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20 Things You Didn't Know About Blood Transfusion

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1. Galen (born 129 AD), a physician, surgeon, and philosopher, believed blood to be 1 of 4 humors, substances that also include black bile, yellow bile, and phlegm.[1] When humors were balanced in an individual, health was ensured. A loss or excess of any humor produced physical or mental illness and disability; this led to the practice of bleeding to remove excess humor and treat disease. Galen was well ahead of his time, as he thought these humors were influenced by dietary intake and activity levels; thus, he promoted the importance of proper diet and regular exercise to promote health over 2000 years ago! Of course, Galen also prescribed drinking dog or weasel blood to cure rabies.

2. Pope Innocent VIII has often been credited with receiving the first blood transfusion around 1492.[1] The translation reporting this "transfusion" recounted that the Pope's blood was exchanged with that of three 10-year-old boys who were promised 1 ducat (approximately $4 at the time) apiece for their participation. The boys died as a result of this transfusion. The pope died days later purportedly from his illness. More recent translations indicated that the blood was not transfused, but imbibed. Actual transfusion was highly unlikely, as circulation was not described or understood for another 136 years!

3. Although William Harvey is credited with the first description of the circulatory system and circulation of blood in 1628,[1] several individuals were instrumental in the development of our understanding. Ibn al-Nafis described blood flow through the pulmonary circulation and coronary arteries in 1242, and Columbo described cardiac contraction in 1559.[2] As so often happens, those who receive credit for a discovery build on the work of earlier scholars who often sink into oblivion.

4. In 1628, Johannes Colle hypothesized that blood transfusion might prolong life, and in 1639, Francis Potter, a vicar, reportedly developed a series of feather quills and tubes for transfusion in chickens, as he postulated that transfusion would cure disease.[3] Although Potter may have been the first to actually perform a transfusion in animals, he was better known as the author of a tract that identified 666 as the number of the beast.

5. In 1665, Richard Lower published the first report of a successful blood transfusion between dogs.[4] He clearly described the surgical technique used to place quills in the carotid artery of the donor animal and the jugular vein of the recipient animal and the success of not 1 but 3 separate transfusions. In 1666, Jean Baptiste Denis, a philosopher and educator, transfused lamb blood into 4 men to cure their ailments. The first patient was treated for mental illness, and the first 3 transfusions were considered successful, as the men did not die; however, after the death of the fourth man, Denis was sued by the widow. Apparently, even in the 17th century, lawsuits were often a consequence of poor outcomes.

6. The first human-to-human transfusion was performed in 1818 by James Blundell, a physician, obstetrician, and physiologist, to treat a man with a gastric carcinoma.[5] The patient rallied after the transfusion of 14 ounces (420 mL) of blood but died 2 days later. Blundell performed several more human-to-human transfusions over the next decade and recounted the experience of the first successful transfusion in the *Lancet* in 1829. This article described the successful treatment of postpartum hemorrhage with 8 ounces (240 mL) of blood transfused from his assistant. Although Dr Blundell later reported classic signs of transfusion reactions after subsequent transfusions in other patients, he continued to recommend transfusion for dying patients, particularly for postpartum hemorrhage. Ostensibly, transfusion reactions were an acceptable alternative to death from hemorrhage.

7. Coagulation in the devices used to transfer the blood from donor to

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recipient was a primary complication in early transfusions. Sir Thomas Smith developed a defibrinating technique to prevent coagulation.[6] This procedure was performed using a wire egg beater and a hair sieve among other unsterile instruments. Sir Thomas transfused blood that had been defibrinated into an infant with hemolytic disease of the fetus/newborn in 1873. Sir Thomas may have been a role model for television hero MacGyver, as he had the imagination to use commonplace objects to achieve unusual outcomes.

8. James Lacy described the anticoagulant effect of black bohea tea in 1722, when he administered this solution intravenously to a canine.[7] We now know that oxalate was formed by enzymatic action as tea steeped; in this century, we understand that oxalate inhibits coagulation by binding with calcium. More than a century later, Dr Braxton Hicks, a prominent obstetrician, promoted the use of chemical substances to produce anticoagulation and improve the success of blood transfusions. In 1869, he published a report describing the use of phosphate of soda as an anticoagulant for 4 cases requiring transfusion. The use of the anticoagulant, sodium citrate, was introduced in 1918 by James Graham, paving the way for storage of donated blood. Modern approved anticoagulants such as acid citrate dextrose, citrate phosphate dextrose, and citrate phosphate dextrose adenine were developed from these earlier substances. Without these, we might still be performing direct transfusion from donor to recipient, which might make massive transfusion challenging.

9. In 1900, Landsteiner identified 3 blood groups in humans, which he designated as groups A, B, and C.[8] Soon after in 1901, Decastello and Sturli identified a fourth group. Two other independent scientists also found and reported 4 groups of blood in humans, Jansky in 1907 and Moss in 1910. Of course, they developed their own designations for blood groups (Table). Unfortunately, the Moss nomenclature was most commonly used in Britain, France, and some parts of the United States, while elsewhere, the Jansky system was used. In 1922, Dr Landsteiner proposed an international classification system to remove the confusion of multiple nomenclatures; this was acknowledged in 1927. However, the Moss system, in addition to the international system, remained in widespread use until the 1950s! Can you imagine trying to decide whether you should transfuse type A or type IV?

10. In 1939, Levine and Stetson[9] published a short case study describing a serious reaction in a postpartum patient transfused with her husband's blood; both were type O. Further study found that the patient's blood reacted with 80% of 104 independent samples of type O blood but not with the remaining 20%. These physicians hypothesized the presence of a fetal immune property inherited from the father that produced antibody formation in the mother. Landsteiner and Weiner[10] identified another human blood antigen in 1940 that they named Rh, as the presence of this antigen produced an agglutination reaction when Rhesus monkey blood was added. Exchange transfusion was subsequently developed to manage what is now known as RhD hemolytic disease of the newborn. In 1963, the first anti-D immunoglobulin to prevent maternal sensitization was tested,[11] and the 14% of pregnancies at risk for hemolytic disease of the newborn in the 1960s decreased to 0% to 1% in the 1980s when the value of anti-D prophylaxis had been acknowledged and administration was routine.[12] It is truly amazing how the discovery of the Rh antigen in 1940 led to nearly universal prophylaxis and prevention only 40 years later!

11. Although currently there are 9.7 million blood donors in the United States, in the 1930s, there was a shortage of live blood donors.[13] Russian physicians tried transfusion of blood from those recently deceased to their ailing patients.[14] Transfusion from cadavers was also reported in the 1960s by a pathologist, Dr Jack Kevorkian, and colleagues; they reported full recovery of 7 patients after transfusion of cadaver blood.[15] Other clinicians attempted transfusion of placental blood; however, bacterial contamination was an issue. The use of cadaver blood was never really accepted, and neither was Dr Kevorkian's future brainchild, assisted suicide with terminal patients.

12. With World War II, the United States military needed units of blood at the front lines to treat those with combat injuries.[14] Officials realized that transporting large quantities of freshly donated blood was not possible. Enter Edwin Cohn, a professor of physical chemistry at Harvard Medical School. Cohn, at the urgent request of the US government, began working to

TABLE Nomenclature for Blood Groups in Humans During Early 20th Century

Landsteiner	Jansky	Moss	International System
1901	**1907**	**1910**	**1927**
Type C	Type I	Type IV	Type O
Type A	Type II	Type II	Type A
Type B	Type III	Type III	Type B
	Type IV	Type I	Type AB

Adapted with permission from Farr AD. Blood group serology—the first four decades. *Med Hist*. 1979;23:215–226.

isolate plasma protein fractions found in human blood. Cohn discovered that transfusion of fraction V, which was abundant with albumin, reduced deterioration due to hemorrhage by increasing circulating volume. Albumin shipments were sent to Pearl Harbor to treat those injured after the Japanese attacked; there were only a few adverse reactions in the almost 90 patients who received the newfound product. Later in 1951, Cohn developed the first cell separator, which permitted the separation of whole blood down into its different constituents; Cohn called the end products "component therapy." Apparently, necessity really was the mother of invention.

13. Donated blood today is tested for up to 15 infectious diseases.[16] Testing donated blood had its origins with the development of the American Society of Hematology in 1958. The society leaders wanted to determine the cause of "serum hepatitis" after transfusion in World War II soldiers.[17] The hepatitis B antigen (then called the Australia antigen, or Au) was discovered, albeit 30 years later. Further investigations revealed the presence of Au in 10% of blood donors with leukemia but only in 0.1% of healthy blood donors. This finding led to the hypothesis that the Au antigen was associated with leukemia. Only later, through studies performed in institutions housing individuals with Down syndrome, who were genetically prone to leukemia, did they find that the Au antigen was actually associated with crowded living environments. Subsequently, the hepatitis B antigen was discovered, and an initial screening test for donated blood was developed. In addition, the hepatitis B vaccine was developed, and eventually, hepatitis C was identified. Talk about a slow motion domino effect!

14. Dr Robert Beal, known for his work with the Australian Red Cross Blood Service, said, "Blood transfusion is like marriage: it should not be entered upon lightly, unadvisedly or wantonly or more often than is absolutely necessary."[18] Truer words were never spoken. Since the inception of blood donation and transfusion, multiple transfusion complications have been identified. While infectious diseases like human immunodeficiency virus are known to be associated with transfusion, these are considered a relatively minor risk today. However, immune-mediated and non–immune-mediated reactions that include transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, transfusion-associated circulatory overload, posttransfusion purpura, and iron overload are more prevalent than infectious ones. Allergic reactions that include pruritus and urticaria occur in 1% to 3% of all transfusions; febrile transfusion reactions occur in 1:330 packed cell transfusions and 1:20 platelet (PLT) transfusions, while more serious transfusion-associated lung injury occurs in 1:5000 transfusions.[19] Transfusion of even 1 unit of packed red blood cells (PRBCs) increases risk for mortality by nearly 2.5 times.[20] And this is a practice meant to save lives!

15. One unit of donated blood can benefit several people through the separation and preservation of blood components (PRBCs, PLTs, fresh frozen plasma (FFP), and cryoprecipitate). Each component has different storage requirements and shelf life, the expiration date from the time of donation. Packed red blood cells can be kept refrigerated for up to 42 days.[13] Platelets are kept at room temperature for up to 5 days, and FFP and cryoprecipitate can remain frozen for a year. Current blood bank practices include rotation of older components to trauma centers so they will be used prior to expiration, thereby reducing waste. However, PRBCs and PLTs develop a predictable "storage lesion" over time, a combination of biological and morphological changes in cells linearly related to storage time. This storage lesion is associated with serious consequences that include impaired circulation, decreased oxygenation, compromised immune response, and systemic inflammation after transfusion.[21,22] Severely injured patients treated at trauma centers may require up to 100 units of blood during resuscitation.[13] If 1 unit of older PRBCs has a storage lesion, imagine the effect of 100 units!

16. Roughly 60 years ago, the US government established the Armed Services Blood Program for oversight of the collection and distribution of blood and blood components to the US armed forces.[23] However, protocols were not developed until prior to the Korean War, when collection points were established in California and Japan. Military physicians decided to use only Rh-negative type O blood for transfusion, as this type of blood was associated with the fewest adverse reactions. Only 4 major transfusion reactions were reported out of an astounding 50,000 transfusions performed by 1952; these reactions were found to be associated with use of locally obtained blood, instead of that from the blood program. The Armed Services Blood Program currently has 81 active blood banks and can be found on Facebook, Twitter (@MilitaryBlood), YouTube, Pinterest, and Flickr!

17. Blood substitutes have been sought since physicians believed in humor, and early replacements included milk and wine administered intravenously.[1] The use of saline infusion began with an experiment in frogs 1884,[24] and Lactated Ringer's solution was developed over the next decade. In 1966, perfluorochemicals were developed, and their oxygen-carrying capacity was investigated. This was

followed by the development of hemoglobin-based products. However, none of these products have been approved for use by the Food and Drug Administration after extensive testing. To date, there is no substitute for "the real thing."

18. Blood transfusions have become ubiquitous in clinical practice, and many believe that the primary risk of transfusion is transmission of infectious diseases. However, not everyone wants to avoid transfusion. Many athletes have been found guilty of "blood doping," which consists of administration of erythropoietin; use of a hemoglobin-based blood substitute or oxygen therapeutic approved for use in animals only; and/or administration of blood transfusions, either stored autologous blood or that from another individual.[25] This can be an expensive undertaking. According to the 2011 National Blood collection and Utilization Survey Report,[26] the average cost for 1 unit of leukocyte-reduced PRBCs was $225.42, but only $57.91 for a unit of FFP. The winner of the highest cost award was a unit of leukocyte-reduced, apheresis PLTs at a whopping $535.17! These costs are astounding when you consider that blood is donated by altruistic individuals. Perhaps there should be a rewards program; donate 10 units of blood, get a free transfusion.

19. Administration of blood components, rather than whole blood, has been accepted as standard practice, as it was thought to promote efficient use of a scarce resource. However, there were few studies evaluating the benefits to component therapy compared with whole blood transfusion. Researchers now suggest transfusion of blood components in a 1:1:1 ratio, meaning 1 unit of PRBCs to 1 unit of FFP to 1 unit of PLTs, as this mimics the composition of whole blood.[27] This ratio of components results in transfusion with a hematocrit of 29%, a PLT count of 88,000 per microliter, and 65% coagulation factor activity in 660 mL.[28] Compare that with transfusion of a unit of fresh warm blood preserved with citrate phosphate dextrose solution, which has a hematocrit of 33% to 43%, a PLT count of 130,000 to 350,000 per microliter, and 86% coagulation factor activity. One investigator described this 1:1:1 transfusion strategy as one that, "… at best provides an anemic, thrombocytopenic, coagulopathic, and cold product to a patient population that is at increased risk of mortality with hypothermia, acidosis, anemia, and coagulopathy."[27] So … who's ready for a 1:1:1 component transfusion?

20. Thirty million blood components are transfused annually in the United States.[13] Evidence-based guidelines have been developed as data from high-quality randomized clinical trials have become available.[29] However, these guidelines are not universally implemented; often, each institution developed its own specific protocols, and those were not strictly followed. Available guidelines commonly include identified prompts or triggers for transfusion of different components and include evaluation of hemoglobin, hematocrit, PLT count, and international normalized ratio. Unfortunately, guidelines are not always accepted or followed![30] According to Goethe, "knowing is not enough; we must apply. Willing is not enough; we must do."

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