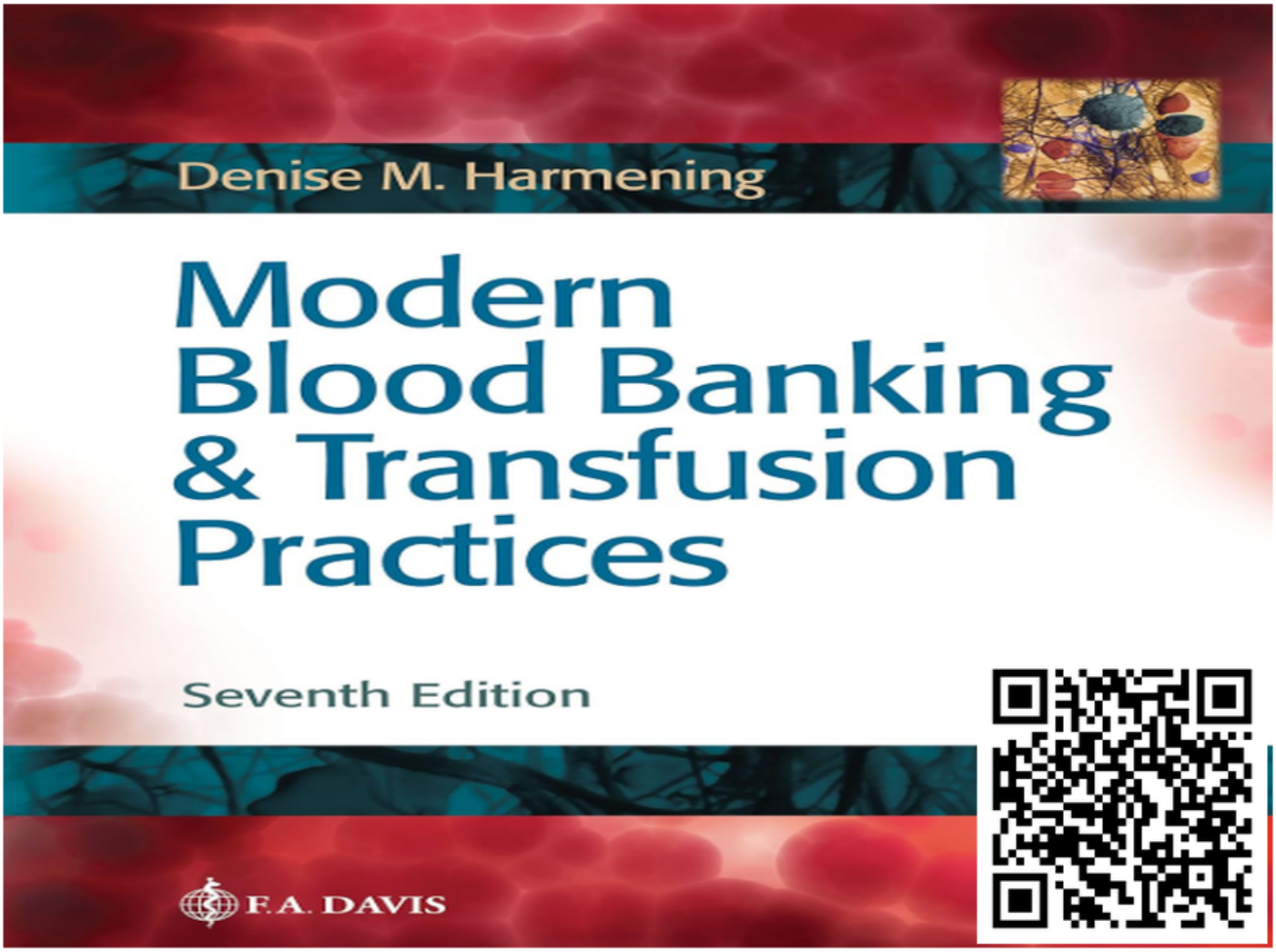
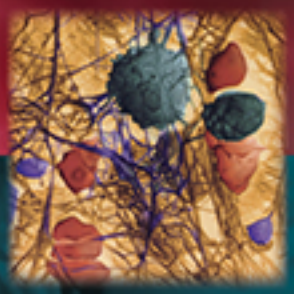


Denise M. Harmening



Modern Blood Banking & Transfusion Practices

Seventh Edition

F.A. DAVIS

Antigen-Antibody Characteristic Chart*

ANTIGENS

Antigen System	Antigen Name	ISBT Name	Antigen Freq. % W	Antigen Freq. % B	RBC Antigen Expression at Birth	Antigen Distrib. Plasma/RBC	Demonstrates Dosage	Antigen Modification Enzyme/Other
Rh	**D	RH1	85	92	strong	RBC only	no	Enz. ↑
	**C	RH2	68	27	strong	RBC only	yes	Enz. ↑
	**E	RH3	29	22	strong	RBC only	yes	Enz. ↑
	**c	RH4	80	97	strong	RBC only	yes	Enz. ↑
	**e	RH5	98	99	strong	RBC only	yes	Enz. ↑
	ce/f	RH6	64	92	strong	RBC only	no	Enz. ↑
	Ce	RH7	70	27	strong	RBC only	no	Enz. ↑
	C^w	RH8	1	rare	strong	RBC only	yes	Enz. ↑
	G	RH12	86	92	strong	RBC only	no	Enz. ↑
	V	RH10	1	30	strong	RBC only	no	Enz. ↑
	VS	RH20	1	32	strong	RBC only	no	Enz. ↑ AET → ZZAP →
Kell	K	KEL1	9	rare	strong	RBC only	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
	k	KEL2	98.8	100	strong	RBC only	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
	Kp^a	KEL3	2	rare	strong	RBC only	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
	Kp^b	KEL4	99.9	100	strong	RBC only	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
	Js^a	KEL6	.01	20	strong	RBC only	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
	Js^b	KEL7	99.9	99	strong	RBC only	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
	†Kx	–	99.9	99.9	weak	RBC low	occ	Enz. → AET^+ ↓ ZZAP $↓^{++}$
Duffy	FY^a	FY1	65	10	strong	RBC only	yes	Enz. ↓ AET ↓ ZZAP ↓
	FY^b	FY2	83	23	strong	RBC only	yes	Enz. ↓ AET ↓ ZZAP ↓
		FY3	100	32	strong	RBC only	no	Enz. → AET → ZZAP →
		FY5	100	32	expressed (on cord cells)	RBC only	no	Enz. → AET → ZZAP →
		•FY6	100	32	expressed (on cord cells)	RBC only	no	Enz. ↓ AET → ZZAP ↓

*This chart is to be used for general information only. Please refer to the appropriate chapter for more detailed information.
AET = 2-aminoethylisthiouronium bromide; ↑ = enhanced reactivity; → = no effect; ↓ = depressed reactivity; occ = occasionally; CGD = chronic granulomatous disease; HDN = hemolytic disease of the newborn; HTR = hemolytic transfusion reaction; NRBC = non-red blood cell; RBC = red blood cell; WBC = white blood cell; ZZAP = dithiothreitol plus papain.
• No human antibody to FY6 has been reported.
† It has been found that Kx is inherited independently of the Kell system; consequently it is no longer referred to as K15.
**Frequency in Asians: D 99%, C 93%, E 39%, c 47%, e 96%

ANTIBODIES

Stimulation	Serology		Comp.	Immunoglobin Class		Optimum	Clinical Significance		Comments
	Saline	AHG	Binding	IgM	IgG	Temperature	HTR	HDN	
RBC	occ	yes	no	occ	yes	warm	yes	yes	Very rarely IgA anti-D may be produced; however, this is invariably with IgG.
RBC	occ	yes	no	occ	yes	warm	yes	yes	
RBC/NRBC	occ	yes	no	occ	yes	warm	yes	yes	Anti-E may occur without obvious immune stimulation.
RBC	occ	yes	no	occ	yes	warm	yes	yes	
RBC	occ	yes	no	occ	yes	warm	yes	yes	Warm autoantibodies may appear to have anti-e-like specificity.
RBC	occ	yes	no	occ	yes	warm	yes	yes	
RBC	occ	yes	no	occ	yes	warm	yes	yes	
RBC/NRBC	occ	yes	no	occ	yes	warm	yes	yes	Anti-C^w may occur without obvious immune stimulation.
RBC	occ	yes	no	occ	yes	warm	yes	yes	
RBC	occ	yes	no	occ	yes	warm	yes	yes	Antibodies to V and VS can present problems in the black population where the antigen frequencies are in the order of 30 to 32.
RBC	occ	yes	no	occ	yes	warm	yes	yes	
RBC	occ	yes	some	occ	yes	warm	yes	yes	Some antibodies to Kell antigens have been reported to react poorly in low ionic media.
RBC	no	yes	no	rarely	yes	warm	yes	yes	
RBC	no	yes	no	no	yes	warm	yes	yes	Kell system antigens are destroyed by AET and by ZZAP.
RBC	rarely	yes	no	rarely	yes	warm	yes	yes	
RBC	rarely	yes	no	rarely	yes	warm	yes	yes	Anti-K1 has been reported to occur following certain bacterial infections.
RBC	no	yes	no	no	yes	warm	yes	yes	
RBC	no	yes	no	occ	yes	warm	yes	yes	The lack of Kx expression on RBCs and WBCs has been associated with the McLeod phenotype and CGD.
RBC	rare	yes	some	rare	yes	warm	yes	yes	Fy^a and Fy^b antigens are destroyed by enzymes. Fy (a–b–) cells are resistant to invasion by *P. vivax* merozoites, a malaria-causing parasite.
RBC	rare	yes	some	rare	yes	warm	yes	yes	
RBC	no	yes	rarely	no	yes	warm	yes	yes	FY3 and 5 are not destroyed by enzymes.
RBC	no	yes	?	no	yes	warm			FY5 may be formed by interaction of Rh and Duffy gene products. FY6 was described using a monoclonal antibody which reacts with most human red cells except Fy(a–b–). This antigen is responsible for susceptibility of cells to penetration by *P. vivax.*

(Continued on inside back cover)

Modern Blood Banking & Transfusion Practices

Seventh Edition

Denise Harmening, PhD, MT(ASCP)

Director of the Online Masters of Science in Clinical Laboratory Management

Professor, Department of Medical Laboratory Science

College of Health Sciences

Rush University

Chicago, Illinois, USA

F.A. DAVIS

Philadelphia

F. A. Davis Company
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Developmental Editor: Karen Gulliver
Art and Design Manager: Carolyn O'Brien
Content Project Manager: Megan Suermann

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To all students—full-time, part-time, past, present, and future—who have touched and will continue to touch the lives of so many educators. . . .

It is to you this book is dedicated in the hope of inspiring an unquenchable thirst for knowledge!

Foreword

Blood groups were discovered more than a century ago and have a rich and varied history, including being recognized as the first markers of human diversity used to study population migration and admixture. The study of blood groups has also made important contributions to biology: for instance, the Colton blood antigens are carried on a membrane protein called aquaporin, which was the first water channel discovered in mammals. Rh-associated glycoprotein (RhAG) was the first mammalian ammonia transporter recognized, and the Kidd blood group protein was the first urea transporter discovered. All have related protein family members present in many tissues and organs. *Modern Blood Banking & Transfusion Practice* is an introduction to the role of blood groups in transfusion therapy, in which blood groups are the core of compatible blood transfusion.

Today, the Internet has truly facilitated access to new knowledge in all areas of science, and the field of transfusion medicine is no exception! Now, with knowledge mobile on every device, we are in an age of information explosion. However, to take advantage of the continual flow of new information generated by blood transfusion scientists and to apply it to everyday work in the blood bank, requires a solid knowledge base. It can be difficult to select one book that covers all the information that technologists in training need to know about blood transfusion science to build that foundation. It requires a well-thought-out systematic presentation of information for training. Dr. Denise Harmening has produced that single volume, now in its seventh edition! This impressive legacy is a testament to the success of her approach and experience as an educator, administrator, researcher, and author, and is also reflected in her membership on the "Medscape" Pathology Editorial Advisory Board.

She has gathered a group of experienced scientists and teachers who, along with herself, cover all the important areas of blood transfusion science. The book is divided into five sections. The chapters included in Part I, "Fundamental Concepts," provide a firm base on which the student can learn the practical and technical importance of the other chapters. The chapters in Part II, "Blood Groups and Serologic Testing," and Part III, "Transfusion Practices," provide information for medical technologists without overwhelming them with esoteric and clinical details. Part IV covers leukocyte antigens and relationship (parentage) testing. The chapters in Part V, "Quality Management and Compliance," complete the scope of transfusion science. Although designed primarily for medical technologists, the book is also well suited to pathology residents, hematology fellows, and others who want to review principles of blood banking and transfusion practices.

Dr. Harmening indicates that this seventh edition will be her last revision. I speak for the profession in commending and thanking her for the major contribution she has made to the education of blood bankers. Importantly, the principles outlined here will remain; some details may change and new blood group antigens will be recognized, but the basic foundation will remain relevant in this "collectors" edition.

Connie M. Westhoff, SBB, PhD
Executive Scientific Director
Immunohematology and Genomics
New York Blood Center

Preface

This book is designed to provide the medical technologist, blood bank specialist, and resident with a concise and thorough guide to transfusion practices and immunohematology. This text, a perfect "crossmatch" of theory and practice, provides the reader with a working knowledge of routine blood banking. Forty-four contributors from across the country have shared their knowledge and expertise in 29 comprehensive chapters. More than 500 illustrations and tables facilitate the comprehension of difficult concepts not routinely illustrated in other texts. In addition, color plates provide a means for standardizing the reading of agglutination reactions.

Several features of this textbook offer great appeal to students and educators, including chapter outlines and educational objectives at the beginning of each chapter; case studies, review questions, and summary charts at the end of each chapter; and an extensive and convenient glossary for easy access to definitions of blood bank terms.

A blood group antigen-antibody characteristic chart is provided on the inside cover of the book to aid in retention of the vast amount of information presented, and serves as a review of the characteristics of the blood group systems. Original, comprehensive step-by-step illustrations of ABO forward and reverse grouping help the student to master this important testing, which represents the foundation of blood banking.

The seventh edition is divided into the following sections:

- Part I: Fundamental Concepts
- Part II: Blood Groups and Serologic Testing
- Part III: Transfusion Practices
- Part IV: Leukocyte Antigens and Relationship Testing
- Part V: Quality Management and Compliance

In Part I, the introduction to the historical aspects of red blood cell and platelet preservation serves as a prelude to the basic concepts of genetics, immunology, and molecular biology. In Part II, four chapters focus on blood groups and four on routine blood bank practices, which include "The Antiglobulin Test," "Detection and Identification of Antibodies," "Pretransfusion Testing," and "Blood Bank Testing Technologies and Automation."

Part III, "Transfusion Practices," includes a chapter titled "Cellular Therapy in the Transplant Setting" and covers the more traditional topics of donor screening, transfusion-transmitted diseases, component preparation, transfusion therapy, transfusion reactions, and apheresis. Certain clinical situations that are particularly relevant to blood banking are also discussed in this section, including hemolytic disease of the fetus and newborn, autoimmune hemolytic anemias, and tissue banking.

The human leukocyte antigen (HLA) system and relationship testing are discussed in Part IV of the book. In Part V, "Quality Management and Compliance," a chapter titled "Patient Blood Management" is discussed. The chapters on quality management, transfusion safety and federal regulatory requirements, laboratory information systems, and legal and ethical considerations complete the scope of practice for transfusion services.

This book is a culmination of the tremendous efforts of many dedicated professionals who participated in this project by donating their time and expertise because they care about the blood bank profession. The book's intention is to foster improved patient care by providing the reader with a basic understanding of modern blood banking and transfusion practices. The seventh edition is designed to generate an unquenchable thirst for knowledge in all medical laboratory scientists, blood bankers, and practitioners, whose education, knowledge, and skills provide the public with excellent health care.

Denise Harmening, PhD, MT(ASCP)

Editorial Reviewers

We especially thank our editorial reviewers for assisting with manuscript, art, and page proof review.

Regina M. Leger, MSQA, MT(ASCP)SBB, CMQ/OE(ASQ)
Director, Specialist in Blood Banking (SBB) Program
Lead Technologist, Special Immunohematology Lab
American Red Cross Blood Services
Southern California Region
Pomona, California, USA

Justin Richard Rhees, MS, MLS(ASCP)^{CM}, SBB^{CM}
Assistant Professor, Medical Laboratory Sciences
Weber State University
Ogden, Utah, USA

Gale Suwe, BS, MT(ASCP)SBB
Instructor, Specialist in Blood Bank Technology Program
Rush University
Chicago, IL USA

Contributors

Robert W. Allen, PhD
Chair & Director School of Forensic Sciences
Center for Health Sciences
Oklahoma State University
Tulsa, Oklahoma, USA

Lucia M. Berte, MA, MT(ASCP)SBB, DLM; COA(ASQ)CMQ/OE
President
Laboratories Made Better! P.C.
Quality Systems Consultant
Broomfield, Colorado, USA

Maria P. Bettinotti, PhD, dip. ABHI
Assistant Professor of Medicine
Director, Immunogenetics Laboratory
Johns Hopkins
Baltimore, MD, USA

Susanne Bishop, MS, MLS(ASCP)^{CM} SBB^{CM}
Assistant Professor
Division of Medical Laboratory Science
College of Allied Health Professionals
University of Nebraska Medical Center
Omaha, Nebraska, USA

Theresa Bostock, MS, MT(ASCP)SBB
Laboratory Director
Orange Regional Medical Center
Middletown, New York, USA

Michele R. Brown, PhD, MS, MLS(ASCP)^{CM} SBB^{CM}
Assistant Professor & Program Director, Healthcare Simulation
Department of Health Services Administration, School of Health Professions
Simulation Associate, Office of Interprofessional Simulation for Innovative Clinical Practice
University of Alabama
Birmingham, Alabama, USA

Lorraine Caruccio, PhD, MT(ASCP)SBB
Formerly, National Institutes of Health
Rockville, Maryland, USA

JoAnn Christensen, MS, MT(ASCP)SBB
Director, IRL East Area 2
NY-Penn, NE PA, and Greater Alleghenies Regions
American Red Cross
West Henrietta, New York, USA

Judy Ellen Ciaraldi, BS, MT(ASCP)SBB, CQA(ASQ)
Consumer Safety Officer
Division of Blood Applications
Office of Blood Research and Review
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Rockville, Maryland, USA

Julie L. Cruz, MD, FACP
Medical Director
Versiti-Indiana Blood Center
Indianapolis, Indiana, USA

Meghan Delaney, DO, MPH
Chief, Pathology and Laboratory Medicine
Children's National Health System
George Washington University Medical School
Washington, DC, USA

Helene DePalma, MS, MT(ASCP)SBB, CQA(ASQ)
Associate Professor
City University of New York-York College
Jamaica, New York, USA

Laurie Gillard, MS, MLS(ASCP)^{CM} SBB
Director of the Specialist in Blood Banking Program
Assistant Professor, Department of Medical Laboratory Science
Rush University
Chicago, Illinois, USA

Ralph E. B. Green B. App. Sci, FAIMLS, MACE
Formerly, Associate Professor
Discipline and Program Leader
Discipline of Laboratory Medicine
School of Medical Sciences
RMIT University
Melbourne, Australia

Steven F. Gregurek, MD
Transfusion Medicine Medical Director
Valley Health System
Las Vegas, Nevada, USA

Denise Harmening, PhD, MT(ASCP)
Director of the Online Masters in Clinical Laboratory Management
Professor, Department of Medical Laboratory Science
College of Health Sciences
Rush University
Chicago, Illinois, USA

Elizabeth A. Hartwell, MD, MT(ASCP)SBB
Associate Professor, Department of Pathology and Immunology
Baylor College of Medicine
Associate Medical Director
Baylor St. Luke's Medical Center
Houston, Texas, USA

Virginia C. Hughes, PhD, MLS(ASCP)SBB
Associate Professor
Department of Medical Laboratory Sciences
College of Health Sciences
University of Delaware
Newark, Delaware, USA

Melanie S. Kennedy, MD
Clinical Associate Professor Emeritus
Department of Pathology
College of Medicine
The Ohio State University
Columbus, Ohio, USA

Scott A. Koepsell, MD, PhD
Department of Pathology and Microbiology
University of Nebraska Medical Center
Omaha, Nebraska, USA

Barbara Kraj, PhD, MLS(ASCP)CM MBCM
Associate Professor and Program Director
School of Medical Diagnostics and Translational Science
Old Dominion University
Norfolk, VA, USA

Regina M. Leger, MSQA, MT(ASCP)SBB, CMQ/OE(ASQ)
Director, Specialist in Blood Banking (SBB) Program
Lead Technologist, Special Immunohematology Lab
American Red Cross Blood Services
Southern California Region
Pomona, California, USA

Nadine Lerret, PhD, MLS(ASCP)CM
Assistant Professor, Clinical Chemistry Course Director
Department of Medical Laboratory Science
Rush University
Chicago, Illinois, USA

Beth L. Manning, BS, MT(ASCP)SBBCM
Marshfield Clinic Health System
Transfusion Services
Marshfield, Wisconsin, USA

Holli Mason, MD
Director, Transfusion Medicine and Serology
Director, Pathology Residency Training Program
Harbor UCLA Medical Center
Associate Clinical Professor
David Geffen School of Medicine at UCLA
Torrance, California, USA

Richard H. McBride, Jr, MS, MT(ASCP)SBB
Chief, Blood and Plasma Branch
Division of Blood Components and Devices
Office of Blood Research and Review
Center for Biologics Research and Review
Food and Drug Administration
Silver Spring, Maryland, USA

Matthew Montgomery, MD
Assistant Medical Director
Hoxworth Blood Center
University of Cincinnati
Cincinnati, Ohio, USA

Gerald P. Morris, MD, PhD
Department of Pathology
University of California, San Diego
San Diego, California, USA

Angela K. Novotny, MT(ASCP)SBBCM
Manager, Blood Bank
The University of Texas Medical Branch
Galveston, Texas, USA

Donna L. Phelan, BA, MT(HEW), CHS(ASHI)
Technical Supervisor
HLA Laboratory
Barnes-Jewish Hospital
St. Louis, Missouri, USA

Mark D. Pool, MD
Assistant Professor of Pathology, Rush Medical College
Blood Center Medical Director, Rush University Medical Center
Chicago, Illinois, USA

Justin Richard Rhees, MS, MLS (ASCP)CM, SBBCM
Assistant Professor
Medical Laboratory Sciences
Weber State University
Ogden, Utah, USA

Karen Rodberg, MBA, MT(ASCP)SBB
Director, Reference Services
American Red Cross Blood Services
Southern California Region
Pomona, California, USA

Kathleen Sazama, MD, JD, MS, MT(ASCP)
Formerly, Chief Medical Officer
LifeSouth Community Blood Centers, Inc.
Gainesville, Florida, USA

Jayanna Slayten, MS, MT(ASCP)SBB^{CM}
Blood Bank Supervisor
Indiana University Health Blood Bank
Indianapolis, Indiana, USA
And Adjunct Faculty, University of Texas Medical Branch
Specialist in Blood Banking Program
Galveston, Texas USA

Phyllis Straff, MS(ISM), MT(ASCP)
Laboratory Information Systems Project Manager
Dept of Pathology and Laboratory Medicine
Rush University, College of Health Sciences
Chicago, Illinois, USA

Gale Suwe, BS, MT(ASCP)SBB
Instructor
Rush University
Specialist in Blood Banking Program
Chicago, Illinois, USA

Ann Tiehen, MT(ASCP)SBB
Formerly, Education Coordinator
North Shore University Health System
Evanston Hospital
Department of Pathology and Laboratory Medicine
Evanston, Illinois, USA

Kathleen S. Trudell, MLS(ASCP)^{CM} SBB^{CM}
Clinical Coordinator, Immunohematology
Division of Medical Laboratory Science
College of Allied Health Professions
University of Nebraska Medical Center
Omaha, Nebraska, USA

Heather M. Vaught, BS, MLS(ASCP)^{CM} SBB^{CM}
Director, Transfusion Medicine Laboratory
Indiana University Health Pathology Laboratory
Indianapolis, Indiana, USA

Phyllis S. Walker, MS, MT(ASCP)SBB
Formerly, Manager, Immunohematology Reference Laboratory
Blood Centers of the Pacific
San Francisco, California, USA

Elizabeth F. Williams, MHS, MT(ASCP)^{CM}, SBB
Associate Professor, Clinical Educational Coordinator
Department of Clinical Laboratory Sciences
School of Allied Health Professions
LSUHSC Health Sciences Center
New Orleans, Louisiana, USA

Laurie Wolf, MLS(ASCP)SBB^{CM}
Transfusion Service Manager, Pathology and Laboratory Medicine
The University of Kansas Health System
Kansas City, Kansas USA

Jules G. Zinni, MLS(ASCP)^{CM} MB^{CM}
Medical Technologist, Blood Bank
Northwestern Memorial Hospital
Chicago, Illinois, USA, USA

Reviewers

Leslie M. Allshouse, MEd, MBA, MLS(ASCP)CM
Program Director and Senior Instructor, Medical Laboratory Science Program
University of Delaware
Newark, Delaware, USA

Karen Bowers, RT, MEd
Instructor, Medical Laboratory Technology Science Program
College of New Caledonia
Prince George, British Columbia, Canada

Maritza Cintron, MPA, BS
Technician Program Director, Medical Laboratory
Marion Technical College
Ocala, Florida, USA

Christina Camillo, MS, MLS(ASCP)CM
Instructor and Clinical Coordinator, Health Sciences
Salisbury University
Salisbury, Maryland, USA

Guyla Evans, PhD, MLS(ASCP)CM, SC(ASCP)CM
Clinical Assistant Professor, Clinical Laboratory Science
East Carolina University
Greenville, North Carolina, USA

Candice Suzanne Grayson, MS, MA, MLS(ASCP)CM
Program Director, Medical Laboratory Technology Program
Community College of Baltimore County
Baltimore, Maryland, USA

Andrea Hoffmann Fontenot, MLS(ASCP)SBBCM
Assistant Professor, Medical Laboratory Technician Program
Delgado Community College
New Orleans, Louisiana, USA

Kerry Harbert, MA, MT(ASCP)
Associate Professor, Medical Laboratory Science
West Virginia University
Morgantown, West Virginia, USA

Hillary Harris, MLS(ASCP)
Medical Laboratory Scientist
Indiana University Health University Hospital,
Indianapolis, Indiana, USA

Elizabeth Hart, MA, CLS
Senior Lecturer, Medical Laboratory Science
University of Massachusetts Dartmouth
Dartmouth, Massachusetts, USA

Phyllis Ingham, EdD, Med, MT(ASCP)
Program Director, Clinical Laboratory Technology/Phlebotomy
West Georgia Technical College
Waco, Georgia, USA

Rebecca Lawson, MS, MLS(ASCP)CM, AHI(AMT)
Staff Associate, Health Sciences and Distance Learning Division
Adjunct Instructor, Clinical Laboratory Technologies
SUNY Broome Community College
Binghamton, New York, USA

Teresita Padilla-Benevieds, MSc, PhD
Instructor and Faculty Diversity Scholar, Biochemistry and Molecular Pharmacology
University of Massachusetts
Worcester, Massachusetts, USA

Art Phillips, MS, MT(ASCP) BB
Adjunct Lecturer, Biology–Medical Technology Program
The College of Staten Island (CUNY)
Staten Island, New York, USA

Kal Randhawa, MLT, Med
Faculty, Medical Laboratory Science
British Columbia Institute of Technology
Barnaby, British Columbia, Canada

Carol Rentas, PhD, MEd, MT(ASCP)
Director, Undergraduate MLS Programs, Integrative Health Sciences
George Washington University
Ashburn, Virginia, USA

Justin Richard Rhees, MS MLS(ASCP)CM, SBBCM
Assistant Professor, Medical Laboratory Sciences
Weber State University
Ogden, Utah, USA

Ann Christine Ridder, MBA, MLS(ASCP)CM
Clinical Education Program Director
School of Clinical Laboratory Science
Augusta Health
Fishersville, Virginia, USA

Brenda Schoffstall, PhD, MT(ASCP)
Associate Professor, Biology
Barry University
Miami, Florida, USA

Judith A. Seidel, MT(ASCP)SBB
Clinical Instructor, Clinical Laboratory Science Program, Academic Affairs
Indiana University Health
Indianapolis, Indiana, USA

Kelly D. Shirley, MAEd, MLS(ASCP)^{CM} SBB^{CM}
Education Coordinator, School of Clinical Laboratory Science
Carolinas College of Health Sciences
Charlotte, North Carolina, USA

Tasha T. Simpson MSc, C (ASCP)^{CM}, MLS(ASCP^{i})^{CM}
Assistant Professor, Medical Laboratory Sciences
Andrews University
Berrien Springs, Michigan, USA

James Kyle Taylor, PhD, MLS(ASCP)^{CM}
Department Head, Medical and Clinical Laboratory Sciences
Auburn University at Montgomery
Montgomery, Alabama, USA

Lorraine Torres, EdD, MT(ASCP)
Program Director, Clinical Laboratory Science Program
The University of Texas at El Paso
El Paso, Texas, USA

Kathleen Winker, MT(ASCP)
Program Director, MLT – Health and Public Safety
Blackhawk Technical College
Monroe, Wisconsin, USA

Jeff Wolz, MA, MT(ASCP)
Director, MLS Program
Arizona State University
Phoenix, Arizona, USA

Contents

Procedures Available on Davis*Plus*

*The following procedures can be found on the textbook's companion website at Davis*Plus.

Related Chapter	Procedure
Chapter 5: The Antiglobulin Test	• Procedure 5–1: Direct Antiglobulin Test • Procedure 5–2: Indirect Antiglobulin Test
Chapter 6: The ABO Blood Group System	• Procedure 6–1: Determination of the Secretor Property
Chapter 10: Detection and Identification of Antibodies	• Procedure 10–1: Plasma Inhibition Studies
Chapter 11: Pretransfusion Testing	• Procedure 11–1: Preparation of Washed "Dry" Button of RBCs for Serologic Tests • Procedure 11–2: Model One-Tube-Per-Donor-Unit Crossmatch Procedure • Procedure 11–3: Saline Replacement Procedure

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	• Procedure 21–10: EDTA/Glycine Acid (EGA) Method to Remove Antibodies From RBCs
	• Procedure 21–11: Separation of Transfused From Autologous RBCs by Simple Centrifugation: Reticulocyte Harvesting

Also available at Davis*Plus* (http://davisplus.fadavis.com/): Polyagglutination, by Phyllis S. Walker, MS, MT(ASCP)SBB.

Fundamental Concepts

Part I

Chapter 1

Red Blood Cell and Platelet Preservation: Historical Perspectives and Current Trends

Denise M. Harmening, PhD, MT(ASCP) and Michelle R. Brown, PhD, MS, MLS(ASCP)^{CM}SBB^{CM}

OBJECTIVES

1. List the major developments in the history of transfusion medicine.
2. Describe several biological properties of red blood cells (RBCs) that can affect post-transfusion survival.
3. Identify the metabolic pathways that are essential for normal RBC function and survival.
4. Define the hemoglobin-oxygen dissociation curve, including how it is related to the delivery of oxygen to tissues by transfused RBCs.
5. Explain how transfusion of stored blood can cause a shift to the left of the hemoglobin-oxygen dissociation curve.
6. State the temperature for storage of RBCs in the liquid state.

Continued

OBJECTIVES—cont'd

7. Define *storage lesion* and list the associated biochemical changes.
8. Explain the importance of 2,3-diphosphoglycerate (2,3-DPG) levels in transfused blood, including what happens to levels post-transfusion and which factors are involved.
9. Name the approved anticoagulant preservative solutions, explain the function of each ingredient, and state the maximum storage time for RBCs collected in each.
10. Name the additive solutions licensed in the United States, list the common ingredients, and describe the function of each ingredient.
11. Explain how additive solutions are used and list their advantages.
12. Explain rejuvenation of RBCs.
13. List the name and composition of the FDA-approved rejuvenation solution and state the storage time following rejuvenation.
14. Define the platelet storage lesion.
15. Describe the indications for platelet transfusion and the importance of the corrected count increment (CCI).
16. Explain the storage requirements for platelets.
17. Explain the swirling phenomenon and its significance.
18. List the two major reasons why routine platelet storage is limited to 5 days in the United States.
19. List the various ways that blood banks in the United States meet the FDA regulation requiring that blood establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices.
20. Explain the use and advantages of platelet additive solutions (PASs), and name two that are approved for use in the United States.

Introduction

People have always been fascinated by blood: Ancient Egyptians bathed in it, aristocrats drank it, authors and playwrights used it as themes, and modern humanity transfuses it. The road to an efficient, safe, and uncomplicated transfusion has been difficult, but great progress has been made. This chapter reviews the historical events leading to the current status of how blood is stored. A review of red blood cell (RBC) biology serves as a building block for the discussion of red blood cell preservation, and a brief description of platelet metabolism sets the stage for reviewing the platelet storage lesion. Current trends in red blood cell and platelet preservation research are presented for the inquisitive reader.

Historical Overview

In 1492, blood was taken from three young men and given to the stricken Pope Innocent VII in the hope of curing him; unfortunately, all four died. Although the outcome of this event was unsatisfactory, it is the first time a blood transfusion was recorded in history. The path to successful transfusions that is so familiar today is marred by many reported failures, but our physical, spiritual, and emotional fascination with blood is primordial. Why did success elude experimenters for so long?

Clotting was the principal obstacle to overcome. Attempts to find a nontoxic anticoagulant began in 1869, when Braxton Hicks recommended sodium phosphate. This was perhaps the first example of blood preservation research. Karl Landsteiner in 1901 discovered the ABO blood groups and explained the serious reactions that occur in humans as a result of incompatible transfusions. His work in the beginning of the 20th century won a Nobel Prize.

Next came devices designed for performing the transfusions. Edward E. Lindemann was the first to succeed. He carried out vein-to-vein transfusion of blood by using multiple syringes and a special cannula for puncturing the vein through the skin. However, this time-consuming, complicated procedure required many skilled assistants. It was not until Unger designed his syringe-valve apparatus that transfusions from donor to patient by an unassisted physician became practical.

An unprecedented accomplishment in blood transfusion was achieved in 1914 when Hustin reported the use of sodium citrate as an anticoagulant solution for transfusions. Later, in 1915, Lewisohn determined the minimum amount of citrate needed for anticoagulation and demonstrated its nontoxicity in small amounts. Transfusions became more practical and safer for the patient.

The development of preservative solutions to enhance the metabolism of the RBCs followed. Glucose was evaluated as early as 1916, when Rous and Turner introduced a citrate-dextrose solution for the preservation of blood. However, the function of glucose in RBC metabolism was not understood until the 1930s. Therefore, the common practice of using glucose in the preservative solution was delayed. World War II stimulated blood preservation research because the demand for blood and plasma increased. During World War II,

the pioneer work of Dr. Charles Drew on developing techniques in blood transfusion and blood preservation led to the establishment of a widespread system of blood banks.[1] In February 1941, Dr. Drew was appointed director of the first American Red Cross blood bank at Presbyterian Hospital.[1] The pilot program Dr. Drew established became the model for the national volunteer blood donor program of the American Red Cross.[1]

In 1943, Loutit and Mollison of England introduced the formula for the preservative acid-citrate-dextrose (ACD). Efforts in several countries resulted in the landmark publication of the July 1947 issue of the *Journal of Clinical Investigation,* which devoted nearly a dozen papers to the topic of blood preservation. Hospitals responded immediately, and in 1947 blood banks were established in many major cities of the United States; subsequently, transfusion became commonplace.

The daily occurrence of transfusions led to the discovery of numerous blood group systems. Antibody identification surged to the forefront as sophisticated techniques were developed. The interested student can review historic events during World War II in Kendrick's *Blood Program in World War II,* Historical Note.[2] In 1957, Gibson introduced an improved preservative solution called *citrate-phosphate-dextrose* (CPD), which was less acidic and eventually replaced ACD as the standard preservative used for blood storage.

Frequent transfusions and the massive use of blood soon resulted in new problems, such as circulatory overload. Component therapy has helped these problems. In the past, a single unit of whole blood could serve only one patient. With component therapy, however, one unit may be used for multiple transfusions. Today, health-care providers can select the specific component for their patient's particular needs without risking the inherent hazards of whole blood transfusions. Health-care providers can transfuse only the required fraction in the concentrated form, decreasing the possibility of overloading the circulatory system. Appropriate blood component therapy now provides more effective treatment and more complete use of blood products. Extensive use of blood during this period, coupled with component separation, led to increased comprehension of erythrocyte metabolism and a new awareness of the problems associated with RBC storage.

Current Status

AABB, formerly the American Association of Blood Banks, estimates that 6.8 million volunteers donate blood each year. Based on the 2015 National Blood Collection and Utilization Survey (NBCUS) approximately 12.6 million units of red blood cells (RBCs) were collected, and around 11.4 million were transfused.[3] This represents a decline of 11.6% and 13.9%, respectively since 2013.[4] With an aging population and advances in medical treatments requiring transfusions, the demand for blood and blood components is expected to continue to be high. It is estimated that one in three people will need blood at some point in their lifetime.[4] These units are donated by fewer than 10% of healthy Americans who are eligible to donate each year.[4] Volunteers can donate at blood drives conducted at their place of work, school, and church, as well as at community and hospital-based blood centers. Volunteer donors are not paid and provide nearly all of the blood used for transfusion in the United States.

Traditionally, the amount of whole blood in a unit has been 450 mL ± 10% of blood (1 pint). More recently, 500 mL ± 10% of blood is being collected.[5] These units are collected from donors with a minimum hematocrit of 38%.[5] Modified plastic collection systems are used when collecting 500 mL of blood, with the volume of anticoagulant preservative solution being increased from 63 to 70 mL. The total blood volume of most adults is 10 to 12 pints, and donors can replenish the fluid lost from the 1-pint donation in 24 hours. The donor's red blood cells are replaced within 1 to 2 months after donation.[4] A volunteer donor can donate whole blood every 8 weeks. (Refer to Chapter 13 on Donor Selection.)

Units of the **whole blood** collected can be separated into three components: **packed RBCs**, **platelets**, and **plasma.** In recent years, less whole blood has been used to prepare platelets because of the increased utilization of **apheresis** platelets. Hence, many units are converted only into RBCs and plasma. The plasma can be converted by **cryoprecipitation** to a clotting factor concentrate that is rich in fibrinogen. A unit of whole blood–prepared RBCs may be stored for 21 to 42 days, depending on the anticoagulant preservative solution used when the whole blood unit is collected and whether a preserving solution is added to the separated RBCs. Donated blood is free. However, there is a cost associated with collection, testing, processing, storing, and shipping of the blood components. The donation process consists of three predonation steps. Donors receive the following (Box 1–1):

1. Educational reading materials
2. A donor health history questionnaire
3. An abbreviated physical examination

BOX 1–1

The Donation Process

Step 1: Educational Materials

Educational material (such as the AABB pamphlet "An Important Message to All Blood Donors") that contains information on the risks of infectious diseases transmitted by blood transfusion, including the symptoms and signs of AIDS, is given to each prospective donor to read.

Step 2: The Donor Health History Questionnaire

A uniform donor history questionnaire, designed to ask questions that protect the health of both the donor and the recipient, is given to every donor. The health history questionnaire is used to identify donors who have been exposed to diseases that can be transmitted in blood (e.g., variant Creutzfeldt-Jakob, West Nile virus, malaria, babesiosis, or Chagas disease).

Step 3: The Abbreviated Physical Examination

The abbreviated physical examination for donors includes blood pressure, pulse, and temperature readings; hemoglobin or hematocrit level; and the inspection of the arms for skin lesions.

The donation process, especially steps 1 and 2, has been carefully modified over time to allow for the rejection of donors who may transmit transfusion-associated disease to recipients. For a more detailed description of donor screening and processing, refer to Chapter 13.

The nation's blood supply is safer than it has ever been because of the donation process and extensive laboratory testing of blood. Current infectious disease screening tests performed on each unit of donated blood are listed in Table 1–1. For a more detailed description of transfusion-associated disease, refer to Chapter 14.

RBC Biology and Preservation

Three areas of RBC biology are crucial for normal erythrocyte survival and function:

1. Normal chemical composition and structure of the RBC membrane
2. Hemoglobin structure and function
3. RBC metabolism[6]

Defects in any or all of these areas will result in RBCs surviving fewer than the normal 120 days in circulation.

Table 1–1 Current Donor Screening Tests for Infectious Diseases

Test	Date Test Required
Syphilis	1950s
Hepatitis B surface antigen (HBsAg)	1971
Hepatitis B core antibody (anti-HBc)	1986
Hepatitis C virus antibody (anti-HCV)	1990
Human immunodeficiency virus antibodies (anti-HIV-1/2)	1992[1]
Human T-cell lymphotropic virus antibody (anti-HTLV-I/II)	1997[2]
Human immunodeficiency virus (HIV-1) NAT*	1999
Hepatitis C virus (HCV) NAT*	1999
West Nile virus NAT	2004
Trypanosoma cruzi antibody (*anti-T. cruzi*)	2007
Hepatitis B virus (HBV) NAT	2009
Babesia microti antibody and NAT (recommended)	2012
Zika virus NAT	2016

NAT = nucleic acid amplification testing
*Initially under IND starting in 1999.
[1]Anti-HIV-1 testing implemented in 1985.
[2]Anti-HTLV testing implemented in 1988.

RBC Membrane

The RBC membrane represents a semipermeable lipid bilayer supported by a mesh-like protein cytoskeleton structure (Fig. 1–1).[7] Phospholipids, the main lipid components of the membrane, are arranged in a bilayer structure comprising the framework in which globular proteins traverse and move. Proteins that extend from the outer surface and span the entire membrane to the inner cytoplasmic side of the RBC are termed *integral* membrane proteins. Beneath the lipid bilayer, a second class of membrane proteins, called *peripheral* proteins, is located and limited to the cytoplasmic surface of the membrane forming the RBC cytoskeleton.[7]

Advanced Concepts

Both proteins and lipids are organized asymmetrically within the RBC membrane. Lipids are not equally distributed in the two layers of the membrane. The external layer is rich in glycolipids and choline phospholipids.[7] The internal cytoplasmic layer of the membrane is rich in amino phospholipids.[7] The biochemical composition of the RBC membrane is approximately 52% protein, 40% lipid, and 8% carbohydrate.[6]

As mentioned previously, the normal chemical composition and the structural arrangement and molecular interactions of the erythrocyte membrane are crucial to the normal length of RBC survival of 120 days in circulation. In addition, they maintain a critical role in two important RBC characteristics: deformability and permeability.[8]

Deformability

To remain viable, normal RBCs must also remain flexible, deformable, and permeable. The loss of adenosine triphosphate (ATP) (energy levels) leads to a decrease in the phosphorylation of spectrin and, in turn, a loss of membrane deformability.[6] An accumulation or increase in deposition of membrane calcium also results, causing an increase in membrane rigidity and loss of pliability.[8] These cells are at a marked disadvantage when they pass through the small (3 to 5 μm in diameter) sinusoidal orifices of the spleen, an organ that functions in extravascular sequestration, and removal of aged, damaged, or less deformable RBCs or fragments of their membrane. The loss of RBC membrane is exemplified by the formation of *spherocytes* (cells with a reduced surface-to-volume ratio; Fig. 1–2) and *bite cells*, in which the removal of a portion of membrane has left a permanent indentation in the remaining cell membrane (Fig. 1–3). The survival of these forms is also shortened.

Permeability

The permeability properties of the RBC membrane and the active RBC cation transport prevent colloid hemolysis and control the volume of the RBCs. Any abnormality that increases permeability or alters cationic transport may

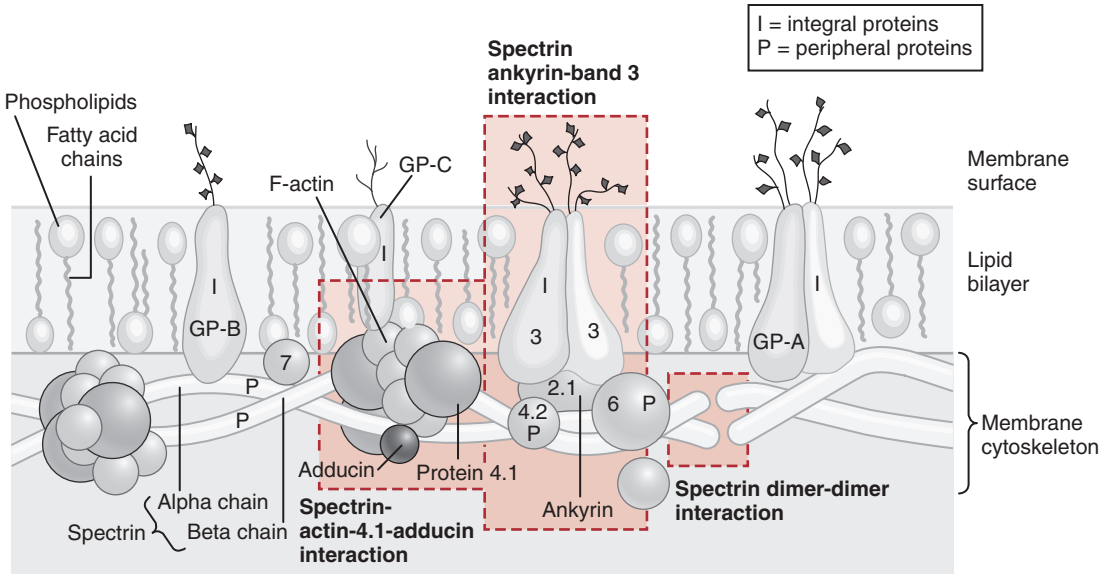

Figure 1–1. Schematic illustration of red blood cell membrane depicting the composition and arrangement of RBC membrane proteins. GP-A = glycophorin A; GP-B = glycophorin B; GP-C = glycophorin C; G = globin. Numbers refer to pattern of migration of SDS (sodium dodecyl sulfate) polyacrylamide gel pattern stained with Coomassie brilliant blue. Relations of protein to each other and to lipids are purely hypothetical; however, the positions of the proteins relative to the inside or outside of the lipid bilayer are accurate. (Note: Proteins are not drawn to scale and many minor proteins are omitted.) *(Reprinted with permission from Harmening, DH: Clinical Hematology and Fundamentals of Hemostasis, 5th ed., FA Davis, Philadelphia, 2009.)*

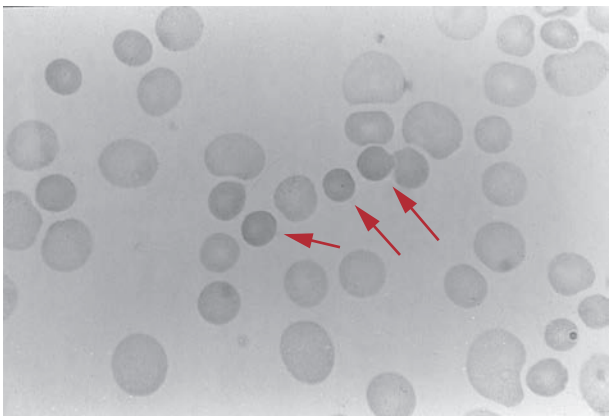

Figure 1–2. Spherocytes.

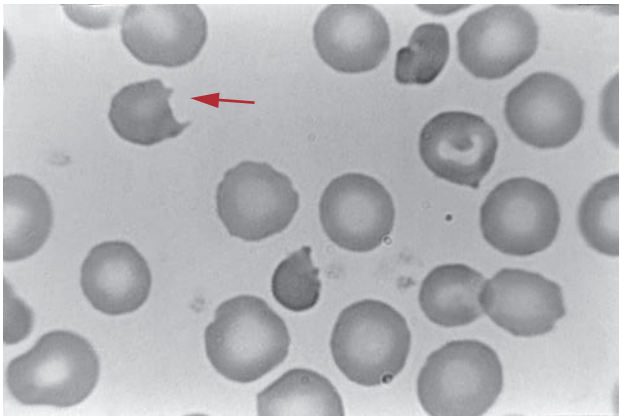

Figure 1–3. "Bite" cells.

decrease RBC survival. The RBC membrane is freely permeable to water and anions.[9] Chloride (Cl^-) and bicarbonate (HCO_3^-) can traverse the membrane in less than a second. It is speculated that this massive exchange of ions occurs through a large number of exchange channels located in the RBC membrane. The RBC membrane is relatively impermeable to cations such as sodium (Na^+) and potassium (K^+).

RBC volume and water homeostasis are maintained by controlling the intracellular concentrations of sodium and potassium.[9] The erythrocyte intracellular-to-extracellular ratios for Na^+ and K^+ are 1:12 and 25:1, respectively.[6] The 300 cationic pumps, which actively transport Na^+ out of the cell and K^+ into the cell, require energy in the form of ATP. Calcium (Ca^{2+}) is also actively pumped from the interior of the RBC through energy-dependent calcium-ATPase pumps.[6] Calmodulin, a cytoplasmic calcium-binding protein, is speculated to control these pumps and to prevent excessive intracellular Ca^{2+} buildup, which changes the shape and makes it more rigid.[6] When RBCs are ATP-depleted, Ca^{2+} and Na^+ are allowed to accumulate intracellularly, and K^+ and water are lost, resulting in a dehydrated rigid cell that is subsequently sequestered by the spleen, resulting in a decrease in RBC survival.[9]

Metabolic Pathways

The RBCs' metabolic pathways that produce ATP are mainly anaerobic because the function of the RBC is to deliver oxygen, not to consume it. Because the mature erythrocyte has no nucleus and there is no mitochondrial apparatus

for oxidative metabolism, energy must be generated almost exclusively through the breakdown of glucose.

Advanced Concepts

RBC metabolism may be divided into the anaerobic glycolytic pathway and three ancillary pathways that serve to maintain the structure and function of hemoglobin (Fig. 1–4): the pentose phosphate pathway, the methemoglobin reductase pathway, and the Luebering-Rapoport shunt. All of these processes are essential if the erythrocyte is to transport oxygen and to maintain critical physical characteristics for its survival. Glycolysis generates about 90% of the ATP needed by the RBC. Approximately 10% is provided by the pentose phosphate pathway. The methemoglobin reductase pathway is another important pathway of RBC metabolism, and a defect can affect RBC post-transfusion survival and function. Another pathway that is crucial to RBC function is the Luebering-Rapoport shunt. This pathway permits the accumulation of an important RBC organic phosphate, **2,3-diphosphoglycerate** (2,3-DPG). The amount of 2,3-DPG found within RBCs has a significant effect on the affinity of hemoglobin for oxygen and therefore affects how well RBCs function post-transfusion.

Hemoglobin-Oxygen Dissociation Curve

Hemoglobin's primary function is gas transport: oxygen delivery to the tissues and carbon dioxide (CO_2) excretion. One of the most important controls of hemoglobin affinity for oxygen is the RBC organic phosphate 2,3-DPG. The unloading of oxygen by hemoglobin is accompanied by widening of a space between β chains and the binding of 2,3-DPG on a mole-for-mole basis, with the formation of anionic salt bridges between the chains.[10] The resulting conformation of the deoxyhemoglobin molecule is known as the *tense (T) form*, which has a lower affinity for oxygen.[6] When hemoglobin loads oxygen and becomes oxyhemoglobin, the established salt bridges are broken, and β chains are pulled together, expelling 2,3-DPG. This is the *relaxed (R) form* of the hemoglobin molecule, which has a higher

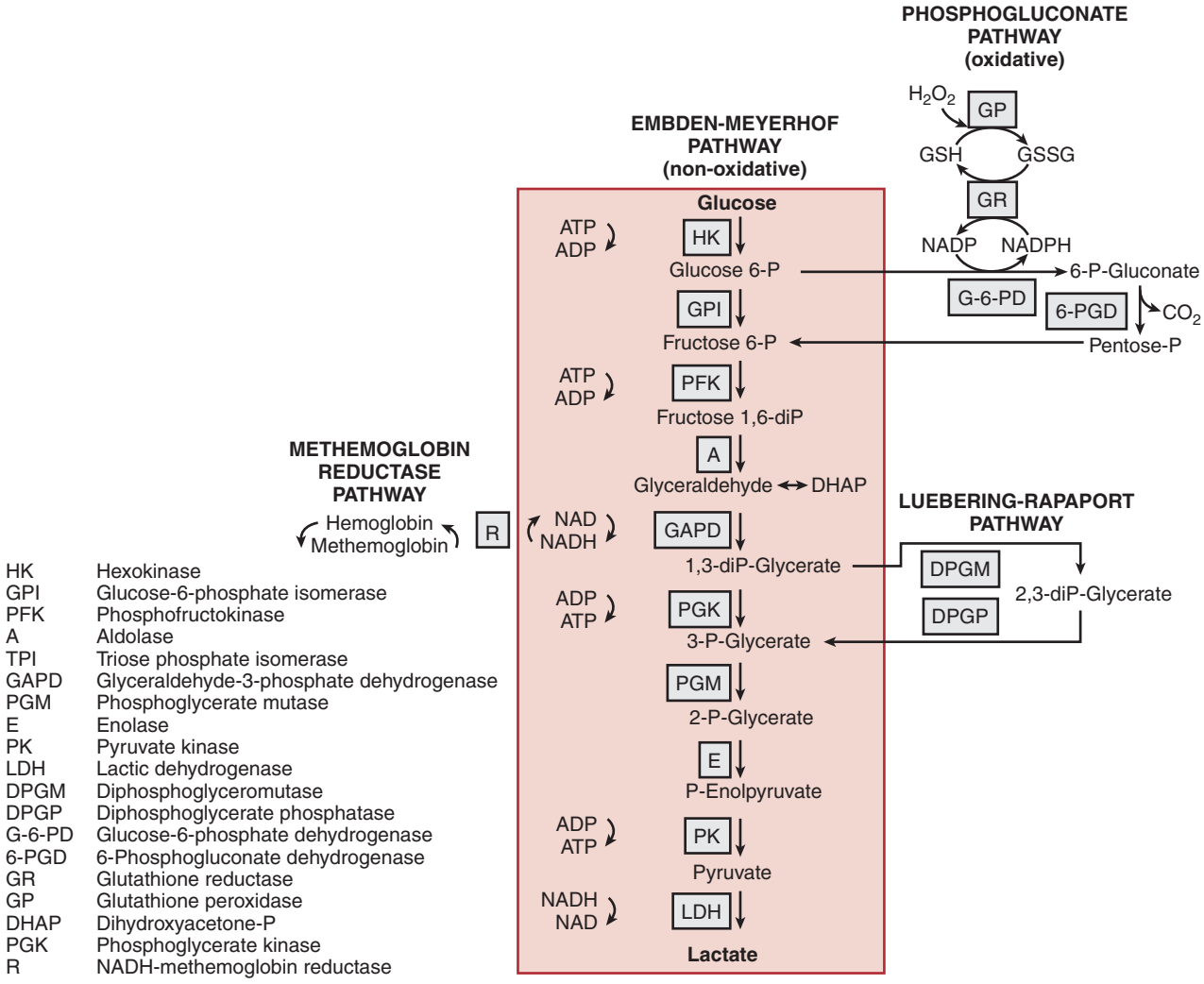

Figure 1–4. Red blood cell metabolism. *(Reprinted with permission from Hillman, RF, and Finch, CA: Red Cell Manual, 7th ed., FA Davis, Philadelphia, 1996.)*

affinity for oxygen.[6] These **allosteric changes** that occur as the hemoglobin loads and unloads oxygen are referred to as the *respiratory movement*. The dissociation and binding of oxygen by hemoglobin are not directly proportional to the partial pressure of oxygen (pO_2) in its environment but instead exhibit a **sigmoid-curve** relationship, known as the *hemoglobin-oxygen dissociation curve* (Fig. 1–5).

The shape of this curve is very important physiologically because it permits a considerable amount of oxygen to be delivered to the tissues with a small drop in oxygen tension. For example, in the environment of the lungs, where the pO_2 tension, measured in millimeters of mercury (mm Hg), is nearly 100 mm Hg, the hemoglobin molecule is almost 100% saturated with oxygen. As the RBCs travel to the tissues, where the pO_2 drops to an average of 40 mm Hg (mean venous oxygen tension), the hemoglobin saturation drops to approximately 75% saturation, releasing about 25% of the oxygen to the tissues.[6] This is the normal situation of oxygen delivery at a basal metabolic rate. The normal position of the oxygen dissociation curve depends on three different **ligands** normally found within the RBC: H^+ ions, CO_2, and organic phosphates. Of these three ligands, 2,3-DPG plays the most important physiological role. Normal hemoglobin function depends on adequate 2,3-DPG levels in the RBC. In situations such as hypoxia, a compensatory **shift to the right** of the hemoglobin-oxygen dissociation curve alleviates the tissue oxygen deficit. This rightward shift of the curve, mediated by increased levels of 2,3-DPG, decreases hemoglobin's affinity for the oxygen molecule and increases oxygen delivery to the tissues. A **shift to the left** of the hemoglobin-oxygen dissociation curve results, conversely, in an increase in hemoglobin-oxygen affinity and a decrease in oxygen delivery to the tissues. With such a dissociation curve, RBCs are much less efficient because only 12% of the oxygen can be released to the tissues.[6] Multiple transfusions of 2,3-DPG–depleted stored blood can shift the oxygen dissociation curve to the left.[10]

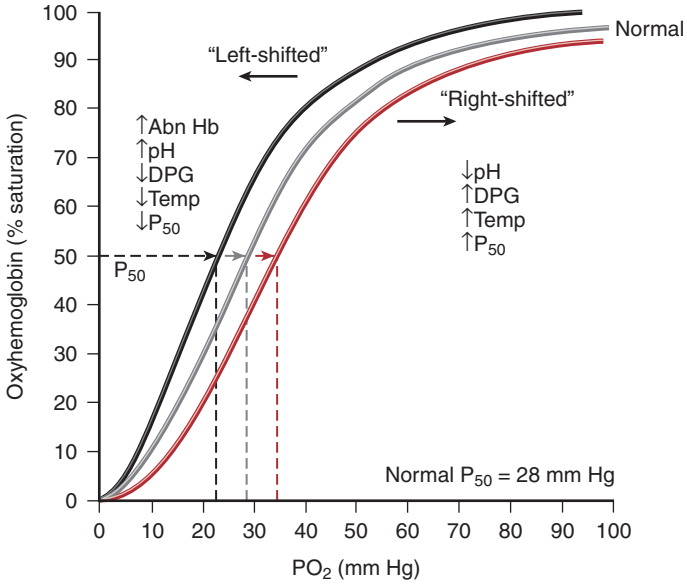

Figure 1–5. Hemoglobin-oxygen dissociation curve. *(Reprinted with permission from Harmening, DH: Clinical Hematology and Fundamentals of Hemostasis, 5th ed., FA Davis, Philadelphia, 2009.)*

RBC Preservation

The goal of blood preservation is to provide viable and functional blood components for patients requiring blood transfusion. RBC viability is a measure of **in vivo** RBC survival following transfusion. Because blood must be stored from the time of donation until the time of transfusion, the viability of RBCs must be maintained during the storage time as well. The U.S. Food and Drug Administration (FDA) requires an average 24-hour post-transfusion RBC survival of more than 75%.[11] In addition, the FDA mandates that red blood cell integrity be maintained throughout the shelf-life of the stored RBCs. This is assessed as free hemoglobin less than 1% of total hemoglobin.[11] These two criteria are used to evaluate new preservation solutions and storage containers. To determine post-transfusion RBC survival, RBCs are taken from healthy subjects, stored, and then labeled with radioisotopes, reinfused to the original donor, and measured 24 hours after transfusion. Despite FDA requirements, the 24-hour post-transfusion RBC survival at outdate can be less than 75% and in critically ill patients is often less than 75%.[12,13]

To maintain optimum viability, blood is stored in the liquid state between 1°C and 6°C for a specific number of days, as determined by the preservative solution(s) used. The loss of RBC viability has been correlated with the **storage lesion**, which is associated with various biochemical changes[14] (Table 1–2).

Advanced Concepts

Because low 2,3-DPG levels profoundly influence the oxygen dissociation curve of hemoglobin,[14] DPG-depleted

Table 1–2 RBC Storage Lesion

Characteristic	Change Observed
Viable cells (%)	Decreased
Glucose	Decreased
ATP	Decreased
Lactic acid	Increased
pH	Decreased
2,3-DPG	Decreased
Oxygen dissociation curve	Shift to the left (increase in hemoglobin and oxygen affinity; less oxygen delivered to tissues)
Plasma K^+	Increased
Plasma hemoglobin	Increased

RBCs may have an impaired capacity to deliver oxygen to the tissues. As RBCs are stored, 2,3-DPG levels decrease, with a shift to the left of the hemoglobin-oxygen dissociation curve, and less oxygen is delivered to the tissues. It is well accepted, however, that 2,3-DPG is re-formed in stored RBCs after in vivo circulation, resulting in restored oxygen delivery. The rate of restoration of 2,3-DPG is influenced by the acid-base status of the recipient, the phosphorus metabolism, the degree of anemia, and the overall severity of the disorder.[6] It has been reported that within the first hour after transfusion, most RBC clearance occurs.[13] Approximately 220 to 250 mg of iron are contained in one RBC unit.[15] Therefore, rapid RBC clearance of even 25% of a single unit of blood delivers a massive load of hemoglobin iron to the monocyte and macrophage system, potentially producing harmful effects.[12]

Despite the biochemical, structural, and functional changes that occur to RBCs during storage, there is no significant difference in rates of death between patients who were transfused with only fresh blood versus those patients who were transfused with the oldest blood available.[16]

Anticoagulant Preservative Solutions

Table 1–3 lists the approved anticoagulant preservative solutions for whole blood and RBC storage at 1°C to 6°C. The addition of various chemicals, along with the approved anticoagulant preservative CPD, was incorporated in an attempt to stimulate glycolysis so that ATP levels were better maintained.[17] One of the chemicals, adenine, incorporated into the CPD solution (CPDA-1) increases ADP levels, thereby driving glycolysis toward the synthesis of ATP. CPDA-1 contains 0.25 mM of adenine plus 25% more glucose than CPD. Adenine-supplemented blood can be stored at 1°C to 6°C for 35 days; the other anticoagulants are approved for 21 days. Table 1–4 lists the various chemicals used in anticoagulant solutions and their functions during the storage of red blood cells.

Table 1–3 Approved Anticoagulant Preservative Solutions

Name	Abbreviation	Storage Time (Days)
Acid citrate-dextrose (formula A)*	ACD-A	21
Citrate-phosphate dextrose	CPD	21
Citrate-phosphate-double-dextrose	CP2D	21
Citrate-phosphate-dextrose-adenine	CPDA-1	35

*ACD-A is used for apheresis components.

Advanced Concepts

It is interesting to note that blood stored in all CPD preservatives also becomes depleted of 2,3-DPG by the second week of storage. The reported pathophysiological effects of the transfusion of RBCs with low 2,3-DPG levels and increased affinity for oxygen include an increase in cardiac output, a decrease in mixed venous (pO_2) tension, or a combination of these.[18] The physiological importance of these effects is not easily demonstrated. This is a complex mechanism with numerous variables involved that are beyond the scope of this text.

Stored RBCs regain the ability to synthesize 2,3-DPG after transfusion, but levels necessary for optimal hemoglobin-oxygen delivery are not reached immediately. Approximately 24 hours are required to restore normal levels of 2,3-DPG after transfusion.[18] The 2,3-DPG concentrations after transfusion have been reported to reach normal levels as early as 6 hours post-transfusion.[18] Most of these studies have been performed on normal, healthy individuals. However, evidence suggests that, in the transfused subject whose capacity is limited by an underlying physiological disturbance, even a brief period of altered oxygen hemoglobin affinity is of great significance.[12] It is quite clear now that 2,3-DPG levels in transfused blood are important in certain clinical conditions. Some studies demonstrate that myocardial function improves following transfusion of blood with high 2,3-DPG levels during cardiovascular surgery.[18] Several investigators suggest that the patient in shock who is given 2,3-DPG–depleted erythrocytes in transfusion may have already strained the compensatory mechanisms to their limits.[18,19–21] Perhaps for this type of patient, the poor oxygen delivery capacity of 2,3-DPG–depleted cells makes a significant difference in recovery and survival.

It is apparent that many factors may limit the viability of transfused RBCs. One of these factors is the plastic material used for the storage container. The plastic must be sufficiently permeable to CO_2 in order to maintain higher pH levels during storage. Glass storage containers are no longer used in the United States. Currently, the majority of blood is stored in polyvinyl chloride (PVC) plastic bags. One issue associated with PVC bags relates to the plasticizer di(ethylhexyl)-phthalate (DEHP), which is used in the manufacture of the bags. It has been found to leach from the plastic into the lipids of the plasma medium and RBC membranes of the blood during storage. However, its use or that of alternative plasticizers that leach are important because they have been shown to stabilize the RBC membrane and therefore reduce the extent of hemolysis during storage. Another issue with PVC is its tendency to break at low temperatures; therefore, components frozen in PVC bags must be handled with care. In addition to PVC, polyolefin containers, which do not contain DEHP, are available for some components, and latex-free plastic containers are available for recipients with latex allergies.[5]

Table 1–4 Chemicals in Anticoagulant Solutions

Chemical	Function	Present In			
		ACD-A	CPD	CP2D	CPDA-1
Citrate (sodium citrate/citric acid)	Chelates calcium; prevents clotting.	X	X	X	X
Monobasic sodium phosphate	Maintains pH during storage; necessary for maintenance of adequate levels of 2,3-DPG.	X	X	X	X
Dextrose	Substrate for ATP production (cellular energy).	X	X	X	X
Adenine	Production of ATP (extends shelf-life from 21 to 35 days).				X

ACD-A = acid citrate-dextrose (formula A); CPD = citrate-phosphate dextrose; CP2D = citrate phosphate double dextrose; CPDA-1 = citrate-phosphate-dextrose-adenine; 2,3-DPG = 2,3-diphosphoglycerate; ATP = adenosine triphosphate

Additive Solutions

Additive solutions (AS) are preserving solutions that are added to the RBCs after removal of the plasma with or without platelets. Additive solutions are now widely used. One of the reasons for their development is that removal of the plasma component during the preparation of packed RBCs removed much of the nutrients needed to maintain RBCs during storage. This was dramatically observed when high-hematocrit RBCs were prepared. The influence of removing substantial amounts of adenine and glucose present originally in, for example, the CPDA-1 anticoagulant preservative solution, led to a decrease in viability, particularly in the last 2 weeks of storage.[16]

Packed RBCs prepared from whole blood units collected in primary anticoagulant preservative solutions can be relatively void of plasma with high hematocrits, which causes the units to be more viscous and difficult to infuse, especially in emergency situations. Additive solutions (100 mL to the packed RBCs prepared from a 450-mL blood collection) also overcome this problem. Additive solutions reduce hematocrits from around 65% to 80% to around 55% to 65% with a volume of approximately 300 to 400 mL.[22] The ability to pack RBCs to fairly high hematocrits before adding additive solution also provides a means to harvest greater amounts of plasma with or without platelets. Box 1–2 summarizes the benefits of RBC additive solutions.

Currently, four additive solutions are licensed in the United States:

1. Adsol (AS-1; Fenwal Inc.)
2. Nutricel (AS-3; Haemonetics Corporation)
3. Optisol (AS-5; Terumo Corporation)
4. SOLX (AS-7; Haemonetics Corporation)

BOX 1–2

Benefits of RBC Additive Solutions

- Extends the shelf-life of RBCs to 42 days by adding nutrients
- Allows for the harvesting of more plasma and platelets from the unit
- Produces a packed RBC of lower viscosity that is easier to infuse

The additive solution is contained in a **satellite bag** and is added to the RBCs after most of the plasma has been expressed. All three additives contain saline, adenine, and glucose. AS-1, AS-5, and AS-7 also contain mannitol, which protects against storage-related hemolysis, whereas AS-3 contains citrate and phosphate for the same purpose.[22] All of the additive solutions are approved for 42 days of storage for packed RBCs.[22] Table 1–5 lists the currently approved additive solutions.

Advanced Concepts

Table 1–6 shows the biochemical characteristics of RBCs stored in the additive solutions after 42 days of storage.[22,23,24] Additive system RBCs are used in the same way as traditional RBC transfusions. Blood stored in additive solutions is now routinely given to newborn infants and pediatric patients, although some clinicians still prefer CPDA-1 RBCs because of their concerns about one or more of the constituents in the additive solutions.[25]

None of the additive solutions maintain 2,3-DPG throughout the storage time. As with RBCs stored only with primary anticoagulant preservatives, 2,3-DPG is depleted by the second week of storage.[23]

Table 1–5 Additive Solutions in Use in North America

Name	Abbreviation	Storage Time (Days)
Adsol (Fenwal Inc.)	AS-1	42
Nutricel (Haemonetics Corporation)	AS-3	42
Optisol (Terumo Corporation)	AS-5	42
SOLX (Haemonetics)	AS-7	42

Table 1–6 Red Blood Cell Additives: Biochemical Characteristics

	AS-1	AS-3	AS-5	AS-7
Storage period (days)	42	42	42	42
pH (measured at 37°C)	6.6	6.5	6.5	6.6
24-hour survival*(%)	83	85.1	80	80
ATP (% initial)	68	67	68.5	91%
2,3-DPG (% initial)	6	6	5	**1.5 μmol/L/g Hb
Hemolysis (%)	0.5	0.7	0.6	0.3

*Survival studies reported are from selected investigators and do not include an average of all reported survivals.
**Reported by researchers using different units

Freezing and Rejuvenation

RBC Freezing

RBC freezing is primarily used for autologous units and the storage of rare blood types. **Autologous transfusion** (*auto* meaning "self") allows individuals to donate blood for their own use to meet their needs for blood transfusion (see Chapter 16, "Transfusion Therapy").

The procedure for freezing a unit of packed RBCs is not complicated. It involves the addition of a cryoprotective agent to RBCs that are less than 6 days old. Glycerol is used most commonly and is added to the RBCs slowly with vigorous shaking, thereby enabling the glycerol to permeate the RBCs. The cells are then rapidly frozen and stored in a freezer. The usual storage temperature is below –65°C, although storage (and freezing) temperature depends on the concentration of glycerol used.[23] Two concentrations of glycerol have been used to freeze RBCs: a high-concentration glycerol (40% weight in volume [wt/vol]) and a low-concentration glycerol (20% wt/vol) in the final concentration of the cryopreservative.[23] Most blood banks that freeze RBCs use the high-concentration glycerol technique.

Table 1–7 lists the advantages of the high-concentration glycerol technique in comparison with the low-concentration glycerol technique. See Chapter 15 for a detailed description of the RBC freezing procedure.

Currently, the FDA licenses frozen RBCs for a period of 10 years from the date of freezing; that is, frozen RBCs may be stored up to 10 years before thawing and transfusion.[26] Once thawed, these RBCs demonstrate function and viability near those of fresh blood. Experience has shown that 10-year storage periods do not adversely affect viability and function.[27] Table 1–8 lists the advantages and disadvantages of RBC freezing.

Advanced Concepts

Transfusion of frozen cells must be preceded by a deglycerolization process; otherwise, the thawed cells would be accompanied by hypertonic glycerol when infused, and RBC lysis would result. Removal of glycerol is achieved by systematically replacing the cryoprotectant with decreasing concentrations of saline. The usual protocol involves washing with 12% saline, followed by 1.6% saline, with a final wash of 0.2% dextrose in normal saline.[5] A commercially available cell-washing system, such as those manufactured by several companies, has traditionally been used in the deglycerolizing process. Excessive hemolysis is monitored by noting the hemoglobin concentration of the wash supernatant. Osmolality of the unit should also be monitored to ensure adequate deglycerolization. Traditionally, because

Table 1–7 Advantages of High-Concentration Glycerol Technique Over Low-Concentration Glycerol Technique

Advantage	High Glycerol	Low Glycerol
1. Initial freezing temperature	–80°C	–196°C
2. Need to control freezing rate	No	Yes
3. Type of freezer	Mechanical	Liquid nitrogen
4. Maximum storage temperature	–65°C	–120°C
5. Shipping requirements	Dry ice	Liquid nitrogen
6. Effect of changes in storage temperature	Can be thawed and refrozen	Critical

Table 1–8 Advantages and Disadvantages of RBC Freezing

Advantages	Disadvantages
Long-term storage (10 years)	A time-consuming process
Maintenance of RBC viability and function	Higher cost of equipment and materials
Low residual leukocytes and platelets	Storage requirements (–65°C)
Removal of significant amounts of plasma proteins	Higher cost of product

a unit of blood is processed in an **open system** (one in which sterility is broken) to add the glycerol (before freezing) or the saline solutions (for deglycerolization), the outdating period of thawed RBCs stored at 1°C to 6°C has been 24 hours.[23] Generally, RBCs in CPD or CPDA-1 anticoagulant preservatives or additive solutions are glycerolized and frozen within 6 days of whole blood collection.[23]

Closed-system devices have been developed that allow the glycerolization and deglycerolization processes to be performed under sterile conditions.[27] RBCs prepared from 450-mL collections and frozen within 6 days of blood collection with CPDA-1 can be stored after thawing at 1°C to 6°C for up to two weeks when prepared in a closed system.[23]

RBC Rejuvenation

Rejuvenation of RBCs is the process by which ATP and 2,3-DPG levels are restored or enhanced by metabolic alterations. Currently, FDA-approved rejuvenation solution contains phosphate, inosine, and adenine.[22] Rejuvenated RBCs may be prepared up to three days after expiration when stored in CPD, CPDA-1, and AS-1 storage solutions.[22] Currently, rejuvenated RBCs must be washed before infusion to remove the inosine (which may be toxic) and transfused within 24 hours or frozen for long-term storage.[22] The rejuvenation process is expensive and time-consuming, thus it is not used often; however, the process is invaluable for preserving selected autologous and rare units of blood for later use.

Current Trends in RBC Preservation Research

Advanced Concepts

Research and development in RBC preparation and preservation is being pursued in five areas:

1. Development of improved additive solutions
2. Development of procedures to reduce and inactivate the level of pathogens that may be in RBC units
3. Development of procedures to convert A, B, and AB type RBCs to O type RBCs
4. Development of methods to produce RBCs through bioengineering (blood pharming)
5. Development of RBC substitutes

Improved Additive Solutions

Research is being conducted to develop improved additive solutions for RBC preservation. One reason for this is because longer storage periods could improve the logistics of providing RBCs for clinical use.

Procedures to Reduce and Inactivate Pathogens

Research is being conducted to develop procedures that would reduce the level of or inactivate residual viruses, bacteria, and parasites in RBC units. One objective is to develop robust procedures that could possibly inactivate all pathogens that may be present, including new and emergent viruses. Amustaline (S-303) pathogen reduction system is currently being studied and has demonstrated adequate post-transfusion viability according to FDA criteria.[28] This nucleic acid-targeted pathogen inactivation technology was developed to reduce the risk of transfusion-transmitted infectious disease with RBC transfusions.[29] Areas of concern that must be addressed before pathogen inactivation technologies are approved for use with RBCs in the United States are potential toxicity, immunogenicity, cellular function, and cost. Currently, the FDA has not approved any Pathogen Reduction Technology (PRT) for use with RBCs.[29]

Formation of O Type RBCs

The inadequate supply of O type RBC units that is periodically encountered can hinder blood centers and hospital blood banks in providing RBCs for specific patients. Research over the last 30 years has been evaluating how A and B type RBCs can be converted to O type RBCs, the universal donor.[30] The use of enzymes that remove the carbohydrate moieties of the A and B antigens is the mechanism for forming O type RBCs.[30] The enzymes are removed by washing after completion of the reaction time.

Blood Pharming

Creating RBCs in the laboratory (**blood pharming**) is another area of research that has the potential to increase the amount of blood available for transfusion. In 2008, the Defense Advanced Research Projects Agency (DARPA) awarded Arteriocyte, a bioengineering company, a contract to develop a system for producing O-negative RBCs on the battlefield.[31] The company, which uses proprietary technology (NANEX) to turn hematopoietic stem cells (HSCs) from umbilical cords into type O, Rh-negative RBCs, sent its first shipment of the engineered blood to the FDA for evaluation in 2010.[31] FDA approval is required before human trials can begin. Cultured RBCs generated from in vitro hematopoietic stem

cells has been reported as well.[32] However, this has not proven practical for routine transfusion. The challenges associated with blood pharming are scalability or large-scale production and cost-effectiveness.

RBC Substitutes

Scientists have been searching for a substitute for blood for over 150 years. Blood substitutes continue to be of interest because of their potential to alleviate shortages of donated blood. In the 1980s, safety concerns about **HIV** led to renewed interest in finding a substitute for human blood; and more recently, the need for blood on remote battlefields has heightened that interest.[33] The U.S. military is one of the strongest advocates for the development of blood substitutes, which it supports through its own research and partnerships with private-sector companies.[33] Today the search continues for a safe and effective oxygen carrier that could eliminate many of the problems associated with blood transfusion, such as the need for refrigeration, limited shelf-life, compatibility, immunogenicity, transmission of infectious agents, and shortages. Box 1–3 lists the potential benefits of artificial oxygen carriers. Since RBC substitutes are drugs, they must go through extensive testing in order to obtain FDA approval. Safety and efficacy must be demonstrated through clinical trials. Table 1–9 outlines the different phases of testing.

Current research on blood substitutes is focused on two areas: **hemoglobin-based oxygen carriers** (HBOCs) and **perfluorocarbons** (PFCs).[34,35] Originally developed to be used in trauma situations such as accidents, combat, and surgery, RBC substitutes have, until recently, fallen short of meeting requirements for these applications.[34] Despite years of research, RBC substitutes are still not in routine use today. South Africa, Mexico, and Russia are the only countries in which blood substitutes are approved for clinical use. None have received FDA approval for clinical use in the United States, although specific products are still in phase III clinical trials.

BOX 1–3

Potential Benefits of Artificial Oxygen Carriers

- Abundant supply
- Readily available for use in prehospital settings, battlefields, and remote locations
- Can be stockpiled for emergencies and warfare
- No need for typing and crossmatching
- Available for immediate infusion
- Extended shelf-life (1 to 3 years)
- Can be stored at room temperature
- Free of bloodborne pathogens
- At full oxygen capacity immediately
- Do not prime circulating neutrophils, reducing the incidence of multiorgan failure
- Can deliver oxygen to tissue that is inaccessible to RBCs
- Have been accepted by Jehovah's Witnesses
- Could eventually cost less than units of blood

Table 1–9 Phases of Testing

Phase	Description of Testing
Preclinical	In vivo and animal testing.
Phase I	Researchers test drug in a small group of people (20 to 80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
Phase II	The drug is given to a larger group of people (100 to 300) to see if it is effective and to further evaluate its safety.
Phase III	The drug is given to large groups of people (1,000 to 3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug to be used safely.
Phase IV	Postmarketing studies to gather additional information about the drug's risks, benefits, and optimal use.

Hemoglobin-Based Oxygen Carriers

HBOC commercial development focused on "oxygen therapeutic" indications to provide immediate oxygenation until medical or surgical interventions could be initiated. Early trauma trials with HemAssist® (BAXTER), Hemopure® (HbO_2Therapeutics), and PolyHeme® (NORTHFIELD Laboratories) for resuscitating hypotensive shock all failed due to the safety concerns of cardiac issues and increased mortality.

Although several HBOCs have progressed to phase II and III clinical trials, currently none have been approved for clinical use in humans in the United States.[36,37] A 2008 meta-analysis of 16 clinical trials involving 3,711 patients and five different HBOCs found a significantly increased risk of death and myocardial infarction associated with the use of HBOCs.[37] As a result, in 2008, the Food and Drug Administration (FDA) put all HBOC trials in the United States on clinical hold due to the unfavorable outcomes.[35] However, Hemopure (HBOC-201) and PolyHeme are still in phase III clinical trials in the United States and Europe.[38] Hemopure was approved for clinical use in South Africa in 2001 to treat adult surgical patients who are anemic, and in Russia for acute anemia.[34] Many HBOCs have been researched; however, the majority have been discontinued due to complications of cardiac toxicity, gastrointestinal distress, neurotoxicity, renal failure, and increased mortality.[34] Table 1–10 summarizes some of the many HBOCs developed.

However, some experts believe that HBOCs hold more promise than PFCs.[33,39]

Table 1–11 lists the advantages and disadvantages of HBOCs.

Perfluorocarbons

Perfluorocarbons are synthetic hydrocarbon structures in which all hydrogen atoms have been replaced with fluorine. They are chemically inert, are excellent gas solvents, and

Passenger lymphocytes Donor lymphocytes in the transplanted organ or HPC (hereditary progenitor cell) product.

Paternity index Term that refers to a statement of "weight" concerning the probability a tested individual, who cannot be excluded as the parent of the child, is the true parent. The paternity index represents a likelihood ratio that compares two mutually exclusive hypotheses. The numerator of the ratio reflects the probability the tested alleged parent is the true parent of the child and the denominator reflects the probability someone random and unrelated to the alleged parent is the true parent.

Patient blood management A multidisciplinary systems-based process encompassing all processes related to blood transfusion to limit and prevent inappropriate or unnecessary transfusions while promoting strategies to reduce the overall transfusion requirements of patients. Also: a multidisciplinary process to apply strategies to avoid or at least minimize a patient's transfusion needs from the preoperative period through discharge.

Perfusion Supplying an organ or tissue with nutrients and oxygen by passing blood or another suitable fluid through it.

Perioral paresthesia Tingling around the mouth occasionally experienced by apheresis donors, resulting from the rapid return of citrated plasma, which contains citrate-bound calcium and free citrate.

Peroxidase An enzyme that hastens the transfer of oxygen from peroxide to a tissue that requires oxygen; this process is essential to intracellular respiration.

Phagocytosis Ingestion of microorganisms, other cells, and foreign particles by a phagocyte.

Phenotype The outward expression of genes (e.g., a blood type). On blood cells, serologically demonstrable antigens constitute the phenotype, except those sugar sites that are determined by transferases.

Phenylthiocarbamide (PTC) A chemical used in studying medical genetics to detect the presence of a marker gene. About 70% of the population inherits the ability to taste PTC, which tastes bitter; the remaining 30% finds PTC tasteless. The inheritance of this trait is due to a single dominant gene of a pair.

Phlebotomy The procedure used to draw blood from a person.

Phosphoglyceromutase A red blood cell enzyme.

Phototherapy Exposure to sunlight or artificial light for therapeutic purposes.

Plasma The liquid portion of whole blood, containing water, electrolytes, glucose, fats, proteins, and gases. Plasma contains all the clotting factors necessary for coagulation but in an inactive form. Once coagulation occurs, the fluid is converted to serum.

Plasma cell A B lymphocyte–derived cell that secretes immunoglobulins or antibodies.

Plasmapheresis A procedure using a machine to remove only plasma from a donor or patient.

Plasma protein fraction (PPF) Also known as Plasmanate; sterile pooled plasma stored as a fluid or freeze-dried and used for volume replacement.

Plasmid Bacterial circular genetic element, 2 to 4 kb long, that replicates independently from the chromosome. Used as vectors in recombinant DNA technology to carry up to 15 kb foreign DNA into host cells. A vast selection of plasmids are commercially available that are useful for different purposes, such as DNA sequencing, protein expression in bacteria, and protein expression in mammalian cells.

Plasminogen A protein in many tissues and body fluids important in preventing fibrin clot formation.

Plasmodium *See* Malaria.

Plasmodium knowlesi A parasite that causes malaria in monkeys.

Platelet A round or oval disk, 2 to 4 μm in diameter, that is derived from the cytoplasm of the megakaryocyte, a large cell in the bone marrow. Platelets play an important role in blood coagulation, hemostasis, and blood thrombus formation. When a small vessel is injured, platelets adhere to each other and to the edges of the injury, forming a "plug" that covers the area and initially stops the blood loss.

Platelet concentrate Platelets prepared from a single unit of whole blood or plasma and suspended in a specific volume of the original plasma; also known as *random-donor platelets*.

Plateletpheresis A procedure using a machine to remove only platelets from a donor or patient.

Platelet refractoriness Failure to yield an increase in recipient's platelet count on transfusion of suitably preserved platelets. HLA alloimmunization is a common cause.

Point mutation A change in a base in DNA that can lead to a change in the amino acid incorporated into the polypeptide; identifiable by analysis of the amino acid sequences of the original protein and its mutant offspring.

Polarity (3′ and 5′ ends) Also called DNA "directionality," determines the direction of DNA replication and transcription. Results from the antiparallel way that the two strands of nucleotides ran in opposite directions. The labels 3′ and 5′ refer to the number assigned by convention to the deoxyribose carbon atom linked to either hydroxyl or phosphate group in DNA molecule.

Polyacrylamide gel A polymer of acrylamide, used as a matrix for gel electrophoresis that provides better resolution than agarose electrophoresis.

Polyagglutination A state in which an individual's red blood cells are agglutinated by all sera, regardless of blood type.

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