1 Introduction: Two Centuries of Progress in Transfusion Medicine

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'States of the body really requiring the infusion of blood into the veins are probably rare; yet we sometimes meet with cases in which the patient must die unless such operation can be performed.' So begins James Blundell's 'Observations on transfusion of blood' published in *The Lancet*, marking the origins of transfusion medicine as a clinical discipline. Blundell (Figure 1.1) was a prominent London obstetrician who witnessed peripartum haemorrhage and whose interest in transfusion had begun as early as 1817 during his medical education in Edinburgh. He established that transfusions should not be conducted across species barriers and noted that resuscitation from haemorrhage could be achieved using a volume of transfusion that was smaller than the estimated blood loss. Despite life-saving results in some patients, clinical experience with transfusion was restricted by lack of understanding of ABO blood groups – a barrier that would not be resolved for another century.

The Nobel Prize-winning work of Karl Landsteiner (Figure 1.2) established the primacy of ABO blood group compatibility and set the stage for safer transfusion practice. Twentieth-century transfusion was advanced by the leadership of many physicians, scientists and technologists and repeatedly incorporated new diagnostics (monoclonal antibodies, genomics) and new therapeutics (plasma fractionation, apheresis and recombinant proteins) to improve patient care.

Today, the field of transfusion medicine is composed of a diverse range of disciplines including the provision of a safe blood supply; the fields of haemostasis, immunology, transplantation and cellular engineering; apheresis technology; treatment using recombinant and plasma-derived plasma proteins; and the daily use of blood components in clinical medicine (Figure 1.3). Without transfusion resources, very little of modern surgery and medicine could be accomplished.

For decades, the challenge of transmitting new information in transfusion fell to Dr Patrick Mollison (Figure 1.4) whose textbook became the standard of its era. Mollison highlighted the importance of both laboratory practice (immunohaematology, haemostasis, complement biology) and clinical medicine in our field. *Practical Transfusion Medicine*, here in its fifth edition, seeks to build on that tradition and to give readers the foundation knowledge required to contribute both academically and clinically to our discipline. For readers about to enjoy the content of this book, the following provides a sampling of the topics presented within the text by leading experts in our field.

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Figure 1.1 James Blundell.

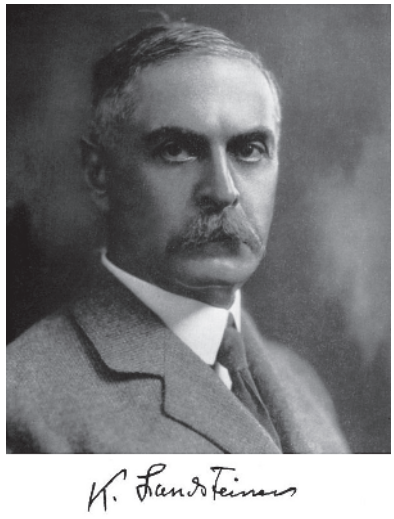

Figure 1.2 Karl Landsteiner.

Blood Donation Worldwide

Each year, approximately 100 million blood donations are made worldwide (Figure 1.5). A safe and adequate blood supply is now an essential infrastructure requirement of any modern national healthcare system. The recruitment and retention of healthy blood donors is a vital activity of the field and the challenges and responsibilities faced by stewards of the blood supply are presented to readers in Chapters 18–22. Whilst the economically advantaged nations of the world have established all volunteer donor programmes with great success, data from the World Health Organization presented in Chapter 24 document that blood donation rates per capita in many low-income nations are insufficient to meet their needs. More research and investment is required so that all regions of the world can rely upon an adequate supply of safe blood.

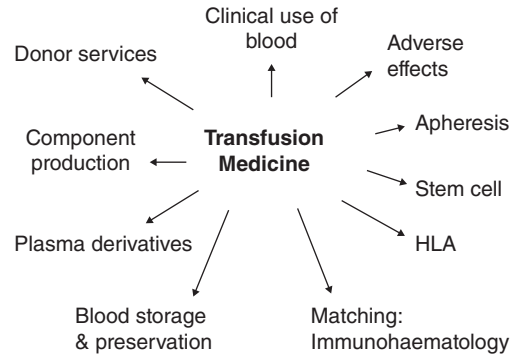

Figure 1.3 The range of transfusion medicine.

Figure 1.4 Patrick Mollison. *Source:* Garratty, Transfusion 2012;52:684–85. Reproduced with permission of John Wiley & Sons.

Changing Landscape of Transfusion Risks

During the final two decades of the twentieth century, intense focus on screening blood donations for infectious diseases led to substantial progress in blood safety and a significant reduction in the risk of transfusion-transmitted diseases (Figure 1.6). Chapters 15–17 present an authoritative summary of this success. We currently enjoy a grace period when the risk of transfusion-transmitted infections is at an all-time low. However, progressive encroachment of humans upon the animal kingdom is expected to result in the emergence of new infections that cross species barriers. Haemovigilance, robust screening technologies and chemical pathogen inactivation are all being applied to address this concern and are reviewed within the text.

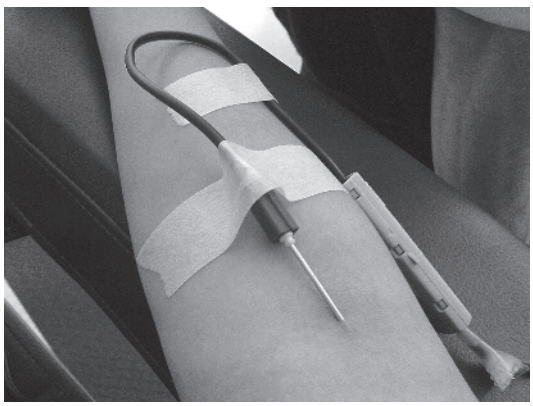

Figure 1.5 Blood donation.

With the advent of the twenty-first century, the landscape of transfusion risk shifted its emphasis towards non-infectious hazards (Figure 1.7). Recent years have focused on improved understanding and prevention of transfusion-related acute lung injury, a topic covered in detail in Chapter 10. More recently, we have learned that circulatory overload from

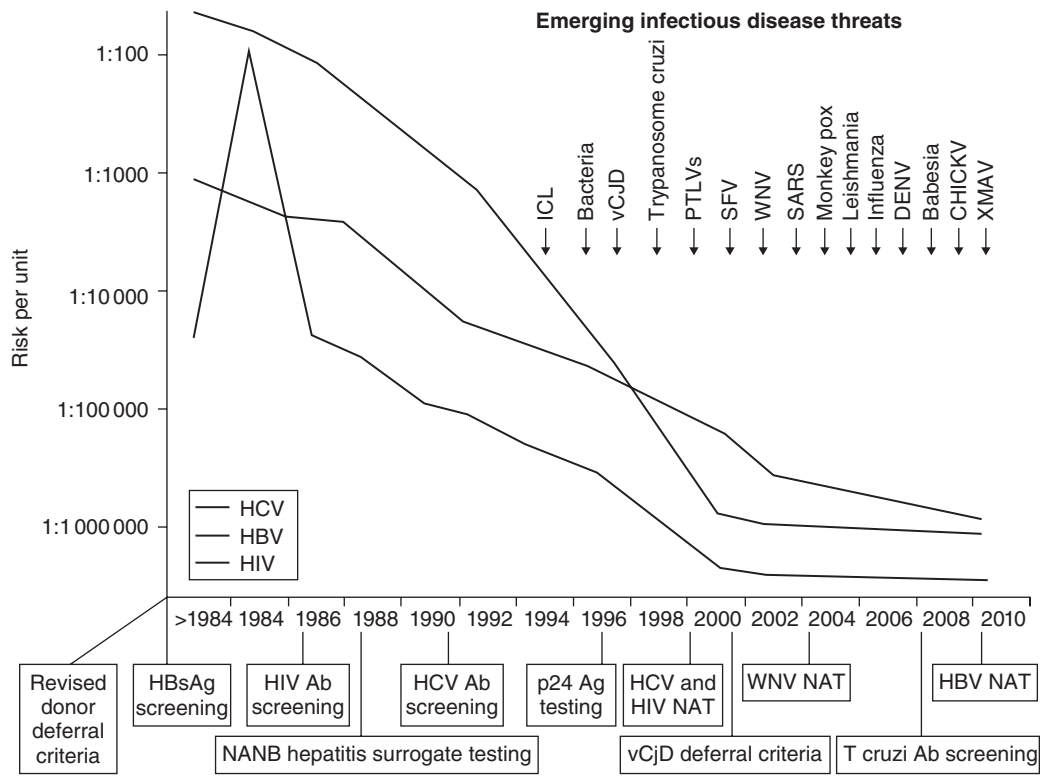

Figure 1.6 Risks of transfusion-transmitted infections over time.

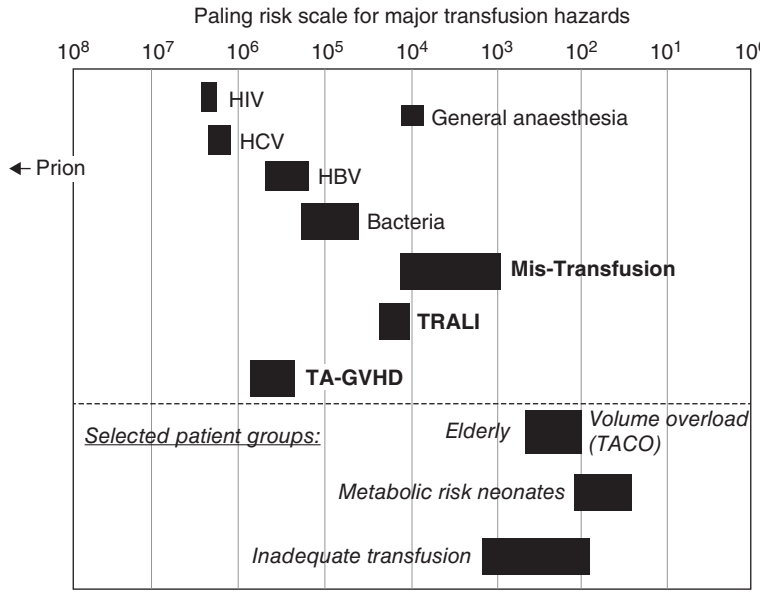

Figure 1.7 Paling scale of transfusion risk.

excessive transfusion is far more common than previously recognised. Yet Blundell himself specifically warned of it in his first description of transfusion: 'to observe with attention the countenance of the patient, and to guard … against an overcharge of the heart' [1]. In addition, haemolytic reactions remain a serious hazard of transfusion. It is quite surprising that despite unimagined advances in internet connectivity, most nations still do not have a system for sharing patient blood group results or antibody profiles between hospitals, thereby failing to share information that would prevent acute and delayed reactions. Much can still be done to further reduce non-infectious hazards of transfusion. Readers will find that Chapters 7–17 provide state-of-the-art summaries of our current understanding regarding the full range of adverse effects and complications of transfusion.

Immunohaematology

Knowledge of the location and functional role of red cell surface proteins that display blood group epitopes has brought order out of what was once a chaotic assembly of information in blood group serology (Figure 1.8). Readers will enjoy an up-to-date treatment of this topic in Chapters 2–6.

Today, red cell genomics has become a practical clinical tool and DNA diagnostics in immunohaematology extends far beyond the reach of erythrocyte blood groups. Genotyping has always been the preferred method for defining members of the human platelet antigen system and is well established for HLA genes in the field of histocompatibility (Figure 1.9). The clinical practice of transfusion medicine is now supported by DNA diagnostics targeting a wide range of genes, including those coding for complement proteins, human neutrophil antigens, haemoglobin polymorphisms and coagulation factors.

Despite advances in defining antigens, both clinical illness and blood group incompatibilities remain dominated by antibody responses of the patient. A robust form of antibody analysis and better control of the immune response remain important frontiers of our field. The ability to downregulate specific alloimmune responses would revolutionise the approach to

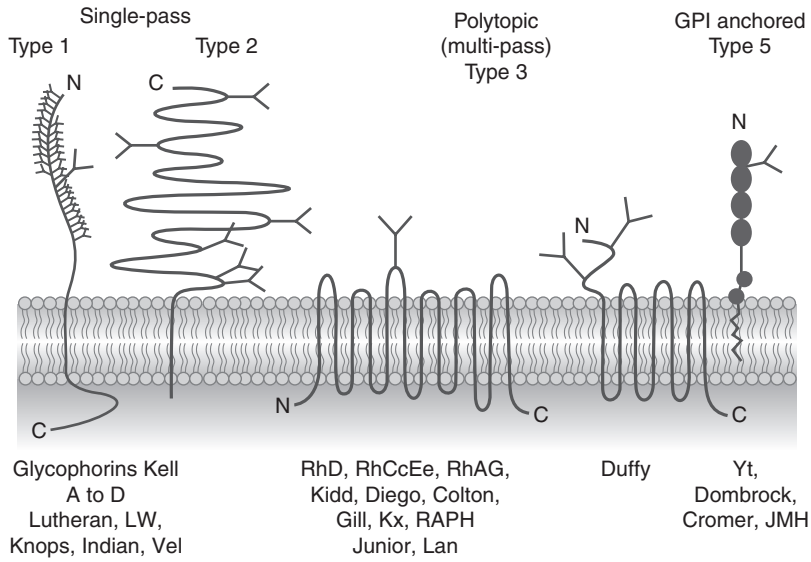

Figure 1.8 Red blood cell antigens. *Source:* Daniels G, Bromilow I. Essential Guide to Blood Groups, 3rd edn. Wiley: Chichester, 2014. Reproduced with permission of John Wiley & Sons.

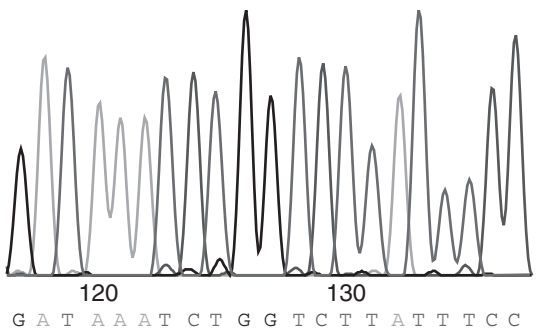

Figure 1.9 DNA sequence.

solid organ transplantation, haemophilia complicated by inhibitors, platelet refractoriness, red cell allosensitisation, haemolytic disease of the newborn and a host of other challenges that confront transfusion specialists every day.

In the meantime, we can offer patients powerful, yet nonspecific immune suppressants. And while the focus of many treatments is on reduction of pathological antibodies, it is increasingly clear that antibodies themselves do not injure tissues nearly as much as the complement proteins that antibodies attract. Complement is at the centre of a wide variety of disorders, including drug-mediated haemolysis or thrombocytopenia, severe alloimmune or autoimmune haemolysis, cryoglobulinaemic vasculitis, HLA antibody-mediated platelet refractoriness and organ rejection, paroxysmal nocturnal haemoglobinuria, atypical haemolytic-uremic syndrome, hereditary angioedema, glomerulonephritis and age-related macular degeneration. With the development in the future of better agents to suppress complement, it can be anticipated that the focus of treatment may shift from removal of pathological antibodies to control of their effect.

Clinical Use of Blood Components: Evolution Based on Evidence

Recent years have witnessed a growing body of evidence derived from clinical research and focused on the proper use of blood components (Figure 1.10). While such research has lagged for plasma products, progress has been made

for both red cells and platelets. Ever since the landmark publication of the TRICC trial by Hebert and others [2], clinical investigators have repeatedly challenged the traditional 100 g/L haemoglobin threshold for red cell transfusion. There are now at least 11 well-designed, sufficiently powered randomised controlled trials documenting that a conservative haemoglobin threshold for red cell transfusion is as beneficial for patient outcomes as a more liberal threshold (Figure 1.11). These studies cut across a broad range of patient categories from infants to the elderly. As a result, in hospitals worldwide, red cell use is more conservative and transfusions are now withheld in nonbleeding patients until the haemoglobin concentration falls to 70 g/L. Looking ahead, we anticipate that future clinical research will seek to further refine the indication for red cells by addressing the fact that the haemoglobin concentration is but one dimension of tissue oxygenation and that the decision to transfuse red cells should include measures of both oxygen delivery and tissue oxygen consumption.

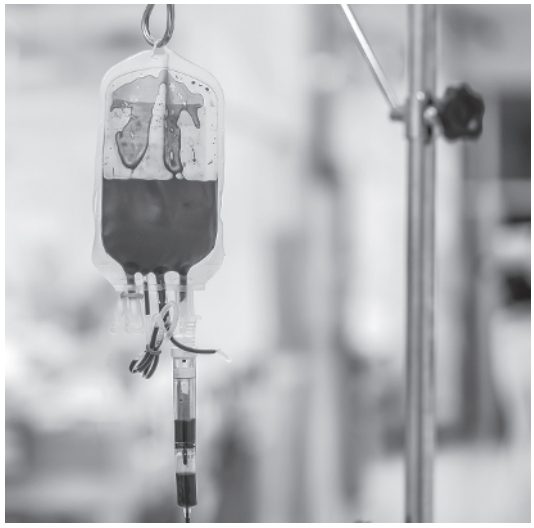

Figure 1.10 RBC transfusion. *Source:* REX by Shutterstock. © Garo.

The last decade has also witnessed evidence-based refinements in the indication for platelet transfusion. The modern era of evidence begins with the work of Rebulla et al [3] who documented that a platelet threshold of 10×10^9/L was equivalent to 20×10^9/L for prophylactic platelet transfusions. Further advances came with the TRAP trial [4], demonstrating that reducing the number of leucocytes (and not the number of donors) was key to preventing HLA alloimmunisation, and the PLADO trial [5] which demonstrated that the traditional dose of platelets (approximately equivalent of that found in 4–6 units of whole blood) resulted in the same outcome as transfusion of three units or

Randomised trials of RCB transfusion threshold

Author	Name	Setting	Trigger	'n'
Hebert, 1999	TRIC	Adult ICU	7 vs 9	836
Kirpalami, 2006	PINT	Infants <1 kg	10 vs 12	457
Lacroix, 2007	---	Paediatric ICU	7 vs 9.5	637
Hajjar, 2010	TRAC	Cardiac surgery	8 vs 10	502
Cooper, 2011	CRIT	Acute MI (pilot)	8 vs 10	45
Carson, 2011	FOCUS	Hip surgery elderly	8 vs 10	2,016
Villaneuva, 2013	---	UGI bleed	7 vs 9	921
Walsh, 2013	RELIEVE	Older patients ICU	7 vs 9	100
Robertson, 2014	---	Traumatic brain	7 vs 10	200
Holst, 2014	TRISS	Septic shock	7 vs 9	998
Murphy, 2015	---	Cardiac surgery	7.5 vs 9	2,007

Figure 1.11 Trials examining the RBC transfusion threshold.

12 units as judged by the proportion of days with grade 2 or higher bleeding. Finally, the TOPPS trial [6] revealed that there was little value to prophylactic platelets among clinically stable patients undergoing autologous bone marrow transplantation. The goal now is to conduct more research on platelet transfusion outside the context of haematological malignancy. While we still have much more to do if we are to refine the clinical use of the traditional blood components, Chapters 34–37 on patient blood management and 45–46 in the section on developing the evidence base for transfusion should give readers a solid foundation upon which to improve clinical decisions regarding transfusion.

Urgent Transfusion

Care of the haemorrhaging patient has always been an essential aspect of transfusion practice. The tragedies of war and human conflict have repeatedly stimulated research focused on urgent transfusion during haemorrhage. Demand for knowledge in this area sadly continues and is amplified within violent societies by civilian trauma from firearms and in other societies by automobile injury. This is an area of changing practice patterns and readers will welcome the up-to-date focus found in Chapters 26 and 27. With the advent of increasingly complex surgery and deployment of life support systems such as extracorporeal membrane oxygenators, massive transfusion is no longer restricted to trauma. In fact, recent studies document that the majority of massive transfusion episodes are associated with surgical and medical conditions unrelated to trauma [7]. More research in these patient groups is needed.

Patients Requiring Chronic Transfusion Support

Chapters 29 and 30 address the needs of patients with haematological disorders who often require chronic transfusion support (Figure 1.12). Patients with haemoglobinopathies, thalassaemia, myelodysplastic syndromes, aplastic anaemia, refractory anaemia, congenital and acquired haemolytic anaemia and those with chronic bleeding disorders such as hereditary haemorrhagic telangiectasia depend upon transfusion to sustain them. Worldwide, the numbers of individuals with severe uncorrectable anaemia is enormous. For these conditions, blood transfusion is seen at its raw, primal best: the sharing of blood from those in good health to those in need.

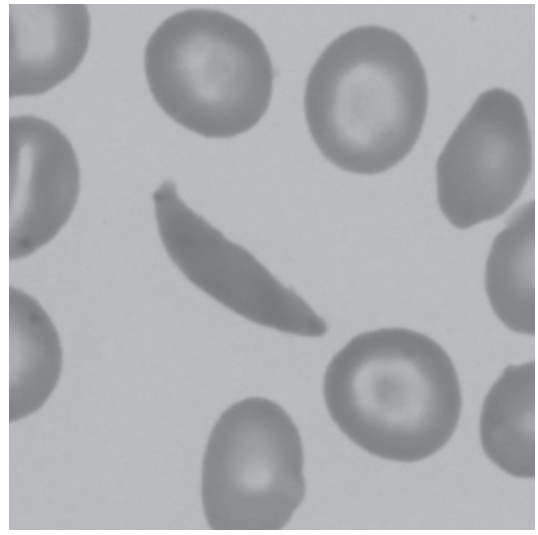

Figure 1.12 Sickle cell anaemia.

Obstetric, Neonatal and Paediatric Transfusion Medicine

Care of the low-birthweight, premature infant remains very challenging. Anaemia and thrombocytopenia result from physiology unique to these youngest of patients, as described in Chapter 33. Neonatal and paediatric transfusion medicine is filled with customary practices often based more on tradition than evidence. We applaud those who have conducted controlled trials that are summarised within the text, and look forward to additional clinical research designed to answer fundamental questions that confront the paediatric transfusion specialist.

Haemostasis and Transfusion

No area of transfusion medicine has seen such explosive recent innovation as the field of haemostasis. A wide range of anticoagulants is now available and the balance between anticoagulation, haemostasis and thrombophilia has become more complex. Transfusion therapy continues a long evolution from plasma replacement to the targeted use of a growing number of plasma-derived or recombinant products that influence haemostasis. Tools and treatments used in the past and then put aside, such as viscoelastic testing and antifibrinolytics, have made a strong resurgence and are finding new positions in the evaluation and treatment of bleeding. Additional haemostasis agents, which we will need to clinically master, are on the way. Chapters 25, 28 and 31 address these topics and will give readers new information on the important role of transfusion in the care of patients with disorders of haemostasis and thrombosis.

Figure 1.13 Cryopreservation in liquid nitrogen.

Cellular Therapies, Transplantation, Apheresis

Cellular therapy is a major growth area in transfusion medicine. The ability to mobilise haematopoietic progenitor cells, then harvest them safely in bulk numbers, process, freeze and successfully reinfuse them as a stem cell tissue transplant has completely revolutionised the field of bone marrow transplantation (Figure 1.13). Other therapeutic areas, such as treatment with harvested and manipulated dendritic cells, mesenchymal cells, T-cells and antigen-presenting cells, have progressed far more slowly. Nevertheless, with advances in gene engineering, the potential to treat illnesses with autologous reengineered cellular therapies is very bright. Chapters 38–44 present a detailed account of the current state of the art in cellular therapies as well as a glimpse of where this field is heading.

The Future

This fifth edition of this textbook concludes, as have previous editions, with reflections on the future of the field. While speculation on the future is never easy, our own view is that the ability to perform targeted gene editing is one of the most promising current research endeavours. CRISPR (clustered regularly interspaced short palindromic repeats) technology allows for the targeted excision of DNA at any known sequence (Figure 1.14).

Short tandem repeat DNA sequences (eventually renamed as CRISPR) were originally discovered as part of normal bacterial defence against viruses. Several genes in bacteria, called CRISPR-associated genes (cas), were found to code for nucleases specific for these repeat sequences, thereby disrupting viral genomes within bacteria. One of these cas genes, *Cas9*, was found to work efficiently within eukaryotic cells as a nuclease

Figure 1.14 CRISPR technology allows targeted excision of DNA. *Source:* Shutterstock. © GeK.

that could be guided by RNA to a specific DNA target. This RNA guide can be synthesised to match the cellular DNA area of choice. By delivering the *Cas9* nuclease and the guiding RNA into a cell, the genome of that cell can be disrupted or edited in a controlled manner.

One example of the application of CRISPR technology has focused on haemoglobin F production [8]. The *BCL11A* gene is the natural suppressor of haemoglobin F. *BCL11A* is turned on after birth, resulting in active downregulation of haemoglobin F transcription. CRISPR technology has been used to disrupt the promoter region of the *BCL11A* gene, thus removing its suppression with a resulting increase in haemoglobin F production. This approach has an obvious potential application in sickle cell disease where even a small increase in haemoglobin F expression can ameliorate clinical symptoms. One can imagine the *ex vivo* manipulation of autologous CD34-positive cells using CRISPR technology followed by their transplantation into the sickle cell patient so as to produce a posttransplant phenotype with higher haemoglobin F expression (Figure 1.15).

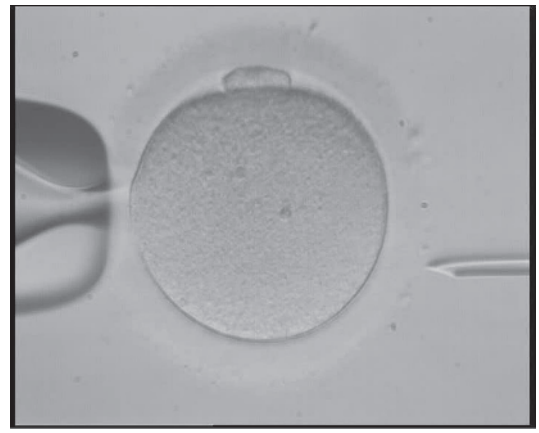

Figure 1.15 Cellular therapies of the future.

Conclusion

James Blundell would immediately recognise a red cell transfusion if he saw one today. However, the great part of what we do would be incomprehensibly advanced and far beyond his understanding. In a similar way, the technologies of the future will revolutionise medical care in ways we can hardly imagine. Let us look forward to a time when we can reflect back on nonspecific immune suppression, apheresis therapy, blood group incompatibilities and one-dimensional laboratory triggers for transfusion care as practices that we needed to understand today so that we could achieve the promise of tomorrow.

References

1 Blundell J. Observations on transfusion of blood. Lancet 1828;**II**:321–4.

2 Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;**340**:409–17.

3 Rebulla P, Finazzi G, Marangoni F et al. The threshold for prophylactic platelet transfusions

in adults with acute myeloid leukemia. N Engl J Med 1997;**337**:1870–5.

4 TRAP Trial Investigators. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. N Engl J Med 1997;**337**:1861–9.

5 Slichter SJ, Kaufman RM, Assmann SF et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 2010;**362**:600–13.

6 Stanworth SJ, Hudson CL, Estcourt LJ et al. Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis. Haematologica 2015;**100**:740–7.

7 Dzik WS, Ziman A, Cohen C et al. Survival after ultramassive transfusion: a review of 1360 cases. Transfusion 2016;**56**:558–63.

8 Canver MC, Smith EC, Sher F et al. BCL11A enhancer dissection by Cas9-mediated in situ saturating mutagenesis. Nature 2015;**527**:192–7.