Yesterday

- The earliest attempts to transfuse blood in the US were led by surgeons, especially trauma surgeons in the military. The discovery of the ABO blood group antigens by Karl Landsteiner in 1901 led to an understanding of the immunological components of transfusion and improved transfusion results. More detailed blood cell typing evolved over the 20th century. The development of anticoagulant-preservation solutions in the early 20th century allowed blood to be stored. The replacement of glass bottles with sterile, interconnected plastic blood containers in the 1960s made therapy using blood components, rather than whole blood, possible. By the 1950s, the risk of transmission of blood-borne infectious agents such as hepatitis was just beginning to be appreciated.

- The NIH developed an automated blood cell separator that could rapidly collect different types of blood cells. For example, the device made it possible to collect platelets to support cancer chemotherapy, and eventually to collect stem cells for transplantation and cellular therapies.

- In the 1970s, NIH-funded studies of post-transfusion hepatitis led to the establishment of one of the first biorepositories dedicated to blood safety.

- Studies at the NIH identified a protein on the surface of red blood cells that allowed malarial parasites to infect the cells. This was the first demonstration of a function for a red cell surface antigen, and has led to promising malarial vaccine research.

- In the early 1980s, the global AIDS epidemic emerged. A significant number of people were infected by receiving blood or blood products contaminated with human immunodeficiency virus (HIV), the retrovirus that causes AIDS. Development of a screening test led to dramatic improvements in blood safety as well as understanding of HIV.

- The NIH funded the Retrovirus Epidemiology Donor Study (REDS) at selected blood centers throughout the country from 1989 to 2003 to determine the prevalence and incidence of HIV among blood donors and the risks of transmitting HIV and other viruses via transfusions.

- A new technology, nucleic acid amplification testing (NAT), greatly improved detection of HIV in donated blood. Previous HIV screening tests relied on detecting circulating antibodies.

Development of antibodies may take three weeks or more after viral infection. During this “window period” the antibody tests could yield negative results for infected blood. NAT reduced the window period for HIV to as little as 11 days and the window period for hepatitis C virus (HCV) from about 70 to 10 days.

- In 2003, the NAT procedure was rapidly modified to detect the West Nile virus (WNV). In just 9 months, a test for WNV was developed and approved by the Food and Drug Administration. During the past 7 years over 1,500 blood donors with acute WNV infections were identified before their donations entered the blood supply.

Today

- NAT is now used to screen virtually all whole blood and plasma donations collected in the United States for HIV, HCV, and WNV. Since NAT was introduced, the risk of HIV and HCV infection associated with blood transfusion has been reduced to about 1 in 1.5-2.0 million blood units.

- REDS-II is now under way to improve the safety and availability of the U.S. blood supply. Its primary objectives are to monitor the appearance of newly discovered infectious agents in the blood supply, determine the causes of transfusion reactions of unknown etiology, assess the effectiveness of new donor screening methods, and evaluate the donation process to improve the adequacy of the blood supply.

- Current REDS-II protocols are (1) evaluating the risks of transfusion-transmitted infectious agents, (2) comparing the incidence of transfusion-related acute lung injury (TRALI), a potentially life-threatening syndrome, in recipients who receive blood that contains human leukocyte antigen (HLA) antibodies with the incidence in recipients who receive blood without the antibodies, (3) exploring why some blood donors may fail to provide an accurate or complete health history during initial screening, and (4) evaluating the effects of the frequency of blood donation and the amount of blood donated on iron and hemoglobin status in donors.

- In response to the critical need for a program to monitor the US blood supply for signs of transfusion-transmitted infectious disease (TTID) and to understand current TTID risk factors and their relative prevalence among donors, REDS-II is launching a national TTID marker and risk evaluation study at the three largest blood collection organizations in the U.S., collectively...
representing about 60 percent of all blood donors and donations in the country.

- An international study in REDS-II is conducting epidemiological, laboratory, and survey research on blood donors in selected countries seriously affected by AIDS to ensure the safety and availability of blood for transfusion. The World Health Organization estimates that even today 5 to 10 percent of AIDS cases globally are acquired from blood transfusions.

- An NIH-led working group is helping to identify and design research studies to evaluate whether xenotropic murine leukemia virus-related virus (XMRV), a newly identified retrovirus, may pose a threat to blood safety.

- Dengue virus, which infects 50-100 million people worldwide and causes more than 25,000 deaths annually, can be transmitted via blood transfusion. An NIH-funded study is screening blood donors in Puerto Rico for dengue virus. The researchers will conduct follow-up studies of donors who test positive. The study will accelerate the implementation of appropriate screening for dengue virus.

- The NIH is funding the development of blood tests to screen for microorganisms that cause the disease babesiosis. Babesia microorganisms are endemic in the northeast US, are transmitted via transfusion, and can lead to illness or death in immunocompromised patients who receive blood that contains them.

- Investigators are working to develop tests to detect transmissible spongiform encephalopathies, such as Creutzfeldt-Jakob disease (CJD) and new variant CJD, and to develop methods to inactivate or remove abnormal prion proteins from blood components.

- While transfusions unquestionably save the lives of many patients, they can cause immunological and other non-infectious complications. Some studies suggest that the way donated blood is processed and the amount of time it is stored may contribute to the development of non-infectious complications. The NIH is funding nine research projects to determine if the safety and efficacy of red blood cell transfusions vary depending on how long the cells have been stored. One of the projects is the first large, multi-center, randomized clinical trial to compare outcomes in heart surgery patients who receive transfusions of red blood cells that have been stored for shorter or longer periods.

**Tomorrow**

- Newly developed technologies will routinely be used to provide rapid and accurate detection of infectious agents transmissible in blood, such as HIV, HCV, and hepatitis B virus. New and improved tests will be accessible for agents such as Chagas disease and malaria and for emerging agents that pose a threat to transfusion safety.

- New tests will allow blood collection services to discern between individuals who have circulating HIV antibodies due to HIV infection and those who have antibodies due to previous immunization with an HIV vaccine.

- A wide range of safe and effective blood substitutes may become available that would be extremely useful when blood is not immediately available or is in short supply, such as in the case of a rare blood type or a major disaster. The substitutes would be free of infectious agents and would pose no major risks of toxicity to recipients.

- NIH funded investigators reported in 2007 the development of a new, rapid screening assay to detect common causes of acute infection by measuring gene expression in blood cells (http://bloodjournal.hematologylibrary.org/cgi/content/full/109/5/2066). For example, influenza was distinguished from common bacterial infections with 95% accuracy and Escherichia coli from Staphylococcus aureus with 85% accuracy. This approach could provide a fast and effective method to diagnose common infections in donated blood.

- Several pathogen reduction technologies (PRTs) have been developed by commercial companies, with initial support from the NIH and the Department of Defense, to remove infectious agents from blood products. As PRTs are further developed and found to be effective and safe, they may change the paradigm for addressing infectious threats to blood safety from a strategy of screening donors and blood to one of eliminating infectious agents from the blood supply.

- Improved understanding of stem cell biology may enable researchers to derive large quantities of mature and functional blood cells from hematopoietic stem cells and other precursor cells, which could speed the development of effective new transfusion therapies.

**For additional information:**

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