MODERN BLOOD BANKING AND TRANSFUSION PRACTICES

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FOREWORD

Blood transfusion science is one of the newest branches of medical laboratory science. Blood groups were only discovered approximately 80 years ago and most of them have only been recognized in the last 30 years. Although transfusion therapy was used soon after the ABO blood groups were discovered, it was not until after World War II that blood transfusion science really started to become an important branch of medical science in its own right. Thus, compared with many branches of medicine, or even pathology, blood transfusion science is an infant, growing fast, changing continually, and presenting a great potential for research and future development.

To be able to grow, our young infant needs to be nurtured with a steady flow of new knowledge generated from research. This knowledge then has to be applied at the bench. To understand and best take advantage of the continual flow of new information being generated by blood transfusion scientists, and to apply it to everyday work in the blood bank, technologists (and pathologists) need to have a good understanding of basic immunology, genetics, biochemistry (particularly membrane chemistry), and the physiology and function of blood cells. To apply new concepts they need technical expertise and enough flexibility to reject old dogma when necessary and accept new ideas when they are supported by sufficient scientific data.

High standards are always expected and strived for by technologists who are working in blood banks or transfusion service. I very much believe that technologists should understand the principles behind the tests they are performing, rather than performing tasks like a machine does. Because of this, I do not think that "cook book" technical manuals have much value in *teaching* technologists; they do have a place as reference books in the laboratory. Over the years (too many to put in print) that I have been involved in teaching medical technologists, it has been very difficult to

select *one* book to cover all that technologists in training need to know about blood transfusion science, without confusing them. Classic texts used regularly in teaching SBB students and pathology residents often contain too much information for the average medical technologist, especially those in training. They contain certain sections that can, and perhaps should, be read, but sometimes even these sections may serve to confuse learners rather than help and stimulate them. Some of them are written to be encyclopedic reference tomes, and others contain a great deal of clinical material or esoterica that are unnecessary for medical technologists who are not yet greatly experienced in blood transfusion practice.

Dr. Harmening Pittiglio has produced a single volume that covers everything a student of medical technology needs to know about blood transfusion science. She has been involved in teaching medical technologists for most of her career, and after seeing how she has arranged this book, I would guess that her teaching philosophies are close to those of my own. She has gathered together a group of experienced scientists and teachers who together with her cover all the important areas of blood transfusion science.

The chapters on the basic principles of cell preservation, genetics, and immunology provide a firm base for the learner to understand the practical and technical importance of the other chapters. The chapters on the blood groups and transfusion practice provide enough information for medical technologists, without overwhelming them with esoterica and clinical details.

Although this book was primarily designed for medical technologists, I believe it is admirably suited to pathology residents, hematology fellows, and others who want to review any aspect of modern blood transfusion science.

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PREFACE

This book is designed to provide the medical technologist or blood bank specialist with a concise and thorough guide to transfusion practices and immunohematology. A problem-oriented approach to the subject matter has been incorporated to provide the practitioner with a working knowledge of modern, routine blood banking.

An introduction to the historical aspects of blood transfusion and preservation is presented as a prelude to current procedures utilized in donor phlebotomy, component preparation, and blood storage and preservation. In addition, new approaches to the above are discussed as an introduction to current research. Federal regulations have also been included in an attempt to clarify the issues of required quality control procedures for the routine blood bank laboratory.

Basic physiology as affected by blood loss will be examined as well as the pathophysiology of the red cells utilized in transfusion, both routine and massive. Consideration will be given to red cell metabolism, hemoglobin structure and function, and assessment of the need for transfusion therapy in a variety of clinical situations (e.g., trauma, chronic anemia, hemorrhagic disorders, and leukemia). A discussion of the adverse effects of blood transfusion will be incorporated in light of previously evaluated clinical disorders.

A thorough and current overview of blood group serology will be presented in the text in terms of basic immunology, inheritance and synthesis of blood group systems, and serologic activity of the associated antibodies. Certain clinical situations that are particularly relevant to blood banking will be discussed in detail, including hemolytic transfusion reactions, hemolytic diseases of the newborn, and autoimmune hemolytic anemia. In addition, a detailed discussion of compatibility testing and autoantibodies will be emphasized as it pertains to the clinical situations already described. Both federal and AABB regulations will be cited throughout the text as well as references at the conclusion of each chapter for further consideration. Finally, this text will also include chapters on human leukocyte antigens (HLA) and paternity testing, two areas that are often neglected in other texts.

This book is intended to bring about improved patient care by providing the reader with a basic understanding of the function of blood, the involvement of blood group antigens and antibodies, the principles of transfusion therapy, and the physiologic mechanisms of blood loss and replacement. It has been designed to generate an "unquenchable thirst for knowledge" in all medical technologists, blood bankers, and practitioners whose education, knowledge, and skills provide the public with excellent health care.

D. Harmening Pittiglio, Ph.D., M.S., MT(ASCP)

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CHAPTER 1

BLOOD PRESERVATION: HISTORICAL PERSPECTIVES AND CURRENT TRENDS

DENISE HARMENING PITTIGLIO, PH.D., MT(ASCP)

HISTORICAL ASPECTS

Man has always been fascinated by blood. Ancient Egyptians bathed in it. Aristocrats drank it. Authors and playwrights used it as themes. And modern man transfuses it. The road to an efficient, safe, and uncomplicated transfusion technique has been at best rough. But great progress is being made.

In 1492 blood was taken from three young men and was given to the stricken Pope Innocent VII in the hope of curing him. All four died. For the first time, a blood transfusion was duly recorded in history. The path to the successful transfusions so familiar today is marred by many reported failures. But man's physical, spiritual, and emotional fascination with blood is primordial. Why did success elude experimenters for so long?

Clotting was the principal obstacle. 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 went further. He discovered the ABO blood groups and explained the serious reactions that occur in humans as a result of incompatible transfusions.

Next came appropriate devices designed for performing the transfusions. 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. But 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 and glucose as a diluent and 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 red cell followed. Glucose was tried as early as 1914, but its function in red cell 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. 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 blood preservation. Hospitals responded immediately, and in 1947 blood banks were established in many major cities of the United States. Transfusion became commonplace. The daily occurrence of transfusions led to the discovery of numerous blood group systems. And antibody identification surged to the forefront as sophisticated techniques were developed. The interested student can review historical events during World War II in Kendrick's *Blood Program in World War II, Historical Note.*[1]

Frequent transfusions and the massive use of blood soon resulted in new problems, such as circulatory overload. Component therapy has solved these. Before, a single unit of whole blood could serve only one patient. With component therapy, however, one unit may be used for multiple transfusions. Today, the physician can select the specific component for his patient's particular needs without risking the inherent hazards of whole blood transfusions. He can transfuse only the required fraction in concentrated form, without overloading the circulation. 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 compo-

nent separation, led to increased comprehension of erythrocyte metabolism and a new awareness of the problems associated with red cell storage.

RED BLOOD CELL METABOLISM

The goal of blood preservation is to provide viable and functional blood components for patients needing blood transfusion. Research in this area has focused on maintaining red cell viability during storage and lengthening red cell post-transfusion survival. These are paramount considerations in blood preservation research.

Viability is a measure of in vivo red cell survival following transfusion. Seventy percent survival of transfused red cells after 24 hours is the lower limit for a successful transfusion. This arbitrary figure was first introduced by Rous and associates[2] in 1947. As storage time increases, red cell viability decreases. As a result, blood has always been assigned a limited, predetermined storage or shelf-life.

The loss of red cell viability has been correlated with the "lesion of storage," which is associated with various biochemical changes. These changes include a decrease in pH, a buildup of lactic acid, a decrease in glucose consumption, a decrease in ATP (adenosine triphosphate) levels, and a loss of red cell function, expressed as a shift to the left of the hemoglobin-oxygen dissociation curve or an increase in hemoglobin-oxygen affinity.

Viability is usually associated with both red cell ATP levels and membrane integrity. If viability can be maintained, the storage time of blood can be increased and the 70-percent post-transfusion survival of red cells ensured. Survival time of transfused red cells has been shown to correlate with ATP levels.[3] When ATP levels fall below approximately 1.5 μmole per g hemoglobin, viability is markedly impaired. In fact, Dern and coworkers[3] have established 1.5 μmoles per g hemoglobin as the minimum acceptable ATP level for 70-percent post-transfusion survival of red cells stored in acid-citrate-dextrose (ACD) and citrate-phosphate-dextrose (CPD) preservatives (Fig. 1-1). Therefore, any preservative that does not maintain ATP levels above approximately 1.5 μmole per g hemoglobin is unlikely to maintain adequate viability of stored red cells. Adequate ATP levels are necessary for maintenance of (1) red cell membrane integrity and deformability; (2) red cell volume, by sustaining the Na^+/K^+ ATPase pumps; (3) hemoglobin function; (4) adequate amounts of red cell reduced pyridine nucleotides; and (5) red cell plasma-lipid exchange.

Red cells generate energy almost exclusively through the breakdown of glucose, since the metabolism of the anucleated erythrocyte is more limited than that of other body cells. The adult red cell possesses little ability to metabolize fatty acids and amino acids. Additionally, mature erythrocytes contain no mitochondrial apparatus for oxidative metabolism. The red cell's metabolic pathways are mainly anaerobic, as one expects, since the function of the red cell is to deliver oxygen, not to consume it. Red cell cellular energetics may be divided into the *anaerobic glycolytic pathway* and three ancillary pathways that serve to maintain the function

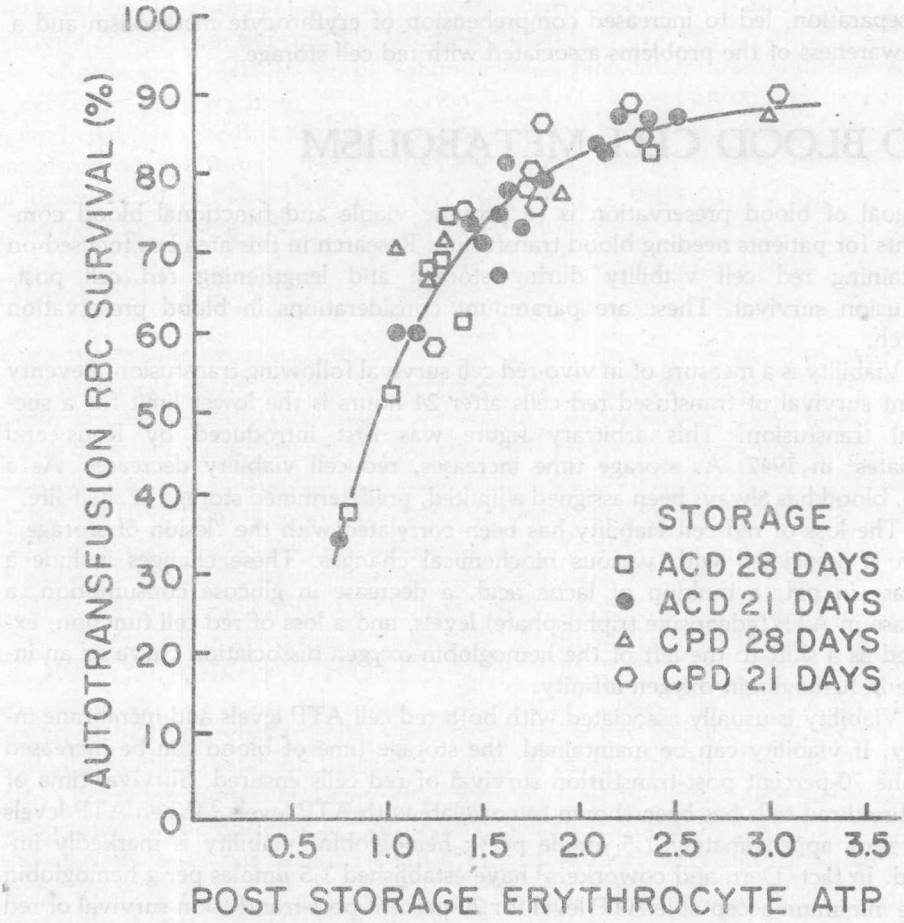

FIGURE 1-1. ATP levels and post-transfusion RBC survival.

of hemoglobin[4] (Fig. 1-2). All of these processes are essential if the erythrocyte is to transport oxygen and maintain those physical characteristics required for its survival in circulation.

Ninety percent of the ATP needed by red blood cells is generated in glycolysis, the erythrocyte's main metabolic pathway. Approximately 10 percent of the red cell's ATP is provided by the *pentose phosphate pathway*, which couples oxidative metabolism with pyridine nucleotide and glutathione reduction. The activity of this pathway increases following increased oxidation of glutathione or retardation of the glycolytic pathway.[5]

When the pentose phosphate pathway is functionally deficient, the amount of reduced glutathione becomes insufficient to neutralize intracellular oxidants. This results in globin denaturation and precipitation as aggregates (Heinz bodies) within the cell.[4] If this process results in sufficient membrane damage, cell destruction occurs.

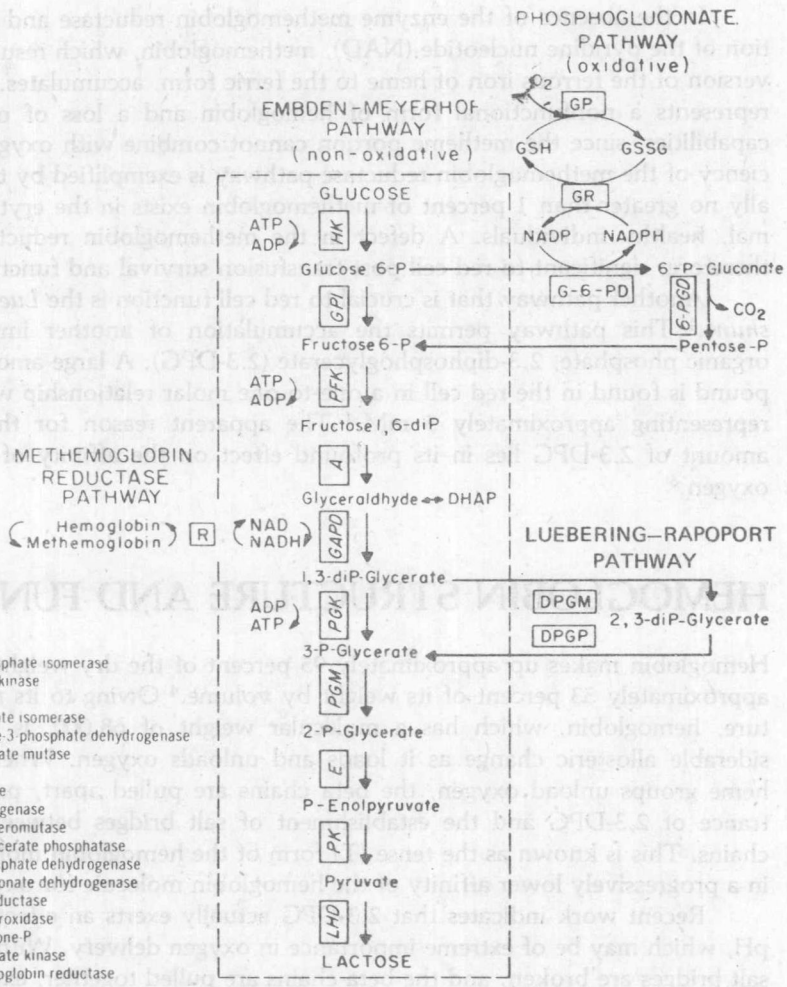

FIGURE 1-2. Pathways of red cell metabolism.

Such oxidative destruction of the red cells usually occurs as a result of an increased oxidant load with a latent decrease in pathway capacity. It is clear, therefore, that some activity in this pathway is essential for normal red cell survival.

The *methemoglobin reductase pathway* is another important component of red cell metabolism. Two methemoglobin reductase systems are important in maintaining hemoglobin in a reduced functional state. Both pathways are dependent on the regeneration of reduced pyridine nucleotides and are referred to as NADH methemoglobin reductase and NADPH methemoglobin reductase. Of the two pathways, there is a physiologic preference for the NADH methemoglobin reductase activity. This pathway is necessary to maintain the heme iron of hemoglobin in the ferrous (Fe^{++}) functional state.