An Introduction to IMMUNOHEMATOLOGY

Second Edition

BRYANT

NEVILLE J. BRYANT
A.R.T., F.A.C.B.S.
Chief Technologist
Blood Transfusion Laboratory
Toronto Western Hospital
Toronto, Ontario, Canada

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1 Goldthorne Avenue
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Apartado 26370—Cedro 512
Mexico 4, D.F., Mexico

Rua Coronel Cabrita, 8
Sao Cristovao Caixa Postal 21176
Rio de Janeiro, Brazil

9 Waltham Street
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Preface

This second edition of *An Introduction to Immunohematology* has been expanded to encompass considerably more information than was contained in the first edition. It is hoped that the additional material will provide a source of reference for laboratories and will serve to whet the appetites of students whose curiosity requires a more detailed explanation of the science and its peculiarities.

Once again, objectives have been included—this time with each chapter—as have sets of examination questions so that the student may test his or her knowledge of each section. In this edition, answers to these questions have been provided at the end of the text.

In preparing this book, I have used the 8th edition of the *Technical Manual* of the American Association of Blood Banks (1981) as a constant source of reference. In the majority of cases, the techniques included are those recommended by the American Association of Blood Banks.

This new edition has been highly referenced with respect to authors of original papers, and it is hoped that this inclusion will prove useful to those requiring such references for the additional data they contain and to students in the preparation of reading assignments, papers or theses.

Despite these changes, the basic purpose of the book remains unchanged: to introduce the newcomer to the major information available and to provide, collected in one place, the essentials of the subject matter. As such, it is my hope that the book will continue to be used as a guide to the fascinating, intricate science that immunohematology has become.

NEVILLE BRYANT

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To these and to all others who have helped in one way or another, I express my gratitude. The responsibility for the book's shortcomings and errors is, of course, exclusively my own.

A Brief History of Blood Transfusion

The possibility of transferring blood from the vessels of one individual directly into those of another was considered, although not seriously, as early as the sixteenth century. The positive era of blood transfusion really began when William Harvey, at a lecture on anatomy at the College of Physicians, England, described the circulation of blood in 1616. Some years later, in 1665, the first animal-to-animal blood transfusions were successfully performed by an English physiologist, Richard Lower, who kept exsanguinated dogs alive by transfusion of blood from other dogs.

In 1667, Jean Baptiste Denys, a Montpellier philosopher, mathematician and personal physician to Louis XIV, successfully transfused nine ounces of blood from the carotid artery of a lamb into the vein of a young man. Subsequent transfusions using animal blood were also performed by Denys, but most of them were unsuccessful; in some cases, patients began to pass black urine. Finally, the wife of a patient who died following three transfusions took legal action against Denys, charging him with murder. A long legal battle ensued, and while Denys was exonerated, from this time on transfusions were prohibited except with the sanction of the Faculty of Medicine in Paris. Then, in 1678, an edict of the French Parliament declared transfusion unlawful, and this decision caused similar edicts to be passed in other countries.

During the next 150 years, little was written or done about transfusion until 1818. That year James Blundell, an English obstetrician and physiologist, advocated the use of blood transfusion as a means of furnishing blood to women who were exsanguinated at childbirth. In October 1818, Blundell gave the first transfusion from man to man. (This is, in fact, disputed by supporters of Philip Syng Physick, who, it is stated, transfused human beings with human blood before Blundell. Physick's aversion to publication may well have denied him the distinction of having been the first to successfully perform person-to-person transfusions.)

The immunologic era was introduced in 1900, when Karl Landsteiner discovered the blood groups by noting the agglutinating properties of the erythrocytes of some persons with the serum of others. This agglutination phenomenon had, in fact, already been noted by S. G. Shattock in 1899 but was interpreted to be the result of rheumatic fever. Other diseases were subsequently held responsible for agglutination by the same investigator.

Landsteiner isolated three groups, which he called 1, 2 and 3. Decastello and Sturli, his pupils, discovered the group we now call AB in 1902, yet

considered it exceptional because it lacked agglutinins. Only in 1906 did Jansky recognize that it, too, was physiologic and representative of the fourth blood group.

Jansky recommended the use of roman numerals to signify the blood groups. The numeral "I" was used for the group we now call "O," "II" represented the group we now call "A," "III" represented the group we now call "B" and "IV" was used for the group discovered by Decastello and Sturli. In 1910, Moss, unaware of Jansky's report, independently classified the groups but reversed groups I and IV, which led to confusion. In 1921, the American Medical Association recommended the adoption of the Jansky classification on the basis of priority. This decision held only until 1928, when the League of Nations adopted the present international ABO classification.

Up until 1914, there was no knowledge of how to store blood. When a patient required a transfusion, it was necessary for the donor to lie next to the patient and for the blood to be directly transferred. Various anticoagulants, such as phosphate, hirudin and peptone, were tried; blood was defibrinated and oxalated, yet in all cases poor results were obtained. Agote, in 1915, introduced sodium citrate as an anticoagulant, and soon afterward it was independently introduced for the same purpose in the United States by Lewisohn. This considerably simplified transfusion practices, since it allowed for the collection and storage of blood prior to transfusion. In 1916, Rous and Turner published studies on the preservation of stored blood. Their results were applied by Oswald Robertson, who conceived of and operated the first blood bank in France during World War I.

Hektoen (1907a, 1907b) is credited with being the first to suggest the tremendous importance of blood grouping for transfusion (a surprising fact in retrospect, since this was the first practical application of Landsteiner's discovery). Ottenberg (1911) was probably the first to actually select compatible blood for transfusion, and Moss published his suggested compatibility test method in 1914. Biologic pretransfusion tests, however, were still carried out as late as 1931. Various techniques were applied, including the infusion of 10 to 20 ml of blood 15 minutes prior to transfusion; the blood was considered "compatible" if no untoward reaction occurred.

In 1908, Ottenberg and Epstein suggested that the blood groups were inherited, and this was established beyond doubt by von Dungern and Hirszfeld in 1910. The exact manner of inheritance was explained by Bernstein in 1925. Blood grouping had now spilled over into the field of genetics, and had also become of significance in forensic medicine in cases of disputed paternity.

In 1927, Landsteiner and Levine discovered the MN system and the P system through the direct immunization of animals with human red cells. While these systems did not affect the transfusion of blood, they were of tremendous genetic and anthropologic significance.

The second most important contribution to the history of the blood groups was made by Levine and Stetson (1939) and Landsteiner and Weiner (1940) through the discovery of the Rh system and its role in the disease known as erythroblastosis foetalis (hemolytic disease of the newborn). Knowledge of this system increased rapidly in the early 1940's and, indeed, continues to increase today.

The period of 1944 through 1946 saw the introduction of three important new tests that allowed for the detection of antibodies that were capable of red cell sensitization yet were incapable of causing agglutination. Bovine albumin was first used for this purpose in 1945. Later in the same year,

Coombs, Mourant and Race introduced the antiglobulin test, which was based on a method described by Moreschi (1908). In 1946 it was shown that certain proteolytic enzymes could also be used to detect these sensitizing antibodies. The use of these tests resulted in the discovery of several new blood group systems. In 1946, the Kell system was discovered by Coombs, Mourant and Race, and the Lewis system was described by Mourant. The Duffy system (Cutbush, Mollison and Parkin) and the Kidd system (Allen, Diamond and Niedziela) were described in 1950 and 1951, respectively. The Lutheran system, also described in this time period, was detected by means of direct agglutination tests (Callender, Race and Paykoc, 1945).

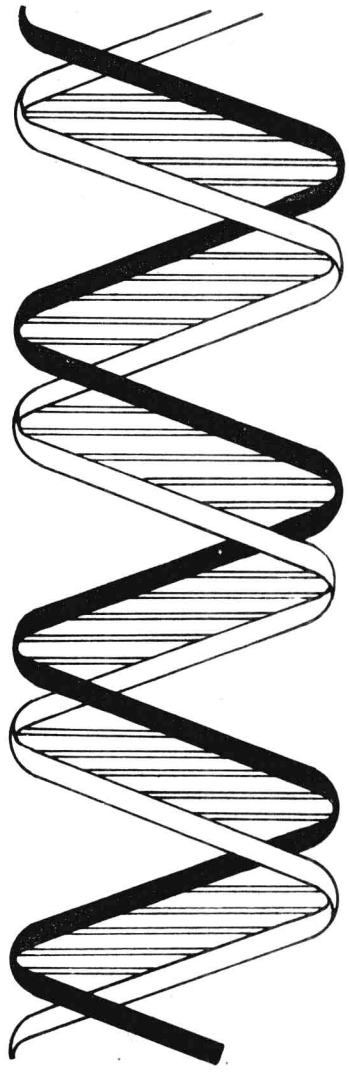
Since 1951, the literature on these and other blood group systems has expanded to encyclopedic proportions. Each major system has been found to be increasingly complex, with seemingly endless red cell polymorphism. Blood transfusion, once considered to be of use only in cases of dire emergency, is now commonplace—yet there are still innumerable problems to surmount. While radical surgical procedures are now possible, the hazard of alloimmunization remains. While we have learned to recognize some of the factors involved, there is little doubt that the best *in vitro* tests are poor mimics of what happens *in vivo*. Other hazards, including those resulting from bacterial contamination, circulatory overload and disease transmission, although reduced, still remain with us. Perhaps most important, however, is the sobering fact that blood transfusion, being in effect a tissue transplantation, is a surgical operation of a special nature, and once performed is virtually impossible to undo.

In spite of these and other risks, blood transfusion is the most frequently employed form of clinical therapy, and it is clearly evident that because of it, millions of lives have been saved or at least extended.

Contents

Section One

BASIC GENETICS



Our main purpose is to provide blood for transfusion that is as safe as our knowledge and technical ability can make it. To this end, we apply the principles of *immunology* to a study of *hematologic* disorders. Thus, ours is an allied science — aptly named *immunohematology*.