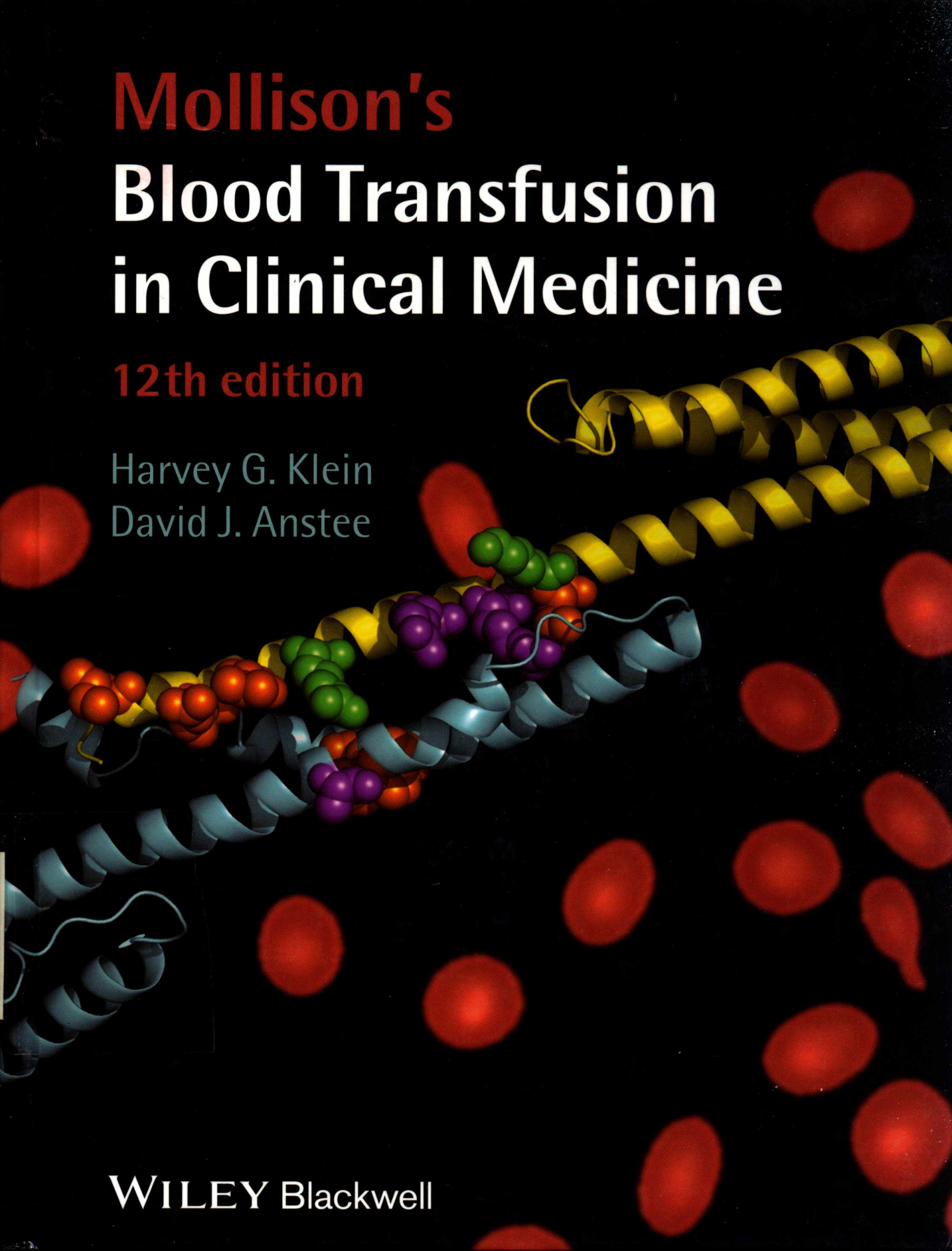
Mollison's Blood Transfusion in Clinical Medicine

12th edition

Harvey G. Klein
David J. Anstee



WILEY Blackwell

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Cover image: The crystal structure of the red cell spectrin tetramer complex (PDB: 3LBX; J. Ipsaro et al. 2010, Crystal structure and functional interpretation of the erythrocyte spectrin tetramerization domain complex. Blood 115: 4843) is superimposed on a blood smear from a hereditary elliptocytosis patient (blood smear photograph courtesy of Patrick Gallagher, Yale University). Selected sites where hereditary elliptocytosis mutations occur are indicated using space-filling spheres on ribbon diagrams of α (yellow) and β (cyan) spectrin. Side chains of mutated sites are color coded based on observed tetramer binding affinity changes (Gaetani et al. 2009, Blood 111: 5712 and Nicolas et al. 1998, Biochem J. 332:81) as highly destabilizing (orange), moderately destabilizing (magenta), and similar to wild type (green). (Image provided by David Speicher and Sandra Harper, The Wistar Institute).
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Preface to twelfth edition

Eight years have passed since the last edition of Mollison's textbook was published. It seems like yesterday. This is the first edition to be revised without the considered advice of Professor Patrick Mollison whose death in November 2011 marked the end of an era. Pat was a pioneer of blood transfusion, a valued mentor and friend, and an encyclopaedic reference regarding the scientific underpinnings of the therapeutic use of blood. In this edition we have included his obituary as well as his preface to the first edition of this textbook from 1951.

Mollison's textbook has been an icon. *Blood Transfusion in Clinical Medicine* arose from the concept of the transfusionist as both scientist and expert consultant. In its early years, this text provided the primary, and often the sole, reference for detailed information and practical experience in blood transfusion. A generation of scientists and clinicians sought and found in its pages those fine points of immunohaematology that helped them manage their patients and satisfy their intellectual curiosity. The 21st century has witnessed an explosion of scientific knowledge and available information. The two are not identical. We have noted previously the proliferation of textbooks, handbooks, systematic reviews and specialty journals. Increased access to the Internet has made electronic media the source of choice for many practising physicians. Yet the very availability of this vast and rising tidal wave of information, much of it uncritically reviewed, poses its own problems. The current authors determined to distil from this mass of information the relevant biology and technology for a timely, comprehensive and clinically useful textbook – without altering the spirit and character that has made Mollison's textbook a cherished companion.

Mollison's textbook has documented the development of transfusion practice and its scientific basis for more than half a century. We have endeavoured to preserve the historical context and have retained many of the early references for those who are disposed to examine the roots of the discipline. Whereas the early editions focused mainly on the recognized red cell blood groups and their clinical implications, we have, edition upon edition, expanded the scope to include the other elements of blood and an understanding of the clinical situations in which they play a role. Whereas situating insights that are beginning to flow from the sequencing of the human genome alongside the 'comparative precision of differential agglutination' may seem jarring at first, this text strives to continue the tradition of integrating biology, technology, clinical practice, and history that characterized the original book and all subsequent editions. Mollison's text has traditionally been used as a source of 'classic' studies and information not available elsewhere, and we have been careful to retain that information in this edition.

Since the last edition, major changes in practice and advances in our understanding have occurred in some aspects of the field, but not in others. Informatics and computational biology have revolutionized the approach to basic science. Advances in DNA-based technology, from recombinant proteins to reprogrammed cells, are redefining the discipline of transfusion medicine and opening a new, vast, yet related field of regenerative medicine. Mobilization and selection of haematopoietic progenitor cells for transplantation have become commonplace as has manipulation of mononuclear cells by culture and gene insertion to offer innovative therapies for a wide range of diseases. This edition has been revised to reflect this remarkable progress. We have not attempted to remake this edition into an exhaustive textbook. By intent, we have eschewed separate chapters on medicolegal issues, detailed methods of blood collection storage, administrative practices, quality systems, facilities management and cost – benefit analysis. We have however integrated elements of these important topics into discussions of clinical problems.

In summary, we have endeavoured to provide the reader with a useful, somewhat opinionated, science-based clinical text on the broad subject of transfusion medicine. We anticipate that this volume will be used most frequently by the physician specialist practising in

transfusion medicine. However, we hope that the book will have equal appeal to the non-specialist (and non-physician) and would be particularly gratified if it finds favour among those doctoral and postdoctoral students with a burgeoning interest in the past, present and future of blood transfusion in clinical medicine.

We are indebted to many people for advice, support and assistance. DJA owes particular thanks to Sherrie Ayles, Nick Burton, Geoff Daniels, Kirstin Finning, Gary Mallinson, Tosti Mankelow, Peter Martin, Clare Milkins, Robin Knight, and Steve Parsons. HGK thanks the many physicians and scientists who provided critique, helpful comments and invaluable expert advice, particularly Drs Mark Brecher, George Garratty, David Stroncek, Franco Marincola, Maria Bettinotti, and Richard Weiskopf. HGK is especially grateful to John I. Gallin and David K. Henderson, who provided him the time and opportunity to work on this edition, and to Sigrid Klein, without whose support it would not have been completed.

We owe a special debt of gratitude to Jennifer Seward and to Maria Khan of Wiley Blackwell, who kept the book on track.

Harvey G. Klein
David J. Anstee
2014

Preface to eleventh edition

The huge challenge of revising this seminal work has been both daunting and immensely rewarding. Mollison's textbook is an icon. *Blood Transfusion in Clinical Medicine* arose from the concept of the transfusionist as both scientist and expert consultant. For many years, this text provided the primary, and often the sole, reference for detailed information and practical experience in blood transfusion. A generation of scientists and clinicians sought and found in its pages those fine points of immunohaematology that helped them manage their patients and satisfy their intellectual curiosity. The last two decades have witnessed an explosion of scientific knowledge, the proliferation of textbooks, handbooks, systematic reviews and specialty journals, not to mention immediate access to manuscripts not yet in print via the Internet. The current authors determined to distil from this mass of information the relevant biology and technology for a timely, comprehensive and clinically useful textbook – without altering the spirit and character that has made Mollison's textbook a cherished companion.

Mollison's textbook has recorded the development of blood transfusion practice and its scientific basis for more than half a century. The first edition focused mainly on the recognized blood groups and their clinical implications. Immunohaematology was confined largely to the red cell. The marvellous complexity of blood was defined by agglutination, and subsequently by the mixed lymphocyte reaction, lymphocytotoxicity and serum protein electrophoresis. Red cell survival, a tool both for investigating clinical problems and for exploring fundamental information regarding haemolytic processes and red cell pathology, was estimated 'with the comparative precision of differential agglutination'. Whole blood was still transfused by the bottle. Today, tens of millions of units of blood components are transfused annually. The immune response is analysed by a wide array of sophisticated techniques and the diversity of human blood is routinely examined at the molecular level. Circulating cells and their survival still teach us about immunology and cellular biology, but we can now track the persistence of transfused lymphocyte subpopulations with molecular assays of microchimerism. This text endeavours to continue the tradition of integrated biology, technology and clinical practice that characterized the original book and all subsequent editions.

Since the last edition, major changes in practice and advances in our understanding have occurred in some aspects of the field, but not in others. The human genome has been sequenced. Informatics and computational biology have revolutionized the approach to biodiversity. Advances in DNA-based technology, from microarrays to recombinant proteins, have had a major impact on many aspects of blood transfusion practice. Transfusion medicine now involves mobilization and selection of haematopoietic progenitor cells for transplantation, storage of umbilical cord blood, and manipulation of mononuclear cells by culture and gene insertion to offer potential therapies for a wide range of diseases. This edition has been revised to reflect this remarkable progress. Enormous advances in protein structure determination have occurred since the last edition and these too are reflected in the revised edition. It is particularly satisfying to record the three-dimensional structure of the glycosyltransferase responsible for the ABO blood groups just over a century after Landsteiner's discovery made safe blood transfusion a possibility. In contrast, Mollison's text has traditionally been used as a source of 'classic' studies and information not available elsewhere, and we have been careful to retain that information in this edition.

We have not attempted to remake this edition into an exhaustive textbook. By intent, we have eschewed separate chapters on medicolegal issues, detailed methods of blood collection, administrative practices, quality systems, facilities management and cost–benefit analysis. Instead, we have integrated elements of these important topics into discussions of clinical problems.

In summary, we have endeavoured to provide the reader with a comprehensive and authoritative clinical text on the broad subject of transfusion medicine. We anticipate that this volume will be used most frequently

by the physician specialist practising in transfusion medicine. However, we hope that the book will have equal appeal to the non-specialist (and non-physician) and would be particularly gratified if it finds favour among those doctoral and postdoctoral students with a burgeoning interest in the past, present and future of blood transfusion in clinical medicine.

We are indebted to many people for advice, support and assistance. DJA owes particular thanks to Sherrie Ayles, Nick Burton, Geoff Daniels, Kirstin Finning, Gary Mallinson, Tosti Mankelow, Peter Martin, Clare Milkins, Robin Knight, Steve Parsons and Joyce Poole. HGK thanks the many physicians and scientists who provided critique, helpful comments and invaluable expert advice, particularly Drs James Aubuchon, Mark Brecher, George Garratty, Dennis Goldfinger, Brenda Grossman, David Stroncek, Franco Marincola, Maria Bettinotti, Paul Holland, Paul Schmidt, Jay Menitove, Paul Mintz, Gary Moroff, Peter Page, Edward Snyder, Richard Weiskopf and Charles Bolan, and to Mr Boyd Conley and Ms Patricia Brooks for technical assistance. HGK is especially grateful to John I. Gallin and David K. Henderson, who provided him the time and opportunity to work on this edition, and to Sigrid Klein, without whose support it would not have been completed.

We owe a special debt of gratitude to Professors Patrick Mollison, C. Paul Engelfriet and Marcela Contreras, upon whose solid foundation this edition was built, and to Maria Khan of Blackwell Publishing, who kept the book on track.

Harvey G. Klein
David J. Anstee
2005

Preface to first edition

Blood was once regarded as a fluid of infinite complexity, the very essence of life. The blood of each person seemed to carry in it the secrets of individuality. As recently as 1666 it was natural for Mr Boyle, in writing to Dr Lower, to speculate in the following terms about the possible effect of cross-transfusion: '. . . as whether the blood of a mastiff, being frequently transfused into a bloodhound, or a spaniel, will not prejudice them in point of scent'.

If each person's blood were as individual as this, transfusion would indeed be complex and would deserve to rank as the most refined branch of medicine. However, this early view of the subtlety of transfusion was eclipsed at the beginning of the century by the discovery that the blood of all human beings could be divided into four groups. It seemed that, provided blood of the same group was transfused, one person's blood was indistinguishable from another's. Indeed, it came to be believed that people who belonged to the common group O could give their blood to anyone whatsoever. This point of view reached its widest acceptance in the early 1940s, when hundreds of thousands of bottles of group O blood were given as a general panacea for the injuries of war, with remarkably satisfactory effects. As a result of this experience, a generation of medical men has grown up believing that blood transfusion is one of the simplest forms of therapy.

And yet, this view of the interchangeability of blood has to be reconciled with the growing knowledge of its immense complexity. There are so many possible combinations of blood group antigens that the commonest of them all occurs in only 2% of the English population. Indeed, such is the individuality of the blood that, in Race's striking phrase, certain combinations 'may never have formed the blood of an Englishman'.

The explanation of this apparent paradox – the potential complexity of transfusion and its actual simplicity – lies in the fact that many blood group factors are so weakly antigenic in man that they are not recognized as foreign by the recipient. However, it can no longer be maintained that a knowledge of the ABO system constitutes an adequate equipment for the transfusionist, for the role of some of the other systems is by no means negligible. Thus, a book on blood transfusion requires a special account of blood groups, in which the emphasis laid on any one of the antigens depends upon the part that it plays in incompatibility.

A good understanding of the effects of transfusion requires two further accounts: one of the regulation of blood volume and of the effects of transfusion on the circulation, and one of the survival of the various elements of blood after transfusion. The survival of transfused red cells has become a matter of special interest. Red cells survive for a longer period than any of the other components of blood, and their survival can be estimated with comparative precision by the method of differential agglutination. A study of the survival of transfused red cells has proved to be of great value in investigating haemolytic transfusion reactions. In addition, it has contributed strikingly to fundamental knowledge in haematology by demonstrating the diminished survival of pathological red cells and the existence of extrinsic haemolytic mechanisms in disease. Transfusions are now not uncommonly given for the purpose of investigation as well as of therapy.

This book is thus composed mainly of an account of blood groups from a clinical point of view and of descriptions of the effects of transfusion on the circulation and of the survival of transfused red cells; it also contains chapters designed to fill in the remaining background of knowledge about the results of transfusion in man. Finally, it contains a rather detailed account of haemolytic disease of the newborn. It is addressed to all those who possess an elementary knowledge of blood transfusion and are interested in acquiring a fuller understanding of its effects.

In preparing this book I have had the help and advice of many friends. Dr J.V. Dacie read through almost all the typescript and made innumerable suggestions for improvements. Dr A.C. Dornhorst gave me the most extensive help in writing about the interpretation of red

cell survival cures, and he is responsible for the simple rules for estimating mean cell life, which I hope that many besides myself will find useful; he has also read through the book during its preparation and given me the benefit of his very wide general knowledge. Dr J.F. Loutit, Dr I.D.P. Wootton and Dr L.E. Young are amongst those who have read certain sections and helped me with their expert advice.

I am even more indebted to Miss Marie Cutbush, who has given an immense amount of time to helping to prepare this book for the press and has, on every page, suggested changes to clarify the meaning of some sentence. In addition, she has most generously encouraged me to quote many joint observations which are not yet published.

Miss Sylvia Mossom was responsible for typing the whole book, often from almost illegible manuscript. I am indebted to her for her skill and patience.

The *British Medical Journal, Clinical Science* and *The Lancet* have been so good as to allow the reproduction of certain figures originally published by them.

Professor P.L. Mollison
1951

In memoriam: Patrick Loudon Mollison

Professor Mollison died on November 26, 2011; he was born in 1914. He was educated at Rugby School, Guys Hospital, Cambridge University, and St Thomas's Hospital (medical school) in London. After qualifying in 1938, he became a house physician at St Thomas's. World War II broke out in 1939 and a young Dr Mollison was sent to work at the South London Blood Supply Depot. While there his activities included treatment of patients with concentrated red blood cells (RBCs) instead of whole blood (component therapy was not used routinely until several decades later) and dried human plasma. He also became interested in the clinical significance of the newly described Rh factor (hemolytic transfusion reactions and hemolytic disease of the fetus and newborn). Publications of this work appeared in 1940 to 1943. Also, in 1943 he published his first paper on RBC survival and the description of a new anticoagulant/preservative which became known as ACD (sometimes with slight modifications) and was used for the next 30 years. I must add that Prof. Mollison always reminded us that he was not the first to acidify the citrate solution, but others thought it would be toxic. From 1943 to 1946 he served in the Royal Army Medical Corps where he continued his work on optimal preservation of blood and treatment of wartime casualties. While in the military he traveled to Germany, India, Africa, and Burma. These trips led to publications (in 1946) on treatment of starvation in prisoners of the Belsen Concentration Camp and blood groups of the Burmese.

In 1948 he became Director of the newly formed Medical Research Council (MRC) Blood Transfusion Unit at Hammersmith Hospital in London. He stayed at Hammersmith Hospital until 1960 when he, and the unit, moved to St Mary's Hospital in Paddington, London, where the unit was renamed the Experimental Haematology Research Unit, with Dr Mollison as Director of the Department of Haematology at the hospital. In

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1963, London University conferred on Dr Mollison the title of Professor of Haematology. He retired in 1979 (compulsory at 65 at that time in the UK).

Professor Mollison was a pioneer in many areas, including fundamental contributions to our understanding of the factors involved in successful preservation of donor RBCs in the fluid and frozen state; survival of RBCs in vivo; applications of radioisotopes for in vivo and in vitro studies; the clinical significance, and insignificance, of some blood group antibodies and the factors that affect their significance; hemolytic disease of the fetus and newborn, including pathogenesis, treatment, and prophylaxis; the role of complement in immunohematology (the very first paper in the first edition of **TRANSFUSION** was Polley MJ, Mollison PL. The role of complement in the detection of blood group antibodies: special reference to the antiglobulin test. Transfusion 1961;1:9–22). His textbook, *Blood Transfusion in Clinical Medicine*, was first published in 1951; the 12th edition will be available in 2012. The 9th and 10th editions had co-authors (Paul Engelfriet and Dame Marcela Contreras), and the 11th and 12th editions had Harvey Klein and David Anstee as co-authors. This book was the "bible" for many immunohematologists and some of us still would give it this status. The book contains original seminal data that are still difficult to find elsewhere in one place. Much of the earlier editions of the book was based on about 200 separate publications by Mollison's group. Luckily, much of this extensive research experience is still retained in the recent edition.

Professor Mollison received many prestigious awards. In 1963 he was elected a Fellow of the Royal Society, the highest honor bestowed on British scientists from all disciplines. In 1979 he was honored by Her Majesty Queen Elizabeth by being made a Commander of the Order of the British Empire. He received several awards from the AABB, including their two top awards, the Bernard Fantus Lifetime Achievement Award (1987) and the Karl Landsteiner Memorial Award (1960). Other prestigious awards included the Philip Levine Award of the American Association of Clinical Pathologists (1973), the Ochlecker Medal from the German Association of Blood Transfusion and Immunohematology (1974), and the Presidential Award from the International Society of Blood Transfusion (2000). Professor Mollison was President of ISBT from 1960 to 1964.

I would like to finish this obituary with a few personal reminiscences of Pat Mollison. I knew him for about 50 years. I first met him when I was working in Prof. Sir John Dacie's (then Dr Dacie) Haematology Department in the Hammersmith Hospital. Mollison's MRC unit was quite close in the same hospital, close enough for me to regularly visit the unit for advice and ask questions about their research. The unit was small; the staff at that time was an Australian research assistant Marie Cutbush (later to become Marie Crookston), Dr Nevin Hughes-Jones, two technicians (Ann Thomas and Denise Hunter), a secretary, and various fellows over the years (e.g., Drs Eloise Giblett and Hugh Chaplin from the United States). When Marie married and left for Canada, she was replaced by Margaret Polley. I will always be grateful for the help and stimulus these people gave to me. In retrospect, I am amazed that Dr (not Prof. at that time) Mollison would personally sacrifice valuable time to go over serologic problems with me, even coming up to the BT lab one evening to help me with a particularly difficult case involving cardiac surgery using the relatively new 'heart/lung machine.' I also remember him taking me to a patient's bedside to watch him inject some purified Lewis blood group substance, obtained from Prof. Walter Morgan (Lister Institute), into a patient with Lewis antibodies (no institutional review boards in those days). I tell these stories to illustrate another facet of Pat Mollison. He was not only a great scientist, but also a true gentleman, whose lack of pomposity benefited me considerably. His kindness and his seminal work on immune RBC survival/destruction and the clinical significance/insignificance of blood group antibodies laid a foundation for my own career. In my opinion, Pat Mollison was the one person who had the most impact on blood transfusion medicine in the past 100 years and that includes Karl Landsteiner. I am proud to be a disciple and still try to preach his gospel.

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Contents

Blood donors and the withdrawal of blood

Bloodletting was once the treatment for almost all maladies and, when carried out in moderation, caused little harm. This chapter includes a discussion of therapeutic phlebotomy, but is mainly concerned with the withdrawal of blood or its constituent parts from healthy donors for transfusion to patients. The chapter addresses qualification of the donor, statistics regarding collection and use, blood shortages and conditions that disqualify donors. Complications of blood donation including iron loss, syncope and needle injuries, and other less common adverse events are discussed. Some applications of therapeutic phlebotomy and blood withdrawal during neonatal exchange transfusion are outlined.

Blood donation

The blood donor

General qualifications

Qualification of blood donors has become a lengthy and detailed process, a 'donor inquisition' some would say. Yet blood collection depends on this system of safeguards to protect the donor from injury and the recipient from the risks of allogeneic blood (see Chapters 15 and 16). Sensitive screening tests have been considered the cornerstone of blood safety for more than four decades. However, testing represents only one component of this system. Additional 'layers of safety' include detailed donor education programmes prior to recruitment, pre-donation informational literature, stringent donor screening selection and deferral procedures, post-donation product quarantine, and donor tracing and notification when instances of disease transmission are detected. Each element plays a role in preventing 'tainted' units from entering the blood inventory. Most transfusion services use evidence-based standards and regulations for the selection of donors, such as those published in the AABB 'Standards' and the United Kingdom 'Red Book', (UKBTS/NIBSC Liaison Group 2005; AABB 2012) and quality systems to assure excellence in all phases of their application (Roback 2008). Other standards derive from 'expert opinion' and 'common sense'; these latter policies need to be revisited as scientific information becomes available.

Blood donors should have the following general qualifications: they should have reached the age of consent or an age judged suitable by local regulation, most often 18 years, but lower in some countries such as the USA and the UK; donors should enjoy good health, have no history of serious illness, weigh enough to allow safe donation of a 'unit' and not recognize themselves as being at risk of transmitting infection (see below). Ideally, donation should be strictly voluntary and without financial incentive (see Chapter 16); however emerging evidence from studies in Sub-Saharan Africa suggests that in some developing countries, the prevalence of markers for HIV, HCV and HBV is the same for family-replacement donors as for voluntary non-remunerated donors. Some blood services impose an arbitrary upper limit on age, commonly 65 years; however, it seems curiously subjective to exclude donors on the basis of age alone if they are otherwise in good health (Schmidt 1991; Simon *et al.* 1991). Furthermore, it is the younger donor who is at increased risk of reactions following phlebotomy (Eder *et al.* 2008). The Blood Collection Service should provide informational literature for prospective blood donors. After information and counselling about criteria for donor selection, donors should consent in writing to the terms of donation, including the use of the donated blood, the extent of testing, the use of testing results (including donor notification of positive results) and the future use of any stored specimens. Donors should be told about the possibility of delayed fainting and about other significant risks of the donation procedure.

Mollison's Blood Transfusion in Clinical Medicine, Twelfth Edition. Harvey G. Klein and David J. Anstee.

Blood donation has potential medicolegal consequences. If a donor becomes ill shortly after giving blood, the illness may be attributed to blood donation. For this reason, among others, it is important to ensure that donors have no history of medical conditions such as brittle diabetes, hypertension, poorly controlled epilepsy and unstable cardiopulmonary disease that might be associated with an adverse event following phlebotomy. Pregnancy might be adversely affected by the donation process and ordinarily excludes a donor. Donors who become ill within 2 weeks of donation should be encouraged to inform the transfusion service, which may wish to discard the donated blood, recall any plasma sent for fractionation or follow up recipients of the blood components as appropriate. Donors who develop hepatitis or HIV infection within 3–6 months of donation should certainly inform the Blood Collection Service.

Donor interview – an evolving inquisition

The donor interview, once an informal set of locally-derived questions administered by well-intentioned volunteers, has become an increasingly detailed set of validated questions designed to qualify the 'raw material' of blood components. The process is highly regulated. Interviewers must be trained and qualified to administer questions and evaluate responses. Screening should be conducted in a setting sufficiently unhurried and private as to permit discussion of confidential information. With current practices in the USA, approximately 2% of volunteer donors still disclose risks that would have led to deferral if known at the time of donation (Sanchez *et al.* 2001). Non-disclosure of deferrable risks is complex. Donors may rationalize failure to acknowledge distant risk behaviour or may truly misinterpret screening questions. Some degree of non-disclosure is probably an inherent part of pre-donation screening (Glynn *et al.* 2001; O'Brien *et al.* 2009). Introduction of standardized and validated questionnaires and the application of interactive computer-assisted audiovisual health history may reduce errors and misinterpretations during conduct of the donor interview (Zuck *et al.* 2001).

Physical examination

Blood collectors perform a limited physical examination designed to protect donor and recipient. Screeners routinely assess the donor's general appearance and defer those who do not appear well or are under the influence of alcohol. Pre-donation pulse and blood pressure in the 'normal range' are often used as screening standards, although variances have been granted for healthy athletes. The scientific rationale supporting specific values for pulse and blood pressure is surprisingly weak and may not predict or prevent cardiovascular or cerebrovascular events in prospective blood donors (see below). Blood collectors are re-evaluating the usefulness of these screening measures. Body weight and temperature are measured by some collection services. Both arms are examined for evidence of illicit drug use and for lesions at the venepuncture site.

Volume of donation

The volume of anticoagulant solutions in collection bags is calculated to allow for collection of a particular volume of blood, which, in the UK, is 450 ± 45 ml. In the USA often 500 ml, but in no case more than 10.5 ml/kg including the additional volume of 20–30 ml of blood collected into pilot tubes. There is concern that even these volumes may contribute to delayed fainting in smaller donors. From donors weighing 41–50 kg, only 250 ml of blood is collected into bags in which the volume of anticoagulant solution has been appropriately reduced. In some countries, the volume collected routinely is less than 450 ml, for example 350–400 ml in Turkey, Greece and Italy, and 250 ml in some Asian countries such as Japan, where donors tend to be smaller. Commercial plasma collectors routinely weigh the donor and calculate a safe volume based on the estimated blood volume.

Record-keeping

It should be possible to trace the origin of every blood donation and records should be kept for several years, depending on the guidelines for each country. In many countries, a system employing unique bar-coded eye-readable donation numbers is now in use. This system makes it possible to link each donation to its integral containers and sample tubes and to the particular donor session record. Information concerning previous donations, such as records of blood groups and microbiology screening tests, antibodies detected, donor deferrals and adverse reactions are important for subsequent attendances. Electronic storage of donor information greatly facilitates accurate identification, release, distribution and traceability of units of blood and blood products. An international code, ISBT 128, is intended to be used by all countries for the accurate identification of donors and donations (Doughty and Flanagan 1996). These records must be protected from accidental destruction, modification or unauthorized access.

Frequency of donors in the population

Although in many Western countries, some 60% of the population consists of healthy adults aged 18–65 years and thus qualified to be blood donors, the highest annual frequency of donation in the world corresponds to about 10% of the population eligible to give blood donating once per year, as in Switzerland (Linden *et al.* 1988; Hassig 1991). The frequency in most developing countries is less than 1% (Leikola 1990).The number of units collected per 1000 US inhabitants of usual donor age (18–65) was 84.1 in 2006, 88.0 in 2001, and 80.8 in 1999. Although these numbers compare favourably with the rate of 72.2 per 1000 in 1997, they pale in comparison with the 100 units per 1000 population collected in Switzerland. As treacherous as it may be to interpret these figures, the numbers suggest that US collecting facilities are generally improving efficiency. Data from the American National Red Cross indicate that the average volunteer donates about 1.7 times a year. Losses from outdated red cells accounted for 5.3% of the supply but, given the fact that red cells can be transfused only to compatible recipients, the number of usable units outdated appears to be extremely small. More than 99% of group O units and 97% of group A units were transfused (National Blood Data Resource Center 2001, 2007 National blood Collection and Utilization Survey).

Blood utilization and shortages

Despite the constant rise in collections, blood collectors report frequent shortages and emergency appeals for blood are disturbingly common. Some 16 million units of red cells and 13 million units of platelets are collected annually in the US and the numbers continue to rise (2007 National blood Collection and Utilization Survey). With the current shelf life, the blood supply more closely resembles a pipeline than a bank or reservoir. A few days of under collection can have a devastating effect on supply. Although most national supermarket chains have developed efficient bar code-based information systems to monitor perishable inventory on a daily basis, few national blood services have as accurate an accounting of blood component location and availability by group and type. Furthermore, there is little general agreement about what constitutes a shortage. Measures of postponed surgery and transfusion, as well as increased rates of RhoD-positive transfusions to RhoD-negative recipients provide some indication of shortage at the treatment level. In a national survey in the US in 2006, 6.9% of hospitals surveyed reportedly delayed elective surgery for 1 day or more, and 13.5% experienced at least 1 day in which non-surgical blood needs could not be met (National Blood Collection and Utilization Survey 2007). A separate government-sponsored study revealed seasonal fluctuations of blood appeals and cancellations of surgery for lack of platelet transfusion support (Nightingale *et al.* 2003). In the former survey, red cell transfusion reached an all-time high, an increase of more than 30% during the previous nine years.

Blood utilization in the US approached 49 units per 1000 of the population, a number not different from that of the previous two surveys and a suggestion that red cell use may have reached a steady-state. However demographics in developed countries are changing and with them, patterns of donation and usage. Ordinarily, more blood is donated by younger age groups, whereas more is used by the elderly (Cobain *et al.* 2007). The shift to older donors mirrors the aging of the population (Zou *et al.* 2007). In Finland, 70- to 80-year-olds have an eightfold higher RBC consumption than 20- to 40-year-olds (Ali *et al.* 2009). The US decennial census 2000 projects that, by the year 2030, the population of Americans over the age of 65 will increase from 12% to 20%; this figure will be even higher in most countries in Western Europe (Kinsella and Velkoff 2001). Variation in RBC use per capita among countries can be explained largely by the age distribution differences of the populations rather than by the different national treatment standards. Given these projections, developed countries may expect blood shortages to become a way of life, unless substantial resources are invested in donor recruitment and retention or methods are adapted to serve the changing population demographic. In developing countries, this is already the case.

The shrinking donor pool: the safety vs. availability conundrum

Donor deferrals and miscollected units have an increasing role in blood shortages. In a 1-year study at a regional blood centre, nearly 14% of prospective donors were ineligible on the day of presentation and more than 3.8% of donations did not result in the collection of an acceptable quantity of blood (Custer *et al.* 2004). Short-term deferral for low haemoglobin (Hb), about 10% of all prospective donors, remains the overwhelming reason for the deferral of female donors in all age groups, representing more than 50% of all short-term deferrals. In first-time female donors, low Hb accounted for 53–67% of deferrals within different age groups, and for repeat female donors 75–80% of deferrals. In both first time and repeat male donors aged 40 years and older, the most common reason for short-term deferral was blood

pressure or pulse outside allowed limits. For persons aged 16–24 years, regardless of sex and donation status, the most common reason for lengthy deferral was tattoo, piercing or other non-intravenous drug use needle exposure. For 25- to 39-year-old female donors, needle exposure was also the most common reason, whereas for male donors, travel to a malarial area was more common. For all ages over 40, the most common reason for long-term deferral was travel to a malarial area.

Measures introduced to increase blood safety may have the unintended consequence of decreasing blood availability. Results from demographic studies indicate that certain donor groups or donor sites present an unacceptable risk of disease transmission. For example, blood collectors no longer schedule mobile drives at prisons or institutions for the disabled because of the recognized high prevalence of transfusion-transmissible viruses. Few would argue the risk–benefit analysis of these exclusions. More questionable were the temporary exclusions of US soldiers exposed to multiple tick bites at Fort Chaffee, Arkansas, and the lengthy deferrals of veterans who served in Iraq and Kuwait because of the fear that they might harbour *Leishmania donovani*, an agent infrequently associated with transfusion risk. Donors who have received human growth hormone injections have been indefinitely deferred because of the possible risk of transmitting Creutzfeldt–Jakob disease (CJD); however, relatives of patients with 'sporadic' CJD are still deferred in the US (except for preparation of plasma fractions) despite evidence of their safety. There have been five case–control studies of more than 600 CJD cases, two look-back studies of recipients of CJD products, two autopsy studies of patients with haemophilia and mortality surveillance of 4468 CJD deaths over 16 years without any link to transmission by transfusion (Centers for Biologic Evaluation and Research, US Food rand Drug Administration 2002). Although the impact of this deferral on the US blood supply has been negligible, the indefinite deferral of donors who resided in the UK for a total of 3 months or longer between 1980 and 1996, and the complicated deferral policy for residents and visitors to the European continent, designed to reduce a calculated risk of transmission of the human variant of 'mad cow disease' (variant Creutzfeldt–Jakob disease, vCJD), has had a substantial impact, a loss of as much as 10% by some estimates, particularly on apheresis donors (Custer *et al.* 2004). With the recognition of emerging and re-emerging infectious diseases, additional donor exclusions appear to be on the horizon (Stramer *et al.* 2009).

Donor medications constitute another significant area of deferral losses. Certain medications, for example etretinate (Tegison), isotretinoin (Accutane), acitretin (Soriatane), dutasteride (Avodart) and finasteride (Proscar), have been identified as posing potential risk to transfusion recipients because of their teratogenic potential at low plasma concentrations. Such exclusions have little impact on blood safety but each shrinks the potentially eligible volunteer donor pool.

More troublesome, although not as numerous, are donor deferrals resulting from false-positive infectious disease screening tests. This problem has been recognized since the introduction of serological tests for syphilis. However, during the past 15 years, the introduction of new screening tests and testing technologies has resulted in numerous deferrals for 'questionable' test results and either complex re-entry algorithms or no approved method to requalify such donors. Surrogate tests used for screening have proved particularly troublesome (Linden *et al.* 1988). However, even specific tests result in inappropriate deferrals. Of initial disease marker-reactive donations, 44% proved to be indeterminate or false positive (Custer *et al.* 2004). Each year an estimated 14000 donors are deferred from donating blood for an indefinite period because of repeatedly reactive enzyme immunoassay (EIA) screening tests for human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and several hundred donors are deferred for apparently false-positive nucleic acid testing (NAT) results (L Katz MD, personal communication).

Conditions that may disqualify a donor

Carriage of transmissible diseases

The most important infectious agents transmissible by transfusion are the hepatitis viruses B and C, HIV, human T-lymphotropic viruses (HTLVs), bacteria and the agents causing malaria. Increasing attention is being paid to the risks of 'emerging' agents and newly recognized infectious risks of transfusion such as dengue, *Coxiella burnetii*, babesiosis and vCJD. Steps that should be taken to minimize the risk of infecting recipients with the agents of these and other diseases involve exclusion based on geographical residence, signs and symptoms of disease, high-risk activity and demographics associated with risk transmission; see Chapter 16. Donors who have been exposed to an infectious disease and are at risk of developing it should be deferred for at least the length of the incubation period.

Recent inoculations, vaccinations, etc.

To avoid the possibility of transmitting live viruses (e.g. those of measles, mumps, rubella, Sabin oral polio vaccine, yellow fever, smallpox), donors should not give blood during the 3 weeks following vaccination. In subjects immunized with killed microbes or with antigens (cholera, influenza, typhoid, hepatitis A and B, Salk polio, rabies, anthrax, tick-borne and Japanese encephalitis) or toxoids (tetanus, diphtheria, pertussis), the interval is normally only 48 h. These recommendations apply if the donor is well following vaccination. Plasma from recently immunized donors may be useful for the manufacture of specific immunoglobulin preparations. Donors who have received immunoglobulins after exposure to infectious agents should not give blood for a period slightly longer than the incubation period of the disease in question. If hepatitis B immunoglobulin has been given after exposure to the virus, donation should be deferred for 9 months to 1 year; similarly, if tetanus immunoglobulin has been given, donation should be deferred for 4 weeks. When rabies vaccination follows a bite by a rabid animal, blood donations should be suspended for 1 year. In developed countries, tetanus and diphtheria immunoglobulin is derived from human sources. However, horse serum is still used in some parts of the world. Donors who have received an injection of horse serum within the previous 3 weeks should not donate blood because traces of horse serum in their blood might harm an allergic recipient. The administration of normal human immunoglobulin before travelling to countries where hepatitis A is endemic is not a cause for deferral.

Group O subjects may develop very potent haemolytic anti-A following an injection of tetanus toxoid, typhoid-paratyphoid (TAB), vaccine or pepsin-digested horse serum, which may contain traces of hog pepsin. In the past, the use of such subjects as 'universal donors' sometimes led to severe haemolytic transfusion reactions in group A subjects. Platelet concentrates collected by apheresis from subjects with hyperimmune anti-A should not be used for transfusion to group A or AB patients in view of the large volume of plasma needed to suspend the platelet concentrate (Daniel-Johnson *et al.* 2009).

Ear-piercing, electrolysis, tattooing, acupuncture

All of these procedures carry a risk of transmission of hepatitis or HIV infection when the equipment used is not disposable or sterilized, and blood donation should then be deferred for 12 months. In the UK and some US facilities, donors are accepted if the acupuncture is performed by a registered medical practitioner or in a hospital. Cosmetic procedures such as eye lining are performed with disposable needles and single-use packets of ink. Although the association between tattooing and exposure to hepatitis C is generally acknowledged (Haley and Fischer 2003), less clear is whether a tattoo performed by licensed and inspected facilities carries more risk than a trip to the dentist's surgery.

'Allergic' subjects

Subjects who suffer from very severe allergy are unacceptable as donors because their hypersensitivity may be passively transferred to the recipient for a short period (see Chapter 15). Subjects with seasonal allergy (e.g. hay fever) may donate when not in an active phase of their hypersensitivity. A screening test for immunoglobulin E (IgE) antibodies would not help to identify those allergic individuals with an increased chance of passively transferring their hypersensitivity (Stern *et al.* 1995).

Blood transfusions and tissue grafts

Donations should not be accepted for at least 12 months after the subject has received blood, blood components or grafts. Donors who have received transfusion in the UK are being deferred indefinitely in part as a precaution against transmission of vCJD.

Surgery and dental treatment

When surgery has been carried out without blood transfusion, donation may be considered when the subject has fully recovered. Uncomplicated dental treatments and extractions should not be a cause for prolonged deferral, as utensils are sterilized and the risk of bacteraemia persisting for more than 1 h is negligible (Nouri *et al.* 1989).

Medication

Many subjects taking medication are not suitable as donors because of their underlying medical condition. Others are unsuitable as donors because the drugs they are taking, for example anticoagulants or cytotoxic agents, may harm the recipients (Mahnovski *et al.* 1987). Subjects who have taken aspirin within the previous week are unsuitable when theirs are the only platelets to be given to a particular recipient. Ingestion of oral contraceptives or replacement hormones such as thyroxine is not a disqualification for blood donation. On the other hand, recipients of human growth hormone (non-recombinant) should be permanently deferred from blood donation as should subjects who have used illicit injected drugs. Deferral for specific medication use is usually an issue of medical discretion; the US Armed Services Blood Program