# IN A DIFFERENT VEIN

Thomas F. Zuck, M.D.

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It is 7:45 on a typical Friday night in 200 BC in Athens when a patient arrives at the local emergency health care facility (usually in a gymnasium) with multiple stab wounds and evidence of what we now recognize as hypovolemic shock---typically with a very rapid pulse due to a sudden and excessive blood loss. To increase the patient's blood volume to permit therapeutic bleeding, he was infused intravenously with milk, at the time not an uncommon therapy in this clinical setting. Quizzical expressions about blood letting in a patient presenting with hemorrhage are understandable; however, it was the standard therapy of the day. The goal was to transfuse fluids, among them milk, to permit more rigorous bleeding. Hippocrates opined in the 4th century BC that all cures involved the equilibrium of humors through "vomiting, sweating, defecation, or bleeding." His advice was "bleed in the acute affections." Despite the bleeding in this case, the patient was reported to do well for a few hours, probably due to the expansion of his blood volume provided by the milk. But, he was subjected to additional therapeutic bleeding and died the next morning. Presumably he did so because of his inability to deliver sufficient oxygen to his tissues. This was due, in part, to the therapeutic bleedings which lowered his hemoglobir, the primary carrier of oxygen by the blood of man.

The setting is now over 2200 years later, at 10:30 on a typical Saturday night in New York City. Ambulance sirens blare as harbingers of what is about to arrive at the accident ward. Within minutes, the trauma patients arrive, on gurneys, that are stretchers on wheels. It may not always be one or two patients—at times it may be many more. When they arrive, the first task for staff is triage: that is, to sort those seriously injured from those with minor injuries and the dead. A concomitant task is to determine which of those seriously injured will require a blood transfusion. If such requirements are urgent, the blood bank will be asked to issue group 0, Rh negative blood, donated by a so-called "universal donor." In many busy accident wards, particularly in some of our larger cities, in order to have it immediately available, a stock of group 0 Rh negative blood is maintained in the accident ward itself.

Tonight, we will trace the highlights of how transfusion medicine matured from Grecian times to today. This history is at times confusing because medical authorities are not always in

agreement. Yet, today transfusions have become a major part of the practice of medicine. Worldwide annual transfusions has been estimated at 16 million gallons, representing 128 million donations of 450 to 500 ml (about a pint) . These are made available to patients by a blood bank industry that generates revenues of over 18 billion dollars annually. Over eighty percent of blood is transfused in developed countries.

Early therapy with the blood of animals could not really be considered transfusions as we know them today, although there is a common thread in ancient rituals that celebrated blood as a mysterious vital principle. This mysticism is typified by a passage in Leviticus 17:11, "the life of the flesh is in the blood." Similarly, in Deuteronomy XII:11 it is stated that "...blood is the life." Also, in Deuteronomy XII:23, it is held that blood is reserved for a jealous deity and to "avoid the temptation of eating blood." But, blood was given orally by Egyptians to treat acute bleeding, without success for obvious reasons. In fact, until the 17th century, all blood was given , exclusively by mouth as it was considered a tonic. Again, negative results are not surprising. Roman patients also were physically emersed in vats filled with the blood of bulls. These emersions were intended to transmit what was characterized as the "youth and vigor" of donor bulls. But they also failed to be life-saving, again for obvious reasons.

The ensuing centuries were truly the dark ages of transfusion medicine. The second medical text ever produced on Gutenberg's printing press in 1462 was a "Bloodletting Calendar" containing elaborate charts for the optimal timing of therapeutic bleeding. While on his deathbed in 1492, Pope Innocent VIII was said to have been transfused with the blood of three young boys. The donors were said to have died after making their contribution of the transfusions. Incidentally, the Pope also died. In some versions of the story, the Pope was said to have taken the blood by mouth. This strategy would have been consistent with the practices of the late 15th century. Some historians doubt that administration of blood to the Pope occurred at all. Although we shall never know, even its possibility is an interesting footnote in the history of transfusion medicine.

Although, there is controversy about the "first transfusion," the seminal infusion of human blood is believed to have taken place in 1615 in Saxony. A young physician was said to have administered blood from a "young vital man" to a "weak, cachectic, old man," intending to impart the "fountain of life" to the recipient. The recipient died nonetheless.

Traditional practices changed little until the description of the circulation by Harvey in 1628 and the realization that blood moved in vascular streams. Richard Lower is credited with performing the first direct transfusion in dogs in 1665. The initial report of transfusion of animal blood into man was published in France. Jean Dennis successfully gave nine ounces, about half a

pint, of lambs blood to a man suffering from madness. The rationale for administering a blood transfusion for madness is not at all clear. In any event, Dennis continued to transfuse the mad patient with animal blood from which therapy the patient eventually died. Dennis was charged with murder, brought at the insistence of the patient's wife. That he was the personal physician to Louis XIV may have contributed to his acquittal. The widow brought a civil suit against Dennis, but again he was exonerated. However, in dismissing the suit the court stipulated "that for the future no transfusion should be made on any human body but by the approbation of the physicians of the Parisian Faculty." On the whole this had a chilling effect as the Parisian faculty "strongly disapproved" of experiments involving transfusion. One French Academy member described transfusion as a "monster methodology, a barbaric practice, reminiscent of cannibalism."

As a sign of the time, transfusion was actually prohibited by the French Parliament. It was also prohibited in Rome and the Royal Society in England deprecated it, without actually banning it. Thus, at this time the practice of transfusion medicine might have been as hazardous for the physicians as it clearly was for the patients.

In the ensuing years, many transfusions of animal blood into man were reported. Patients tolerated the first transfusion well and only showed red cell destruction of subsequent infusions. Some of these patients were said to have passed wine-colored urine "as if it had been mixed with soot of chimneys." The wine color was caused by the red hemoglobin freed when the animal red blood cells were destroyed. The first transfusions were tolerated because man does not have so-called naturally occurring antibodies to animal blood. However, once having been transfused, patients would make antibodies that would destroy subsequent transfusions of blood from the same animal species. Other novel transfusions were proposed. It was even suggested by the physician to the Baron of Brandenberg that reciprocal transfusions between husband and wife might settle marital discord. I was unable to confirm whether this recommended novel strategy was ever actually employed.

The premodern age of transfusion emerged when James Blundell became concerned about the deaths from hemorrhage associated with childbirth. He wrote "(a) few months ago I was requested to visit a woman who was sinking under uterine hemorrhage... she died in the course of two hours. Reflecting afterwards on this melancholy scene..., I could not forbear considering, that the patient might very probably have been saved by transfusion; and that...the vessels might have been replenished by means of the syringe with facility and promptitude." In December, 1818, Blundell began injecting human blood into patients, most extremely ill. In the ensuing eleven years, he transfused ten critically ill patients, five of whom survived.

Blundell's work evoked interest in transfusion in England, Europe, and beyond. As

evidence, in 1832, a young Russian physician, Andrei Wolff, transfused whole blood to a mother hemorrhaging following a traumatic delivery---and she survived. But, the details are incompletely recorded. Wolff previously had studied with Blundell in England and for his first transfusion in Russia presumably used some of Blundell's devices that he had brought to Russia from England. Additional transfusions are also attributed to Wolff, but their documentation is too poor to cite as precedent.

One problem imposed significant practical limits to early transfusion practice. Blood outside the circulation clots in three to five minutes. It is for this reason that many early transfusions flowed through tubing inserted into a donor's artery or vein and infused directly into a vein of the recipient. Even with this strategy, the blood in the tubing frequently clotted and it was difficult to determine how much blood actually had been transfused. As might be expected, misadventures were not uncommon.

Late in the 19th century interest was again aroused by the prospect of transfusing all matter of materials, earlier lessons apparently forgotten! This occurred despite Blundell's admonition that man should receive only the blood of man. Milk was again attempted in the belief that the fat globules could be converted into red blood cells. All of this interest in surrogate materials finally came to an end with the introduction of normal saline which is a 0.9 percent solution of sodium chloride, common table salt, in water. Saline quickly became the standard replacement for acute blood loss, especially in emergent situations. And so it remains today. Infusions of various liquids as substitutes for blood at the time were eventually abandoned.

The modern era in transfusion medicine was ushered in early in the 20th century when Landsteiner observed that the sera of some people caused the red blood cells of others, but not their own, to clump. This clumping has the technical term of "agglutination." In his original article he wrote "(i)n a number of cases (Group A) the serum reacts with the corpuscles of another group (B) , but not, however, on those of group A, while, again the corpuscles of A will be influenced likewise by serum B. The serum of the third group (C) agglutinates the corpuscles of both A and B, while the corpuscles of C will not be influenced by the sera of A and B." Landsteiner later changed "C" to "O", which we know it as today. The fourth and final member of this blood system was described by Decastello and Sturli. These red cells possessed both A and B reactivity on their cell membranes and were, not surprisingly, designated "group AB." Thus, human red cell membranes express antigens for A or B, or both (cells termed group AB) , or none, cells that are termed group 0. These blood groups are part of what, not surprisingly, became known as the ABO system. Among the many red blood cell antigen systems, only in the ABO system do people develop antibodies to the antigens that they do not express. These are termed "naturally occurring" antibodies. For example, people of blood group A make anti-B and group 0

people make both anti-A and anti-B. The ABO system has turned out to be more complex than the four antigenic patterns initially identified and described here. There are literally dozens of what are termed "subtypes" that are beyond scope of this presentation.

Somewhat less than 50 percent of people are Group 0 and are known as "universal donors" because their red cells can be transfused into any patients. It is for this reason that early transfusions were successful in about one-half of recipients given without regard for blood groups. Successful transfusion of other groups depended on chance ABO compatibility of donor and recipient.

The red blood cells of man have, or "express" in the blood bankers jargon, many other blood groups in addition to those of the ABO system. For the most part, these are of interest only to transfusion medicine specialists. However, one of them, the Rh system, is discussed here because it is one of the more interesting. In 1939, the Rh system was recognized in a distinct manner. Landsteiner and Wiener were able to immunize, that is cause antibodies to be formed, in pigs and rabbits when these animals were injected with red blood cells from Rhesus monkeys. It turned out that these antibodies also clumped 85 percent of human red blood cells but failed to do so in the remaining 15 percent. The antigen on the red blood cell membrane was termed Rhesus, or "Rh" for short. An interesting aspect of Rh system antigens expressed on red blood cells is a disease that occurs in some newborns. An Rh-negative mother can conceive an Rh-positive child if it received a father's Rh positive gene. During the latter parts of pregnancy and after delivery, the mother may make antibodies to the babies Rh-positive red blood cells that leaked into her bloodstream. These antibodies can destroy the red blood cells of future Rh-positive fetuses, that is, infants in utero, and make them anemic, sometimes seriously so. Several regimens have been recommended to prevent the mother from forming Rh antibodies during or after the first pregnancy of an Rh-positive infant. They all center around injecting Rh antibodies to the mother based on the general principal that humans do not make antibodies if their body recognizes it already has done so. This strategy is effective in preventing ninety percent or Rh-negative mothers from making Rh antibodies that could affect future Rh-positive fetuses.

In the past 100 years many blood group antigens and systems of related antigens other than ABO and Rh have been described. In fact, with the exception of identical twins, the red blood cells of every living person are unique to that person by the distinct combination of blood group antigens expressed by their red cells.

In some situations, blood grouping effected matters quite aside from matching donors and recipients for transfusion. In a famous case of the mid-1920's, vitriolic arguments ensued over disputed parentage of two babies. Their mothers had been in the maternity ward together and

nothing seemed awry until the father of one found a surname other than his own inked on their baby's buttocks. As it turned out, all efforts to establish identity failed until ABO grouping proved unequivocally the babies had been switched—-the father and mother who were group 0 could not have borne a group A baby. The conflict was resolved amicably.

In addition to the description of the ABO system, practical blood transfusion had to await the development of effective anticoagulants, solutions that prevent blood from clotting once it is outside the circulation. For the technically oriented, one of the most commonly used anticoagulants in blood banking, sodium citrate, does this by binding the plasma calcium. Free calcium ions are required for blood to clot. Practical and effective anticoagulants that also preserved red cells were first described in 1914 when a nutrient, the sugar glucose, was added to the citrate. These advances made blood transfusions practical in World War I. Indeed, in 1917, the Allied armies began to use citrated blood that was introduced by a Canadian Army medical officer. However, its use was not common, only a few thousand were actually transfused throughout the entire war.

During the years when blood banking, as a discipline, developed between and during the two world wars, all manner of strange and unusual events were reported. In Germany in 1935, a Jewish physician who himself served as the donor for a direct transfusion to an Aryan patient was sent to a concentration camp for "defiling the blood of the German race." Of equal improbability, a wounded soldier in the Pacific theater noted that he was the donor of the blood whose plasma he was receiving. He had donated the unit while home on leave. And, in a somewhat more macabre development, it was in the late 1930's that cadaver blood came into use in Europe. The infamous Dr. Kevorkian became known as "Dr. Death" when he helped terminal patients die and then transfused their cadaver blood.

The first blood bank in the United States was opened by Fantus in 1937 in Chicago's Cook County Hospital. The first community blood center in Europe was started in 1938 in Barcelona. It became the European model for blood centers.

Wars have provided much of the impetus for developing strategies for deploying and managing blood for transfusion. In the late 1930's, the Spanish Republican Army collected 9,000 liters of blood in citrate-dextrose anticoagulant for the treatment of battle casualties in that Civil War. But, it was World War II that caused blood banking to develop rapidly through vital efforts to save the lives of wounded soldiers. During the war, primitive blood banking matured into an increasingly sophisticated medical specialty. For it was during the war that physicians began to understand that serious blood loss required the replacement of red blood cells, not simply saline solutions or plasma. Between 1941 and 1945, the American Red Cross provided 13 million pint

bottles of blood to the war effort, much converted to dried plasma that could be reconstituted in the field with saline solutions. Whole blood was also sent to Europe and the Pacific. Over 68,500 gallons (548,000 pints, the safe amount of blood that can be drawn from smaller donors) of blood were distributed by the British in World War II. In the 1940's the British developed a National Blood Service to manage its nation's blood supply. In contrast, immediately after the war, the American Red Cross closed its blood centers and discontinued its various contractual relationships. However, in 1947 it announced it would begin to collect blood again. It did so initially by opening a regional blood center in Rochester, New York. Its overall plan was to place all regional collection facilities nationwide under Red Cross management, without regard for the management in place at the time. As might be expected, existing non-Red Cross regional blood centers resisted and a struggle based on collection philosophy emerged. The Red Cross believed that a donor should give to the community without regard to whom the blood eventually was transfused—-the so-called philosophy of community responsibility. In response to these Red Cross activities, the American Association of Blood Banks was formed in Dallas in 1947. This association espoused the philosophy that blood donation was an individual responsibility and that credits against future blood needs should accrue to a blood donor. Despite the controversy, blood centers proliferated. In 1949, blood procurement centers were comprised of 1,500 hospitals, 31 American Red Cross centers, and 46 non-hospital community blood centers, for a total of more than 1,600 blood collection facilities in the United States. The number of these facilities grew dramatically in the next thirteen years. In 1962, the aggregate number of blood banks was over 4,500 collecting more than six million units of blood. Today about one-half of the blood is collected by regional Red Cross centers and about one-half by non-Red Cross regional centers, of which Hoxworth is prototypical. A modest amount is still collected by hospital-based blood banks, but, due to the increasing complexity of collecting and testing blood for transfusion and complying with the required good manufacturing practices, hospital collections continue to dwindle.

By today's standards some of the early transfusion medicine practices seem quaint. To quote from Lewisohn, "(w)hen the blood was introduced at Mount Sinai Hospital in 1938, the open glass beaker was replaced by a Mason jar with a metal cover in which the blood was kept in the blood bank. Immediately before its use, the metal cover was removed and the blood was filtered through a few layers of sterile gauze into an open beaker and then poured into a sterile flask which led to the patients vein." In 1939, Loutet and Mollison from England described acid-citrate-dextrose an anticoagulant-preservative solution, better known for obvious reasons as ACD. Many observers of the history of blood banking believe the development this solution was a seminal advance in blood banking. As World War II emerged, blood for transfusion was

collected in sterile glass bottles. Upon storage, the red cells would sediment, leaving what was termed "packed cells" in the lower part of the bottle and plasma at the upper part. These two could be separated and given to different patients, depending upon their medical needs. This practice initiated so-called "component therapy," which is giving a patient only that component of blood they need rather than whole blood.

In this era, glass bottles served well, but fever and chills were common due to the not infrequent bacterial contamination of the drawn blood. The introduction of polyvinyl resin plastic bags in 1952 became a seminal development in blood banking. These bags greatly improved sterilization methodologies. Further, the configuration of integral multiple bag container systems connected by sterile tubing improved whole blood separation techniques. Thus, the plastic bag ushered in the era of complete component therapy. It was technically a rather simple matter to place a unit of blood drawn into a plastic bag into a large centrifuge and separate the red cells from the plasma by centrifugation, that is, spinning. If separation is done within hours of the drawing of the blood, the plasma can be frozen, and is termed "fresh-frozen plasma," which is invaluable in replacing coagulation factors.

Normally, a series of biochemical reactions among plasma proteins separated from the circulation coagulates to form a clot to stanch bleeding. Patients missing one or more of these proteins, or factors, cannot control bleeding effectively. Of these. Factor VIII is perhaps the most famous due to its absence in the some male members of the Royal House of Spain. These patients are termed hemophiliacs, literally "love of blood." If plasma is freshly frozen shortly after collection and thawed under appropriate conditions, a white precipitate forms that is rich in Factor VIII and termed cryoprecipitate, or "cryo" in the blood banker's jargon. Cryo changed the lives of hemophiliacs permanently worldwide, although, tragically it concomitantly transmitted the human immunodeficiency virus, or HIV, the causative agent of the acquired immunodeficiency syndrome, or AIDS. This appearance was a very dirty trick by nature. AIDS can be avoided, as can all other plasma-derived infections by the use of recombinant, or cloned proteins, including Factor VIII. These are proteins that are expressed by non-human cells into which the genetic code for a human protein has been inserted. For example, there are several expression systems in different cell lines for human Factor VIII. Infectious diseases are not transmitted by recombinant proteins grown in vitro in cell lines rather than man or animals. For those hemophiliacs not yet infected with HIV, recombinant Factor VIII is strongly indicated, if not mandated.

But a second blood component has even more extensive application than Factor VIII---the blood platelet---with millions of units transfused annually in this country. Blood platelets are cells without nuclei and are about one-fourth the size of a red blood cell. They develop in the

bone marrow. Their primary function is to stick, or adhere, to the edges of wounds or other bleeding sites, and to each other, to form a temporary cellular plug to staunch bleeding. After platelets have initiated the control of bleeding, the various coagulation factors, among them Factor VIII, interact to create the fibrin clot which each of us has seen many times.

A variety of fairly common diseases require platelet support. Among the better known are the leukemias, the uncontrolled proliferation of one of the various types of white cells. Chemotherapy is given to control or eradicate the proliferation. But, in the process the platelet precursor cells are also destroyed and patients bleed because there are too few platelets to form the temporary plug described.

Fortunately, platelets for transfusion can be harvested in two ways. In the first, and for years the most common, they can be separated from a donation of whole blood by centrifugation much the way plasma is separated from red cells. Unfortunately, it takes the platelets from several donations of whole blood——generally between four and six—-to yield sufficient platelets to stanch bleeding in an adult patient. Thus, the platelets from several donations are "pooled," that is mixed together, to provide the cells needed for one transfusion. Further, they have a much shorter half-life in the circulation than do the red cells---four to seven days'—compared with about hundred twenty days for red cells. This creates the need for platelets to be transfused frequently.

The second method of harvest is termed apheresis. In this process, the donors are connected through needles and sterile tubing to equipment that by centrifugation separates the various components. Those components not needed are returned to the donor. As an example, the blood bank may only wish to collect platelets. They can be separated by centrifugation and all the rest of the blood is returned to the donor. Although the donor has to be connected to the equipment for much longer than for single unit donation of whole blood, enough platelets to treat a recipient, or in some cases two or more recipients, can be obtained by a single apheresis collection taking less than two hours. Platelets obtained by apheresis have the additional advantage of presenting a single infectious disease risk to the recipient, whereas pooled platelet concentrates presents a risk from each donor. In the United States, apheresis platelets have become the more common strategy to provide platelets to patients with low counts.

Transmission of infectious diseases has been one of the major difficulties that dogged transfusion specialists for decades, although not necessarily a concern of the general public. But, it became a very public concern, some might say "panic," with the emergence of AIDS in the 1980's. In the early days after the appearance of AIDS, many patients refused transfusions. Some enlisted friends to donate on their behalf—-so called "directed donations." As an aside,

because they often were "first time" donors whose blood had never been tested for the array of diseases for which blood banks test, directed donations paradoxically were actually less safe than blood from repeat donors whose blood previously was found negative for infectious diseases. Very early in the AIDS epidemic, the only method for screening out donors who might have AIDS was asking about histories of homosexuality or intravenous drug abuse, that is, risky behavior. Many infected donors lied when asked these questions, and, predictably, infected units continued to be donated and transfused. A strategy termed "confidential unit exclusion" was developed through which a donor could request in confidence that his unit not be transfused—-no questions asked. A donor could donate, say, in a corporate drive, exercise unit exclusion and protect an unwitting recipient. And, he or she would not be ostracized by their peers by admitting risky behavior. The frequent use of these strategies to interdict potentially infected units confirmed the wisdom of their use.

In the mid-1980s the first tests for antibodies to the AIDS viruses became available. Their availability not only improved the safety of the blood supply, but confirmed once again that people infected with HIV continued to donate blood. Over time, the sensitivity of these tests to detect antibodies to the AIDS virus were improved significantly. However, there is a lag time between when a person is infected and the appearance of detectable antibodies. People who donated in this interval were said to be in a "window" of undetectability. Despite improvements in testing, it is not possible to eliminate this window period. Even today, as we test for the nucleic acids of the virus and thus reduce the infection rate of blood from the AIDS virus to one in several million transfusions---extremely rare "window cases" still occur.

Although AIDS is the preeminent transfusion risk in the public's mind, other diseases transmitted by transfusion remained difficult for many years. Hepatitis, an infectious inflammation of the liver, posed major problems. Before tests for specific viruses were developed, blood was tested by what are termed surrogate tests. These were primarily enzyme assays reflecting liver function that may become deranged with significant infection. There are many viruses than can infect the liver, but those of most interest here are termed with rather an alphabet soup as "A," "B," and "C." Although it was not initially understood to be so, hepatitis A is transmitted by the so-called "fecal-oral" route---a rather unpleasant medical concept and very different from injection. Hepatitis A historically caused confusion, but it is now known to have no relevancy to transfusion medicine. Hepatitis B, initially referred to as the "Australian antigen," was recognized early and studied extensively. Tests that were not particularly sensitive were used initially to screen blood for transfusion. After 1975, the Food and Drug Administration required a third-generation, and vastly more sensitive, test be used to screen blood. As noted, currently, blood is screened by highly sensitive nucleic acid techniques.

But even as blood donations that tested positive for hepatitis B were excluded with increasingly sensitive techniques, post-transfusion hepatitis still occurred. Because the causative agent of this hepatitis was neither A nor B, it was caller non-A, non-B hepatitis. Although it tended to be less severe than hepatitis B, it remained a significant concern. The agent causing the great majority of non-A, non-B hepatitis was cloned by a commercial test manufacturer in 1988 and it was termed the "hepatitis C" virus. Ability to test donated blood soon followed, and the transfusion-transmitted hepatitis era had essentially ended. Other hepatitis viruses can be transmitted by transfusion, but they are rare. As one reflects on the history of essentially eliminating hepatitis transmitted by transfusion, it stands as one of medicines more significant accomplishments.

For many years in the United States blood donors; commonly were paid a modest stipend for donating. Unfortunately, this practice tended to attract people who were both down and out and often not in the best of health. Commercial paid donor centers were frequently located in the less savory parts of communities and often near saloons. It was well-known that recipients of blood from paid donors had ten times the hepatitis rates as recipients of volunteer blood. One could argue that the Food and Drug Administration was somewhat tardy in requiring all blood donations to be labeled as "paid" or "volunteer" in 1978. But, once the Agency ruled, almost overnight, blood from paid donors disappeared from hospital blood bank shelves and concomitantly these transfusion-transmitted hepatitis rates dropped dramatically.

Asking friends to be a "directed donor" was a practice spawned by the AIDS crisis. People who were scheduled for an elective invasive procedure that might require blood transfusion were terrified to receive banked blood given by a stranger. They were convinced that their friends would be safer and they asked them to donate for their benefit. In fact, donation by a directed donor is only equally as safe if the donor has previously given blood for the community. It quickly became clear that the infectious disease transmission rates from first-time directed donors was much higher than the repeat volunteer donors. These donors might not be able to admit risky behavior to their friends. Some blood centers wisely would only accept directed donations from donors who had previously given to the community blood supply. However, at the height of the AIDS scare and before viral nucleic acid testing, directed donations proved difficult to discourage.

But, perhaps no area of transfusion medicine is surrounded by more mystique than the prospect of the availability of "artificial blood." Another term frequently used in the lay literature is "blood substitute." Actually neither term is completely accurate. Blood is an extremely complex organ, supporting many physiologic functions in mammals. Most artificial blood candidates have been designed primarily to carry respiratory gases---oxygen from the lungs to the cells and carbon

dioxide from the cells to the lungs. But, in contrast to many developments in medical care, public curiosity about the do-ability of developing blood substitutes is very high. This curiosity has been fueled in no small part by the emergence of AIDS which not only presented risks, but severely damaged the public's confidence in the safety of the nation's blood invasive procedure that might require blood transfusion were terrified to receive banked blood given by a stranger. They were convinced that their friends would be safer and they asked them to donate for their benefit. In fact, donation by a directed donor is only equally as safe if the donor has previously given blood for the community. It quickly became clear that the infectious disease transmission rates from first-time directed donors was much higher than the repeat volunteer donors. These donors might not be able to admit risky behavior to their friends. Some blood centers wisely would only accept directed donations from donors who had previously given to the community blood supply. However, at the height of the AIDS scare and before viral nucleic acid testing, directed donations proved difficult to discourage.

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One blood substitute uses some form of hemoglobin, which we have seen is the oxygen-carrying component of human red blood cells. Hemoglobin products use purified human or bovine (that is, cow) hemoglobin to carry oxygen from the lungs to the tissues.

Problems with a hemoglobin-based blood substitutes quickly became evident during early clinical trials. First, hemoglobin freed of the environment of the red cell is a very inefficient carrier of oxygen, the reason, after all, for transfusing either red cells or a blood substitute. Second, despite purification strategies, free hemoglobin displays disturbing toxicity, primarily to the kidneys. Third, hemoglobin-based substitutes are not easily sterilized. This places enormous burdens on the purity of their manufacturing processes. Fourth, these preparations have a brief life in the vascular system: five to twelve hours compared to one hundred and twenty days for hemoglobin contained in red blood cells. Finally, these solutions have a limited shelf-life under

refrigeration and the costs of freeze-drying to extend storage, although an effective process, are very high. If their use was reserved for emergencies, such as managing trauma, a high outdate rate could be anticipated and would further escalate the costs.

An early clinical trial in 1978 with a 99.9 percent pure solution of unmodified hemoglobin caused disastrous reactions in eight healthy male volunteers, although fortunately no long-term adverse effects were exhibited. It became clear, that to be clinically useful, hemoglobin would have to be chemically modified. Currently, there is only one clinical trial of a modified hemoglobin-based blood substitute ongoing in this country. It is a Phase III trial, which is FDA lingo for the final clinical studies required for approval. It is planned to transfuse up to six units of a product called Polyheme into 600 patients. It is noteworthy that two hemoglobin-based products are in very limited use in Europe where licensing is less stringent than in the United States. Their impact is said to have been minimal.

The second blood substitute is based on a perfluorocarbon class of compounds. They are composed of carbon, fluorine and bromine in various chemical configurations. Perfluorocarbons are widely known as PFCs. Oxygen is highly soluble in PFCs and they carry oxygen as a direct proportion to the amount of oxygen the patient is breathing. Unfortunately, PFCs are not water soluble and thus must be infused as an emulsion which limits the duration of their circulation. Nonetheless, PFCs have several striking advantages. First, no matching is required between the blood of the recipient and the PFC. Second, because they are completely synthetic, PFC do not transmit infectious diseases. Third, commercial manufacture, although complex, would not depend upon donations of human blood. These preparations also have short half-lives---five to seven hours. Despite their attractiveness, none of these preparations is either licensed for use or currently under clinical trials. In the best known clinical trial in the early 1980's by Gould and colleagues, the emulsion infusions were found to be ineffective in delivering oxygen to the tissues. No preparation is under development in this country currently. In summary, sixteen blood substitute trials have been undertaken in the United States since 1916——none successfully.

In conclusion, the emergence of AIDS has exerted enormous pressure on blood services to provide both effective and safe blood components. We believe these public expectations have largely been met. Although blood transfusions are not "100 percent safe" they are "as safe as reasonably achievable." It is difficult to imagine the progression from the transfusion of milk in early Grecian times to the highly sophisticated component therapy of donated blood and therapeutic proteins made with recombinant technology of today.

But, I would like to leave you with a message. If you need a transfusion, accept it. Despite all the terrible press given blood banking about the hazards of blood transfusions

following the emergence of AIDS, safety is now on your side---by a very, very large margin!