infused proteins might overwhelm cellular immune mechanisms and blunt the antibody responses to subsequent encounters with the proteins of infecting microbes. As discussed in later chapters, some hemophilia physicians had difficulty distinguishing between the immune depletion due to HIV infection and the changes in the immune system resulting from prior treatments with clotting proteins.

The next important advance in the use of blood as a therapeutic material came in the early part of the 20th century with the development of methods to prevent blood clotting [19]. These generally involved the addition of sodium citrate to the blood, but it took several years before it was recognized that the citrate solution had to be sterile to avoid inducing fever in transfusion recipients. Once blood clotting could be safely prevented, blood storage became feasible. In 1937, Fantus established the first blood bank at Cook County Hospital in Chicago [20]. It was called a bank because it was envisioned that blood would be deposited by healthy individuals and subsequently withdrawn by those in need. To maintain a positive balance, donors needed to be recruited; they could be motivated to donate either as an altruistic act or with a monetary reward. Initially, many donors were paid, but with the advent of World War II, volunteer donors came to provide the majority of the blood required [21]. After the War, the American Red Cross established regional blood centers across the United States, and they were supplemented by more than 4000 hospital and community blood banks.

During the years after World War II, the number of persons receiving blood transfusions dramatically increased due, in part, to major campaigns to recruit blood donors and the development of better methods for blood collection, storage, and administration. However, as more patients were transfused, adverse reactions became more common. Perhaps the most frequent was fever, which complicated 1–3% of all transfusions. This was due to the presence of antibodies in the patient's blood that attacked the white cells transfused with the donor blood [22]. The products released by disrupted white cells provoked chills and fever in the transfusion recipient. In addition, allergic reactions were reported in 3% of transfusions [23], possibly due to the sensitivity of the recipient to foods or drugs in the donor blood. This could occur if blood from someone who had recently eaten strawberries was given to a person allergic to this fruit. Another type of reaction, known as transfusion-related acute lung injury, occurred when a type of white cell known as a neutrophil was activated by antibodies in the donor's blood [24]. The products released by these neutrophils injured the lungs [25]. Today, these sorts of reactions have become less frequent because most donor blood is filtered to remove the white cells prior to transfusion. Currently, most severe reactions are due to human errors in typing, cross-matching, or mislabeling of blood products. Infusion of mislabeled or misdirected blood can result in the rapid destruction of the infused red cells and a fatal or near-fatal outcome for the recipient.

Blood transfusions can be harmful in other ways. For example, transfusions were shown to increase the risk of death more than twofold when given to people who have had acute heart attacks [26]. In individuals undergoing colorectal cancer surgery, transfusions during the procedure were associated with significant increases in cancer recurrence, postoperative infection, the need for surgical re-intervention, and mortality [27]. The quality of the blood transfused might also contribute to poor transfusion outcomes. Current guidelines permit storage of blood for up to 6 weeks; during storage, the capacity of the red cells to deliver oxygen declines, some of the cells break apart (hemolyze), and the risk of bacterial contamination might increase [28]. Initially, some studies showed that rates

of survival after heart surgery were better in patients receiving transfused blood stored less than 2 weeks [29], but more recent trials found no greater organ dysfunction in those receiving transfusions with older versus fresh blood [30,31].

Contracting infection from contaminated blood is another major problem associated with transfusion. As previously noted, blood must be collected, stored, and infused using sterile precautions. If the donor is infected, or if the stored blood becomes contaminated by bacteria, then the organisms will be transmitted to the recipient. Transmission of hepatitis virus from donors to recipients was first reported in 1943 by Paul Beeson, who described jaundice in seven patients that appeared within 1–4 months after transfusion [32]. It was soon recognized that the risk of transfusion-transmitted hepatitis was greatest if the blood donors were drug abusers or prisoners, especially those with a history of using shared needles. These people usually donated because they were paid for their blood or, in the case of prisoners, rewarded with freedom from confinement. To decrease financial motivation for giving blood, the Red Cross and other blood collectors initiated a policy of no monetary compensation for blood donations and discontinued blood drives at prisons.

In addition to hepatitis, malaria and a variety of other infectious agents can be transmitted by transfusion [33–36a,b]. The Table lists viruses, parasites, and other microbial agents reported to have been transmitted by transfusion (coronavirus transmission is suspected but not established):

Viruses	**Parasites**
HIV 1 and 2	Babesiosis
Hepatitis A, B, C, D, E, and G	Chagas disease
Parvovirus B19	Malaria
Zika virus	
Coronaviruses (SARS, MERS)?	**Spirochetes**
Prions	Syphilis
TSE (mad cow disease)	

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; TSE, transmissible spongiform encephalopathy.

Because many of these microbes can reside in the tissues and blood for months to years without inducing symptoms,[1] the donors might not appear ill at the time of the blood donation. Unfortunately, there are no currently approved methods for sterilizing the blood itself, but several companies are working on various pathogen (germ) reduction techniques; some involve adding chemicals to the blood and exposing it to ultraviolet light to kill viruses and bacteria [37].

Because procedures to safely sterilize blood are still unavailable, blood banks have adopted extensive screening procedures to detect infections in donors and

1. For example, hepatitis viruses. Zika virus may produce no symptoms while remaining in the blood for about a week (Center for Disease Control and Prevention, quoted by C Saint Louis in The New York Times, February 20, 2016, p. A5.)

in the donated blood. For example, people are deferred if they have been diagnosed or treated for malaria within the previous 3 years, have an unexplained febrile illness occurring within 1 year of exposure to malaria, or even lived in a malarious area within the previous year. Potential donors now complete questionnaires and are deferred or the blood is not used for transfusion if donors are classified into any of the following categories:

Donor Deferral List 2014

- Anyone who has ever used intravenous (IV) drugs (illegal IV drugs)
- Men who have had sexual contact with other men[a]
- Anyone with a positive test result for HIV (AIDS virus)
- Men and women who have sex for money or drugs
- Anyone who has had hepatitis since age 11 years
- Anyone who has had babesiosis or Chagas disease[b]
- Anyone who has taken Tegison for psoriasis[c]
- Anyone who has risk factors for Creutzfeldt–Jakob disease (CJD) or who has a blood relative with CJD[b]
- Anyone who spent >3 months in the United Kingdom during 1980–96[d]
- Anyone who underwent transfusion in the United Kingdom or France since 1980[d]
- Anyone who has spent 5 years in Europe since 1980[d]

Notes:
[a]The FDA has proposed amending the ban on blood donation by gay and bisexual men to a 1-year deferral (2015) [38].
[b]The microbes that cause these diseases might be circulating in donor blood.
[c]Tegison might cause fetal abnormalities if transfused during pregnancy.
[d]"Mad cow disease" was reported in these countries.

Blood banks also perform extensive testing for a number of infectious agents; the currently required or recommended tests of donor blood are shown in the chart. Note that most of the testing was not initiated until 1985 (the peak year of HIV infection) or thereafter:

Agent	Year initiated
Human immunodeficiency virus	1985
Human T-cell leukemia virus	1988
Hepatitis B virus	1971
Hepatitis C virus	1990
Syphilis	1950s
West Nile virus	2003
Chagas disease agent	2007

The indications for blood transfusions include acute blood loss that is sufficiently severe to alter the function of vital organs; this might be due to surgery, injury, pregnancy, or diseases such as ulcers or cancer. Transfusions are also prescribed for individuals who are unable to make blood, and they are administered when the blood level falls to less than half the normal amount [39]. Infants born with certain heart and lung defects might also need transfusions, as do

some individuals with sickle cell anemia. There are several other indications for transfusion; for example, blood is required for many cardiovascular procedures requiring the use of mechanical devices.

To collect sufficient quantities of blood to meet the various medical needs, the current completely voluntary system depends on donations by large groups from schools and businesses (blood drives), as well as donations by individuals. Because of all the mentioned reasons for donor deferral, it is estimated that only 38% of the population is eligible to give blood and only a fraction of those actually donate [40]. Extensive advertising and public service announcements are used to enlist volunteer donors (Fig. 3.1).

Currently, most physicians have adopted conservative policies for prescribing transfusions and only order blood for patients likely to fare poorly because of a low blood count [41]. The use of transfusions in the United States has declined by 30% since 2009, from 15 million units to 11 million units, and

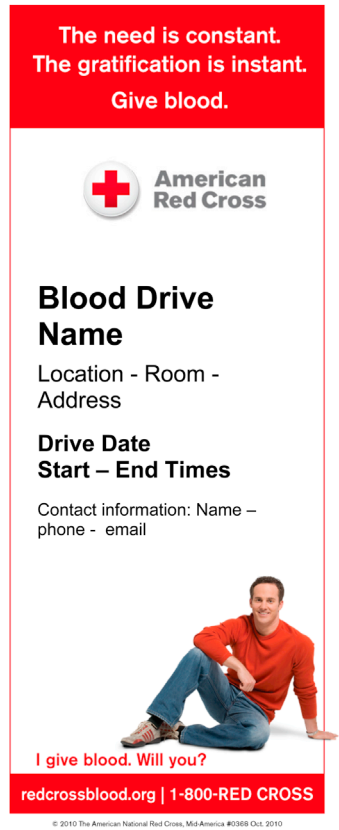

FIGURE 3.1 Donor recruitment poster of the American Red Cross.

blood bank revenue has decreased from $5 billion to $1.5 billion [42]. There are alternatives to the use of banked blood; for example, prior to surgery anemic patients can be treated with a hormone, erythropoietin, to increase their blood counts, and during surgical procedures shed blood can be recycled back to the patient.

Blood donation is a unique form of altruistic behavior, one in which the donor does not receive the tangible rewards customarily given for other virtuous acts [43]. Most people agree to donate because they feel a sense of moral obligation and responsibility to the community [44]. Repeat donors probably also experience pleasurable internal feelings associated with the knowledge that they are contributing to restoring the health of others. In the 1970s, there was a third group of persons who regularly donated blood. These were men who had sex with men, and they constituted a sizeable percentage of repeat donors, especially on the West Coast. Their motivation to donate is unclear, but it could have been due to a need to counterbalance their negative social image with a positive contribution to society, or to show that their blood was just as good and beneficial as blood from anyone else. Those who donated blood in the late 1970s and early 1980s were almost certainly not aware that they had become infected with HIV. In the following chapters we see how blood from HIV-positive homosexual men became the fatal link between hemophilia and acquired immunodeficiency syndrome (AIDS).

KEY POINTS

- There are many references to blood in our vocabulary, religious life, and social interactions.
- Most of the knowledge about blood composition, blood groups, collection, and storage accrued during the past two centuries.
- Innate and adaptive immune systems defend against invading microorganisms, but occasionally they construe transfused blood products as foreign proteins and inactivate them.
- Technical improvements led to a remarkable increase in the number of blood transfusions after World War II.
- Recent studies suggest that the benefits of transfusion are limited, and blood conservation procedures have been widely adopted.
- It is now recognized that blood can be a vehicle for the transmission of an extensive variety of infectious agents.
- Although drug abusers and prisoners were excluded from donating blood, a sizeable percentage of the blood donors in the 1970s were men who had sex with men.
- Although there are no methods for sterilizing blood, screening of donors and donated blood for several microbial organisms is now routine, and infected units are not used for transfusion.

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