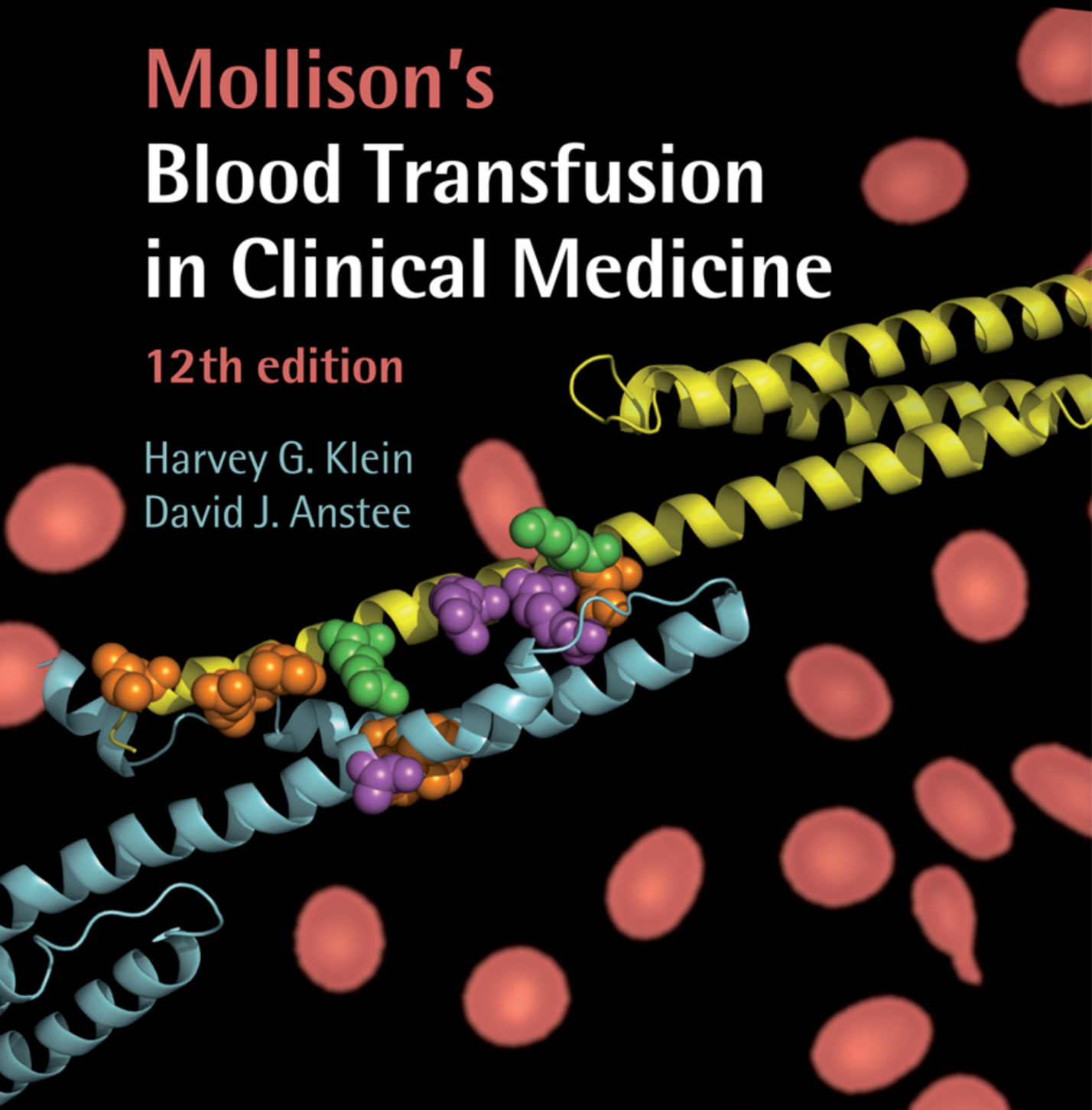
Mollison's Blood Transfusion in Clinical Medicine

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.

George Garratty, PhD, FRCPath
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1 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 14 000 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

has made its drug deferral list available online (http://militaryblood.dod.mil/library/policies/downloads/medication_list.doc).

Donors with relatively minor red cell abnormalities

In some populations, a considerable number of donors have an inherited red cell abnormality. The three conditions most likely to be encountered are: glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, sickle trait (HbAS) and thalassaemia trait.

G-6-PD deficiency

This is the most common red cell enzyme defect; hundreds of molecular variants have been catalogued. Although most G-6-PD-deficient red cells have only slightly subnormal survival and lose viability on storage with adenine at only a slightly increased rate (Orlina *et al.* 1970), some enzyme variants render the cells unsuitable for transfusion. With the African variant Gd^{A-} – present in 10% of African–Americans, a relatively small number of red cells are severely affected. However, the Mediterranean variant $Gd^{Mediterranean}$ and others render the red cell particularly sensitive to oxidative stress. If the recipient of one of these units develops an infectious illness or ingests fava beans or one of any number of drugs (phenacetin, sulfonamides, vitamin K, primaquine, etc.), rapid destruction of the donor's G-6-PD-deficient cells may result. Neonatologists avoid using G-6-PD-deficient blood for exchange transfusion, and subjects who have evidenced G-6-PD-related haemolysis should be permanently deferred from donation (Beutler 1994).

Sickle trait (HbAS)

Sickle trait red cells survive normally in healthy subjects, even after storage. However, in patients subject to various types of hypoxic stress, these cells survive poorly. HbS polymerizes at low oxygen tension and the cells are trapped in the spleen (Krevans 1959) and in leukoreduction filters during red cell preparation (Stroncek *et al.* 2002; Bryant *et al.* 2007). Blood from donors with sickle cell trait should not be used for infants or for patients with sickle cell disease who undergo exchange transfusion. Patients, other than those with sickle Hb, who require general anaesthesia should have no problems if transfused with HbAS red cells provided that adequate oxygenation is maintained. Red cells from subjects with HbAS are usually unaffected by collection via apheresis, but those with sickling haemoglobinopathies should not donate by apheresis and are not suitable for intraoperative salvage. If blood from donors with sickle cell trait is glycerolized for storage in the frozen state, extra wash solution must be used during the deglycerolization procedure (Castro *et al.* 1981).

Thalassaemia trait

This is associated with little or no reduction in red cell lifespan in most subjects with a normal Hb concentration and these subjects may be accepted as donors.

Special conditions in which normally disqualified donors may donate

In some circumstances, a donor may give blood or components to be used for a special purpose, even although the requirements for normal donation are not met. For example, a donor who is mildly anaemic or who has recently given birth may give plasma or platelets by apheresis; the plasma may be needed for reagent preparation, for example HLA antibodies, or the platelets may be needed for transfusion to the newborn infant. Donors at risk for carrying malaria may give plasma for fractionation. The usual interval between donations may be waived for important medical indications. The donor age limitation and a number of other screening criteria may be modified for components directed to the recipient of the donor's bone marrow. In every case, medical evaluation should ensure that there is no increased risk to the donor's health and that the value of the component outweighs any perceived increase in risk. Under these circumstances, informed consent regarding the variance and documentation of the circumstances is mandatory.

Donation of whole blood

Frequency of donation

The volume lost from a single unit donation is replaced within 48–72 h. Red cell mass recovers more slowly, requiring 3–6 weeks (Figure 1.1). Some collection services bleed donors no more than two or three times a year; most do not bleed women who are pregnant or those who have been pregnant within the previous 6 weeks. The primary objective of this policy is to protect the donor from iron deficiency.

There is a wide variation in the recommended minimum interval between donations. For example in the US, in line with World Health Organization (WHO) recommendations, the interval can be as short as 8 weeks and a maximum of 3 litres of blood per year may be collected (American Association of Blood Banks 2003). Premenopausal women should not donate as frequently

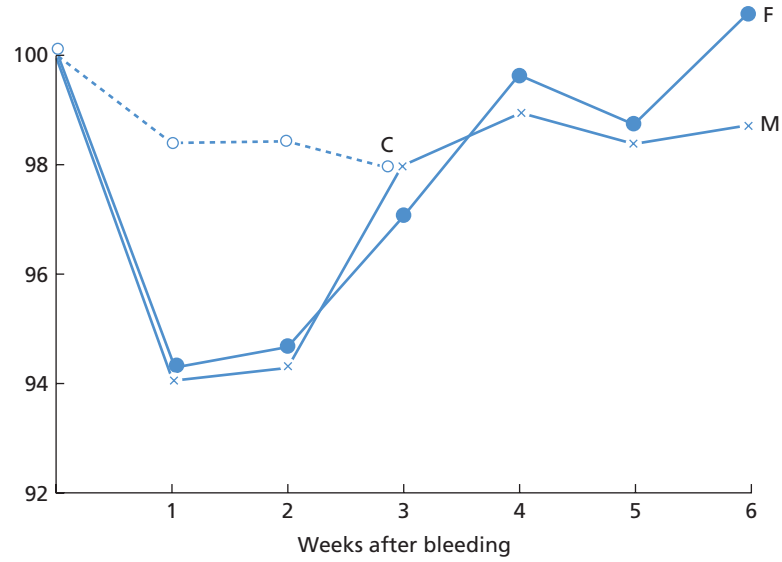

Figure 1.1 Mean Hb concentration in seven women (F) and seven men (M) at weekly intervals after being bled about 8% of blood volume. The dotted line indicates the change in mean Hb concentration for four men and four women who were not bled (C) (Source: Wadsworth 1955. Reproduced with permission of John Wiley & Sons Ltd.).

as men (see below). In the Netherlands, men are bled every 3 months and women every 6 months.

Because few red cells are lost during platelet and plasmapheresis, these procedures may be performed more often and at shorter intervals. Standards vary by country; in the USA plateletpheresis donors may be drawn every 48 h up to twice per week and 24 times per year. Commercial plasmapheresis donors are bled even more frequently; however, physical examination is more rigorous and laboratory testing more extensive for these donors. As combinations of components, such as two-unit red cells, are drawn by apheresis, volumes and intervals become individualized, but generally limited by the loss of red cells.

Effect of blood donation on iron balance

Failure to meet the Hb standard is the most common reason for donor disqualification and iron deficiency, as a result of frequent donation, most often causes rejection.

Kinetics of iron loss

More than one-half of the total iron in the body is in the form of Hb. Adult males have approximately 1000 mg of storage iron, whereas adult females typically have only 250–500 mg. A twice-per-year blood donor loses more blood than does the average menstruating woman, whose annual loss does not normally exceed 650 ml. In men, iron lost from a 450-ml donation (242 ± 17 mg) is made up in about 3 months by enhanced absorption of dietary iron. For women (217 ± 11 mg), almost 1.5 years would be required to replace iron lost at donation. Based on these data, the interval between donations would appear to be no less than 3 months for men and 6 months or more for women (Finch 1972). However, even when these intervals are observed, blood donation seems to cause iron deficiency. Generally, iron stores are adequate between the first and second donations. Thereafter, an increase in iron absorption is necessary to sustain the increased plasma iron turnover and maintain iron balance (Garry *et al.* 1995). In total, 8% of males who donate four or five times per year and 19% of those who donate every 8 weeks will become iron deficient. If these male donors continue to donate, some may still meet the Hb and/or Hct standard for donation, but develop red cell indices consistent with iron deficiency. Some men will qualify to donate even although their Hb is substantially below their baseline value; others will be deferred as their Hb level drops below the 12.5-g requirement (Simon *et al.* 1981). In a group of healthy young men who gave blood every 2 months and received no iron therapy, one-third had no stainable iron in the marrow after four donations (Lieden 1975). In another study of donors deferred because of low Hb concentration, more than 70% had evidence of iron deficiency (Finch *et al.* 1977). Similarly, even male donors who gave blood only twice per year had a significant fall in mean ferritin levels accompanied by a lower Hb, red cell count and mean corpuscular Hb

concentration (MCHC) if they had donated more than 10 times (Green *et al.* 1988). Iron stores are exhausted in virtually all female donors regardless of the frequency of blood donations (Conrad *et al.* 1981).

Oral iron supplementation

The suggestion that repeat blood donors receive iron supplementation raises a number of scientific, medical and ethical questions of which the scientific ones are most easily answered. Oral iron supplementation, if prescribed in sufficient doses and if taken by the donor, can increase annual donation frequency without the risk of iron deficiency (Bianco *et al.* 2002). The suboptimal doses found in daily multivitamins will not. In a study of donors who had given blood either 15 times or 50 times at the rate of five donations per year and had received a supplement of 600 mg of Fe^{2}+ after each donation, about 75% had no stainable iron in the marrow (Lieden 1973). These subjects were not anaemic and had normal serum iron levels. In a further study in which blood was donated every 2 months, resulting in an average daily loss of 3.5 mg of iron, iron stores were not maintained at the initial level, even when the subjects received 100 mg of iron per day (Lieden 1975). On the other hand, in 12 regular blood donors with subnormal serum ferritin levels who gave blood every 8 weeks, the ingestion of 5600 mg of iron between phlebotomies was sufficient to restore serum ferritin levels to normal and to provide a small store of iron in the bone marrow (Birgegard *et al.* 1980). Despite this finding, some experts believe that frequent bleeding even with iron supplementation is not justified and that the maximum annual rate of donation should be twice for men and once for women (Jacobs 1981).

When the interval between donations is 3 months or less, iron supplementation in the form of ferrous iron may be given to try to prevent iron deficiency. In the past, ferrous sulphate and ferrous gluconate have been prescribed but some preparations are not well-absorbed, cause gastrointestinal disturbances in many donors, and are potentially fatal if ingested in large doses by children. For all of these reasons, carbonyl iron, a small particle preparation of highly purified metallic iron with high bioavailability and almost no risk of accidental poisoning in children, seems better suited for this purpose. A series of studies by Gordeuk and co-workers (1990) showed that, with a regimen of 100 mg of carbonyl iron taken daily at bedtime for 56 days, the minimum interval between donations in the US is well-tolerated and provides enough absorbable iron to replace whatever is lost at donation in 85% of donors. A higher dose of carbonyl iron given for a shorter period of time (600 mg of iron three times daily for 1 week) caused gastrointestinal side-effects similar to those seen with ferrous sulphate (Gordeuk *et al.* 1987). In a controlled trial designed to prevent iron deficiency in qualifying female blood donors, women who received carbonyl iron (100 mg at bedtime for 56 days) increased their mean number of donations per year from 2.4 to 3.6 while increasing their iron stores (Bianco *et al.* 2002).

Iron supplementation programmes are difficult to implement and maintain (Skikne 1984). Even ongoing programmes may have limited effectiveness if the iron preparation is unpalatable or poorly absorbed (Monsen *et al.* 1983). Many blood collectors remain reluctant to become 'community clinics', whereas others raise concerns about prescribing medication for normal volunteers in order to extract additional donations. Finally, some physicians are concerned about overlooking occult gastrointestinal malignancy as the stool turns dark with the iron preparation and occult blood may be lost without the resulting anaemia. This has been estimated to be a very low risk (Bianco *et al.* 2002).

Laboratory monitoring of iron status

Laboratory monitoring can help manage the repeat blood donor. In normal, well-nourished subjects, serum ferritin concentration is a good indicator of iron stores (Worwood 1980), although red cell ferritin may be a better indicator of body iron status (Cazzola and Ascari 1986). Red cell ferritin is affected only slightly by factors other than tissue iron stores (e.g. inflammation, increased red cell turnover), whereas these factors may cause a rise in serum ferritin. Several studies of ferritin estimations in large series have confirmed that iron stores may be seriously depleted in blood donors (Finch *et al.* 1977; Bodemann *et al.* 1984; Skikne 1984). For serial blood donors who have complete blood counts performed, a progressive drop in the red cell indices [mean cell volume (MCV), MCHC] provides an even easier and less expensive method of following functional iron status (Leitman *et al.* 2003). An isolated low MCV determination may result from a haemoglobinopathy rather than iron deficiency more than 30% of the time depending upon the ethnicity of the donor population (Bryant *et al.* 2009).

Screening test to detect anaemia

Subjects should be tested before donation to make sure that they are not anaemic. A common test is to allow a drop of blood to fall from a height of 1 cm into a selected solution of copper sulphate and thus to determine its Hb

concentration from the specific gravity. A more accurate, portable photometric method avoids some of the environmental hazards of the copper sulphate technique at a higher cost (James *et al.* 2003). In some countries, such as France, the Hb level is no longer determined before donation. Instead, the Hb level and the packed cell volume (PCV) of blood donations are estimated. Donors found to be anaemic are recalled for investigation.

The lowest acceptable Hb levels for male and female blood donors, defined by the specific gravity of whole blood, correspond reasonably well with limits defined by conventional spectrophotometric analysis of venous samples. In a series of 200 healthy subjects, the range (mean ± 2 SD) was 121–165 g/l for males and 120–147 g/l for females (Bain and England 1975). Similar values were reported in a review of normal Hb concentrations based on published data (Garby 1970). Haematologic differences have been found between African–Americans and white people; reference standards for Hb, PCV and MCV differ among ethnic groups (Beutler and West 2005).

A common practice is to accept male donors whose blood contains at least 135 g Hb/l as judged by a copper sulphate solution of specific gravity 1.055, and female donors whose Hb concentration is not less than 125 g/l as measured by a copper sulphate solution of specific gravity 1.053. If a donor fails the copper sulphate test, rapid microhaematocrit or Hb determinations can be done at the donor station from skin-prick blood, using accurate portable photometry instruments (Cable 1995). In London, these supplementary determinations revealed that in approximately 50% of cases a donation can be taken, thus saving the donor from unnecessary anxiety (James *et al.* 2003). When donors are found to be anaemic (2–3% of London donors, mostly women), venous samples are taken and retested by conventional haemoglobinometry. Donors who are confirmed as anaemic should be referred to their general practitioner. In the US, the minimum acceptable level of Hb for donors is 125 g Hb/l (American Association of Blood Banks 2003).

The copper sulphate technique, although easy and convenient is being phased out, in part because of the environmental hazard and risk to screening personnel, and in part because of its poor accuracy and reproducibility. Errors in technique in using the copper sulphate method include incorporation of air bubbles or the use of an inadequate height for dropping the blood, which tend to underestimate the Hb concentration so that donors may be rejected unnecessarily. On the other hand, in rare cases in which the plasma protein concentration is greatly raised, anaemic donors may be accepted as normal, each extra g/dl of plasma protein being equivalent to 0.7 g/dl Hb (Mannarino and MacPherson 1963). Falsely high positive results in the copper sulphate method may also be due to a high white cell count associated with granulocyte mobilization or leukaemia.

The source of the blood sample may determine acceptance or rejection of a donor in borderline cases. Based on microhaematocrit methods, blood obtained by ear lobe puncture was found to give values about 6% higher than those obtained simultaneously by fingerprick puncture (Avoy *et al.* 1977), and blood from fingerprick was found to have an Hb value 2% lower than that of venous blood obtained simultaneously (Moe 1970). Ear lobe sampling is unreliable and is now considered obsolete in the US.

Noninvasive technology using reflectance spectroscopy for estimating hemoglobin concentration has been introduced as a possible screening technique. If successful, the method may eliminate the fingerstick and change the process of donor screening.

Hb regeneration after normal blood donation

In 14 normal healthy subjects bled of about 400 ml of blood (8% of their blood volume), circulating reticulocytes increased minimally but significantly, and peaked on the ninth day after bleeding. The Hb level was lowest 1 or 2 weeks after bleeding, and increased rapidly thereafter, reaching predonation levels at 3–4 weeks (Figure 1.1). In a study in which total red cell volumes were measured in subjects who had donated about 190 ml of red cells, about 50 ml of red cells were restored after 1 week and restoration was almost complete at 6 weeks (Heaton and Holme 1994).

Untoward effects during or shortly after venesection

When light-headedness and bruising at the venepuncture site are included, some 11–36% of blood donors will suffer a phlebotomy-related reaction (Newman 1997; Trouern-Trend *et al.* 1999; Newman 2003). The majority of these reactions are mild. However, a small number, some of which are avoidable, result in donor injury and disability. Reaction rates are higher in autologous donors, some of whom have significant degrees of medical debility (see Chapter 17).

Blood pressure and pulse measurement: predictive and protective?

Blood pressure and pulse in the normal range have been traditional screening standards for assuring that prospective blood donors are healthy and for predicting donors

at increased risk for cardiovascular and neurovascular adverse events. 'Normal' for this purpose has relied more on consensus definition than on scientific rationale. The older literature is equivocal. Poles and Boycott (1942) reported no relationship between low initial blood pressure and syncopal episodes, whereas other studies reported weak correlation (Boynton and Taylor 1945; Callahan 1963). Recent studies have not confirmed a relationship between blood pressure and fainting at the extremes of the range used for accepting donors (Wiltbank *et al.* 2008; Trouern-Trend *et al.* 1999; Eder *et al.* 2009). However before discarding blood pressure measurement as one indicator of donor health, consider that the recent studies were conducted in the era when AABB standards for blood pressure were in place and few data concerning donors with systolic pressure >180 or diastolic pressure <80 are available. Prospective donors who fell outside of this range were deferred.

Fainting or the vasovagal attack

Syncope, the sudden brief loss of consciousness caused by diminished cerebral blood flow, occurs at least once in almost 22% of the population, and 9% have recurrent syncope (Lu *et al.* 2003). Syncope occurs in both children and adults and is responsible for about 6% of emergency room visits and 3% of hospitalizations. Most syncopal events are triggered by standing or emotion and are often referred to as vasovagal reactions. The mere sight of blood being taken from another person can precipitate a 'vasovagal attack' in certain subjects. Withdrawing a sufficient quantity of blood will provoke syncope in everyone. After the loss of as little as 400 ml of blood, some subjects remain predisposed to faint even several hours later if they rise suddenly from a sitting or lying position, or if they remain standing for prolonged periods. In view of this risk, all donors should be observed for at least 15 min after donation and should be questioned about their occupation. Donors in whom fainting would be especially hazardous to themselves or to others (e.g. pilots, surgeons and bus drivers) should probably refrain from work or potentially dangerous hobbies for up to 12 h after giving blood. Donors who experience a delayed faint should be indefinitely deferred from blood donation, regardless of their occupation (Kamel *et al.* 2010).

Pathophysiology

The vasovagal attack appears to be a hypothalamic response mediated by either a central neural pathway or a peripheral pathway associated with the baroreceptors. While blood is being drawn, warning of oncoming fainting may be presaged by a decline in bloodflow rate, as already noted in the seventeenth century (Harvey 1628). Vasovagal reactions are typically biphasic, originating with a stress-induced elevation in pulse and blood pressure, and rapidly followed by the commonly recognized signs and symptoms of fainting. As the syndrome develops, the donor feels weak and dizzy. Clinical characteristics include sweating and pallor, cool extremities, strikingly slow and faint pulse, low or undetectable blood pressure, vomiting and, less commonly, tetany and urinary and faecal incontinence. Loss of consciousness may follow and convulsions are seen occasionally. These effects result primarily from the action of the autonomic system, causing slowing of the heart, vomiting and sweating and, perhaps most important, dilatation of the arterioles, leading to a sudden fall in blood pressure (Barcroft *et al.* 1944). The slow pulse rate (30–60 per min) in the vasovagal attack is the most useful single sign in differential diagnosis.

Donor characteristics and frequency

Estimates of the frequency with which fainting occurs in blood donors vary according to the definition of the term 'faint'. In the Medical Research Council's inquiry (1944), 'fainting' was defined as the manifestation of any of a series of signs or symptoms such as pallor, sweating, dimness or nausea. By this definition, some 5–6% of donors fainted. A similar frequency of vasovagal symptoms (5.3%) was noted by interviewers who solicited this information from 1000 donors 3 weeks after blood donation (Newman 2003). In a series of 10 000 cases, only 2.8% of donors fainted, but the term 'fainting' was applied only to those who lost consciousness or could not stand or sit without doing so (Poles and Boycott 1942). Moderate to severe reactions are reported in 0.08–0.34% of donations (Newman 1997). In a retrospective analysis of 793 293 allogeneic whole blood and apheresis donations in a single year, the prevalence of reactions classified as moderate or severe was 41 in 10 000 donations; 24% of these reactions were delayed (>15 min) and 12% occurred off-site (Kamel *et al.* 2010). Delayed reactions were associated with female sex and with low estimated blood volume. First-time donors were about twice as likely to have reactions as were repeat donors (see also below). Off-site reactions, particularly in female donors, were more likely to be associated with a fall, with head trauma, with other injury, and with the use of outside medical care.

Vasovagal reactions occur more commonly on the first occasion of giving blood. Of course those with severe

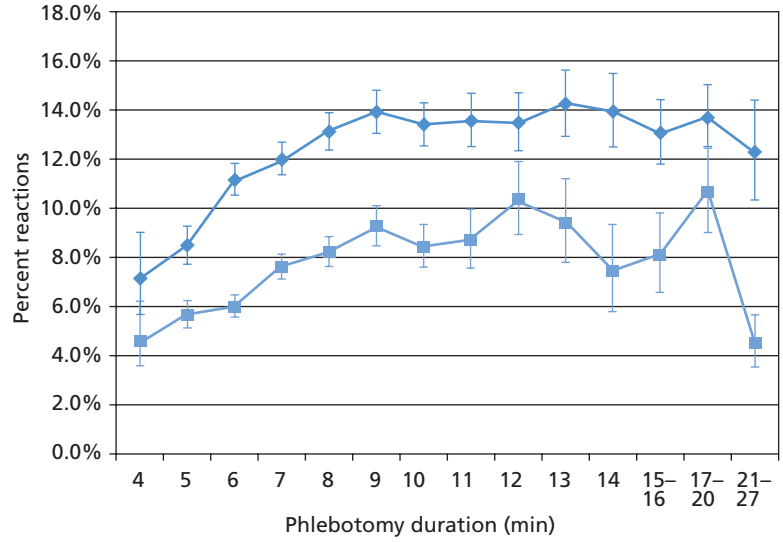

Figure 1.2 Vasovagal reactions in first-time, 17-year-old, Caucasian female blood donors (◆) and in first-time, 17-year-old Caucasian male blood donors (■) at different phlebotomy durations (Source: Newman *et al.* 2008. Reproduced with permission of John Wiley & Sons Ltd.).

reactions are frequently deferred from further donations, and thus the 'repeat donor' is in a selected group. Among 1000 donors studied over a period of several years, more than one-half experienced their only symptoms at the time of their first donation; the incidence of reactions fell progressively over a period of 6 years (Beal 1972). In 40 437 donations studied, fainting was found to be more common in female donors; 4.9% of first-time female donors suffered vasovagal reactions compared with 3.8% of first-time male donors. The figures were less than half in repeat donors of both sexes, 1.9% and 1.1% respectively (Tomasulo *et al.* 1980). However, gender may be a surrogate measure for body weight. In a case–control study, age, weight and first-time donor status were significant predictors of syncope (Trouern-Trend *et al.* 1999).

One early study noted a relation between the incidence of fainting and the amount of blood donated. The incidence was 3.8% in those giving 440 ml, but 8.5% in those giving 540 ml (Poles and Boycott 1942). In normal males from whom 800–1000 ml of blood was taken, the incidence was 11 out of 28, and in those from another series, loss of consciousness was observed in 5 out of 6 (Ebert *et al.* 1941). In experiments in which up to 1500 ml of blood was withdrawn from normal volunteers, fainting could be produced in all subjects if enough blood was withdrawn within a limited time (Howarth and Sharpey-Schafer 1947).

Rapid phlebotomy would seem to be a factor in syncopal reactions, but the opposite appears to be true. Newman *et al.* (2008) compared the rate of vasovagal donor reactions with the duration of whole-blood collections in first-time high school donors. A total of 126 195 first-time, 17-year-old Caucasian donors in 35 American Red Cross blood centres, donated a volume 525 ml, whole blood with phlebotomy intervals ranging from 4 to 27 minutes (velocity, 131–19 ml/min). Vasovagal reactions were higher in females than in males at all duration times (Figure 1.2). The reaction rates increased with longer phlebotomy durations in both females and males, a seeming paradox. It is not clear whether these observations can be extended to other donor populations, age groups, or repeat donors; however deferring young donors with low estimated blood volume represents one approach to protecting donors at increased risk of reactions without jeopardizing the adequacy of the blood supply (Rios *et al.* 2010).

Management of vasovagal reactions: science, custom and myth

Subjects who display these signs but who have not lost blood recover rapidly when they are placed supine and positioned so that the head is lower than the rest of the body (Trendelenburg position). Time-honoured measures include applying an ice pack or cold towel to the (donor's) forehead or back of the neck or using a paper bag rebreathing technique to elevate CO_2 and cerebral blood flow. The effectiveness of such techniques is unknown. Inhalation of ammonia salts adds very little other than irritating the respiratory membranes and the

blood donor. Intravenous infusion, inotropic agents and cholinergic blockade are rarely necessary. Donor room personnel should be cautioned against the precipitous use of external defibrillation and cardiopulmonary resuscitation, as these techniques will invariably cause more harm than good to a donor suffering from a vasovagal attack.

Some consequences of syncope

Syncope can have serious consequences. Seizure activity and tetany have been reported in about 25% of syncopal reactions. Skull and facial bone fractures, scalp lacerations, chipped teeth and extremity fractures have all been reported (Boynton and Taylor 1945; Kamel *et al.* 2010). A retrospective analysis of 178 vasovagal reactions from 194 000 donations found that 10% of these donors sustained a head injury and 6% required additional medical care in an emergency room. One injured donor developed post-concussion syndrome and suffered headaches and other symptoms for more than 1 year (Newman and Graves 2001). Although 12% of the reactions occurred off site, the majority within 1 h of donation. More than 60% occurred at the refreshment table, an observation that should stimulate serious thought about the design and oversight of the donor recovery area.

Pre-donation water ingestion has been used as a simple prophylaxic measure against vasovagal reactions in blood donors. Water ingestion has a pressor effect, enhances tolerance of upright posture by increasing peripheral vascular resistance, and reduces the chance of syncope during orthostatic stress (Lu *et al.* 2003). Using a tilt-table orthostatic stress system, Lu *et al.* (2003) found that drinking 473 ml water enhanced tolerance of upright posture in 22 subjects with no prior history of syncope (Figure 1.3). A 16 oz (473-ml) water drink decreased the vasovagal donor reaction rate in high-school donors by 21%, but to varying degrees in different subpopulations (Newman *et al.* 2007).

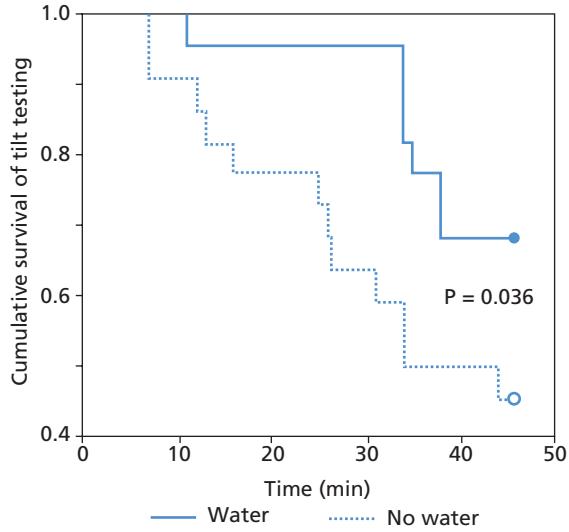

Figure 1.3 Cumulative proportion of subjects remaining free of presyncopal episodes with and without water. At 30 minutes, 95% of those with water compared with 63% of those without water were able to tolerate tilt. At completion of study (45 minutes), 69% with water compared with 45% without water were able to tolerate tilt (Source: Lu *et al.* 2003. Reproduced with permission of Lippincott Williams & Wilkins.).

Some other untoward effects

Bruising

Bruising is one of the commonest complications of blood donation, and is reported in 9–16% of donations (Boynton and Taylor 1945; Newman 1997). In the majority of cases, the haematoma is restricted to a small area in the antecubital fossa. However, very large, incapacitating and painful haematomas develop occasionally following blood donation. Inattention to an enlarging haematoma can result in a forearm compartment syndrome with consequent neural and vascular compromise and massive tissue necrosis. Instruction regarding pressure dressing, cold compresses and medical follow-up can prevent a large bruise from turning into a medical emergency.

Phlebitis and cellulitis

Mild phlebitis at the venepuncture site in the antecubital fossa is common, self-limited and usually of little consequence. Mild discomfort, warmth and local linear or surrounding erythema may be difficult to distinguish from mild cellulitis or reaction to the topical antiseptic, particularly if the latter contains iodine. Despite a seemingly benign appearance, local reactions merit close medical follow-up to prevent extension of these lesions to abscess formation or septic phlebitis. Early application of warm compresses, oral anti-inflammatory agents and administration of antibiotics when indicated are prudent. Newman reports an incidence of local reactions of 1 in 50 000 to 1 in 100 000 (Newman 1997).

Nerve injury

The proximity of cutaneous branches of the medial and ulnar nerves to the large-bore needle access to the antecu-

bital vein makes occasional injury to these structures inevitable. The injuries are generally transient and rarely a source of donor distress. In most instances the donor reports a localized area of numbness or tingling (paraesthesia). In 419 000 donations over a 2-year period, Newman and Waxman (1996) reported an incidence of peripheral nerve injury of 1 in 6300, with 78% of donors reporting their injury on the day of donation. Symptoms were almost evenly divided between paraesthesias and radiating pain, although eight donors reported loss of arm strength. Almost one-quarter of these reports were associated with haematoma formation at the venepuncture site. In total, 70% of donors recovered completely within 1 month; 52 out of 56 recovered completely and four donors reported a small area of persistent numbness.

Puncture of an artery

This leads to an unusually rapid flow of bright red blood; when the needle is withdrawn, there may be severe leakage of blood, followed by extensive bruising. If an arterial puncture is suspected, the needle should be withdrawn immediately and firm pressure applied for at least 10 min, followed by a pressure dressing. If the radial pulse is not palpable, the donor should be referred to a vascular specialist. Rare complications of arterial injury include pseudoaneurysm formation and development of an arteriovenous fistula (Lung and Wilson 1971; Popovsky *et al.* 1994).

Tetany

Tetany is occasionally observed in blood donors (incidence 1 in 1000), characteristically in nervous subjects, and is thought to be due to hyperventilation. Manifestations may include carpopedal spasm, laryngismus, stridulus and a positive Chvostek's sign. Rapid relief can be obtained by rebreathing from a paper bag or inhaling 5% CO_2 from a cylinder, an unlikely method of management in the modern blood centre (Frazer and Fowweather 1942). In an apheresis donor, tetany is almost invariably preceded by tingling and paraesthesias, is the consequence of citrate-induced hypocalcemia, and should be managed by reducing the flow of citrated blood and administration of oral calcium.

Convulsions

These are uncommon. If seizures occur, the donor should be immobilized on the bed or on the floor to prevent injury, and an open airway ensured.

Air embolism during blood donation

When blood is taken into plastic bags that contain no air, there is no possibility of air embolism. On the other hand when blood is drawn into glass bottles (as is still the practice in some countries), air embolism may occur. The prime cause of air embolism in this circumstance is obstruction to the air vent of the bottle (for details and further references, see seventh edition, p. 6). Apheresis devices include inline filters and air detector alarm systems to prevent air from a defective seal from being pumped into a donor.

Fatalities attributed to blood donation

In 1975, the Food and Drug Administration of the USA published regulations requiring the reporting of deaths associated with blood collection, plasmapheresis and transfusion. In the 10 years from 1976 to 1985, three deaths attributed to blood donation were reported out of 100 million units of donated blood. Two deaths were due to myocardial infarction and one was in a patient with phaeochromocytoma (Sazama 1990). In 1999, of 48 deaths reported to the FDA in some 20 million donations, four fatalities occurred in donors. Two of these were donors of autologous units and all deaths were attributed to underlying disease. In 2009, three fatalities following whole blood donation were reported. In two of these cases, donation was ruled out as the cause of death, and in the third case, although the donation could not be definitively eliminated as related to the donor's death, no evidence supported a causal relationship between the donation and subsequent death of the donor.

Potential health benefits of blood donation

For the volunteer donor, the chief benefit lies in the satisfaction of selfless concern for the welfare of others. An obvious potential benefit is the unexpected clue to the diagnosis of a disorder that may be treatable, such as iron deficiency, chronic hepatitis, or in the case of pathogeneic bacteria detected by platelet culture, an underlying infection or occult tumour (Haimowitz *et al.* 2009). However, two studies suggest that there may be more tangible health benefits, particularly for middle-aged men, such as lowering the risk of cardiovascular disease (Meyers *et al.* 1997; Salonen *et al.* 1998). The proffered explanation derives from the so-called 'iron hypothesis': menstrual iron loss protects women against cardiovascular disease; iron stores correlate with cardiovascular disease across European populations and heart failure is a hallmark of disorders of iron surplus (Sullivan 1981). One proposed

mechanism for this association is generation of oxygen-free radicals that induce oxidation of lipids (McCord 1991). However the Johns Hopkins Hospital autopsy registry found less coronary artery disease in hearts from patients with haemochromatosis and haemosiderosis than in hearts of age- and sex-matched controls (Miller and Hutchins 1994).

Salonen and co-workers (1998) conducted a prospective 9-year follow-up study of 2862 men aged 42–60 from eastern Finland, who had participated in the Kuopio Ischemic Heart Disease Risk Factor Study (Salonen *et al.* 1998). Only one man out of 153 who had donated blood in the 24 months prior to baseline examination suffered a myocardial infarction, compared with 316 (12.5%) of the 2529 non-donors. Meyers and co-workers (1997) compared the rate of cardiovascular events of 665 blood donors with that of 3200 non-donors in a telephone survey of a cohort selected from the Nebraska Diet Heart Survey. By multivariate analysis, non-smoking men who had donated at least once in the previous 3 years had a significantly lowered risk of cardiovascular events; no additional benefit was derived from longer or more frequent donation. Numerous cofactors confound these studies, and the validity of this statistical association has been questioned (Ford 1997).

Although the hypothesis remains intriguing, it is premature to suggest that health benefits, other than those attributable to altruism, will derive from blood donors – even for non-smoking middle-aged men.

Directed donations

Directed donations are those given exclusively for named patients, usually by relatives or friends. The use of directed donations contravenes the normal principles of voluntary blood donation, fails to increase safety (Cordell *et al.* 1986; Strauss 1989) and finds medical justification in vanishingly few circumstances: (1) in patients with rare blood groups when the only available compatible donors may be close relatives; (2) in occasional patients awaiting renal transplants, for whom donor-specific transfusions may still play a role (Salvatierra *et al.* 1981; Anderson *et al.* 1985; see also Chapter 14); (3) in infants with neonatal alloimmune thrombocytopenia or haemolytic disease of the newborn, for whom maternal platelets or red cells are occasionally invaluable; (4) in children requiring open-heart or extensive orthopaedic surgery, for whom the total requirements for blood and components can be collected preoperatively, as for autologous transfusion but from designated relatives or parents, thus minimizing the number of donor units to which the children are exposed (Brecher *et al.* 1988); and (5) in patients with leukaemia in relapse after bone marrow transplantation, for whom donor leucocytes are used as adoptive immunotherapy to induce graft-versus-leukaemia (GvL) effect (Sullivan *et al.* 1989; Kolb *et al.* 1990).

The practice of transfusing parental blood to premature newborn infants is not without risks. Mothers may have antibodies against antigens (inherited from the father) on the infant's red cells; platelets or white cells and maternal plasma should not be used. Fathers should not serve as cell donors because they may have antigens present on their red cells, which are incompatible with maternally derived antibodies present in the fetus. Moreover, in view of partial histocompatibility, transfusion of cells from parents and close relatives may result in graft-versus-host disease (GvHD) in the infants, or older children, especially if the infants are immunodeficient (Bastian *et al.* 1984; Strauss 1989). Circumstances such as these, in which blood or platelet suspensions should be irradiated, are described in Chapter 15.

The practice of transfusing parents with blood from their offspring can also be dangerous. Fatal GvHD occurred in two immunocompetent adult patients who were transfused with fresh whole non-irradiated blood from their children during cardiac surgery. In both cases, one of the donors was homozygous for one of the recipient's HLA haplotypes (Thaler *et al.* 1989). When such transfusions are indicated, and except for instances in which adoptive immunotherapy is intended, the components should be treated with 25 Gy gamma irradiation (see Chapter 15).

People who donate for friends and family lose their anonymity and may be subject to influences not placed upon community donors. Such donors may provide less than candid answers to sensitive donor questions, either because they believe that unsafe blood will inevitably be detected by testing procedures or because they wish to conceal information from the recipient or the blood collector. Two examples follow:

1 A 28-year-old male first-time donor qualified to give a unit of blood for his mother's scheduled heart surgery. The unit tested positive for anti-HIV. During a subsequent confidential interview, the donor acknowledged untruthful answers to the high-risk activity questions on the donor interview form. When asked why he would donate for his mother when he was aware of the increased risk of his blood, he responded that any exposure to a transfusion-transmitted disease would surely be detected by testing. He indicated that refusal to donate for his mother would have signalled either lack of filial devotion or a lifestyle

unacceptable to his mother. Furthermore, he interpreted the fact that he had been detected by testing as validation of his approach.

2 A child with a 19-year history of aplastic anaemia was found to harbour a chronic parvovirus B19 infection (Kurtzman *et al.* 1987). Treatment with immune plasma was planned on an investigational protocol. Among numerous donors tested for antibody to this virus, the child's parents were found to have the highest titred plasma. Each had an unremarkable medical history and physical examination. Because both parents qualified to donate blood and insisted that they were the safest donors for their child, units of plasma were drawn and prepared for immunotherapy. Neither parent had donated blood previously. During routine sample testing, extremely high alanine aminotransferase (ALT) levels were detected in specimens from both parents, and subsequent medical evaluation revealed that both parents had chronic hepatitis. After persistent questioning about this finding, the parents recalled several episodes of intravenous drug use some 16 years earlier.

A variant of directed donation is the compulsory 'replacement donation' extracted from relatives and friends of patients admitted to hospital in many countries in the developing world. Such donations are often purchased and are generally less safe than true voluntary donations (Sarkodie *et al.* 2001). However recent information from Ghana indicates that frequency of viral markers in replacement and first-time volunteer donors was similar, although higher than that of repeat donors. A blood unit from replacement donor costs half or less than that from a volunteer donor (Allain *et al.* 2010).

Use of cadaver blood – Dead-icated donors

Administration of cadaver blood seems to be of prime interest to journalists and reporters. The collection of blood from cadavers has been practised in a few centres in Russia (Yudin 1936; Agranenko and Maltseva 1990), and tried and rejected by several centres in Spain and the US shortly thereafter. A fascinating history of the cadaver blood programme in Chicago, and its resurrection in Detroit and Mexico City, has been published (Ramsey and Schmidt 2009). Reports of widespread use of cadaver blood and its benefits have attained mythical proportions.

Therapeutic phlebotomy

Blood centres and transfusion services, with their expertise in safe blood withdrawal and donor management, present a logical setting for performing therapeutic phlebotomy. Even though many subjects referred for therapeutic phlebotomy are as healthy as volunteer donors, and in the case of hereditary haemochromatosis have been volunteer donors, others are true patients who deserve close medical supervision. Blood collected from these procedures may be unsuitable for transfusion because of the patient/donor's underlying medical condition or because the subject fails to qualify as a donor for other reasons. By tradition, therapeutic phlebotomy services have been located in an area separate from volunteer blood donation and have required a medical prescription from an attending physician. However, as otherwise healthy subjects with hereditary haemochromatosis are being identified by screening programmes, the distinction between patient and donor has blurred. Some countries require that blood drawn from such donors (see below) be so labelled, and that the recipient be informed of the source of the transfusion.

Polycythaemia vera

Phlebotomy remains the overwhelming choice for the initial therapy of polycythaemia vera (Streiff *et al.* 2002). Although red cells from such patients survive normally, polycythaemia vera is a clonal, progressive, myeloproliferative disorder and patients are at increased risk for developing leukaemia. As a rule, this blood is not used for transfusion, although the risk of acquiring a graft of malignant cells from the donor seems to be negligible, even in recipients whose immune mechanisms are suppressed by disease or drugs. Although the target level for phlebotomy remains controversial, studies of blood viscosity and thromboembolic disease suggest that patients be maintained at a PCV <44%, a level usually reached by weekly to monthly phlebotomy until iron stores are depleted (Streiff *et al.* 2002).

Other conditions associated with polycythaemia

Erythrocytosis may occur in a variety of congenital states, such as mutations in the erythropoietin receptor gene and in the Hb molecule, in residents of high-altitude locations and in patients with respiratory insufficiency, cyanotic congenital heart disease and a variety of neoplasms. It may be useful to measure oxygen consumption and exercise tolerance to help determine whether therapeutic phlebotomy is helpful in these disorders and, if so, what the target level for phlebotomy should be (Winslow *et al.* 1983; 1985).

Hereditary haemochromatosis

Hereditary haemochromatosis is one of the most common inherited disorders of white people, occurring

in 1 in 250 individuals of northern European descent (Olynyk 1999). It is uncommon in other racial groups, although sporadic cases occur. A point mutation in the HFE gene, Cys282Tyr, is found in 85–100% of white people with the disorder (Gilbert *et al.* 1989). Failure of the HFE gene product to bind to the transferrin receptor on gut mucosal cells leads to inappropriately high gastrointestinal absorption of iron, with progressive iron deposition in the skin, liver, heart and other tissues. Hepatic fibrosis, cirrhosis, endocrine insufficiency, heart failure and arthritis may ensue. Haemochromatosis is associated with a high risk of secondary osteoarthritis and joint replacement. A German study found that 16% of subjects with haemochromatosis had at least one joint replaced, suggesting that a substantial proportion of subjects with haemochromatosis face progressive and severe osteoarthritis warranting joint replacement surgery (Sahinbegovic *et al.* 2010). However, the clinical penetrance of the disorder is variable and a substantial number of subjects with the mutation remain unaffected or asymptomatic for years.

Management of phlebotomy

Phlebotomy remains the most effective therapy for haemochromatosis. If phlebotomy is initiated before the onset of cirrhosis, patients can lead a normal life (Barton *et al.* 1998). Phlebotomy is generally initiated on a weekly basis, with removal of approximately one unit of blood (500 ml) per session. Clinical and laboratory endpoints of induction (weekly) therapy differ widely from centre to centre (Bolan *et al.* 2001). Recent guidelines target a transferrin saturation ranging from less than 20–30% as a guide to the pace of maintenance phlebotomy. However, the transferrin saturation may rebound rapidly after initial iron depletion owing to the dysregulation of iron cycling associated with hereditary haemochromatosis, and may not accurately reflect the true total body iron burden. Monitoring the Hb and MCV in combination provides a reliable, accurate and inexpensive method for indicating the onset of iron-limited erythropoiesis and guiding the endpoints of therapy (Bolan *et al.* 2001; Leitman *et al.* 2003). Furthermore, sustained maintenance of the MCV at exactly this level (5–10% below baseline) was found to keep subjects with hereditary haemochromatosis just on the verge of iron-limited erythropoiesis and could be used to define a phlebotomy interval that prevented iron reaccumulation during maintenance therapy, while allowing Hb levels to rise well into the normal range (above 14 g/dl). Two-unit apheresis affords a rapid method for removing iron on a schedule convenient for most subjects. The efficiency can be seen by comparing twins with haemochromatosis, one of whom was treated with manual single-unit phlebotomy, whereas the other underwent the apheresis procedure (Figure 1.4).

Use of blood for transfusion

Several countries use blood withdrawn from subjects with haemochromatosis for allogeneic transfusion. However in the US, federal regulations require disease labelling of blood derived from therapeutic phlebotomy and additional donation conditions must be met before labelling for hereditary haemochromatosis is waived by the FDA (Guidance for Industry. Variances for Blood Collection from Individuals with Hereditary Hemochromatosis. Rockville MD: Center for Biologics Evaluation

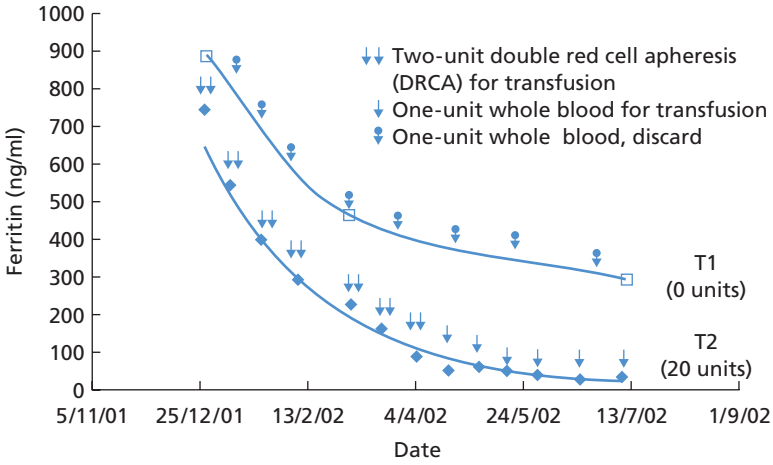

Figure 1.4 Twin brothers with hereditary haemochromatosis undergoing therapeutic phlebotomy. Twin 2 (T2) was treated with two-unit apheresis phlebotomy that resulted in more rapid iron depletion than his twin (T1) who received manual single-unit bleeding. Subject A required fewer treatment visits.