ROSSI'S PRINCIPLES OF TRANSFUSION MEDICINE

FIFTH EDITION

Edited by
Toby L. Simon • Jeffrey McCullough • Edward L. Snyder
Bjarte G. Solheim • Ronald G. Strauss

with website

WILEY Blackwell

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Edited by

Toby L. Simon, MD
Senior Medical Director, Plasma Product Development and CSL Plasma, CSL Behring, King of Prussia, Pennsylvania; and
Clinical Professor of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

Jeffrey McCullough, MD
Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota, USA

Edward L. Snyder, MD, FACP
Professor, Department of Laboratory Medicine, Yale University School of Medicine; and
Director, Blood Bank/Apheresis Service, Yale-New Haven Hospital, New Haven, Connecticut, USA

Bjarte G. Solheim, MD, PhD, MHA
Professor Emeritus, Institute of Immunology, Oslo University Hospital–Rikshospitalet, and University of Oslo, Oslo, Norway

Ronald G. Strauss, MD
Professor Emeritus, Departments of Pathology and Pediatrics, University of Iowa College of Medicine, Iowa City, Iowa, USA;
Associate Medical Director, LifeSource/Institute for Transfusion Medicine, Chicago, Illinois, USA

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Contents

Contributors

Amin Alousi, MD
Associate Professor of Medicine
Department of Stem Cell Transplantation
and Cellular Therapy
The University of Texas
MD Anderson Cancer Center
Houston, TX, USA

Arna Andrews, PhD
Director, Cell Line Development, CSL Behring
Broadmeadows, VIC, Australia

Donald M. Arnold, MD, MSc, FRCPC
Associate Professor, Division of Hematology and Thromboembolism, Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada

Jeffrey A. Bailey, MD, PhD
Assistant Professor, Departments of Medicine and Pathology, Division of Transfusion Medicine; Program in Bioinformatics and Integrative Biology University of Massachusetts Medical School; and UMass Memorial Medical Center, Worcester, MA, USA

Jenna Balestrini, PhD
Postdoctoral Fellow in Anesthesiology
Department of Biomedical Engineering, Department of Anesthesiology, Yale University School of Medicine
New Haven, CT, USA

Richard J. Benjamin, MD, PhD, FRCPath
Chief Medical Officer, Cerus Corp, Concord CA, USA

Melvin Berger, MD, PhD
Senior Director, Medical Research Strategy
CSL Behring, King of Prussia, PA, USA

Alexey Bersenev, MD, PhD
Associate Research Scientist, Department of Laboratory Medicine, Yale University School of Medicine, and Blood Bank, Yale-New Haven Hospital, New Haven CT, USA

Joseph Bertolini, PhD
R&D Director, CSL Behring
Broadmeadows, VIC, Australia

Morris A. Blajchman, MD, FRCP(C)
Professor Emeritus, Departments of Pathology and Medicine, McMaster University, Hamilton
ON, Canada

Martin H. Bluth, MD, PhD
Professor, Department of Pathology
Wayne State University School of Medicine
Detroit, MI, USA

Kevin Boehm, MD
Student, Department of Biomedical Engineering
Department of Anesthesiology, Yale University School of Medicine, New Haven, CT, USA

José O. Bordin, MD
Associate Professor, Department of Hematology and Transfusion Medicine, Universidade Federal de São Paulo, São Paulo, Brazil

Anneke Brand, MD, PhD
Professor of Transfusion Medicine, Sanquin Blood Bank and Department of ImmunoHematology and Blood Transfusion, Leiden University Medical Center, Leiden
The Netherlands

Emanuela Bruscia, PhD
Assistant Professor of Pediatrics, Yale University School of Medicine and Blood Bank, Yale-New Haven Hospital
New Haven, CT, USA

Edwin A. Burgstaler, MT, HP(ASCP)
Development Technologist, Therapeutic Apheresis Treatment Unit, Mayo Clinic, Rochester
MN, USA

Jeffrey L. Carson, MD
Richard C. Reynolds Professor of Medicine
Chief, Division of General Internal Medicine; and Provost— New Brunswick, Rutgers Robert Wood Johnson Medical School, Rutgers Biomedical Health Sciences, Rutgers University, New Brunswick, NJ, USA

Richard Champlin, MD
Professor and Chairman, Department of Stem Cell Transplantation and Cellular Therapy, University of Texas-MD Anderson Cancer Center, Houston, TX, USA

Jocelyn Chandler, MD
Chief Resident, Department of Pathology
Yale University School of Medicine; and Blood Bank Yale-New Haven Hospital, New Haven, CT, USA

Robert D. Christensen, MD
Presidential Professor and Chief, Division of Neonatology, University of Utah School of Medicine
Salt Lake City, UT, USA

Leanne Clifford, BM, MSc
Resident, Department of Anesthesiology, Mayo Clinic
Rochester, MN, USA

Laura Cooling, MD
Associate Professor
Department of Pathology
University of Michigan
Ann Arbor, MI, USA

Michael W. Cripps, MD
Assistant Professor of Surgery, Department of Surgery
Division of Burn/Trauma/Critical Care, University of Texas Southwestern Medical Center, Dallas, TX, USA

Kendall P. Crookston, MD, PhD
Professor, Departments of Pathology and Medicine
University of New Mexico School of Medicine; Regional Medical Director, United Blood Services of New Mexico; and Associate Medical Director, TriCore Reference Laboratories, Albuquerque, NM, USA

Robertson D. Davenport, MD
Associate Professor, Department of Pathology
The University of Michigan Medical School
Ann Arbor, MI, USA

Sarah M. Drawz, MD
Fellow, Department of Laboratory Medicine and Pathology, University of Minnesota
Minneapolis, MN, USA

Amy L. Dunn, MD
Associate Professor, Department of Pediatrics
The Ohio State University; and Director, Hemophilia and Bleeding Disorder Program, Hemophilia Treatment Center, Division of Hematology/Oncology/BMT
Columbus, OH, USA

Anne F. Eder, MD, PhD
Vice President, National Medical Affairs; Biomedical Services, American Red Cross, Adjunct Associate Professor, Georgetown University Medical Center
Washington DC, USA

Lise Estcourt, MA(MEL), MSc, DPhil, MRCP, FRCPath
Consultant Hematologist, NHS Blood and Transplant and The National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford University Hospitals, NHS Foundation Trust and the University of Oxford, Oxford, UK

Emmanuel A. Fadeyi, MD
Associate Professor, Department of Pathology
Wake Forest University School of Medicine
Winston-Salem, NC, USA

Øystein Flesland, MD, PhD
Head of Section, Patient Reporting and Learning Systems Unit, Norwegian Knowledge Centre for the Health Services, Oslo, Norway

Sameh Gaballa, MD
Assistant Professor of Medical Oncology
Division of Hematological Malignancies and Bone Marrow Transplantation
Thomas Jefferson University
Philadelphia, PA, USA

Susan A. Galel, MD
Senior Director of Scientific Affairs, Blood Screening Roche Molecular Systems, Pleasanton, CA; and Associate Professor Emeritus, Department of Pathology Stanford University School of Medicine, Palo Alto CA, USA

Ashley Gard, PhD cand.
Department of Biomedical Engineering, Department of Anesthesiology, Yale University School of Medicine
New Haven, CT, USA

Eric A. Gehrie, MD
Instructor, Department of Laboratory Medicine
Yale University School of Medicine
and Blood Bank, Yale-New Haven Hospital
New Haven, CT, USA

Sergio Giralt, MD
Professor of Medicine, Weill Cornell Medical College
Chief, Adult BMT Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Lawrence Tim Goodnough, MD
Professor of Pathology and Medicine, Co-Director Transfusion Medicine Program, Director, Transfusion Medicine Fellowship Program, Associate Medical Director, Stanford Blood Center
Stanford University Medical Center
Stanford, CA, USA

Morten Grönn, MD
Consultant Neonatologist, Department of Child and Adolescent Medicine, Akershus University Hospital
Nordbyhagen, Norway

Thor Willy Ruud Hansen, MD, PhD
Professor of Pediatrics, Consultant Neonatologist Neonatal Intensive Care, Women and Children's Division, Oslo University Hospital; and Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Paul Hébert, MD
Professor of Medicine, University of Montreal; and Physician-in-Chief, Centre Hospitalier de L'Université de Montréal (CHUM), Montreal, Canada

Peter Hellstern, MD
Director and Professor, Institute of Hemostaseology and Transfusion Medicine, Academic City Hospital
Ludwigshafen, Germany

Jeanne E. Hendrickson, MD
Associate Professor, Departments of Laboratory Medicine and of Pediatrics, Yale University School of Medicine, and Associate Director, Transfusion Medicine Service, Yale-New Haven Hospital, New Haven
CT, USA

Tor Hervig, MD, PhD
Professor, Department of Clinical Science
Department of Immunology and Transfusion Medicine
Haukeland University Hospital, Bergen, Norway

John R. Hess, MD, MPH
Professor, Department of Laboratory Medicine and Hematology, University of Washington
School of Medicine; and Medical Director, Transfusion Service, Harborview Medical Center
Seattle, WA, USA

John B. Holcomb, MD
Professor of Surgery; Chief, Division of Acute Care Surgery; and Director, Center for Translational Injury Research, University of Texas Health Science Center
Houston, TX, USA

Iris Jacobs, MD
Global Clinical Program Director, CSL Behring
King of Prussia, PA USA

Cassandra D. Josephson, MD
Professor, Pathology and Pediatrics, Emory University School of Medicine, Medical Director, Children's Healthcare of Atlanta, Blood Tissue & Apheresis Services, Atlanta, GA, USA

Karen E. King, MD
Associate Professor, Department of Pathology and Oncology, Director, Hemapheresis and Transfusion Support, Associate Director, Transfusion Medicine, The Johns Hopkins University School of Medicine
Baltimore, MD, USA

Joseph E. Kiss, MD
Medical Director, Hemapheresis and Blood Services The Institute for Transfusion Medicine; and Associate Professor of Medicine, Division of Hematology-Oncology, Department of Medicine, The University of Pittsburgh, Pittsburgh, PA, USA

Daryl J. Kor, MD, MSc
Associate Professor, Department of Anesthesiology
Mayo Clinic, Rochester, MN, USA

Mark J. Koury, MD
Professor of Medicine, Division of Hematology/ Oncology, Vanderbilt University, Nashville, TN, USA

Diane Krause, MD, PhD
Professor, Laboratory Medicine, Pathology and Cell Biology, Yale University School of Medicine and Blood Bank, Yale-New Haven Hospital, New Haven, CT, USA

David J. Kuter, MD, DPhil
Chief of Hematology, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School, Boston MA, USA

Jeanne V. Linden, MD, MPH
Director, Blood and Tissue Resources, Wadsworth Center, New York State Department of Health
Albany, NY, USA

Jeffrey McCullough, MD
Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School
Minneapolis, MN, USA

Janice G. McFarland, MD
Medical Director, Platelet and Neutrophil Immunology Laboratory, Blood Center of Wisconsin; and Professor Department of Medicine, Medical College of Wisconsin
Milwaukee, WI, USA

Andrea M. McGonigle, MD
Assistant Professor, Department of Pathology and Laboratory Medicine, Associate Medical Director Transfusion Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA USA

David H. McKenna, MD
Associate Professor of Laboratory Medicine and Pathology, Director, Division of Transfusion Medicine
University of Minnesota Medical School
Minneapolis, MN, USA

Jeffrey S. Miller, MD
Department of Medicine
Division of Hematology, Oncology and Transplantation
Blood and Marrow Transplantation Program
University of Minnesota, Minneapolis, MN, USA

Paul D. Mintz, MD
Director, Division of Hematology Clinical Review
Office of Blood Research and Review, Center for Biologics Evaluation & Research, US Food and Drug Administration, Silver Spring, MD, USA

Shanna Morgan, MD
Medical Director,
American Red Cross-North Central Region
Adjunct Assistant Professor
Laboratory Medicine and Pathology
Division of Transfusion Medicine
University of Minnesota
Assistant Medical Director Blood Bank
Veterans Affairs Hospital, Minneapolis, MN, USA

Michael F. Murphy, MD, FRCP, FRCPath
Professor of Transfusion Medicine and Consultant Haematologist, NHS Blood & Transplant, National Institute of Health Research (NIHR)
Oxford Biomedical Research Centre
Oxford University Hospitals and the University of Oxford, UK

Christian Naper, MD, PhD, MHA
Senior Consultant, Institute of Immunology
Oslo University Hospital–Rikshospitalet and University of Oslo, Oslo, Norway

Andrew Nash, PhD
Senior Vice President, Research, CSL Behring
Broadmeadows, VIC, Australia

Ishac Nazi, PhD
Assistant Professor, Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University Hamilton, ON, Canada

Paul M. Ness, MD
Professor, Pathology, Medicine and Oncology, Director Transfusion Medicine Division, The Johns Hopkin University School of Medicine Baltimore, MD, USA

Laura Niklason, PhD, MD
Professor of Anesthesiology and Biomedical Engineering, Department of Anesthesiology, Yale University School of Medicine, New Haven, CT, USA

Tho D. Pham, MD
Assistant Medical Director of Clinical Services, Stanford Blood Center; and Clinical Instructor, Department of Pathology, Stanford University School of Medicine, Palo Alto, CA, USA

Gregory J. Pomper, MD
Associate Professor, Department of Pathology Wake Forest School of Medicine, Winston-Salem NC, USA

Ralph M. Powers, DDS
Senior Manager, Scientific Affairs, Institute of Regenerative Medicine, LifeNet Health Virginia Beach, VA, USA

Aaron E. Pritchard, MD
Assistant Professor of Pathology, University of New Mexico School of Medicine, Albuquerque, NM, USA

Keith Quirolo, MD
Formerly Department of Hematology/Oncology, UCSF Benioff Children's Hospital, Oakland, Oakland, CA USA

Lawrence Rice, MD
Chief, Division of Hematology, Houston Methodist Hospital; Professor of Medicine, Weill Cornell Medical College; and Adjunct Professor of Medicine, Baylor College of Medicine, Houston, TX, USA

Henry M. Rinder, MD
Professor of Laboratory Medicine and Internal Medicine (Hematology), Yale University School of Medicine and Director, Hematology Laboratories, Yale-New Haven Hospital, New Haven, CT, USA

Ennio C. Rossi, MD
Professor Emeritus of Medicine, Northwestern University School of Medicine, Chicago, IL, USA

Nathan J. Roth, PhD
Director, Global Pathogen Safety, CSL Behring King of Prussia, PA, USA

Alex B. Ryder, MD
Assistant Professor, Departments of Pediatrics and Pathology, University of Tennessee Health Science Center, Le Bonheur Children's Hospital Memphis, TN, USA

Ulrich J. Sachs, MD, PhD
Head and Professor, The Platelet and Granulocyte Laboratory, Institute for Clinical Immunology and Transfusion Medicine, Justus Liebig University Giessen, Germany

Michael Schmidt, MD
Professor, Institute of Transfusion Medicine and Immunohematology, German Red Cross, Frankfurt/M Germany

Wade L. Schulz, MD, PhD
Resident, Department of Laboratory Medicine Yale University School of Medicine and Blood Bank Yale-New Haven Hospital, New Haven, CT, USA

Jerard Seghatchian, MD
Senior Consultant, International Consultancy in Blood Components Quality/Safety Improvement, Audit/ Inspection and DDR Strategies, London, UK

Erhard Seifried, MD, PhD
Director and Professor
Institute of Transfusion Medicine and Immunohematology, German Red Cross, Frankfurt/M Germany

Neil Shah, MD
Clinical Assistant Professor of Pathology and Transfusion Medicine, Medical Director of Referral Testing, Departments of Pathology and Medicine Stanford School of Medicine Stanford, CA, USA

Sujit Sheth, MD
Professor of Clinical Pediatrics, Department of Pediatrics, Weill Cornell Medical College New York, NY, USA

Don L. Siegel, PhD, MD
Professor, Pathology and Laboratory Medicine; and Director, Division of Transfusion Medicine and Therapeutic Pathology, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Joshua Siewert, MSc
School of Management, Department of Biomedical Engineering, Yale University; Department of Anesthesiology, Yale University School of Medicine New Haven, CT, USA

Toby L. Simon, MD
Senior Medical Director, Plasma Product Development and CSL Plasma, CSL Behring, King of Prussia PA; Clinical Professor of Pathology, University of New Mexico School of Medicine,Albuquerque, NM, USA

James W. Smith, MT, BSc
Technical Director, Platelet Immunology Laboratory Michael G. DeGroote School of Medicine McMaster University, Hamilton, ON, Canada

Edward L. Snyder, MD
Professor, Department of Laboratory Medicine Yale University School of Medicine, Director Blood Bank/Apheresis Service, Yale-New Haven Hospital, New Haven, CT, USA

Martha C. Sola-Visner, MD
Associate Professor of Pediatrics, Harvard Medical School, Harvard University; and Attending Neonatologist, Division of Newborn Medicine, Boston Children's Hospital, Boston, MA, USA

Bjarte G. Solheim, MD, PhD, MHA
Professor Emeritus, Institute of Immunology Oslo University Hospital–Rikshospitalet and University of Oslo, Oslo, Norway

Bryan R. Spencer, MPH
Research Scientist, American Red Cross Dedham, MA, USA

Simon J. Stanworth, MA, FRCP, DPhil, FRCPath
Consultant Haematologist, NHS Blood and Transplant and The National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford University Hospitals, NHS Foundation Trust and the University of Oxford, Oxford, UK

Jill R. Storry, PhD
Blood Group Immunology, Clinical Immunology and Transfusion Medicine, University and Regional Laboratories Region Skåne, Lund University Hospital; and Associate Professor, Division of Hematology and Transfusion Medicine, Department of Laboratory Medicine, Lund University Lund, Sweden

Ronald G. Strauss, MD
Professor Emeritus, Departments of Pathology and Pediatrics, University of Iowa College of Medicine, Iowa City, IA, USA, Associate Medical Director, Life Source/ Institute for Transfusion Medicine, Chicago, IL, USA

James R. Stubbs, MD
Chairman, Division of Transfusion Medicine, Department of Laboratory Medicine and Pathology Mayo Clinic, Rochester, MN, USA

Sumati Sundaram, PhD
Post Doctorate Associate in Cell Biology, Department of Biomedical Engineering, Yale University; Department of Anesthesiology, Yale University School of Medicine New Haven, CT, USA

Miho Teruya, MD, MPH
Postdoctoral Fellow, Department of Hematology/ Oncology, Baylor College of Medicine, Houston, TX USA

Alan T. Tinmouth, MD, MSc (Clin Epi), FRCPC
Assistant Professor, Departments of Medicine, and Laboratory Medicine & Pathology, University of Ottawa; Head, General Hematology and Transfusion Medicine, Division of Hematology, The Ottawa Hospital; and University of Ottawa Centre for Transfusion Research Ottawa Hospital Research Institute Ottawa, ON, Canada

Christopher A. Tormey, MD
Associate Professor, Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT; and Director of Transfusion Medicine Veterans Affairs Medical Center West Haven, CT, USA

Darrell J. Triuzi, MD
Professor of Pathology
Director, Division of Transfusion Medicine
University of Pittsburgh Medical Center
Medical Director
Institute for Transfusion Medicine
Pittsburgh, PA, USA

Marc L. Turner, PhD
Professor, Department of Cellular Therapy, University of Edinburgh; and Medical Director, Scottish National Blood Transfusion Service, Edinburgh, Scotland, UK

Eleftherios C. Vamvakas, MD, PhD
Formerly, Rita and Taft Schreiber Chair in Transfusion Medicine; Professor of Pathology and Director of Clinical Pathology, Department of Pathology
Cedars-Sinai Medical Center Los Angeles, CA, USA

Jos J.M. van Roosmalen, MD, PhD
Professor of International Safe Motherhood and Health Systems, Department of Obstetrics, Leiden University Medical Center, Leiden; and Section of Health Care and Culture, Athena Institute, VU University, Amsterdam
The Netherlands

Ralph R. Vassallo, Jr., MD
EVP/Chief Medical and Scientific Officer
Blood Systems, Inc., Scottsdale AZ, USA and
Adjunct Associate Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA
USA

Marieke B. Veenhof, MD
Senior Resident, Obstetrics and Gynaecology
Department of Obstetrics, Leiden University Medical Center, Leiden, The Netherlands

Elliott Vichinsky, MD
Medical Director, Hematology/Oncology, UCSF Benioff Children's Hospital Oakland, Oakland, CA; and Professor of Pediatrics, University of California San Francisco, San Francisco, CA, USA

Jonathan P. Wallis, BA oxon, MB. BS. lond., FRCP(UK), FRCPath
Consultant Haematologist, Department of Haematology, Freeman Hospital, Newcastle upon Tyne, UK

Theodore E. Warkentin, MD, BSc (Med), FRCPC, FACP, FRCP(Edin)
Professor, Departments of Pathology, Medicine and Molecular Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada

Jonathan H. Waters, MD
Chief, Department of Anesthesiology
Magee-Womens Hospital of UPMC, Professor of Anesthesiology and Bioengineering, University of Pittsburgh, Medical Director, Patient Blood Management Program of UPMC
Pittsburgh, PA, USA

Mark J. Weinstein, PhD
Associate Deputy Director for Science, Office of Blood Research and Review, Center for Biologics Evaluation & Research, US Food and Drug Administration, Silver Spring, MD, USA

Robert Weinstein, MD
Professor, Departments of Medicine and Pathology, and Chief, Division of Transfusion Medicine, University of Massachusetts Medical School; and UMass Memorial Medical Center, Worcester, MA, USA

Connie M. Westhoff, SBB, PhD
Director, Laboratory of Immunohematology and Genomics, New York Blood Center, New York
NY, USA

Johanna C. Wiersum-Osselton, PhD
TRIP National Hemovigilance and Biovigilance Office
Leiden, The Netherlands

Elise Wilcox
Student, Department of Biomedical Engineering
Yale University; Department of Anesthesiology
Yale University School of Medicine, New Haven, CT
USA

Michael Wilson, PhD
Senior Director, Molecular Biology, CSL Behring
Broadmeadows, VIC, Australia

Jeffrey L. Winters, MD
Medical Director, Therapeutic Apheresis Treatment Unit, Mayo Clinic, Rochester, MN, USA

Steven E. Wolf, MD
Professor of Surgery and Chairman for Research
Department of Surgery, Division of Burn/Trauma/Critical Care, University of Texas Southwestern Medical Center, Dallas, TX, USA

Gary M. Woods, MD
Assistant Professor, Department of Pediatrics
Eastern Virginia Medical School, Division of Pediatric Hematology/Oncology, Children's Hospital of the King's Daughters, Norfolk VA, USA

Mark H. Yazer, MD
Professor of Pathology, University of Pittsburgh
Associate Medical Director, Centralized Transfusion Service, Institute for Transfusion Medicine
Pittsburgh, PA, USA

Preface

After an interval of six years, we have again focused on the task of updating *Rossi's Principles of Transfusion Medicine* in order to support the continually evolving disciplines of transfusion medicine, blood banking, and cellular therapies. Many of the trends we identified and covered in the last edition have continued to evolve. More extensive use of molecular techniques, increased focus on hemovigilance and donor vigilance, continued maturation of pathogen inactivation technologies, and advances in cellular therapy are but some examples. Many controversies remain, such as the impact of red cell storage on patient well-being and the best approach to follow for the treatment of severe bleeding, particularly in the acute trauma setting.

As before, we welcome back authors from the prior editions as well as introduce new authors to strategically deal with changes in the field, including as a new editor Dr. Jeffrey McCullough. Keeping abreast of changing technology in publishing, we have provided a web connection for all purchasers of the book—both the print and electronic editions. To keep the size of the book manageable, the full list of numbered references is available on the web. Additionally, after each chapter, authors have provided a short list of major reviews or key articles.

We have made one significant organizational change. We removed the section at the end that was called "Delivery of Transfusion and Transplantation Services." Instead, the first section of the book is titled "Contemporary issues in donation and transfusion." After the historical perspective, a new chapter on patient blood management explores in greater detail than before what has been arguably the most transformative movement in the field since the last edition. Teaching the responsible and cautious use of blood components has long been a major part of the role of the transfusion medicine expert. But, somehow in the last five years, the message has resonated as never before and the resulting decline in blood utilization has revolutionized the business model of community and national blood programs as well as reduced dramatically the frequency of blood shortages in the developed world. Recruitment techniques have been refined so that the right number of donors for the right component with the right blood type at the right time has become more important than total numbers. Of course, we do need to remember that the situation in countries with underdeveloped economies is much different. There, the lack of adequate quantities of safe blood components and transfusion services for lifesaving needs is still all too common.

In this same section, there is a new chapter on the technical aspects of transfusion as well as an updated chapter on collection of blood. In consideration of the increased attention focused on both preventing the acute problem of loss of consciousness after donation and the chronic problem of iron depletion in red cell donors, a new separate chapter on adverse effects of donation has been added. Chapters on hemovigilance and donor vigilance and regulatory oversight complete the section. The latter chapter combines material from several chapters in the prior edition covering quality and regulation from both the manufacturing and hospital perspectives on a global basis.

In the second section on transfusion medicine practice, new data on blood components are added and the restrictive use of red cells is further documented. In addition, the chapters on plasma are expanded given the growth in use of plasma derivatives—a trend opposite to the declining use of most cellular components. The third section on apheresis, transplantation, and new therapies has been expanded to keep up with increased activity, particularly in cell and gene therapy. Section IV is devoted to specialized clinical practice, with coverage of the new approaches to treatment of trauma and massive bleeding. The last section covers the hazards of transfusion. As the "big three" viruses (hepatitis B and C and HIV) have come under better control, that material has been placed in one chapter. A new chapter on testing for pathogens complements an expanded chapter on pathogen reduction to highlight approaches to containing infectious threats. The book concludes with chapters on non-infectious hazards of transfusion.

Our publisher, Wiley-Blackwell, was able to provide full support for the coordination and production of this edition. We appreciate all of their efforts, which they have provided efficiently and with high quality.

As we publish the fifth edition, we simultaneously celebrate both the continuity in the field and the new developments and once again emphasize the teamwork of the transfusion medicine professionals at all levels, including medical specialists in all fields who utilize transfusion medicine, technologists, administrators, nurses, and donors. We hope that a new upcoming generation of transfusion medicine specialists will carry on its proud traditions and bring about exciting innovation.

Most importantly, it is our ability to provide help to the patient—who, as the recipient of transfusion medicine products and services, is better able to extend his or her life, improve the quality of that life, or both—that constantly motivates us to move the field forward throughout the world.

We, as an editorial group, recognize the contribution of our invaluable authors and thank our families, colleagues, employers, teachers, and students for their understanding and support during the intense period of time needed for preparation and execution of this, the fifth edition of *Rossi's Principles of Transfusion Medicine*.

List of abbreviations

2-ME	2-mercaptoethanol
2RBC	double red cell collection
AA	aplastic anemia
AABB	(Not spelled out; originally founded as the American Association of Blood Banks)
AAP	American Academy of Pediatrics
aAPC	artificial antigen presenting cell
AAV	adeno-associated virus
Ab	antibody
ABC	America's Blood Centers
ABLE	Age of Blood Evaluation (trial)
ABT	allogeneic blood transfusion
ACCP	American College of Chest Physicians
ACD	acid–citrate–dextrose
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACh	acetylcholine
AChR	acetylcholine receptor molecule
ACI	anemia of chronic inflammation
ACOG	American College of Obstetricians and Gynecologists
ADCC	antibody-dependent cellular cytotoxicity
ADF	actin depolymerizing factor
ADP	adenosine diphosphate
ADSC	adipose-derived stem cell
AFSA	American Society for Apheresis
AGM	aortogonadomesonephros
AHF	antihemophilic factor
AHG	antihuman globulin
AHRQ	Agency for Healthcare Research and Quality
AHSP	alpha-hemoglobin stabilizing protein
aHUS	atypical hemolytic uremic syndrome
AIDS	acquired immune deficiency syndrome
AIHA	autoimmune hemolytic anemia
AIS	absent iron stores
ALAS2	5-aminolevulinic acid synthase
ALCL	anaplastic large-cell lymphoma
ALK	anterior lamellar keratoplasty
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AMKL	acute megakaryoblastic leukemia
AML	acute myelogenous leukemia
AMP	adenosine monophosphate
AMR	Ashwell–Morell receptor
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic antibody
ANH	acute normovolemic hemodilution
APC	antigen-presenting cell
API	alpha$_1$-proteinase inhibitor
aPCC	activated prothrombin complex concentrate
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ARITI	Age of Red Blood Cell in Premature Infants
ASP	antibody specificity prediction
ASRI	American Society for Reproductive Immunology
Atf4	activating transcription factor-4
ATG	antithymocyte globulin
ATP	adenosine triphosphate
AUC	area under the ROC curve
AvWS	acquired von Willebrand syndrome
BAGP	bicarbonate, adenine, glucose, and phosphate
B-ALL	B-cell acute lymphoblastic leukemia
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
BasoEB	basophilic erythroblast
B-CAM	basal cell adhesion molecule
BDD	B-domain-deleted
BECS	blood establishment computer software
BFU-E(s)	burst-forming unit(s)-erythroid
BFU-MK	MK burst-forming unit
BiKE	bispecific killer engager
BMD	Becker muscular dystrophy
BMP	bone morphogenetic protein
BMSC	bone marrow stem cell
BNP	B-type natriuretic peptide
BOS	bronchiolitis obliterans syndrome
BRN	Blood Regulators Network
BSA	body surface area
BSS	Bernard Soulier syndrome
BTHC	butyryl-tri-hexyl citrate
BVDV	bovine viral diarrhea virus
CABG	coronary artery bypass graft
CAD	cold agglutinin disease
CAEV	arthritis-encephalitis virus of goats
CAFC	cobblestone area-forming cell
CAP	College of American Pathologists
CAR	CXCL12 abundant reticular (cell)
CARS	compensatory anti-inflammatory response syndrome
CAR-T cell	T cell expressing a chimeric antigen receptor
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CCAD	Central Cardiac Audit Database
CCI	corrected count increment
CCPD	complement control protein domain

CDA	congenital dyserythropoietic anemia
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDR	complementarity-determining region
CDRH	Center for Devices and Radiologic Health
CD–P–TS	European Committee on Blood Transfusion
CDSS	clinical decision support software
cffDNA	cell-free fetal DNA
CFR	US Code of Federal Regulations
CFU-GM	progenitor cells with the capacity to generate neutrophils in vitro
CGD	chronic granulomatous disease
cGMP	current good manufacturing practice
CH2-THF	methylenetetrahydrofolate
CH3-THF	methyltetrahydrofolate
CHCM	cell hemoglobin concentration mean
ChLIA	chemiluminescent immunoassay
CHMP	Committee for Medicinal Products for Human Use
CHO-THF	formyltetrahydrofolate
CHr	cellular hemoglobin in reticulocytes
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIDP	chronic inflammatory demyelinating polyneuropathy
CJD	Creutzfeldt–Jakob disease
CLET	cultured limbal epithelial transplantation
CLIA	Clinical Laboratory Improvement Amendments
CM	carboxymethyl
CML	chronic myelogenous leukemia
CMP	common myeloid precursor
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
COBLT	Cord Blood Transplant (study)
COM	All Common Checklist
CPB	cardiopulmonary bypass
CPD	citrate–phosphate–dextrose
CPDA	citrate–phosphate–dextrose–adenine
CPOE	computerized physician order entry
CPSI	Canadian Patient Safety Institute
CRASH-2	Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage trial
CREG	cross-reactive group
CRM	cross-reactive material
CRISPR	clustered regularly interspaced short palindromic repeat
CRPS II	chronic regional pain syndrome type 2
CSA	cyclosporine
CSF	circulating steel factor
CTA	cancer-testis antigen
CTL	cytotoxic T-cell
CVAD	central venous access device
CXCL12	stromal-cell derived factor 1
DAF	decay accelerating factor
DARC	Duffy antigen receptor for chemokines
DART	Danish Registration of Transfusion Accidents
DAT	direct antiglobulin test
DBA	Diamond–Blackfan anemia
DC	dendritic cell
DCASGPR	dendritic cell asialoglycoprotein receptor
DDAVP	desmopressin acetate
DEA	diethyleneamine
DEAE	dietlylaminoethyl
DEHP	diethylhexyl phthalate
DFPP	double-membrane filtration plasmapheresis
DFSD	dry fibrin sealant dressing
DHF	dihydrofolate
DHFR	dihydrofolate reductase
DHSt	dehydrated stomatocytosis
DIC	disseminated intravascular coagulation
DITP	drug-induced immune thrombocytopenia
DMD	Duchenne muscular dystrophy
DMS	demarcation membrane system
dsDNA	double-stranded DNA
dsRNA	double-stranded RNA
DTT	dithiothreitol
DVT	deep vein thrombosis
EACA	ε-aminocaproic acid
EBA	European Blood Alliance
EBI	erythroblastic island
ECBS	Expert Committee on Biological Standardization
ECM	extracellular matrix
ECP	extracorporeal photopheresis
EDQM	European Directorate for the Quality of Medicines
EDTA	ethylenediaminetetraacetic acid
EFIC	exception from informed consent
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMP	erythroblast–macrophage protein
EPO	erythropoietin
EPO-α	erythropoietin alpha
EPO-R	erythropoietin receptor
EEA	European Economic Area
EIA	enzyme immunoassay
EIAV	infectious anemia virus of horses
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERMAP	erythrocyte membrane-associated protein
ESC	embryonic stem cell
ET	essential thrombocythemia
EU	European Union
EUHASS	European Hemophilia Safety Surveillance
EVA	ethylene vinyl acetate
EXM	electronic crossmatch
FACT	Foundation for the Accreditation of Cellular Therapy
FADH	reduced flavin adenine dinucleotide
FAST	focused ultrasonographic survey for trauma
FBS	fetal blood sampling
FCR	fraction of cells remaining
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration
FDAAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act

FDA cGMP	US Food and Drug Administration current good manufacturing practice
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	follicular dendritic cell
FDP	fibrin degradation product
FEIBA	factor VIII inhibitory bypass activity
FEP	free erythrocyte protoporphyrin
FFP	fresh frozen plasma
FGS	focal glomerulosclerosis
FH	familial hypercholesterolemia
FLAER	fluorescent aerolysin
FNAIT	fetal/neonatal alloimmune thrombocytopenia
FNHTR	febrile nonhemolytic transfusion reaction
FT/RA	first-time and reactivated (donors)
G6PD	glucose-6-phosphate dehydrogenase
GABA	γ-amino butyric acid
GAD-65	65-kD isoform of glutamic acid decarboxylase
GAG	glycoslyaminoglycan
GBM	glomerular basement membrane
G-CSF	granulocyte colony-stimulating factor
GDP	guanosine diphosphate
GEN	Laboratory General Checklist
GI	gastrointestinal
GLUT1	glucose transporter 1
GM-CSF	granulocyte macrophage colony-stimulating factor
GMP	good manufacturing practice
GP	glycoprotein
GPA	glycophorin A
GPB	glycophorin B
GPI	glycosylphosphatidylinositol
GPS	Goodpasture syndrome
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSH	glutathione
GSL	glycospingolipid
GSS	Gerstmann–Sträusler–Scheinker (disease)
GTP	guanosine triphosphate
GTX	granulocyte transfusion
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
GWA	genome-wide association
HA	hydroxyapatite
HAM (test)	(Not an abbreviation; named after its creator, Thomas Ham)
HBc	hepatitis B core (antigen)
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBSAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCEC	human corneal endothelial cell
HCT	hematopoietic cell transplant
HCT/P	human cells, tissues, and cellular and tissue-based product
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDFN	hemolytic disease of the fetus and newborn
HDV	hepatitis D virus
HE	hereditary elliptocytosis
HELLP	syndrome of hemolysis, elevated liver enzymes, and low platelet count
HES	hydroxyethyl starch
hESC	human embryonic stem cell
HEV	hepatitis E virus
HFMEA	Healthcare Failure Mode and Effect Analysis
HH	hereditary hemochromatosis
HHV	human herpesvirus
HIF	hypoxia-inducible transcription factor
HIPA	heparin-induced platelet activation assay
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HLA	human leukocyte antigen
HMW	high molecular weight
HO1	heme oxygenase-1
HPC	hematopoietic progenitor cell
HRI	heme-regulated inhibitor
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transfusion
HSV	herpes simplex virus
HTA	health technology assessment
HTLV-I	human T-cell lymphotropic virus, type I
HTLV-II	human T-cell lymphotropic virus, type II
HTR	hemolytic transfusion reaction
HUS	hemolytic uremic syndrome
%HYPOm	percentage of hypochromic mature red blood cells
%HYPOr	percentage of hypochromic red blood cells
IAT	indirect antiglobulin testing
IBCT	incorrect blood component transfused
IBR	intraoperative blood recovery
ICAM4	interstitial cell adhesion molecule-4
ICH	International Conference on Harmonization (of Technical Requirements)
ICH	intracranial hemorrhage
ICU	intensive care unit
IDA	iron-deficiency anemia
IDE	iron-deficient erythropoiesis
IDSA	Infectious Disease Society of America
IDT	individual testing
IFAT	immunofluorescent antibody test
IFN	interferon
IGF1	insulin-like growth factor-1
IgG	immunoglobulin G
IgSF	immunoglobulin superfamily
IHN	International Hemovigilance Network
IL	interleukin
IND	investigational new drug
iNKT	invariant natural killer T cell
IPD	individual-patient data
INR	international normalized ratio
IPFA	International Plasma Fractionation Association
iPSC	induced pluripotent stem cell
IPSS	International Prognostic Scoring System
IQPP	International Quality Plasma Program
IRE	iron-responsive element
IRP	iron regulatory protein

ISBT	International Society of Blood Transfusion
ISTARE	International Surveillance Database for Transfusion Adverse Reactions and Events
ISTH	International Society on Thrombosis and Hemostasis
IT	information technology
ITI	immune tolerance induction
ITP	immune thrombocytopenic purpura
IV	intravenous
IVD	in vitro diagnostic
IVIG	intravenous immunoglobulin
JAK2	Janus tyrosine kinase-2
KIR	killer immunoglobulin-like receptor
KLF1	Krüppel-like factor-1
LAK	lymphokine-activated killer
LCL	lymphoblastoid line
LCR	locus control region
LCT	lymphocytotoxicity
LDL	low-density lipoprotein
LEMS	Lambert–Eaton myasthenic syndrome
LESC	limbal epithelial stem cell
LGL	large granular lymphocyte
LHR	long homologous repeat
LIC	liver iron concentration
LISS	low-ionic-strength saline
LMAN	lectin mannose binding
LMW	low molecular weight
LR	leukocyte-reduced *or* leukoreduction
LSC	limbal stem cell
MAG	myelin-associated glycoprotein
MAHA	microangiopathic hemolytic anemia
MAIPA	monoclonal antibody-specific immobilization of platelet antigens
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase
MART	melanoma antigen recognized by T cells
MBP	myelin basic protein
MCFD	multiple coagulation factor deficiency gene
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP	macrophage chemoattractant protein
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MEP	megakaryocytic-erythroid progenitor
MGSA	melanocyte growth-stimulating activity
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MIRL	membrane inhibitor of reactive lysis
MK	megakaryocyte
MMP	matrix metalloproteinase
MODS	multiple-organ dysfunction syndrome
MOF	multiple-organ failure
MOG	myelin oligodendrocyte glycoprotein
MPP	multipotent progenitor
MPV	mean platelet volume
MRI	magnetic resonance imaging
MSC	mesenchymal stem (or stromal) cell
MTP	massive transfusion protocol
MTX	methotrexate
NAAT	nucleic acid amplification testing
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NAIT	neonatal alloimmune thrombocytopenia
NAPTT	non-activated partial thromboplastin time
NAT	nucleic acid testing
NATA	Network for Advancement of Transfusion Alternatives
NBCUS	(AABB) National Blood Collection and Utilization Survey
NCA	national competent authority
NCI	National Cancer Institute
NET	neutrophil extracellular trap
NHLBI	National Heart, Lung, and Blood Institute
NIBSC	National Institute of Biological Standards and Control
NICU	neonatal intensive care unit
NIH	National Institutes of Health
NOD	non-obese diabetic
NPO	*nil per os*
NSAID	nonsteroidal anti-inflammatory drug
NTBI	non-transferrin-bound iron
NYHA	New York Heart Association
OBI	occult hepatitis B infection
OBRR	Office of Blood Research and Review
OCS	open canalicular system
OHI	occult hepatitis infection
OHSt	overhydrated stomatocytosis
OMCL	Official Medicines Control Laboratory
OR	odds ratio
OrthoEB	orthochromatic erythroblast
PAI-1	plasminogen activator inhibitor type 1
PAIgG	platelet-associated IgG
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PAS	platelet additive solution
PASSPORT	Post Approval Surveillance Study of Platelet Outcomes, Release Tested (protocol)
PBM	patient blood management
PBMC	peripheral blood mononuclear cell
PBPC	peripheral blood progenitor cell
PBR	postoperative blood recovery
PBSC	peripheral blood stem cell
PC	platelet concentrate
PCAM	platelet-endothelial cell adhesion molecule-1
PCC	prothrombin complex concentrate
PCH	paroxysmal cold hemoglobinuria
PCL	polycaprolactone
PCP	*Pneumocystis carinii*
PCR	polymerase chain reaction
PDMP	plasma-derived medicinal product
PEG	polyethylene glycol
PEG-rHuMGDF	pegylated recombinant human mega karyocyte growth and development factor
PEI	Paul Ehrlich Institute
PF	platelet factor
PF24	24-hour frozen plasma

PFA-100	platelet function analyzer 100
PfEMP	*Plasmodium falciparum* erythrocyte membrane protein
PGA	polyglycolic acid
PhEur	European Pharmacopeia
PHSA	Public Health Service Act
PICC	peripherally inserted central catheter
PIC/S	Pharmaceutical Inspection Co-operation Scheme and Pharmaceutical Inspection Convention
PIG-A	phosphatidylinositol glycan class A
PIVKA	proteins induced in vitamin K absence or antagonism
PK	penetrating keratoplasty
PKD	pyruvate kinase deficiency
PLA	polylactic acid
PLADO	Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenia Patients
PLGA	polylactic-co-glycolic acid
PMMA	polymethylmethacrylate
PMN	neutrophil
PNH	paroxysmal nocturnal hemoglobinuria
PNM	polymorphonuclear
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (syndrome)
POISE	Perioperative Ischemic Evaluation (trial)
PolyEB	polychromatophilic erythroblast
PPH	postpartum hemorrhage
PPi	pyrophosphate
PPTA	Plasma Protein Therapeutics Association
PRA	panel-reactive antibody
PRAC	Pharmacovigilance Risk Assessment Committee
ProEB	pro-erythroblast
PRP	platelet-rich plasma
PRPP	phosphoribosyl pyrophosphate
PRV	pseudorabies virus
PS	phosphatidylserine
PSA	prostate-specific antigen
PSGL1	platelet sialoglycoprotein ligand-1
PSO	patient safety organization
PT	prothrombin time
PTFE	polytetrafluoroethylene
PTLD	posttransplant lymphoproliferative disease
PTP	posttransfusion purpura
PTR	platelet transfusion refractoriness
PT/PTT	prothrombin time and partial thromboplastin time
PUP	previously untreated patient
PVC	polyvinyl chloride
pVHL	von Hippel–Lindau protein
QA	quality assurance
QAE	quaternary amino ethyl
QALY	quality-adjusted life year
QC	quality control
RA	rheumatoid arthritis
RANTES	regulated on activation, normal T-cell expressed and secreted
RBC	red blood cell
RBC(s), LR	red blood cell(s), leukocytes reduced
RBM15	RNA binding motif protein 15
RCAS1	receptor-binding cancer antigen expressed on SiSo cells
RECESS	Red Cell Duration Study
REF	febrile nonhemolytic transfusion reaction
RFLP	restriction fragment length polymorphism
RhAG	Rh-associated glycoprotein
RhIG	Rh immune globulin
RING	Safety and Effectiveness of Granulocyte Transfusion in Resolving Infection in People with Neutropenia (study)
RIPA	radioimmunoprecipitation assay
RIR	replication-incompetent retrovirus
RISE	REDS-II Donor Iron Status Evaluation
RLS	reporting and learning systems
ROC	receiver operating characteristic
ROS	reactive oxygen species
RP	reticulated platelet
RSV	respiratory syncytial virus
SAA	severe aplastic anemia
SABM	Society for the Advancement of Blood Management
SAG	saline, adenine, and glucose
SAG-M	saline, adenine, glucose, and mannitol
SCD	sickle cell disease
SCF	stem cell factor
scFv	single-chain variable fragment
SCL	stem cell leukemia
SCN	severe congenital neutropenia
sc-TPA	single-chain tissue plasminogen activator
sc-UPA	single-chain urokinase plasminogen activator
S/D	solvent and detergent (*or* solvent–detergent)
SDS-PAGE	sodium dodecyl sulfate–polyacrylamide gel electrophoresis
serpin	serine protease inhibitor
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SMC	smooth muscle cell
SNP	single nucleotide polymorphism
SoGAT	International Working Group on the Standardization of Genomic Amplification Techniques for the Virological Safety Testing of Blood and Blood Products
SOP	standard operating procedure
SP	sulfopropyl
SPRCA	solid-phase red cell adherence
SPS	stiff-person syndrome
SQUID	superconducting quantum interference device
SRA	serotonin release assay
SRF	serum response factor
ssDNA	single-stranded DNA
SSOPH	sequence-specific oligonucleotide probe hybridization
ssRNA	single-stranded RNA
STAT5	signal transduction and activator of transcription-5
sTfR	soluble transferrin receptor
TACO	transfusion-associated circulatory overload
TAD	transfusion-associated dyspnea

TAFI	thrombin-activatable fibrinolysis inhibitor
TA-GVHD	transfusion-associated graft-versus-host disease
TALENS	transcription activator–like effector nucleases
TA-MC	transfusion-associated microchimerism
TAMMv	timed average mean maximum velocity
TAPS	twin anemia–polycythemia sequence
TCD	transcranial Doppler
TCP	tricalcium phosphate
tc-TPA	two-chain tissue plasminogen activator
tc-UPA	two-chain urokinase plasminogen activator
TEE	thromboembolic event
TEG	thromboelastography
TEVG	tissue-engineered vascular graft
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
Th	T helper (cell)
THA	total hip arthroplasty
THF	tetrahydrofolate
TI	tincture of iodine
TIL	tumor-infiltrating lymphocyte
TLR	toll-like receptor
TM	thalassemia major
TMA	thrombotic microangiopathy
TMAA	thrombotic micro-angiopathic anemia
TNC	total nucleated cell count
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TOP	Transfusion of Prematures
TOTM	triethyl hexyl trimellitate
tPA	tissue plasminogen activator
TPMT	thiopurine methyltransferase
TPO	thrombopoietin
TRAIL	TNF-related apoptosis-inducing ligand
TRALI	transfusion-related acute lung injury
TRAP	Trial to Reduce Alloimmunization to Platelets
TRICC	Transfusion Requirements in Critical Care
TRICK	transfusion-related inhibition of cytokines
TRIM	transfusion-related immunomodulation
TRS	(WHO) Technical Report Series
TSO	Transfusion Safety Office
TT	thrombin time
TTI	transfusion-transmissible infection
TTP	thrombotic thrombocytopenic purpura
TTTS	twin-to-twin transfusion syndrome
TWEAK	TNF-like weak inducer of apoptosis
TXA	tranexamic acid
UDHQ	Uniform Donor History Questionnaire
ULR	universal leukocyte reduction
UTR	untranslated region
VATS	Viral Activation by Transfusion Study
VCAM1	vascular cell adhesion molecule 1
vCJD	variant Creutzfeldt–Jakob disease
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VGKC	voltage-gated potassium channel
VKA	vitamin K antagonist
VLBW	very-low-birthweight
VLDL	very-low-density lipoprotein
VMV	visna-maedi virus of sheep
VWD	von Willebrand disease
WAIHA	warm-type autoimmune hemolytic anemia
WAS	Wiskott–Aldrich syndrome
WBC	white blood cell
WBD	whole blood derived
WBIT	wrong blood in tube
WCC	WHO Collaborating Center
WFH	World Federation of Hemophilia
WHIM (syndrome)	warts, hypogammaglobulinemia, infections, and myelokathexis
WHO	World Health Organization
ZFN	zinc finger nuclease
ZnPP	zinc protoporphyrin

About the companion website

This book has a companion website:

www.wiley.com/go/simon/transfusion

The website features the figures from the book, the full text of the book, and all references.

The password for the website is the first word of Chapter 2. Please use all lowercase.

CHAPTER 1

Transfusion in the new millennium

Ennio C. Rossi[1] & Toby L. Simon[2]

[1]Northwestern University School of Medicine, Chicago, IL, USA
[2]Plasma Product Development and CSL Plasma, CSL Behring, King of Prussia, PA; and Department of Pathology, University of New Mexico School of Medicine, Albuquerque, NM, USA

Prehistoric man left drawings of himself pierced by arrows.[1] This means he was as aware of blood as he was of his own limbs. The flint implements he used as tools and weapons distinguished him from other creatures and contributed to the violence of his era. As he hunted food and fought enemies, he observed bleeding and the properties of blood. A cut, received or inflicted, yielded a vivid red color. If the cut was shallow, there was little blood. But if the cut was deep, a red torrent flowing from the stricken victim quickly led to death, with shed blood congealed and darkening in the sun. Fatal hemorrhage was commonplace. Nonetheless, the sight must have been fearful and possibly existential as life flowed red out of the body of an enemy or a wounded animal.[2] It is no wonder, then, that at the dawn of recorded history, blood was already celebrated in religious rites and rituals as a life-giving force.

The cultural expressions of primitive and ancient societies, although separated by time or space, can be strikingly similar. Whether these expressions emerged independently or were diffused about the world by unknown voyagers will probably always remain clouded in mystery.[2] Nonetheless, there is a common thread in the ancient rituals that celebrate blood as a mystical vital principle. In Leviticus 17:11, "the life of the flesh is in the blood," and the Chinese Neiching (ca. 1000 BC) claims the blood contains the soul.[2] Pre-Columbian North American Indians bled their bodies "of its greatest power" as self-punishment,[3] Egyptians took blood baths as a recuperative measure, and Romans drank the blood of fallen gladiators in an effort to cure epilepsy.[4] The Romans also practiced a ceremony called taurobolium—a blood bath for spiritual restoration. A citizen seeking spiritual rebirth descended into a pit, or *fossa sanguinis*. Above him on a platform, a priest sacrificed a bull, and the animal's blood cascaded down in a shower upon the beneficiary. Then, in a powerful visual image, the subject emerged up from the other end of the pit, covered with blood and reborn.[1]

The legend of Medea and Aeson taken from Ovid's *Metamorphoses* and quoted in Bulfinch's *Mythology* [5] also ascribed rejuvenating powers to blood. Jason asked Medea to "take some years off his life and add them to those of his father Aeson." Medea, however, pursued an alternative course. She prepared a cauldron with the blood of a sacrificed black sheep. To this, she added magic herbs, hoarfrost gathered by moonlight, the entrails of a wolf, and many other things "without a name." The boiling cauldron was stirred with a withered olive branch, which became green and full of leaves and young olives when it was withdrawn. Seeing that all was ready,

> Medea cut the throat of the old man and let out all his blood, and poured into his mouth and into his wound the juices of her cauldron. As soon as he had imbibed them, his hair and beard laid by their whiteness and assumed the blackness of youth; his paleness and emaciation were gone; his veins were full of blood, his limbs of vigour and robustness. Aeson is amazed at himself and remembers that such as he now is, he was in his youthful days, 40 years before.

This legend seems to echo the apocryphal story of Pope Innocent VIII, who is said to have received the blood of three young boys in 1492 while on his deathbed. As the story goes, a physician attempted to save the pope's life by using blood drawn from three boys 10 years of age, all of whom died soon thereafter. Some 19th-century versions of this tale suggest the blood was transfused. However, earlier renditions more plausibly suggest that the blood was intended for a potion to be taken by mouth. In any event, there is no evidence the pope actually received any blood in any form.[6,7]

The folklore that flowed with blood was not accompanied by a great deal of accurate information. The ancient Greeks believed that blood formed in the heart and passed through the veins to the rest of the body, where it was consumed. Arteries were part of an independent system transporting air from the lungs. Although Erasistratos (circa 270 BC) had imagined the heart as a pump, his idea was ahead of its time. As long as veins and arteries were dead-end channels transporting blood and air, there was little need for a pump in the system. Although Galen (131–201 AD) finally proved that arteries contain blood, communication with the venous system was not suspected. Blood, formed in the liver, merely passed through the blood vessels and heart on its way to the periphery.[1] These teachings remained in place for 1400 years until they were swept away in 1628 by Harvey's discovery of the circulation.

The realization that blood moved in a circulating stream opened the way to experiments on vascular infusion. In 1642, George von Wahrendorff injected wine[8]—and, in 1656, Christopher Wren and Robert Boyle injected opium and other drugs[9]— intravenously into dogs. The latter studies, performed at Oxford, were the inspiration for Richard Lower's experiments in animal transfusion.

The first animal transfusion

Richard Lower (1631–1691) was a student at Oxford when Christopher Wren and Robert Boyle began their experiments on infusion. In due course, Lower joined their scientific group and studied the

Rossi's Principles of Transfusion Medicine, Fifth Edition. Edited by Toby L. Simon, Jeffrey McCullough, Edward L. Snyder, Bjarte G. Solheim, and Ronald G. Strauss.

intravenous injection of opiates, emetics, and other substances into living animals.[10] In time, the transfusion of blood itself became the objective. The announcement of the first successful transfusion, performed by Richard Lower at Oxford in February 1665, was published on November 19, 1666, in the *Philosophical Transactions of the Royal Society* in a short notation titled, "The Success of the Experiment of Transfusing the Blood of One Animal into Another."[11] The entire notation is as follows:[11]

> This experiment, hitherto look'd upon to be of an almost insurmountable difficulty, hath been of late very successfully perform'd not only at Oxford, by the directions of that expert anatomist Dr. Lower, but also in London, by order of the R. Society, at their publick meeting in Gresham Colledge: the Description of the particulars whereof, and the Method of Operation is referred to the next opportunity.

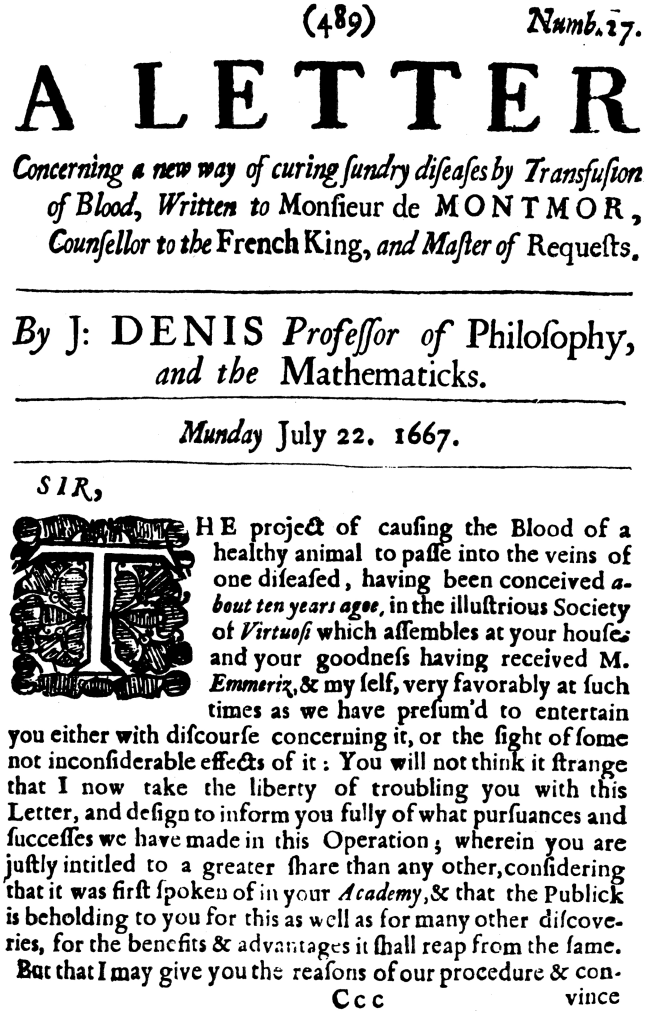
The December 17, 1666, issue of the *Transactions* contained the full description as promised.[12] It was taken from a letter[13] written by Lower to Robert Boyle on July 6, 1666, in which Lower described direct transfusion from the carotid artery of one dog to the jugular vein of another. After describing the insertion of quills into the blood vessels of the donor and recipient dogs, Lower wrote:[13]

> When you have done this you may lay the dogs on their side and fasten them densely together as best you may to insure the connection of the two quills. Quickly tighten the noose around the neck of the receiving animal as in venasection, or at all events compress the vein on the opposite side of the neck with your finger, then take out the stopper and open the upper jugular quill so that while the foreign blood is flowing into the lower quill, the animal's own blood flows out from the upper into suitable receptacles—until at last the second animal, amid howls, faintings, and spasms, finally loses its life together with its vital fluid.
>
> When the tragedy is over, take both quills out of the jugular vein of the surviving animal, tie tightly with the former slipknots, and divide the vein. After the vessel has been divided, sew up the skin, slacken the cords binding the dog, and let it jump down from the table. It shakes itself a little, as though aroused from sleep, and runs away lively and strong, more active and vigorous perhaps, with the blood of its fellow than its own.

These studies inevitably led to the transfusion of animal blood to humans. In England, this occurred on November 23, 1667, when Lower and Edmund King transfused sheep blood into a man named Arthur Coga.[14] Described by Samuel Pepys as "a little frantic," Coga was paid 20 shillings to accept this transfusion, with the expectation that it might have a beneficial "cooling" effect. One week later, Coga appeared before the Society and claimed to be a new man, although Pepys concluded he was "cracked a little in the head."[13] However, this was not the first transfusion performed in a human. The credit for that accomplishment belongs to Jean-Baptiste Denis (1635–1704), who had performed the first human transfusion several months earlier in Paris.

The first animal-to-human transfusion

The founding of the Royal Society in London in 1662 was followed in 1666 by the establishment of the Academie des Sciences in Paris under the patronage of King Louis XIV. The new Academie reviewed the English reports on transfusion with great interest. Denis probably read of Lower's experiments in the *Journal des Savants* on January 31, 1667, and he began his own studies approximately one month later.[15,16] The first human transfusion was then performed on June 15, 1667, when Denis administered the blood of a lamb to a 15-year-old boy (Figure 1.1).



(489) Numb. 27.

A LETTER

Concerning a new way of curing ſundry diſeaſes by Tranſfuſion of Blood, Written to Monſieur de MONTMOR, *Counſellor to the* French King, *and Maſter of* Requeſts.

By J: DENIS *Profeſſor of* Philoſophy, *and the* Mathematicks.

Munday July 22. 1667.

SIR,

THE project of cauſing the Blood of a healthy animal to paſſe into the veins of one diſeaſed, having been conceived *about ten years agoe*, in the illuſtrious Society of *Virtuoſi* which aſſembles at your houſe: and your goodneſs having received M. *Emmeriz*, & my ſelf, very favorably at ſuch times as we have preſum'd to entertain you either with diſcourſe concerning it, or the ſight of ſome not inconſiderable effects of it: You will not think it ſtrange that I now take the liberty of troubling you with this Letter, and deſign to inform you fully of what purſuances and ſucceſſes we have made in this Operation; wherein you are juſtly intitled to a greater ſhare than any other, conſidering that it was firſt ſpoken of in your *Academy*, & that the Publick is beholding to you for this as well as for many other diſcoveries, for the benefits & advantages it ſhall reap from the ſame. But that I may give you the reaſons of our procedure & con-

Ccc vince

Figure 1.1 The first human transfusion. Source: Denis (1967). [17]

Although discovery of the circulation had suggested the idea of transfusion, indications for the procedure remained uninformed. Transfusion was still thought to alter behavior and possibly achieve rejuvenation. The blood of young dogs made old dogs seem frisky; the blood of lions was proposed as a cure for cowardice; and, five months later, Arthur Coga would receive a transfusion of sheep blood because of its presumed "cooling" effect. Denis used animal blood for transfusion because he thought it was "less full of impurities":[17]

> Sadness, Envy, Anger, Melancholy, Disquiet and generally all the Passions, are as so many causes which trouble the life of man, and corrupt the whole substance of the blood: Whereas the life of Brutes is much more regular, and less subject to all these miseries.

It is thus ironic that the symptoms of the first transfusion recipient may have been explained in part by profound anemia; the single transfusion of lamb blood may have produced temporary amelioration owing to increased oxygen transport. Denis described the case as follows:[17]

> On the 15 of this Moneth, we hapned upon a Youth aged between 15 and 16 years, who had for above two moneths bin tormented with a contumacious and violent fever, which obliged his Physitians to bleed him 20 times, in order to asswage the excessive heat.

> Before this disease, he was not observed to be of a lumpish dull spirit, his memory was happy enough, and he seem'd chearful and nimble enough in body; but since the violence of this fever, his wit seem'd wholly sunk, his memory perfectly lost, and his body so heavy and drowsie that he was not fit for anything. I beheld him fall asleep as he sate at dinner, as he was eating his Breakfast, and in all occurrences where men seem most unlikely to sleep. If he went to bed at nine of the clock in the Evening, he needed to be wakened several times before he could be got to rise by nine the next morning, and he pass'd the rest of the day in an incredible stupidity.
>
> I attributed all these changes to the great evacuations of blood, the Physitians had been oblig'd to make for saving his life.

Three ounces of the boy's blood were exchanged for 9 ounces of lamb arterial blood. Several hours later the boy arose, and "for the rest of the day, he spent it with much more liveliness than ordinary." Thus the first human transfusion, which was heterologous, was accomplished without any evident unfavorable effect.

This report stimulated a firestorm of controversy over priority of discovery.[18,19] The letter by Denis was published in the *Transactions* on July 22, 1667, while the editor, Henry Oldenburg, was imprisoned in the Tower of London. Oldenburg, following some critical comments concerning the Anglo-Dutch War then in progress (1665–1667), had been arrested under a warrant issued June 20, 1667. After his release 2 months later, Oldenburg returned to his editorial post and found the letter published in his absence. He took offense at Denis's opening statement, which claimed that the French had conceived of transfusion "about ten years agoe, in the illustrious Society of Virtuosi" (Figure 1.1). This seemed to deny the English contributions to the field. Oldenburg cited these omissions in an issue of the *Transactions* published September 23, 1667, "for the Months of July, August, and September." By numbering this issue 27 and beginning pagination with 489, Oldenburg attempted to suppress the letter by Denis.[18] However, as is evident, this did not ultimately succeed. Nonetheless, subsequent events created even greater difficulties for Denis.

Although the first two subjects who underwent transfusion by Denis were not adversely affected, the third and fourth recipients died. The death of the third subject was easily attributable to other causes. However, the fourth case initiated a sequence of events that put an end to transfusion for 150 years.

Anthony du Mauroy was a 34-year-old man who suffered from intermittent bouts of maniacal behavior. On December 19, 1667, Denis and his assistant Paul Emmerez removed 10 ounces of the man's blood and replaced it with 5 or 6 ounces of blood from the femoral artery of a calf. Failing to note any apparent improvement, they repeated the transfusion 2 days later. After the second transfusion, du Mauroy experienced a classic transfusion reaction:[20]

> His pulse rose presently, and soon after we observ'd a plentiful sweat over all his face. His pulse varied extremely at this instant, and he complain'd of great pains in his kidneys and that he was not well in his stomach.

Du Mauroy fell asleep at about 10 o'clock in the evening. He awoke the following morning and "made a great glass full of urine, of a colour as black, as if it had been mixed with the soot of chimneys."[20] Two months later, the patient again became maniacal, and his wife again sought transfusion therapy. Denis was reluctant but finally gave in to her urgings. However, the transfusion could not be accomplished, and du Mauroy died the next evening.

The physicians of Paris strongly disapproved of the experiments in transfusion. Three of them approached du Mauroy's widow and encouraged her to lodge a malpractice complaint against Denis. She instead went to Denis and attempted to extort money from him in return for her silence. Denis refused and filed a complaint before the Lieutenant in Criminal Causes. During the subsequent hearing, evidence was introduced to indicate that Madame du Mauroy had poisoned her husband with arsenic. In a judgment handed down at the Chatelet in Paris on April 17, 1668, Denis was exonerated, and the woman was held for trial. The court also stipulated "that for the future no Transfusion should be made upon any Human Body but by the approbation of the Physicians of the Parisian Faculty."[21] At this point, transfusion research went into decline, and within 10 years it was prohibited in both France and England.

The beginnings of modern transfusion

After the edict that ended transfusion in the 17th century, the technique lay dormant for 150 years. Stimulated by earlier experiments by Leacock, transfusion was "resuscitated" and placed on a rational basis by James Blundell (1790–1877), a London obstetrician who had received his medical degree from the University of Edinburgh.[22] Soon after graduation, Blundell accepted a post in physiology and midwifery at Guy's Hospital. It was there that he began the experiments on transfusion that led to its rebirth. The frequency of postpartum hemorrhage and death troubled Blundell. In 1818, he wrote:[23]

> A few months ago I was requested to visit a woman who was sinking under uterine hemorrhage. . . . Her fate was decided, and notwithstanding every exertion of the medical attendants, 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.

This opening statement introduced Blundell's epoch-making study titled "Experiments on the Transfusion of Blood by the Syringe"[23] (see Figure 1.2). Blundell described in detail a series of animal

EXPERIMENTS

ON THE

TRANSFUSION OF BLOOD

BY THE

SYRINGE.

By JAMES BLUNDELL, M.D.

LECTURER ON PHYSIOLOGY AT GUY'S HOSPITAL.

COMMUNICATED

By MR. CLINE.

Read Feb. 3, 1818.

Figure 1.2 The beginnings of modern transfusion. Source: Blundell (1818). [23]

experiments. He demonstrated that a syringe could be used effectively to perform transfusion, that the lethal effects of arterial exsanguination could be reversed by the transfusion of either venous or arterial blood, and that the injection of 5 drams (20 cc) of air into the veins of a small dog was not fatal but transfusion across species ultimately was lethal to the recipient.[23] Thus, Blundell was the first to state clearly that only human blood should be used for human transfusion. The latter conclusion was confirmed in France by Dumas and Prevost, who demonstrated that the infusion of heterologous blood into an exsanguinated animal produced only temporary improvement and was followed by death within 6 days.[24] These scientific studies provided the basis for Blundell's subsequent efforts in clinical transfusion.

The first well-documented transfusion with human blood took place on September 26, 1818.[25] The patient was an extremely emaciated man in his mid-thirties who had pyloric obstruction caused by carcinoma. He received 12 to 14 ounces of blood in the course of 30 or 40 minutes. Despite initial apparent improvement, the patient died two days later. Transfusion in the treatment of women with postpartum hemorrhage was more successful. In all, Blundell performed 10 transfusions, of which five were successful. Three of the unsuccessful transfusions were performed on moribund patients, the fourth was performed on a patient with puerperal sepsis, and the fifth was performed on the aforementioned patient with terminal carcinoma. Four of the successful transfusions were given for postpartum hemorrhage, and the fifth was administered to a boy who bled after amputation.[22] Blundell also devised various instruments for the performance of transfusion. They included an "impellor," which collected blood in a warmed cup and "impelled" the blood into the recipient via an attached syringe, and a "gravitator"[26] (Figure 1.3), which received blood and delivered it by gravity through a long vertical cannula.

The writings of Blundell provided evidence against the use of animal blood in humans and established rational indications for transfusion. However, the gravitator (Figure 1.3) graphically demonstrated the technical problems that remained to be solved. Blood from the donor, typically the patient's husband, flowed into a funnel-like device and down a flexible cannula into the patient's vein "with as little exposure as possible to air, cold and inanimate surface."[25] The amount of blood transfused was estimated from the amount spilled into the apparatus by the donor. In this clinical atmosphere, charged with apprehension and anxiety, the amount of blood issuing from a donor easily could be overstated. Clotting within the apparatus then ensured that only a portion of that blood actually reached the patient. Thus, the amount of blood actually transfused may have been seriously overestimated. This may explain the apparent absence of transfusion reactions. Alternatively, reactions may have been unrecognized. Patients who underwent transfusion frequently were agonal. As Blundell stated, "It seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins."[26] Under these circumstances, "symptoms" associated with an "unsuccessful" transfusion might be ascribed to the agonal state rather than the transfusion itself. For a time, the problem of coagulation during transfusion was circumvented by the use of defibrinated blood. This undoubtedly increased the amount of blood actually transfused. However, there were numerous deaths. Interestingly, these deaths were attributed to intravascular coagulation when in actuality they were probably fatal hemolytic reactions caused by the infusion of incompatible blood.[27]

Vol. II.] LONDON, SATURDAY, JUNE 13. [1828-9.

OBSERVATIONS
ON
TRANSFUSION OF BLOOD.

By Dr. Blundell.

*With a Description of his Gravitator.**

States of the body really requiring the infusion of blood into the veins are probably rare; yet we sometimes meet with cases in which the patient must die unless such operation can be performed; and still more frequently with cases which seem to require a supply of blood, in order to prevent the ill health which usually arises from large losses of the vital fluid, even when they do not prove fatal.

* The instrument is manufactured by Messrs. Maw, 55, Aldermanbury.

In the present state of our knowledge respecting the operation, although it has not been clearly shown to have proved fatal in any one instance, yet not to mention possible, though unknown risks, inflammation of the arm has certainly been produced by it on one or two occasions; and therefore it seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins.

The object of the Gravitator is, to give help in this last extremity, by transmitting the blood in a regulated stream from one individual to another, with as little exposure as may be to air, cold, and inanimate surface; ordinary venesection being the only operation performed on the person who emits the blood; and the insertion of a small tube into the vein usually laid open in bleeding, being all the operation which it is necessary to execute on the person who receives it.

The following plate represents the whole apparatus connected for use and in action:—

Tab. 1.

No. 302. Y

Figure 1.3 Blundell's gravitator. Source: Blundell (1828). [26]

Transfusion at the end of the 19th century, therefore, was neither safe nor efficient. The following description, written in 1884, illustrates this point:[28]

> Students, with smiling faces, are rapidly leaving the theatre of one of our metropolitan hospitals. The most brilliant operator of the day has just performed immediate transfusion with the greatest success. By means of a very beautiful instrument, the most complex and ingenious that modern science has yet produced, a skilful surgeon has transfused half a pint, or perhaps a pint, of blood from a healthy individual to a fellow creature profoundly collapsed from the effects of severe hemorrhage. Some little difficulty was experienced prior to the operation, as one of the many stop-cocks of the transfusion apparatus was found to work stiffly; but this error was quickly rectified by a mechanic in attendance. Towards the close of the operation the blood-donor, a powerful and heavy young man, swooned. Two porters carried him on a stretcher into an adjoining room.

In the latter half of the 19th century, there were many attempts to render transfusion a more predictable and less arduous procedure. In 1869, Braxton-Hicks,[29] using blood anticoagulated with phosphate solutions, performed a number of transfusions on women with obstetric bleeding. Many of the patients were in extremis, and ultimately all died. Unfortunately, a detailed description of terminal symptoms was not provided.[29] Some investigators attempted to rejuvenate animal-to-human transfusion, and Oscar Hasse persisted in this approach despite disastrous results. Studies by Emil

Ponfick and by Leonard Landois finally put an end to this practice. Ponfick, in carefully controlled studies, confirmed the lethality of heterologous transfusion and identified the resulting hemoglobinuria along with its donor erythrocyte source. Landois documented the poor results of animal-to-human transfusion and demonstrated the lysis of sheep erythrocytes by human serum in vitro.[8]

Frustration with blood as a transfusion product led to even more bizarre innovations. From 1873 to 1880, cow, goat, and even human milk was transfused as a blood substitute.[30] The rationale derived from an earlier suggestion that the fat particles of milk could be converted into blood cells. Milk transfusion was particularly popular in the United States,[30] where the practice of animal-to-human transfusion was recorded as late as 1890.[31] Fortunately, these astonishing practices were discontinued when saline solutions were introduced as "a life-saving measure" and "a substitute for the transfusion of blood."[32] A passage from an article written by Bull in 1884[32] is particularly instructive:

> The danger from loss of blood, even to two-thirds of its whole volume, lies in the disturbed relationship between the calibre of the vessels and the quantity of the blood contained therein, and not in the diminished number of red blood-corpuscles; and. . . . This danger concerns the volume of the injected fluids also, it being a matter of indifference whether they be albuminous or containing blood corpuscles or not.

Mercifully, volume replacement with saline solutions deflected attention from the unpredictable and still dangerous practice of blood transfusion. Accordingly, transfusions were abandoned until interest was rekindled by the scientific and technical advances of the early 20th century.

The 20th century

The 20th century was ushered in by a truly monumental discovery. In 1900, Karl Landsteiner (1868–1943) observed that the sera of some persons agglutinated the red blood cells of others. This study, published in 1901 in the *Wiener Klinische Wochenschrift* [33] (Figure 1.4), showed for the first time the cellular differences in individuals from the same species. In his article, Landsteiner wrote:[34]

> In a number of cases (Group A) the serum reacts on 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 A and B, while the corpuscles of C will not be influenced by the sera of A and B. The corpuscles are naturally apparently insensitive to the agglutinins which exist in the same serum.

With the identification of blood groups A, B, and C (subsequently renamed group O) by Landsteiner and of group AB by Decastello and Sturli,[35] the stage was set for the performance of safe transfusion. For this work, Landsteiner somewhat belatedly received the Nobel Prize in 1930. But even that high recognition does not adequately express the true magnitude of Landsteiner's discovery. His work was like a burst of light in a darkened room. He gave us our first glimpse of immunohematology and transplantation biology and provided the tools for important discoveries in genetics, anthropology, and forensic medicine. Viewed from this perspective, the identification of human blood groups is one of only a few scientific discoveries of the 20th century that changed all of our lives.[34] Yet the translation of Landsteiner's discovery into transfusion practice took many years.

At the turn of the 20th century, the effective transfer of blood from one person to another remained a formidable task. Clotting, still uncontrolled, quickly occluded transfusion devices and frustrated most efforts. In 1901, the methods used in transfusion were too primitive to demonstrate the importance of Landsteiner's discovery. Indeed, the study of in vitro red cell agglutination may have seemed rather remote from the technical problems that demanded attention. An intermediate step was needed before the importance of Landsteiner's breakthrough could be perceived and the appropriate changes could be incorporated into practice. This process was initiated by Alexis Carrel (1873–1944), another Nobel laureate, who developed a surgical procedure that allowed direct transfusion through an arteriovenous anastomosis.

Carrel[36] introduced the technique of end-to-end vascular anastomosis with triple-threaded suture material. This procedure brought the ends of vessels in close apposition and preserved luminal continuity, thus avoiding leakage or thrombosis. This technique paved the way for successful organ transplantation and brought Carrel the Nobel Prize in 1912. It was also adapted by Carrel[37] and others[38,39] to the performance of transfusion. Crile[38] introduced the use of a metal tube to facilitate placement of sutures, and Bernheim[39] used a two-piece cannula to unite the artery to the vein (Figure 1.5). Because all of these procedures usually culminated in the sacrifice of the two vessels, they were not performed frequently. Direct transfusion was also fraught with danger. In a passage written two decades later, the procedure was recalled in the following manner:[40]

> The direct artery to vein anastomosis was the best method available but was often very difficult or even unsuccessful. And, what was almost as bad, one never knew how much blood one had transfused at any moment or when to stop (unless the donor collapsed). (I remember one such collapse in which the donor almost died—and the surgeon needed to be revived.)

Aus dem pathologisch-anatomischen Institute in Wien.

Ueber Agglutinationserscheinungen normalen menschlichen Blutes.

Von Dr. Karl Landsteiner, Assistenten am pathologisch-anatomischen Institute.

Figure 1.4 Landsteiner's description of blood groups. Source: Landsteiner (1901). [33]

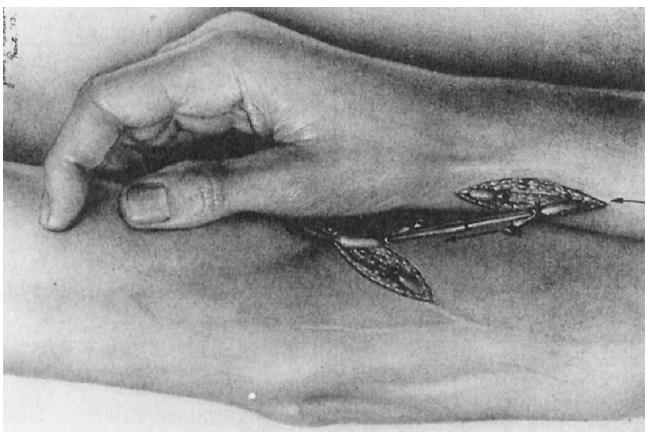


Figure 1.5 Direct transfusion by means of arteriovenous anastomosis through the two-pieced cannula of Bernheim. Source: Bernheim (1917). [39]

A CASE OF FATAL HEMOLYSIS FOLLOWING DIRECT TRANSFUSION OF BLOOD BY ARTERIOVENOUS ANASTOMOSIS.*

WILLIAM PEPPER, M.D.
Instructor in Medicine, University of Pennsylvania.
AND
VERNER NISBET, M.D.
Assistant Instructor in Medicine, University of Pennsylvania; Assistant Director of the William Pepper Laboratory of Clinical Medicine.
PHILADELPHIA.

Figure 1.6 Report of a fatal transfusion reaction. Source: Pepper and Nisbet (1907). [41]

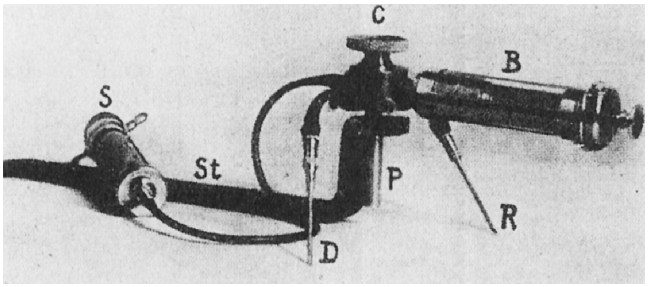


Figure 1.8 Apparatus for Unger's two-syringe, four-way stopcock method of indirect transfusion. Source: Unger (1915). [49]

Despite these many difficulties, direct transfusion through an arteriovenous anastomosis for the first time efficiently transferred blood from one person to another. The process also disclosed fatal hemolytic reactions that were undeniably caused by transfusion[41] (Figure 1.6). However, the relation of these fatal reactions to Landsteiner's discovery was not recognized until Reuben Ottenberg (1882–1959) demonstrated the importance of compatibility testing.

Ottenberg's interest in transfusion began in 1906 while he was an intern at German (now Lenox Hill) Hospital in New York. There, Ottenberg learned of Landsteiner's discovery and in 1907 began pretransfusion compatibility testing.[42] Ottenberg accepted an appointment at Mount Sinai Hospital the next year and continued his studies on transfusion. In 1913, Ottenberg published the report that conclusively demonstrated the importance of preliminary blood testing for the prevention of transfusion "accidents"[43] (Figure 1.7). This was not Ottenberg's only contribution. He observed the Mendelian inheritance of blood groups,[44] and he was the first to recognize the relative unimportance of donor antibodies and consequently the "universal" utility of type O blood donors.[45]

Further advances in immunohematology were to occur in succeeding decades. The M, N, and P systems were described in the period between 1927 and 1947.[46] The Rh system was discovered in connection with an unusual transfusion reaction. In 1939, Levine and Stetson[47] described an immediate reaction in a group O woman who had received her husband's group O blood soon after delivery of a stillborn fetus with erythroblastosis. This sequence of events suggested that the infant had inherited a red cell agglutinogen from the father that was foreign to the mother. At about the same time, Landsteiner and Wiener[48] harvested a rhesus monkey red cell antibody from immunized guinea pigs and rabbits. This antibody agglutinated 85% of human red cell samples (Rh-positive) and left 15% (Rh-negative) unaffected. When the experimentally induced antibody was tested in parallel with the serum from Levine's patient, a similar positive and negative distribution was observed, and the Rh system had been discovered. Other red cell antigen systems were subsequently described, but when Rh immunoglobulin was introduced as a preventive measure for hemolytic disease of the newborn, it became one of the major public health advances of the century.

Despite the introduction of compatibility testing by Ottenberg, transfusion could not be performed frequently as long as arteriovenous anastomosis remained the procedure of choice. Using this method, Ottenberg needed five years (Figure 1.7) to accumulate the 128 transfusions he reported in his study on pretransfusion testing.[43] New techniques, such as Unger's two-syringe method introduced in 1915[49] (Figure 1.8), eventually put an end to transfusion by means of arteriovenous anastomosis. However, transfusions did not become commonplace until anticoagulants were developed and direct methods of transfusion were rendered obsolete.

ACCIDENTS IN TRANSFUSION

THEIR PREVENTION BY PRELIMINARY BLOOD EXAMINATION: BASED ON AN EXPERIENCE OF ONE HUNDRED TWENTY-EIGHT TRANSFUSIONS *

REUBEN OTTENBERG, M.D.
AND
DAVID J. KALISKI, M.D.
NEW YORK

Accidents following transfusion have been sufficiently frequent to make many medical men hesitate to advise transfusion, except in desperate cases. It has been our opinion since we began making observations on this question in 1908 that such accidents could be prevented by careful preliminary tests, leading to the exclusion of agglutinative or hemolytic donors. Our observations on over 125 cases have confirmed this view and we believe that untoward symptoms can be prevented with absolute certainty.

Figure 1.7 Report of the importance of testing before transfusion. Source: Ottenberg and Kaliski (1913). [43]

Anticoagulants, the blood bank, and component therapy

The anticoagulant action of sodium citrate completely transformed the practice of transfusion. Early reports from Belgium[50] and Argentina[51] were followed by the work of Lewisohn[52] that established the optimal citrate concentration for anticoagulation. The work of Weil[53] then demonstrated the feasibility of refrigerated storage. Subsequently, Rous and Turner[54] developed the anticoagulant solution that was used during World War I.[55] Despite its very large volume, this solution remained the anticoagulant of choice until World War II, when Loutit and Mollison[56] developed an acid–citrate–dextrose (ACD) solution. Used in a ratio of 70 mL ACD to 450 mL blood, ACD provided 3 to 4 weeks of preservation of a more concentrated red cell infusion. Thus, the two world wars were the stimuli for the development of citrate anticoagulants and the introduction of indirect transfusion.[46] For the first time, the donation process could be separated, in time and place, from the actual transfusion. Blood drawn and set aside now awaited the emergence of systems of storage and distribution. Again, it was the provision of medical support during armed conflict that stimulated these developments.

A blood transfusion service, organized by the Republican Army during the Spanish Civil War (1936–1939), collected 9000 L of

blood in citrate–dextrose anticoagulant for the treatment of battle casualties.[57] At about that same time, Fantus[58] began operation of the first hospital blood bank at Cook County Hospital in Chicago. His interest had been stimulated by Yudin's report[59] on the use of cadaveric blood in Russia. Apart from certain scruples attached to the use of cadaveric blood, Fantus reasoned that a transfusion service based on such a limited source of supply would be impractical. Accordingly, he established the principle of a "blood bank" from which blood could be withdrawn, provided it had previously been deposited. As Fantus[58] himself stated, "[J]ust as one cannot draw money from a bank unless one has deposited some, so the blood preservation department cannot supply blood unless as much comes in as goes out. The term 'blood bank' is not a mere metaphor." The development of anticoagulants and the concept of blood banks provided an infrastructure upon which a more elaborate blood services organization could be built. World War II was the catalyst for these further developments.

At the beginning of World War II, blood procurement programs were greatly expanded.[46] In Great Britain, an efficient system had been developed through the organization of regional centers. When the war started, these centers, already in place, were able to increase their level of operation. In the United States, the use of plasma in the management of shock had led to the development of plasma collection facilities.[60] The efficient long-term storage of plasma had been further facilitated by the process of lyophilization developed by Flosdorf and Mudd and the introduction of ABO-independent "universal" plasma produced by pooling several thousand units of plasma.[61] In 1940, the United States organized a program for the collection of blood and the shipment of plasma to Europe. The American Red Cross, through its local chapters, participated in the project, which collected 13 million units by the end of the war.[46]

The national program of the American Red Cross ceased at the end of the war. However, many of the local chapters continued to help recruit donors for local blood banks, and in 1948, the first regional Red Cross blood center was begun in Rochester, New York. By 1949–1950 in the United States, the blood procurement system included 1500 hospital blood banks, 1100 of which performed all blood bank functions. There were 46 nonhospital blood banks and 31 Red Cross regional blood centers. By 1962, these numbers had grown to 4400 hospital blood banks, 123 nonhospital blood banks, and 55 American Red Cross regional blood centers, and the number of units collected had grown to between 5 and 6 million per year.[62]

During this time, blood was collected through steel needles and rubber tubing into rubber-stoppered bottles. After washing and resterilization, the materials were reused. On occasion, "vacuum bottles" were used to speed up the collection. However, the high incidence of pyrogenic reactions soon led to the development of disposable plastic blood collection equipment.

In a classic article written in 1952, Walter and Murphy[63] described a closed, gravity technique for whole blood preservation. They used a laminar flow phlebotomy needle, an interval donor tube, and a collapsible bag of polyvinyl resin designed so that the unit could be assembled and ready for use after sterilization with steam. The polyvinyl resin was chemically inert to biologic fluids and nonirritating to tissue. Soon thereafter, Gibson *et al.* [64] demonstrated that plastic systems were more flexible and allowed removal of plasma after sedimentation or centrifugation. In time, glass was replaced with plastic, and component therapy began to emerge. This development was enhanced by the US military's need to reduce the weight and breakage of blood bottles during shipment in the Korean War.

Component and derivative therapy began during World War II, when Edwin J. Cohn and his collaborators developed the cold ethanol method of plasma fractionation.[65] As a result of their work, albumin, globulin, and fibrinogen became available for clinical use. As plastic equipment replaced glass, component separation became a more widespread practice, and the introduction of automated cell separators provided even greater capabilities in this area.

Clotting factor concentrates for the treatment of patients with hemophilia and other hemorrhagic disorders also were developed during the postwar era. Although antihemophilic globulin had been described in 1937,[66] unconcentrated plasma was the only therapeutic material until Pool discovered that Factor VIII could be harvested in the cryoprecipitable fraction of blood.[67] This resulted in the development of cryoprecipitate, which was introduced in 1965 for the management of hemophilia. Pool showed that cryoprecipitate could be made in a closed-bag system and urged its harvest from as many donations as possible. The development of cryoprecipitate and other concentrates was the dawn of a golden age in the care of patients with hemophilia. Self-infusion programs, made possible by technologic advances in plasma fractionation, allowed early therapy and greatly reduced disability and unemployment. This golden age came abruptly to an end with the appearance of the AIDS virus.

Transfusion in the age of technology

In contrast to the long ledger of lives lost in previous centuries because of the lack of blood, transfusion in the 20th century saved countless lives. In 1937, during those early halcyon days of transfusion, Ottenberg wrote:[40]

> Today transfusion has become so safe and so easy to do that it is seldom omitted in any case in which it may be of benefit. Indeed the chief problem it presents is the finding of the large sums of money needed for the professional donors who now provide most of the blood.

It is ironic that Ottenberg's statement should refer to paid donors and foreshadow difficulties yet to come. However, experience to that point had not revealed the problem of viral disease transmission. More transfusions would have to be administered before that problem would be perceived.

After the introduction of anticoagulants, blood transfusions were given in progressively increasing numbers. At Mount Sinai Hospital in New York, the number of blood transfusions administered between 1923 and 1953 increased 20-fold[68,69] (Table 1.1). This increase was particularly notable after the establishment of blood banks. It was during this period that Beeson wrote his classic description of transfusion-transmitted hepatitis.[70] He had been alerted to the problem by the outbreaks of jaundice that followed inoculation programs with human serum during World War II. Thus blood transfusion entered a new era. Blood components not only saved lives but also transmitted disease. The discovery of the Australian antigen[71] and the subsequent definition of hepatitis A virus and B virus (HBV) still left residual non-A and non-B disease,[72] a gap that has been largely filled by the discovery of the hepatitis C virus (HCV).[73] However, it was the outbreak of AIDS that galvanized public attention to blood transfusion.

The AIDS epidemic was first recognized in the United States, and the first case of AIDS associated with transfusion was observed in a 20-month-old infant.[74] Subsequently, the suspicion that AIDS could be transmitted by means of transfusion was confirmed.[75]

Table 1.1 Increase in the Number of Blood Transfusions at Mount Sinai Hospital, New York, 1923–1953

Year	Number of Transfusions
1923	143
1932	477
1935	794
1938	(Blood bank started)
1941	2097
1952	2874
1953	3179

Source: Lewisohn (1955).[68] Adapted with permission of Elsevier.

The human immunodeficiency virus (HIV) was identified,[76] and an effective test to detect the HIV antibody was developed.[76]

Concern for blood safety

Since 1943, transfusion therapy has been shadowed by the specter of disease transmission. In that year, Beeson described posttransfusion hepatitis and unveiled a problem that has grown with time. As transfusion increased, so did disease transmission. In 1962, the connection between paid donations and posttransfusion hepatitis was made.[77] A decade later, the National Blood Policy mandated a voluntary donation system in the United States. And yet, blood usage continued to increase.

Concern about posttransfusion hepatitis was not sufficient to decrease the number of transfusions. Although the use of whole blood declined as blood components became more popular, total blood use in the United States doubled between 1971 and 1980 (Table 1.2).[78–85] This pattern changed as the emergence of AIDS exposed all segments of society to a revealing light.

AIDS probably arose in Africa in the 1960s and spread quietly for years before it was detected. By 1980, an estimated 100,000 persons were infected, and by 1981, when the first cases were reported, a worldwide pandemic lay just beneath the surface. The initial response of the public and officials seemed trifling and insufficient as the outbreak grew to proportions few had foreseen. Criticism was levied against the news media for initially ignoring the story, the government for delay in acknowledging the problem, gay civil rights groups for resistance to epidemiologic measures, research scientists for unseemly competition, blood services for delayed response in a time of crisis, and the US Food and Drug Administration (FDA) for inadequate regulatory activity. Historians with the perspective of time will determine whether there really were more villains than the virus itself.[86]

Table 1.2 Transfusions in the United States (in Millions of Units)[78–85]

Year	Whole Blood and Red Blood Cells	Platelets	Plasma	Total**
1971	6.32	0.41	0.18	6.91
1979	9.47	2.22	1.29	12.98
1980	9.99	3.19	1.54	14.72
1982	11.47	4.18	1.95	17.60
1984	11.98	5.53	2.26	19.77
1986	12.16	6.30	2.18	20.64
1987	11.61	6.38	2.06	20.05
1989	12.06	7.26	2.16	21.48
1992	11.31	8.33	2.26	21.90
1994	11.11	7.87	2.62	21.60
1997	11.52	9.04	3.32	23.88
1999	12.39	9.05	3.32	24.76
2001	13.90	10.20	3.93	28.03
2004	14.18	9.88	4.09	28.15
2006	14.65	10.39	4.01	29.05
2008	15.02	2.28*	4.48	23.24
2011	13.79	3.16*	3.88	20.93

* Platelets reported in apheresis units.
** Includes other components.

The realization that transfusion can transmit an almost invariably fatal disease had a chilling effect on the public. Two major changes in blood services have occurred in the aftermath of the AIDS epidemic. The FDA, using pharmaceutical manufacturing criteria not "tailored to . . . blood banks," became more aggressive in regulatory actions against blood collection establishments.[87] And, finally, blood use moderated for approximately 10 years. Through the 1980s and early 1990s, red cell and plasma transfusion peaked and began to stabilize (Table 1.2). Only platelet use and human progenitor cell transplantation, driven by the demands of cancer chemotherapy, continued to increase.[78–85] Educational programs to encourage judicious use of blood have been initiated, and they have been favorably received by practicing physicians. Use of red cells and plasma fell from 2008 to 2011. This was a combined impact of the great recession reducing healthcare utilization and the widespread use of patient blood management programs intended to reduce blood transfusion. This represents the first time since the end of the Second World War that the growth in transfusion of blood products in the United States and other developed countries stopped and was reversed for a sustained period.

Relentless public pressure for a "zero-risk" blood supply resulted in dividends through continued scientific and technologic improvements. Enhanced sensitivity and better use of serologic testing, along with improved scrutiny of donors, resulted in major reductions in risk of transmitted disease by the mid-1990s.[88] Discovery that pools of units subjected to nucleic acid testing almost closed the window for HIV and HCV virus resulted in application of this testing for both whole blood and plasma donations beginning between 1998 and 2000.[88,89] This, combined with virus reduction and inactivation of the final product, resulted in plasma derivatives that have not transmitted AIDS or hepatitis since 1994.[90] For whole blood and platelet components, risks have become low. A solvent/detergent-treated fresh frozen plasma component has been used in Europe and recently became available in the United States.

With the reduction in the risk of viral transmission, the focus in the developed world has shifted to transfusion-related acute lung injury (TRALI)—possibly from recipient-directed leukocyte antibodies and lipid mediators in transfused plasma—and bacterial infection primarily occurring in room-temperature stored platelets. So that incremental gains can be made against these risks, the use of male plasma only and the culture of platelets before they are released have been implemented. The 2011 blood utilization survey indicated a 28.8% reduction in TRALI, suggesting a significant breakthrough with regard to this risk.[85] Geographic exclusions have been aimed at reducing the potential for variant Creutzfeldt–Jakob disease (vCJD) transmission by transfusion, although in the United States such occurrence seems highly unlikely. In many countries, universal leukocyte reduction has been a response to the vCJD risk. Ironically, universal application of leukocyte reduction is probably ineffective for vCJD but has stimulated controversy over its use for preventing other problems.[91]

Finally, focus on the understanding, management, and prevention of medical errors in general might lead to progress against remaining nemesis hemolytic transfusion reactions caused by