

The genesis of paediatric haematology in the UK

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Summary

Paediatric haematology began to establish itself as a speciality in the UK just over 60 years ago. In that time, clinical trials involving all the specialist centres in the country, and based on scientific advances, have dramatically improved the outlook for children with a range of malignant and non-malignant disorders, but particularly acute leukaemia. As in many specialties, multidisciplinary teams have played a major role in delivering these advances. With these structures in place at a national level, perhaps, of all specialties, paediatric haematology is poised to benefit from the new developments in precision medicine, gene editing and immunotherapy.

Keywords: Paediatric haematology, neonatal haematology.

Introduction: personal perspectives

Wandering career paths, at least to start with

IR: The best thing about being a first-year medical student in Glasgow in the early 1970s, parties aside, was being taught embryology by Ray Scothorne, the Professor of Anatomy. A tall and imposing man, the antithesis of the Gothic department and its largely dead occupants, he made it exciting to learn how tissues and cells organised themselves in such a precise and regulated way during early human development. Under the microscope, the most beautiful cells were in the developing bone and bone marrow. I have never lost interest in the clues that subtle differences in the appearance and behaviour of these cells can provide in deciphering the biological basis of human diseases. After a dalliance with a career in obstetrics/fetal medicine (a complete failure), I undertook training jobs in neonatology and paediatrics at

the Royal Hospital for Sick Children in Glasgow, a haphazard stack of buildings on top of a hill (Fig 1). The paediatric haematologist there was Michael Willoughby, sadly very recently deceased. The work looking after children with blood disorders was interesting, challenging and exciting. The diagnostic lab and, in particular the microscope, was integral to the work. So, I was hooked.

IH: Although my path and Irene's did not directly cross, the themes and main actors were often the same. I always wanted to be a doctor and at an early stage I knew that would be in paediatrics as adult medicine was not for me and I loved working with children. As a student I was taken under the wing of one of the first British oncologists who tragically died as 'a mistake' at the hands of the IRA. Gordon Hamilton-Fairley turned my interest in oncology into a fascination, and he then arranged for me to work for David Weatherall (DJ to everyone) in Liverpool (Fig 2). I was then enthused with haematology by that great man. One of my earliest experiences there was a lecture by Don Pinkel of St Jude's Children's Hospital in Memphis, very much the father of modern childhood leukaemia treatment. Coming out of the lecture I heard conversations that vilified him as putting kids through hell for an incurable disease. Thanks to courageous innovators like him, and supporters like DJ, that landscape is now unrecognisable. I was incredibly lucky to work for such pre-eminent people who were also wonderful human beings. My final beginning was to be houseman to the polymath Sir Cyril Clarke, lepidopterist, geneticist, clinician and Rhesus guru (Fig 3).

Haematology as a stepping stone to paediatric haematology

As there was no specialised paediatric haematology training 40 years ago, IR was sent off to learn adult medicine in a grim provincial hospital, now derelict, where the cardiac arrest trolley was moved between wards on a child's pram. The reward was a haematology post back in Glasgow with Robert Cumming and Brooke Hogg. Looking back, this was excellent 'wood for the trees', consultant-led training, although whether pipe-smoking (not me) was wise in a lab

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Fig 1. Royal Hospital for Sick Children and Queen Mother's Hospital, Yorkhill, Glasgow.

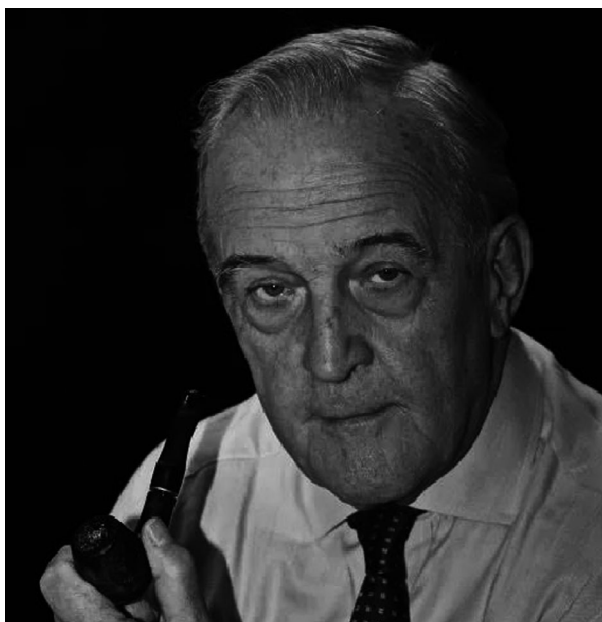


Fig 2. Professor Sir David Weatherall (courtesy of Doug Vernimmen).

full of paper reports and flammable reagents could be questioned. I completed my training in Nottingham, as a Leukaemia Research Fund Lecturer in Haematology, where I worked with Nigel Russell (who had in turn trained with IH) and saw first-hand how to deliver both first-class clinical care and an innovative research programme. I knew I needed more research training and decided to move to London. Before doing this, a senior professor counselled me not to go. 'Why would you exchange all this', he asked, pointing out of the window, 'for the bright lights and pushy academics of London, who will slaughter you?' He was pointing at a sheep in a field. I suppose by way of an answer I moved to the Royal Postgraduate Medical School, initially to a

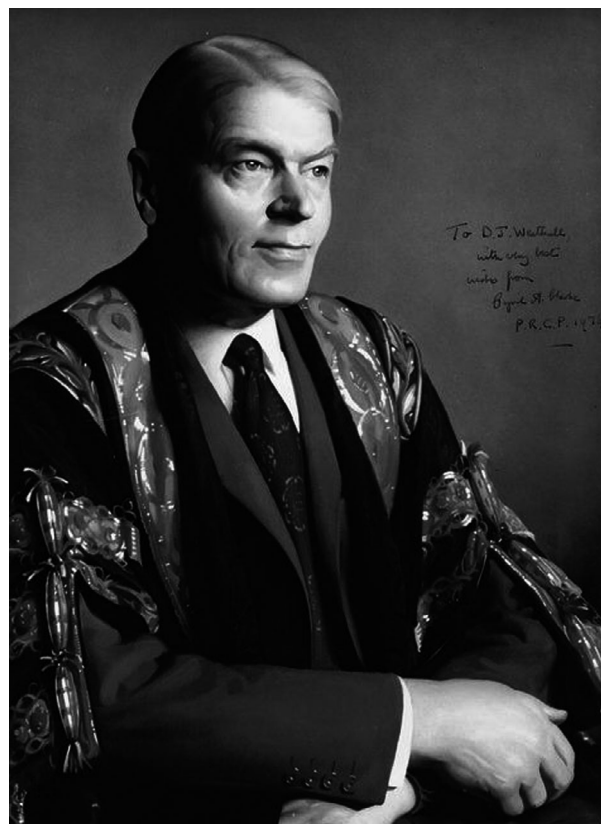


Fig 3. Sir Cyril Clarke. From: Weatherall DJ: Cyril Clarke and the prevention of rhesus haemolytic disease of the newborn, *British Journal of Haematology* 157: 41–46.



Fig 4. Professor Lucio Luzzatto astride his leaving present on his departure in 2004 from the Royal Postgraduate Medical School, by then assimilated into Imperial College London (courtesy of Vera Hanwright and Richard Manning).

research post with Lucio Luzzatto (Fig 4) from whom I learned many things, not least the importance of asking the right question. It was 1988. Fortunately, the sheep farming Nottingham professor was wrong.

Meanwhile, IH went to work with Pat Morris Jones, the first fully trained paediatric oncologist in the UK. One of her greatest contributions was to lead the development of specialist children's cancer centres under the aegis of the UKCCSG (United Kingdom Children's Cancer Study Group). That organisation championed clinical trials in lymphoma and other solid malignancies and later on, after the era of Medical Research Council (MRC) leukaemia trials, they also took on that liquid role. She instilled within me the need for good communication skills, something I was not naturally good at, and she pioneered interactive skills training with her Unit's psychiatrist Peter Maguire. I am proud that serious turf wars never broke out between paediatric oncologists and haematologists and that many like David Weatherall resisted any urge to go down the route of countries like America and 'lock' haematologists into secluded laboratories, never to appear blinking into the light of day. We also recognised the importance of indispensable individual skills and expertise as brought to us from those who came from an adult-treater background. Haematology was fascinating because in those days we did everything. Being able to take the history, examine the patient and then procure samples, make the diagnosis and treat all types of patients with blood disorders, was the epitome of patient management. Like Irene, I struggled to train adequately and chose the full path of years of general paediatrics in Liverpool and Manchester followed by more years of adult-treating haematology, in Liverpool and London [Great Ormond Street (GOS) and Royal Free Hospitals (RFH)]. Spending long periods in neonatal and transfusion medicine and such-like was tough going but an excellent basis for finally taking the paediatric and pathology exams when middle-aged. David I. K. Evans in Manchester generated my long-lasting interest in morphology and also haemophilia (Fig 5). Grant Prentice, Victor Hoffbrand, Ted Tuddenham and Peter Kernoff were first rate clinician-scientists and reinforced my training in research and development, usually through clinical trials, and some basic science relating to haemopoiesis. Judith Chessells was an outstanding clinician with huge experience, a real workaholic whose insight into clinical trials, especially regarding leukaemia, took the outcomes for children to a new level (Fig 6). Roger Hardisty (Fig 7), at GOS also, taught me all I ever knew about platelets and continued my experience with genuine clinician-scientists. I was so lucky that in those days it was possible to create one's own training programme.

Becoming a paediatric haematology consultant

Being appointed as a consultant in Paediatric Haematology at Hammersmith Hospital, London in 1990 was an exciting opportunity for IR, but one only a naive optimist would relish. After all, there were no patients, no clinic, no ward, no junior staff and no other paediatric haematology consultants. All there was, ironically it seemed at the time, was two



Fig 5. Professor D. I. K. Evans (BMJ photo).



Fig 6. Professor Judith Chessells (courtesy of Ian Hann).



Fig 7. Professor Roger Hardisty (courtesy of GOSH).



Fig 8. Hammersmith Hospital Children's BMT Unit 1990 (courtesy of Phil Daly).

purpose-built Bone Marrow Transplant (BMT) beds, newly installed on the general paediatric ward. I seem to remember that John Barrett, now BJH Editor-in Chief but then

Professor of Haematology at the Hammersmith, showed me these BMT rooms, for which he had raised the refurbishment funds, and declaring 'these are for you!' (Fig 8). With John's support, and a fantastic nurse, Phil Daly, the service started from there. Incidentally, business planning was in its infancy and for several years no-one asked for a budget. It took five years before a second consultant, Inderjeet Dokal, was appointed and dramatically improved my working life. Until then, like many consultant paediatric haematologists at the time, I was single-handed and on call virtually all the time. This meant relying hugely on support from colleagues around the country to help with advice on managing difficult cases, including Brenda Gibson in Glasgow, Phil Darbyshire in Birmingham, Judith Chessells, IH and Paul Veys at GOS, John Lilleyman at the Royal London, Tony Oakhill in Bristol and many others. The Hammersmith service grew progressively, surviving threatened closure when paediatric services were reconfigured by moving to St Mary's in 2000 and continues to thrive under the leadership of Josu de la Fuente who took over in 2006.

IH came to Glasgow as a consultant in 1983 and made the mistake of starting on the early morning of January 1st when the city resembled a wasteland. I came to like the place very much and was fortunate to have Tim Eden as my colleague in Scotland, another example of haematologists and oncologists working together and feeding off each others' particular skills, which helped as we were both initially single-handed and overwhelmed. I followed in the footsteps of Michael Willoughby who left as he could no longer manage with limited resources. It was made clear to me on day one that he was greatly missed, and I learned that being popular would never be easy. It did begin a very long battle that continued to the end of my paediatric haematology career, fighting for the things that my patients needed. Brenda Gibson continued that process in Glasgow very successfully. Within weeks and a few months, I was hit by two issues which resound still to this day; my woeful training (despite my best efforts) in perinatal haematology, and the HIV crisis. Dealing with two maternal deaths, with the help of Elizabeth (Liz) Letsky (Fig 9) and her team at Queen Charlotte's was hard enough; we were then faced out of a clear blue sky with a disease with no answers. This current day is redolent with the issues that we had to deal with, and one day all of us from that era hope that ignorant world leaders and others recognise the great existential threats of zoonoses and anti-vaccine pseudo-scientists. After four years in Glasgow, I moved back to GOS in order to be more able to further my interest in clinical trials as well as the other aspects of haematology. This was an era where we were able to make huge advances in almost all areas, thanks to collaborative national and international trials and studies. One very good example is the collaborative approach of Judith Chessells (Fig 6) and Ross Pinkerton and myself (Royal Marsden) on trials that transformed advanced stage B non-Hodgkin lymphoma (NHL) from a lethal disease with a median survival of six weeks, to one that became



Fig 9. Dr Elizabeth Letsky (courtesy of Vera Hanwright and Richard Manning).

curative in more than 80% of cases. It was an exhilarating time, enhanced by developments in stem cell transplants, in particular T-cell depletion technology by another great innovator, Grant Prentice (Fig 10), and subsequently by Paul Veys, Persis Amrolia and others. The synergistic axis between GOS and the RFH was a very fruitful one, the former emphasising the discipline of collaborative peer-reviewed national and international phase III clinical trials, and the latter having an emphasis on discovery science. Roger Hardisty and Judith Chessells promoted the vital development of paediatric clinician-scientists, facilitated by the joint training schemes with Victor Hoffbrand, Grant Prentice and many others at the RFH. Many eminent haematologists mentioned here, and the advances they made, are too numerous to do justice to here but they include the description of the favourable prognosis of high hyperdiploid acute lymphoblastic leukaemia (ALL) (Lorna Secker-Walker and Christine Harrison), development and refining of immunophenotyping and minimal residual disease detection (George Janossy, Dario Campana and Nick Goulden) and factor VIII purification (Ted Tuddenham, Frances Rotblatt and Peter Kernoff).



Fig 10. Professor Grant Prentice (courtesy of Grant Prentice).

Development of the field

Birth of a specialty

An authoritative history of paediatric haematology would require a book on its own and our story is that which coincides with the lifetime of the BSH. Prior to this period there was scant attention paid to our specialty in the literature, with just short sections in Holt's *Diseases of Infancy and Childhood* from 1897 (with a dismal prognosis of most blood disorders emphasised) and then subsequently full texts in the 1940s by, for instance, Kugelmass from New York. In the UK, Sir Leonard Parsons (Fig 11) is regarded as one of the grand old men of British haematology, and the first to take an interest in paediatric blood diseases, having trained at GOS and in Birmingham. His major early contributions during his long career (1905-1950) including haemolytic anaemias, and antenatal paediatrics, were excellently summarised in this journal by Richard Stevens,³¹ himself a great contributor to the specialty whilst at Royal Manchester Children's Hospital. He is greatly missed. Few of us create a whole specialty in our lifetime. However, this was the case when Roger Hardisty was appointed at GOS Hospital as the first Consultant Haematologist in 1958 (Fig 7). Interestingly, paediatric haematology was then a consultative specialty with no



Fig 11. Sir Leonard Parsons (1879–1950) (National Portrait Gallery; Stevens RF. Sir Leonard Parsons and the scientific basis of paediatric haematology, *British Journal of Haematology* 2001;112: 558–60).

dedicated beds. He was head of the haematology laboratories and of the Haemophilia Centre. However, under his leadership the clinical service developed to include not only state-of-the-art inpatient facilities for leukaemia patients, but also other paediatric malignancies, bone marrow failure disorders and bone marrow transplantation. Although perhaps best known for his work on platelet function disorders, Roger Hardisty also made key contributions to childhood leukaemia. He instigated studies into the roles of inherited susceptibility and case clustering³⁴ and wrote the first paper on prognostic factors in childhood leukaemia,¹⁶ later on supervising IH's MD on the subject in the late 1970s. He also described leukaemic involvement of the central nervous system (CNS),¹⁵ a topic he came back to after Judith Chessells joined the department in 1972¹³ moving from the Royal Postgraduate Medical School. This move proved to be key to the future of paediatric haematology in the UK, although probably no-one realised it at the time, as she took over from Roger Hardisty when he retired and the majority of UK paediatric haematologists over the last 40–50 years have benefitted either directly or indirectly from her knowledge, advice and support.



Fig 12. Professor Sir John Lilleyman (BMJ photo).

Other pioneers of paediatric haematology in the UK at that time were Liz Letsky (Fig 9), who moved from GOS Hospital to Queen Charlotte's Hospital in west London in 1983 to found the first perinatal haematology service in the UK, and John Lilleyman (Fig 12) and David Evans, who were key members of the MRC Working Party on Childhood Leukaemia (see below) along with Tim Eden and Pat Morris Jones who were both oncologists. Memorable for her striking black hair and bright chiffon scarves, as well as her extensive knowledge, Liz Letsky willingly shared her unique expertise not only with the authors, but also with the many haematologists and obstetricians from all over the world who sought her advice. She also, incidentally, performed the earliest clinical trials of iron chelation therapy in the UK for patients with thalassaemia.³ Despite her vibrant personality, Liz was very understated about her scientific contributions, and yet it was often her sharp observations that laid the foundations for more basic research into abnormalities of erythropoiesis in fetal life and thalassaemia.³⁸

As the 60s drew to a close it became clear that to tackle what was then the biggest problem in paediatric haematology — the dismal prognosis of childhood leukaemia — hospitals in the UK would have to work together, centralising care on a 'hub-and-spoke' arrangement, and carefully thought out peer-reviewed clinical trials would need to be designed. It would be impossible to describe all of the developments in paediatric haematology since that time without writing several volumes. Instead, we have selected some of the areas where this spirit of working together proved so important for a small and emerging specialty to make a significant impact on outcome for children with blood disorders.

UK childhood leukaemia trials

MRC Working Party on Childhood Leukaemias. Rightly hailed as one of the most remarkable and important success stories

of the last 60 years, the chance of long-term survival for children with ALL has increased from virtually zero to approaching 90%. While not quite as spectacular, outcome for children with acute myeloid leukaemia (AML) has also improved, with overall survival now of 70–75%. This undoubtedly reflects the willingness, since the early 1970s, of paediatric haematologists in the UK and Ireland to work together and, equally importantly, of the MRC to fund this work, at least for the first 30 years. Collaborative working was not always plain sailing, however, as can be deduced from the report of the first trial (UKALL I; 1970–71) which states that 'During preparation of the trial it became evident that the diversity of views and facilities in the co-operating centres would not permit a trial in which prophylactic treatment of the CNS could be a randomised variable. Accordingly, centres were divided into those where all patients received such treatment, those where none received it, and a few where the cases were randomly allocated equally to CNS prophylaxis or no CNS prophylaxis' (Report to the MRC by the Leukaemia Committee and the Working Party on Leukaemia in Childhood²⁸). In those early years, there were only four paediatric haematologists in the UK, all of them on the Working Party — Roger Hardisty, Judith Chessells, Michael Willoughby and David Evans. Most children were looked after by paediatric oncologists, the first fully trained being Pat Morris Jones who sadly died recently, and the numbers of paediatric haematologists were to increase only very slowly over the next 20 years.

Nevertheless, the MRC Working Party on Leukaemia in Childhood went on to deliver more than 20 national studies in ALL and AML. These studies were not unique, in that similar national groups in Europe and the US were all working to improve the outcome for children with leukaemia through carefully designed clinical trials. However, the UK trials provided one of the leading international benchmarks against which others could be compared and they continue to do so.²⁷ The roll call of paediatric haematologists and oncologists who contributed to this work is too long to list but it includes many of the current paediatric haematologists in centres throughout the UK and Ireland.

UKALL trials and their successors. Although hailed as a success today, there were setbacks as well as advances. Analysis of the UKALL II to VI trials showed no improvement in remission or survival over the seven years from 1972 to 1979 despite enrolling nearly 1,500 patients and although the results were somewhat better in UKALL VII (1979–80), the first real jump forward was in UKALL VIII (1980–84) which produced a 15–20% increase in disease-free survival to 54%.²⁰ This, in large part, reflected the value of international as well as national collaboration in childhood leukaemia trials because UKALL VIII had incorporated a protocol tested by the US Children's Cancer Group. There were further improvements in survival in UKALL X (1985–90), though not in UKALL XI; in ALL97 (1997–2002), where event-free survival reached 74%;²⁰ and in ALL 2003 (2003–2011) where

event-free survival approached 90%.⁴¹ In the most recent trial, UKALL 2011 (2012–18) that has yet to fully report, the emphasis has moved towards reducing treatment-related toxicity without compromising these impressive survival results.¹¹ Running parallel to the main UKALL trials, successive relapse trials pointed to the need for new approaches.²⁴ Insights from the T-cell depletion work at the RFH by Grant Prentice and George Janossy²⁶ informed how vital T-cell receptors were in leukaemia cell kill, which led on to research into Chimaeric Antigen Receptor (CAR)-modified T cells. In the short time since the first promising reports appeared, CAR-T cells have already been shown to be curative in relapsed ALL, including innovative studies led by Persis Amrolia at GOS Hospital.¹⁰

Childhood AML. At the same time the Working Party also drove forward clinical trials in childhood AML starting in the early 1970s. The early results were to prove very disappointing with well under 10% survival. Nevertheless, for AML too, national clinical trials were key to the eventual rise in event-free survival rates in the late 1980s to more than 50%.¹⁴ The larger trials (AML 10, AML 12 and AML 15) had both paediatric and adult arms, with the paediatric protocols steered by IH, David Webb, Dick Stevens and Brenda Gibson (Fig 13) in particular^{14,30}. These allowed subgroup analysis based on cytogenetic analysis and the beginnings of risk stratification.⁴⁴ Treatment-related mortality also fell, as in ALL, due to improvements in supportive care. However, as the relapse rate for children with AML has plateaued over the last 30 years, ongoing clinical trials, such as the current international collaborative trial, MyeChild01 (2016), are increasingly important. Meanwhile, work by Gertjan Kaspers and Owen Smith^{6,33} in particular have helped to achieve the incredible curative therapies with simple treatment for acute promyelocytic leukaemia, and have begun to address the difficult area of relapsed AML in children, through international collaborative trials.



Fig 13. Professor Brenda Gibson on the summit of Schiehallion (also the name of the Paediatric Haematology Oncology ward at the Royal Hospital for Children, Glasgow) (courtesy of Brenda Gibson).

Haematopoietic stem cell transplantation (HSCT)

Autologous and allogeneic HSCT programmes really began to expand in the early 1990s, particularly once HSCT was considered as a form of consolidation therapy rather than salvage in AML. The evidence to support this approach was controversial at the time and, in fact, AML 10 found no significant survival advantage of autologous or allogeneic HSCT in first remission for children with AML.⁴ The 1990s also saw the expansion in HSCT as curative therapy for children with genetic disorders, where other curative options were not available, such as immunodeficiencies, Fanconi anaemia and haemoglobinopathies.^{1,2} In the case of haemoglobinopathies, there was considerable debate because alternative therapies, such as life-long transfusion, were available and had to be balanced against life-long cure.²⁹ Paediatric haematologists, both those who transplanted and those who referred patients for transplants, often had very different views about the indications for HSCT and the risks that were or were not acceptable. As unrelated donor and haploidentical donor transplants increased in the 1990s and the 2000s, respectively, decision-making became even more complex as in theory a donor could be found for every child. In response to this, the UKCCSG BMT group was formed to discuss policies and develop guidelines; a national multidisciplinary team was established and, with the passing of the Human Tissue Act,¹⁴ donation of allogeneic bone marrow and peripheral blood stem cells by children and adults was regulated for the first time.

Sickle cell disease

In the 1980s, at the same time as the results for children with ALL, were beginning to improve, a few clinicians in the UK began to raise awareness of another group of children who were frequently in hospital with life-threatening acute and chronic complications and for whom standard medical care appeared to have little to offer. These were children with sickle cell disease. Knowledge about this disease as it affected children in the UK was sparse, and children were usually managed by general paediatricians, many of whom had little experience or knowledge of the condition. In a series of studies in the 1980s and 1990s, Misha Brozovic and Sally Davies carefully described and documented the myriad clinical manifestations of sickle cell disease in children and adults.⁷ Ultimately, their work led to the national neonatal screening programme for haemoglobinopathies in 2006³² and a national network of specialist haemoglobinopathy centres linked 'hub-and-spoke' style to local services so that every child with sickle cell disease has access to expert care from early infancy onwards [<https://www.england.nhs.uk/publication/specialist-haemoglobinopathy-services-specialist-haemoglobinopathy-teams/>]. This network helped to introduce transcranial Doppler screening to virtually all affected children in the UK to identify those at high risk of stroke.

Paediatric haematologists, often working with adult haematologists and other paediatric specialists, also facilitated the recruitment of large numbers of children with sickle cell disease to definitive studies of stroke, lung disease and vaso-occlusive crises and to landmark clinical trials defining the role of transfusion perioperatively¹⁷ and for silent cerebral infarcts,⁸ BMT for severe sickle cell disease⁴² and disease-modifying drugs, including hydroxycarbamide and, more recently, the HbS polymerisation inhibitor voxelotor.⁴⁰

Children with haemophilia

Management of these children was extremely challenging in the 1960s and 1970s. Therapies such as cryoprecipitate and fresh frozen plasma (FFP) had become quite recently available and had many down sides, not least of course the persisting threat of transfusion transmitted infections (TTI). Reactions were common, home therapy with frozen plasma products was usually impossible and dosing was usually more theoretical 'finger in the air' than scientific. The development of factor concentrates made all the difference initially, facilitating home therapy for the first time, until TTI raised its ugly head again. Maybe arrogantly, I believe that a key step forward was the work that Ri Liesner, Kate Khair and I did showing for the first time that even children with established target joints could be stopped bleeding if you persisted.¹⁸ We were hoping to achieve, and eventually did reach, the benchmark achieved some years earlier in the pioneering Swedish work, whereby they aimed for one bleed per year or less in severely affected patients without inhibitors. The latter, along with those children who have severe platelet function inherited defects, remain the greatest challenges. In the early 1980s, all of the great optimism espoused by Peter Jones and others came crashing down with HIV and within a decade by the additional burden of Hepatitis C. In fact, there is a great debt which should be paid to Pharma for the development of safe recombinant products in adequate amounts and with continuing improvements in half-life facilitating easier venous access and home therapy. This development was again critically dependant on the RFH research axis and the work of Ted Tuddenham and his colleagues there in purifying factor VIII,³⁵ leading to its cloning. The other very important development of the sort that only ever seems to occur in medicine when there is a crisis/scandal, was the allocation of much better resources, Haemophilia centres with adequate space and governance, and the crucial role of enhanced practice nurses such as Kate Khair at GOS, whereby ambulatory care could be greatly improved and families could regain control.³⁷

Neonatal haematology

The most dramatic change over the last 60 years has been in the prevalence of Rh haemolytic disease of the newborn (HDN). Many sweltering evenings were spent as senior house

officer in neonatology in the late 1970s performing manual red-cell exchanges of babies severely affected by Rh HDN. Since then, this disease has been virtually eliminated, largely due to the pioneering work of Sir Cyril Clarke, Professor of Medicine at the University of Liverpool, who discovered that administration of prophylactic anti-D to Rh-negative mothers during pregnancy was able to prevent the disease.⁵ Sir David Weatherall pointed out that Sir Cyril always claimed that butterfly genetics, particularly the discovery of supergenes (in mimicry and in the Rh complex) led to his ideas about Rh disease prevention!⁴³ More recently, another major cause of neonatal morbidity and mortality due to alloimmunisation, fetal and neonatal alloimmune thrombocytopenia (FNAIT), has been shown to be potentially amenable to a similar approach, in an initiative driven in large part by a dynamic patient organisation founded in the UK.²³

Paediatric haematology and the importance of research

To both of us, scientific research in paediatric haematology, whether driven by curiosity or immediate clinical translation, is fundamental to the improvements in outcome for children achieved over the last 60 years and fostering the clinician-scientists of the future to continue this work should be a priority. For IR, even while working on the wards or in the clinic, the need to understand the biological and molecular basis of childhood haematological disorders, many of which we now know have their origin before birth, has been an obsession, driven by curiosity as well as improving child health, and steered by inspirational scientists and clinicians. Sparked by Ray Scothorne's embryology lectures and sustained by the lucky chances that took me to work with Garret FitzGerald at Vanderbilt (Nashville) and Lucio Luzzatto at the Royal Postgraduate Medical School, I first had a lab of my own in 1990. Independence brought the chance to interact with neonatologists, fetal medicine specialists, young scientists, now with established groups of their own, and more recently, with the support of Doug Higgs and Georg Hollander, to move to the MRC Weatherall Institute at the University of Oxford to explore in more depth the fetal/embryonic origins of childhood haematological disorders. That I recognised the importance of this is undoubtedly due to the brilliant insights of Sir Mel Greaves, whose work has underpinned all that we now understand about leukaemogenesis in children.¹²

For IH too, the ontogeny of fetal haematopoiesis was a particular interest. Given the opportunity to do basic science lab work by Victor Hoffbrand, the research was ultimately reasonably successful, but it was immediately clear to me that this would certainly not be my forte. I was used to the immediate cut and thrust of clinical medicine and spending many hours meticulously setting up many experiments which did not work, with many weeks apparently wasted, was not for me. It did make me forever admiring of those who can do it successfully. I envy the current generation; this is the

genomic era and the opportunities show no bounds. I have only one bit of advice — grasp the opportunity with both hands and do not be afraid of the new learning that you have to do. That is exciting; I had to do it initially very painfully with the genesis of molecular medicine. The other future has to be with randomised clinical trials. In most instances there is no believable alternative. I was again lucky to work for many years with the Oxford biostatistician group, mainly Sue Richards and Rob Hills who were unfailingly helpful and expert. It was not always easy realising that the Peto's and many others in that group were more intelligent than me, and that some thought all doctors to be stupid, but the collaboration was productive and our results respected throughout the world, thanks largely to them.

Future prospects and challenges

For childhood leukaemias, the increasing complexity of risk stratification, together with the reduction in children failing treatment, mean that collaborative trials across countries and age groups will be needed to tackle resistant disease and avoidable toxicity. This is the strategy of the current MyeChild 01 and of the new ALLtogether trial involving 13 countries, including the UK, which will enrol children and adults (ages 1–45 years), and is currently being piloted in some countries. As information from genomic and epigenomic studies is incorporated into risk-adapted management, development of targeted therapies and refining the application of immunotherapy, it becomes even more important to maintain the lines of communication and collaboration established over the last decade between national groups. Realists can reasonably anticipate that application of 'big data' analyses and artificial intelligence (AI) may also benefit children with leukaemia.³⁹ Optimists might argue that insights from mouse models as well as human studies which are beginning to unlock the clues to pathogenesis within studies of fetal haematopoiesis^{21,25} might lead to childhood leukaemia being a preventable disease within the next 60 years.⁴⁵

The role of HSCT in the management of children with malignant disorders is also increasingly risk-adjusted and personalised to better select those children likely to benefit. HSCT for childhood leukaemia may even be relegated to a minor role as CAR-T cell therapy is refined to optimise efficacy and safety and extend to AML as well as ALL. For non-malignant disorders, the lessons learned from transplanting children with inherited diseases have been valuable starting points for the development of gene therapy and gene editing.^{19,22} It seems likely that all these approaches will proceed in parallel for the next few years until there is good evidence for their long-term safety and benefits. Quieter revolutions include the wider application of whole-genome sequencing both to speed up accurate diagnosis of rare haematological disorders and potentially also the development of novel therapies.³⁶ For haemophilia A at least, it seems likely that prophylaxis with extended half-life FVIII concentrate will remain

as the standard of care for children for some time while refinements to ensure the long-term efficacy and safety of gene therapy continue to be a major avenue of research.³⁷ For patients with inhibitors, recent developments in tolerising and bypassing therapies now hold out hope that the inhibitor patients may at last have a chance for a more normal quality of life.

Finally, what are the challenges facing paediatric haematology, our colleagues and our patients?

Only some of the most important or pressing are mentioned here and, inevitably, reflect our personal perspectives and the benefit of hindsight.

Throughout the last 50 years, paediatric haematology consultants have largely been dual-trained in haematology and paediatrics and have cared for children across the full range of disorders, still able to use the laboratory skills gained (often painfully) during training. This was of course precisely what drew us into the speciality. For paediatric haematology trainees going forward, the challenges will be to decide if, and how, to retain these laboratory skills and whether there is still a role for consultants able to manage all aspects of the speciality. There may not be a choice. In common with other specialities, increasing bureaucracy, often in response to well-meaning new regulations and sometimes in response to unwelcome financial drivers, is now an almost constant frustration and frequently a barrier to maintaining and improving clinical care. These pressures can seem like a 'double whammy' to clinician-scientists. Without the ongoing dialogue between science and the clinic, progress in the most difficult diseases, such as infant leukaemia, will remain frustratingly slow.

The challenge regarding patient management is the need to continue developing clinical trials and ensure funding for expensive new drugs and therapies. Despite stalwart efforts by a significant number of clinicians over the last 30 years, transition management and integration of Teenage and Young Adult services for both malignant and non-malignant disorders still has to be improved. Finally, and above all, we have to constantly be aware of the importance of managing the expectations of families and the children themselves, as eloquently discussed by du Pre and Brierley.⁹

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