Research Opportunities in Transfusion Medicine

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Scope of the Problem
The field of transfusion medicine began 100 years ago, in 1900, with the discovery by Landsteiner of the ABO blood group system. This discovery demonstrated that plasma proteins have defined specificities. These plasma proteins, later termed antibodies, recognize epitopes on red blood cells. These discoveries constituted a starting point for blood banking—collection and storage of blood—and for immunohematology, the serological investigation of blood group antigens (Figure 1). During the past 3 to 4 decades, significant advances have been achieved in improving the blood supply with respect to availability, safety, and fractionation into components, such as red blood cells, platelet concentrates, and plasma proteins.

Donors currently donate approximately 12 million units of blood annually in the United States. Without these donations, many procedures and treatments, such as hematopoietic stem cell transplantation, complex cardiac and orthopedic surgery, and organ transplantation, would not be possible. A safe and adequate blood supply is a fundamental necessity to support state-of-the-art medical and surgical therapies. However, resources are now needed to translate advances in the biology of hematopoietic cells into newer cellular therapies and to investigate the unique immunological effects that result from transfusion of blood cells. This article discusses current status and progress in several aspects of transfusion medicine, including adequacy and safety of the blood supply, appropriate use of transfusion therapy, development of novel cellular therapies, and manipulation and prevention of immune responses.

Major Advances
Advances in transfusion medicine that have occurred during the past 25 years include reduction in risk of virally transmitted disease, pharmaceutical production of recombinant clotting factors, isolation and storage of stem and progenitor cell populations for transplantation, and genetic characterization of blood group antigens.

Reduction in transfusion-transmitted viral disease was achieved by a conversion from paid to volunteer donors, by improvement in donor screening, and by improvement of assays that detect viruses in donor blood. Since implementation of nucleic acid testing of donor blood, the estimated risks of hepatitis B (1 per 63,000 units), hepatitis C (1-3 per 1 million units), and human immunodeficiency virus (HIV) (1-2 per 1 million units), are now minuscule (Figure 2). At the same time, pasteurization and solvent-detergent treatment have virtually eliminated risk of HIV and hepatitis transmission through clotting factor concentrates and other plasma derivatives.

Advances have also been made in hematopoietic stem and progenitor cell transplantation for both hematologic and nonhematologic malignancies. The realization that stem and progenitor cells circulate in peripheral blood and that these cells can be mobilized from bone marrow using cytokines has led to outpatient cytopheresis procedures. Transfusion medicine specialists are now involved in collection, in vitro manipu-
1900 1920 1940 1960 1980 2000
Whole blood transfusions were the mainstay of transfusion therapy until the 1950s. Fractionation of plasma into derivatives such as albumin and clotting factor concentrates was introduced in the 1940s. Using centrifugation, whole blood was separated on a wide scale in the 1960s into various cellular and acellular components. Beginning in the 1970s, platelet and granulocyte products were also prepared using apheresis. During the 1980s, various steps were undertaken to reduce the risk of infectious disease transmission, including the development of recombinant clotting factor proteins. During the past 2 decades, it became possible to isolate different cell populations from bone marrow and peripheral and placental blood with defined functional properties. This led to development of cellular therapies for hematopoietic stem cell transplantation and immunotherapy for infectious diseases and cancer. The discovery that hematopoietic stem cells can differentiate into cells of other lineages such as neuronal and hepatic cells suggests the potential for tissue engineering.

Current Scientific Foundation
The indications for transfusion of blood products continue to evolve. The hemoglobin concentration alone is an inadequate indication for red blood cell transfusion but improved clinical guidelines have not yet been defined. The importance of this issue is underscored by evidence that suggests that more liberal use of red blood cell transfusion may possibly harm younger, less severely ill patients in the intensive care unit. It is now possible to develop blood group antigen testing by genetic approaches. Genotyping may lend itself to screening larger numbers of units in the blood supply and may be more amenable to laboratory automation. This development could therefore enhance compatibility testing by selecting donor red blood cell units, which genetically match the red blood cells of the recipient. As a result, alloimmunization would be less likely.

Current Cutting-Edge Research
Current research is aimed at reducing viral transmission of blood products.
Several viral/bacterial inactivation methods are being investigated for cellular products that are not amenable to solvent-detergent treatment or pasteurization.\textsuperscript{14} Also, artificial blood substitutes (now in phase 3 trials) ultimately may have clinical utility, but they are unlikely to replace the volunteer donor blood supply.\textsuperscript{15}

With respect to cell therapies, attempts are under way to define hematopoietic stem cells and to understand stem and progenitor cell replication and differentiation.\textsuperscript{16} These studies may lead to better approaches for ex vivo stem and progenitor cell expansion. Also, stem cell homing (eg, chemokines) and engraftment (eg, facilitator cells) are critical for hematopoietic stem cell transplantation.\textsuperscript{17} Other cell therapies in development include T-cell therapies, for their graft vs tumor effect (ie, residual/recurrent chronic myelogenous leukemia), and the ex vivo generation of dendritic cells, for use in tumor vaccines.\textsuperscript{18,19} Progress also is being made in differentiating the cells (and surface molecules) of the immune system that generate immune responses to foreign and host antigens.\textsuperscript{20,21} As a result, experimental research and clinical trials are ongoing to find ways to either prevent or blunt autoimmune or alloimmune responses by costimulatory molecules (eg, using anti-CD40, CTLA4-Ig).\textsuperscript{22-24}

Critical Needs

Basic principles of quality and risk management support establishment of evidence-based guidelines. A network of clinical research centers in transfusion medicine is essential to improve the effectiveness of the research that this discipline requires. Basic research analyzing the control of hematopoiesis is critical to expansion of hematopoietic cells and important to development of novel cellular therapies. Several issues must be resolved to advance hematopoietic stem cell transplantation. For example, which cells or factors are necessary for long-term engraftment? Which cells exist in the bone marrow environment and how do they influence hematopoietic growth and differentiation? Which factors influence the retention and trafficking of hematopoietic progenitor cells to and from the bone marrow environment?

Alloimmunity is a common consequence of blood cell transfusion. Further studies are needed to elucidate the mechanisms involved in generation of these immune responses. Such studies may focus on definition of target antigens (eg, tumor antigens, antigens in graft-vs-host disease, immune cell types, and the membrane molecules involved), cell origin (eg, host vs donor), the role of cytokines in establishing and perpetuating an alloimmune response, and the role of chemokines and chemokine receptors in homing immune cells. To date, few animal models exist that can be used to study alloimmune responses to blood cell elements. A special need exists to develop murine models to take advantage of existing reagents; the ability to inactivate murine background genes and knock-in human genes may be useful to study the induction, prevention, and modulation of immune-hematological responses. Such models may help define the role of specific immune cells (eg, T cells, dendritic cells), the role of donor vs host antigen-presenting cells, and the role of certain receptors (eg, Fcγ).

Forecast of Major Advances

Current problems with blood shortages can be solved by finding ways to increase blood donations, by establishing donor criteria that maintain a safe blood supply without turning away safe donors, and by more accurately defining the indications for transfusions. Blood group genotyping will improve compatibility testing and selection of appropriate donor blood. In addition, genotyping will more precisely define fetal risk for neonatal hemolytic disease. Transfusion safety will be further enhanced by improved genetic testing of donated blood for known pathogens and by use of viral/bacterial inactivation steps suitable for cellular products. While reduction in the transmission risk of hepatitis B, hepatitis C, and HIV infection during the past 15 years is a major advantage, it is important to continue surveillance for newly emerging viruses and other pathogens (eg, prions, associated with variant mad cow disease) (Figure 2).\textsuperscript{25}
Advances in cell and molecular biology of immune and hematopoietic cells will make it possible to isolate and grow cells in vitro for specific cell therapies. Such therapies will include hematopoietic stem and progenitor cell populations with optimal engraftment and minimal graft-vs-host disease, dendritic cells for tumor vaccines, T-cell populations defined for their antitumor/antiviral effects, and stem and progenitor cells that are rendered resistant to infectious disease or genetically modified to correct genetic disorders. Since hematopoietic stem cells are capable of differentiating into cells of different lineage (eg, liver cells), it may possible to generate human tissue and blood cells in vitro for therapeutic applications. Further understanding of alloimmune responses after transfusion may lead to ways to mitigate or prevent unwanted consequences of transfusion, such as graft-vs-host disease and refractoriness to platelet transfusion. Collectively, this interdisciplinary research effort will translate into safer and more effective transfusion therapy with a wide range of applications.

**References**