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Transfusion Medicine



An international journal published
for the British Blood Transfusion Society

Fifty Years of Blood Transfusion

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Transfusion Medicine

An international journal published for the British Blood Transfusion Society

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Transfusion Medicine

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Fifty Years of Blood Transfusion

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Foreword

Dr Gunson is an ideal author for this work. He makes reference to the many people who have made a notable impact on the blood service but modestly makes no reference to his own significant contribution. He is internationally recognized for his work in transfusion medicine and his vision was one of the driving forces behind the creation of the truly national blood service that now exists. All those associated with the Blood Transfusion Service, whether colleagues, donors or patients, owe him a great debt of gratitude.

I am honoured to have been asked to contribute the Foreword to this book. Although it deals with the history of one of our great public institutions, the National Blood Transfusion Service, it is really a testament to the generosity of the people in this country and an unequalled example of human nature at its best. That the Service is, this year, celebrating its 50th anniversary is due to one simple fact: millions of individuals are prepared to give their blood so that other, unknown, persons can have the medical treatment they require. This is often the difference between life and death for the recipient of that gift. The National Blood Service has a worldwide reputation for quality and safety that is second to none and this is built on our system of voluntary, unpaid blood donors.

I think it extremely unlikely that those early pioneers, about whose work Drs Gunson and Dodsworth write so eloquently, could ever have hoped to see a nationwide network of nearly 2 million donors giving 2.5 million donations per year, or could have imagined the complex and sophisticated medical and scientific disciplines that would develop from their early work.

As Chairman of the National Blood Authority, I am conscious of the magnificent traditions of the past that the new national service has inherited but, as the contents of this history show, the blood service has always existed in a constantly evolving world. This is particularly apparent now, and in looking to the future we must build on the strengths established over the past 50 years. Many challenges face the blood service today, not the least of which is to keep pace with the ever-increasing demand for blood from hospitals. Our blood supply is amongst the safest in the world but, even so, medical advice is always likely to be that the best transfusion is no transfusion. Safety and quality have always been hallmarks of the Service and we will ensure that standards are maintained.

The blood service is vital to the NHS and is a unique organization within it. It shares with the NHS the commitment of its staff to provide the highest possible professional standards, but is unique in the alliance of these commitments with the generosity of donors. Professor Titmuss wrote about 'The Gift Relationship' in his seminal work published soon after the birth of the National Blood Transfusion Service. The phrase is still accurate nearly 50 years later and will, I believe, still hold good when the history of the first 100 years of the blood service is written.

SIR COLIN WALKER, OBE
Chairman, The National Blood Authority

Preface

The first record of a transfusion of blood to a human being was by Samuel Pepys over 300 years ago when Arthur Coga received a few ounces of blood from a sheep before an audience at the Royal Society. Despite the pioneering work of James Blundell (1824), any measure of success in the administration of blood transfusions had to await the discovery of the ABO blood groups by Landsteiner in 1900. In the 20th century the impetus for using blood transfusion therapy came during two World Wars and the Spanish Civil War.

In 1996 the National Blood Transfusion Service for England and Wales will celebrate its Golden Jubilee. In common with all medical specialities, and to an extent driven by the requirements of these specialities, blood transfusion practice has experienced many changes during the past 50 years. Progress in vascular surgery, chemotherapy, transplantation, the treatment of coagulation disorders and shock from massive blood loss, to name a few examples, has been made possible only with support therapy available from blood and its products. Transfusion medicine, a recent term, is used to describe not only those activities involved with the collection and processing of blood, but also those associated with a number of specialities. There have been contributions to anthropology, biochemistry, forensic medicine, genetics, haematology, immunology, transplantation science, microbiology and virology; yet it remains a small speciality, with only about 4000 employees in England and Wales, of whom 43 are consultant medical staff.

Within the National Health Service the Transfusion Service is unique in having unpaid volunteers as the corner-

stone for the provision of its service to patients. In order to provide maximum safety, quality and efficacy, the Service has had to operate within strict guidelines.

This history of the National Blood Transfusion Service illustrates the development of a speciality that has been recognized relatively recently. Considerable medical and scientific progress has been made but there is a recurring feature which merits attention: on four occasions attempts were made to change the management of transfusion centres from regional to national in order to create a unified Service. Twenty-three years after the first application was made to the former Ministry of Health in 1970 the Department of Health agreed to establish a National Blood Authority.

The history begins with the Lister Institute, founded in 1891. The Institute was to play a major role in the development of the Transfusion Service until 1978, particularly in the field of plasma fractionation. The British Red Cross became involved with blood transfusion in the 1920s and was superseded in 1939 by the Medical Research Council and the Emergency Medical Service. However, since 1946, the National Blood Transfusion Service (known as the National Blood Service since 1993) has been part of the National Health Service and the present publication has been written to mark the 50th anniversary of its foundation.

HAROLD H. GUNSON
HELEN DODSWORTH

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Chapter 1: The Lister Institute

Arguably, the early development of the practice of blood transfusion was dependent upon the activities of the Lister Institute. For over 25 years the Institute was not only responsible for providing facilities for the drying of plasma and introducing and developing plasma fractionation, but it also facilitated research into the immunochemistry of the blood-group antigen-antibody reaction, the investigation of the genetics of blood-group systems and the bulk preparation of blood-grouping antisera. It is pertinent, therefore, to recount an abbreviated history of this world-renowned Institute. The information given in this chapter has been obtained from Chick *et al.* (1971) unless stated otherwise.

The study of infectious diseases made significant progress during the last two decades of the 19th century. Robert Koch developed culture techniques for bacteria and their subsequent examination by microscope. However, it was Louis Pasteur's fundamental work on establishing the principles of immunization against disease, particularly with respect to rabies, that was the major factor leading to the founding of the Lister Institute. In 1888, the French government founded the Institute Pasteur, whose major function was to provide treatment for patients who were at risk of developing rabies.

Earlier, in 1875 the Public Health Act in the UK required the appointment of Medical Officers of Health. In order that persons could be trained for these posts, the College of State Medicine was founded in 1886. Despite this development, those bitten by rabid dogs in 1889 still had to travel to Paris to the Institute Pasteur for treatment which was given free of charge. In the 4 years prior to 1889, 214 patients made this journey.

A commission of eminent scientists led by Sir Henry Roscoe MP for South Manchester and Professor of Chemistry at Owen's College (now the University of Manchester), concluded that Pasteur's treatment of rabies was sound. Following this assessment there was a move during 1889 to create an institute in the UK which would be similar to that of the Pasteur.

The idea was not without its opponents. Pasteur's attenuation of the rabies virus in the spinal cords of rabbits was denounced in many newspapers and some eminent scientists agreed. The Lord Mayor of London, a business man Sir James Whitehead, argued that, of the 60 or so patients threatened with rabies each year, about half would not be able to afford to travel to Paris for treatment. If £25 could be raised for these persons to travel to Paris and stay for 2 weeks for the treatment, the resulting £750 per year would be insignificant in respect to the provision of such an institute in the UK.

This commercial argument prevailed and Sir James

Whitehead established a Committee to raise money for a gift to the Institute Pasteur and funds to enable affected patients to travel to Paris for treatment. During the next 6 months, £3200 had been raised, of which £2000 was sent to the Institute Pasteur. Sir James Whitehead considered the work of the Committee to be at an end.

However, Charles Roy, Professor of Pathology at Cambridge, urged his medical colleagues, who included Lister, the famous surgeon and pioneer of antiseptic surgery, and Roscoe not to abandon the concept of an anti-rabies treatment centre in the UK. He was strongly supported by Dr Sydney Turner who was secretary of the Mastiff Club. The disbanded Committee was reinstated and, despite his previous views, Sir James Whitehead agreed to be chairman. Proposals put forward by Roy and Turner were well received and the Steering Committee became the Executive Committee of the British Institute of Preventive Medicine which was legally incorporated on 25 July 1891.

The chief aims of the Institute were set out in the Memorandum of Association:

- "to study, investigate, discover and improve the means of preventing and curing infective diseases of man and animals;
- to provide instruction and education in preventive medicine to Medical Officers of Health, Medical Practitioners, Veterinary Surgeons and advanced students;
- to prepare and supply, to those requiring them, such special protective and curative materials as have already been found or shall, in future, be found of value in the prevention and treatment of infectious diseases;
- to treat persons suffering with infective diseases or threatened with them, in buildings of the Institute or elsewhere."

A public appeal for funds was begun, but by 1893, despite a grant from the Worshipful Company of Grocers, funds without conditions attached amounted to only £12,000.

In 1893 the Duke of Westminster offered to sell a site on his estate on the embankment at Chelsea Bridge at an advantageous price: this was accepted. Also in 1893, the British Institute of Preventive Medicine and the College of State Medicine were merged. The three-storey building at 101 Great Russell Street, Bloomsbury, in which the College was housed, became the temporary home of the Institute until the accommodation at Chelsea Bridge was completed in 1898.

In December 1898 the First Lord Iveagh gave £500,000 to the nation. Half was given to the poor of Dublin and the other half to the newly constructed Institute. This gift provided

an assured income for the Institute which continued to benefit from its association with the Guinness family for many years.

Ironically, by 1898, the treatment of rabies was not a priority as this disease had been eradicated in the UK. Pasteur's protégé, Armand Ruffer, was appointed interim Director of the Institute during its accommodation in Bloomsbury. In 1894, Ruffer was instrumental in developing a horse antitoxin for diphtheria which was successful in treating the disease and significantly reducing its mortality. Ruffer, himself, developed diphtheria and recovered following injections of the Institute's antitoxin. However, a resulting post-diphtheritic paralysis caused his resignation in 1896. In that year the British Institute for Preventive Medicine was renamed the Jenner Institute of Preventive Medicine.

This name led to a dispute with the manager of a small business in Battersea, trading under the name of The Jenner Institute for Calf Lymph. He insisted that his company should be allowed to deal with any orders for calf lymph vaccine. The Council of the Institute agreed not to market calf lymph as long as the name of Jenner was used. However, following a smallpox outbreak in the early years of the 20th century and the resulting pressure on the Institute to prepare a calf lymph vaccine, the name was changed to the Lister Institute of Preventive Medicine in 1903. This was done to honour the first Chairman of the Governing Body, the Rt Hon. Lord Lister.

One of the main aims of the Institute was the provision of antitoxins. The horses were stabled at a farm called The Poplars at Sudbury near Harrow. However, in 1902 the lease of The Poplars was purchased by the Great Central Railway and the Institute in that year bought the freehold of an estate called Queensberry Lodge at Elstree, Hertfordshire. This purchase had major implications for research into and production of plasma products in the Blood Products Laboratory (now known as the Bio Products Laboratory) which was developed on this site in the 1950s.

In April 1943, Dr (later Sir) Alan Drury was invited to become Director of the Lister Institute. He was, at that time, directing the London Blood Supply Depots and was Chairman of the Medical Research Council's (MRC) Blood Transfusion Research Committee. During the next decade, as will be noted in subsequent chapters, Drury had a major effect on the practice of blood transfusion (Kekwick, 1981).

There were 984 scientists and administrators employed at the Lister Institute between 1898 and 1966. Additionally, 83 persons working at the Lister institute were supported financially by the MRC.

Fifty-eight of the above workers were elected Fellows of the Royal Society and six became Nobel Laureates during their careers (F. M. Burnet, A. Harden, R. L. M. Synge, A. R. Todd, H. H. Dale, A. J. P. Martin). It is not surprising, therefore, that the work of the Institute became recognized internationally.

By 1960 there were six departments at Chelsea Bridge,

biochemistry, biophysics, electron microscopy, experimental pathology, microbiology and virology. The MRC's Trachoma Research Unit was attached to the virology department. The MRC's Blood Group Research Unit and Blood Group Reference Laboratory were housed at Chelsea Bridge. In addition, three research and production departments for vaccines and antisera and the Blood Products Laboratory were based at Elstree.

The involvement of the Lister Institute in the freeze-drying and fractionation of plasma and the work of the Blood Group Reference Laboratory will be described elsewhere. However, two other activities of the Lister Institute which had a major impact on the development of blood-transfusion medicine and science will be mentioned here.

Walter Morgan was appointed to the Lister Institute laboratories in 1929 to develop the standardization of antitoxins in accordance with the Therapeutic Substances Act (1925). His initial research project concerned the nature of the O antigen from the pathogens *Shigella dysenteriae* and *Bacterium typhosum*.

In 1938 he was invited to join Professor Robison's Department of Biochemistry at Chelsea Bridge. He became Head of this department following Robison's death in 1941 and turned his attention to the elucidation of the nature of blood-group antigens. In 1942 he was joined by Winifred Watkins and together they have elucidated the carbohydrate nature of the antigen specificity of ABH, Lewis and P₁. Also, they proposed the biosynthetic pathways in which the ABO, Hh, Lele genes encoded specific glycosyltransferases. These catalyse the sequential addition of sugar residues to common precursor structures to build up the five determinant structures associated with these blood-group systems (Watkins, 1994).

Throughout the early years of the Second World War, human blood-grouping sera had been provided for the blood supply depots by the Galton Serum Unit. Shortly before the war, this unit, directed by Professor R. A. Fisher, moved from University College, London to Cambridge. Initially undergraduates and residents were able to provide adequate quantities of blood for the production of grouping sera. However, with increasing demand the intake of the Royal Air Force proved to be a convenient source of sera. Approximately 200,000 airmen were grouped and their blood groups recorded on their identity discs. This exercise proved useful in the determination of the blood-group distribution in the UK. Several hundred donations were collected from those airmen whose blood was suitable for preparing grouping sera. During the last two years of the war the blood depots were the main source of supply of grouping sera (Medical Research in War, 1947).

At the end of the war the MRC was anxious to support the continuation of research into human blood groups and Dr Robert Race, who was directing the Galton Serum Unit, became Director of the MRC Blood Group Research Unit. In 1946 Alan Drury offered accommodation for this unit at

the Lister Institute at Chelsea Bridge (Kekwick, 1981). Robert Race, with his colleague Ruth Sanger, made many contributions by finding new blood-group systems, particularly Xg, discovering new alleles of existing systems and defining their genetic pathways. Their text-book *Blood Groups in Man* has become renowned worldwide. Following the retirement of Race and Sanger, the unit has been directed with distinction by Dr Patricia Tippett. The MRC closed the unit in 1995 following Dr Tippett's retirement, but some of their research work will continue at the International Blood Group Reference Laboratory in Bristol (IBGRL).

Despite the pre-eminence of the Lister Institute in medical research its financial position began to decline after the Second World War. It was recognized in the Victorian era that a research institute dependent upon private donations was a risky venture. Sir Ray Lankester, Professor of Comparative Anatomy at University College, London, stated as long ago as 1889 that the proposal to create an institute similar to that of the Pasteur could only be expected to succeed with finances from the Government. "We cannot by private subscription maintain an Institution for scientific research", he said "it has been tried. It cannot be done. It is simply out of the question."

For over 70 years the Institute demonstrated that it was possible to finance research with a combination of private funding and the sales of biological products. Rapid inflation and the country's economic situation meant that by the early 1970s the future for the Lister Institute was bleak (Creeth, 1993).

Strenuous efforts to find financial support were made by Professor A. Neuberger, who became Chairman of the Governing Body in 1971, and by Sir Ashley Miles the Director who retired in 1971. Professor D. C. Evans, his successor, who only remained in this post for one year before becoming the Director of the National Biological Standards Institute, endeavoured to reduce expenditure and make the serum and vaccine production at Elstree more profitable.

Walter Morgan was recalled from retirement to be Director in 1972 but, by this time, his efforts together with those of Professor Neuberger to rescue the finances were doomed to failure. By the end of 1974, when the closure of the Institute at Chelsea Bridge had become inevitable, only the group working on blood-group antigens remained. This work was subsequently transferred to the MRC's Clinical Research Centre at Northwick Park Hospital. The MRC Blood Group Research Unit had moved to the Galton Laboratories at University College. The work of the Biophysics Department

was transferred to the University of Bristol (Watkins, 1994).

The Lister Institute at Chelsea Bridge closed on 31 December 1975. The Blood Group Reference Laboratory remained in the purpose-built accommodation in the yard of the Institute until its subsequent transfer to the Radcliffe Infirmary in Oxford.

The closure of the Institute at Chelsea Bridge did not immediately affect operations on the Elstree site. However, in his 1976 Report of the Governing Body, the Chairman warned that if production was not accompanied by research there could not be a long-term future for Elstree. By 1978, the activities of the Lister Institute had terminated at the Elstree laboratories. Professor Neuberger, in his Chairman's statement in the 1978 Report of the Governing Body, commented that there had been several reasons which had led to the closure. These included the costs of improving the facilities to conform with recent legislation, improving the buildings in order that there could be efficient competition, and the necessary research to enable new products to be developed (the Institute had not marketed a new product for many years). In order to correct these deficiencies several million pounds would be required. Even with the sale of the Lister Institute at Chelsea Bridge it would be unlikely that sufficient funds would be available. The Blood Products Laboratory continued to operate, funded by the Department of Health and Social Security (DHSS).

The Institute at Chelsea Bridge and the Elstree Buildings were sold eventually and the proceeds were invested by the Governing Body. A new role for the Institute was sought to utilize its accumulated capital. Having obtained a new Memorandum of Association, the Institute now grants Research Fellowships to applicants selected annually by a Scientific Advisory Committee. The Institute maintains itself as a community by holding an annual meeting of the Fellowship-holders, present and past, in the company of the Governing Body and Members including former scientific staff. At these meetings the Fellows give scientific presentations (Watkins, 1994).

Behind all these changes, including the closures and sales of the properties, was Gordon Roderick who was Secretary of the Institute, having spent many years as Estate Manager at Elstree. By the time of his retirement in 1995 he had seen the Fellowship scheme well established. To recognize his contribution throughout the years of change there is a Travel Scholarship awarded annually in his name (L. Vallet, pers. comm.).

Chapter 2: Towards a National Blood Transfusion Service in England and Wales, 1900-1946

When the Second World War ended it seemed appropriate for the Ministry of Health (MoH) to form a National Blood Transfusion Service (NBTS) by assuming responsibility for the existing blood depots. These depots included four established in 1939 to serve London and administered by the Medical Research Council (MRC) together with 10 others established throughout the country in 1940 and administered by the Emergency Medical Service. The transfer of responsibility, planned to take place in July 1946, had to be postponed until 26 September because so many of the senior MoH staff were on holiday.¹ It is unlikely, however, that the transition from one administrative body to another was noticed in the depots themselves as their functions did not change.

A similar, though independently funded, service known as the Scottish National Blood Transfusion Service (SNBTS) had been set up in Scotland on 11 January 1940 (Masson, 1993).

BLOOD TRANSFUSION DURING THE FIRST WORLD WAR

The roots of our transfusion service antedate the Second World War Blood Supply Depots. Geoffrey Keynes (1983) recalls that he was first made aware of the life-saving properties of blood transfusion in the course of the First World War whilst working as a medical officer on the Western Front. In 1916, during a visit to an American casualty-clearing station staffed by men from Harvard University, he learned several transfusion techniques including direct transfusion from donor's artery to recipient's vein, the transfer of blood from donor to recipient in syringes and transfusion of blood taken from a donor into sodium citrate solution.

Following the independent discoveries of Hustin (1914), Agote (1915) and Lewisohn (1915) that citrate was a safe and effective anticoagulant, citrated blood rapidly fell into disrepute. Febrile reactions to citrated blood were common and it was some time before the causes were traced to bacterial contaminants in the distilled water used to make citrate solutions and also to traces of dried blood in inadequately cleaned transfusion equipment (Lewisohn & Rosenthal, 1933). In fact, more than two decades of controversy were to follow in which the relative merits of 'pure' vs. citrated

blood would be debated (Wain, 1984). Unaware of these problems and governed only by the exigencies of war, Keynes developed a strong preference for citrated blood, finding that in an emergency he could perform the whole process of blood transfusion and surgical procedure single-handedly. Fortunately for Keynes and his colleagues, an American surgeon had introduced the use of citrated blood into the British Army Medical Service: the same surgeon is usually credited with having set up the first blood bank and using blood stored for up to 14 days (Robertson, 1918). There was no doubt in Keynes' mind that blood transfusion not only saved the lives of those who were in shock through loss of blood, but also extended the possibilities of life-saving surgery. Nonetheless, he recalled that blood donation and transfusion were so novel at the time, that the donor, usually a lightly injured man, had to be encouraged to donate with the bribe of an extra fortnight's leave in 'Blighty' (Keynes, 1983).

On his return to London after the war, Keynes joined the surgical team at St Bartholomew's Hospital and was amazed to discover how little importance his colleagues ascribed to the extraordinary therapeutic value of blood transfusion. It proved particularly difficult to persuade his chiefs to allow him to replace blood during an operation, thereby preventing surgical shock; their main objection being that a transfusion would get in the way of the operators. Moreover, their rather negative view of blood transfusion had been supported by an editorial in the *Lancet* (1918) which, though acknowledging the value of blood transfusion in military practice, suggested that there was likely to be much less demand for it in civilian hospitals. The same leading article emphasized the novelty of the procedure by stating that it was unlikely that any English surgeon could have been found, before the First World War, who was able to perform the operation of blood transfusion. Moynihan (later Lord Moynihan), Professor of Surgery in Leeds, challenged the statement, saying that the operation of blood transfusion had been carried out in Leeds for the previous 10 years (Moynihan, 1918). Following a visit to George Crile in Cleveland, Ohio, Moynihan had adopted the direct person-to-person transfusion technique; the latter having been introduced into America by a Frenchman, Alexis Carrel (Crile, 1909).

It is likely that blood transfusion was more widespread than the *Lancet's* leading article suggested. If blood were needed it was donated by relations or friends of the patient, or even by members of a hospital's professional donor panel. Contemporary technology, using blood without an anticoagulant, made the whole operation clumsy, time-consuming and also very expensive, requiring as it did a

¹ A. Landsborough Thomson (MRC) to A. N. Drury, Director of the Lister Institute and the four London Blood Depots. Wellcome Institute, Contemporary Medical Archives (WI, CMA) GC/107/3.

whole team of trained operators. Quite apart from the expense to hospitals and the inconvenience to the medical profession, direct transfusion was unpopular with donors, causing them considerable discomfort and exposing them to unpleasant sights. Additionally, it had the disadvantage of being difficult to regulate. Blood often clotted in the cannula and in the absence of very precise weighing apparatus, it was impossible to assess the volume that had been transfused. Keynes' senior colleagues initially blocked his efforts to set up a donor panel at St Bartholomew's Hospital and in 1924 he complained that "This prevailing uncertainty as to how or where to obtain a blood donor often results in the postponement of the decision to transfuse until the patient has passed from the category of hopeful to that of hopeless" (Keynes, 1924). However, by the time this complaint was published, a most remarkable and public spirited man, Percy Lane Oliver (Fig. 2.1) had founded an independent voluntary donor service which was addressing the problem.

PERCY LANE OLIVER (1878–1944) AND THE BRITISH RED CROSS BLOOD DONOR SERVICE

Oliver was born at St Ives, Cornwall, on 11 April 1878. His family moved to south-east London in 1883 and, at the age of 14, he gained the highest mark of all 449 entrants in the Civil Service entrance examination. However, having a weak heart, he was rejected by the Medical Board and instead of joining the Civil Service accepted the post of assistant librarian to Camberwell Borough Council. In 1901 he transferred to the Town Hall staff where he worked in the finance department until his early retirement in 1933. He was married at St Giles Church, Camberwell, in July 1905 and set up house in the vicinity.

Together with others he founded the Camberwell Division of the Red Cross, becoming Honorary Secretary in 1910. In the early years of the First World War he and his wife made themselves responsible for helping Belgian refugees, meeting them at the docks, taking them to a large house near their home which provided temporary accommodation and caring for them until more permanent housing could be found. His service to refugees was recognized in 1918 when he was awarded the Order of the British Empire.

Oliver enlisted in the Royal Naval Air Service in 1916 and was stationed at Crystal Palace. His Red Cross Division played an important part in rescue operations when the munitions factory at Silvertown exploded in 1917. In the same year, together with his wife, son and daughter, he moved into rented accommodation over the Red Cross Divisional Headquarters in Talfourd Road. During one of the Division's meetings in October 1921, a request for volunteers to give blood was received from King's College Hospital. Oliver, together with several other members of the Service, went to the hospital where one of their number, Sister Linstead, was

found to have blood compatible with that of the patient. The other members returned to the divisional headquarters to await the outcome. They were most impressed when Sister Linstead rejoined them none the worse for her 'ordeal'. She was able to report that not only had the patient benefited from her donation, but also that her blood had been taken in a most expert manner and the process had been simple and painless.

ORGANIZATION OF A DONOR PANEL

The incident made a great impression on Oliver who realized that many patients had neither relations nor friends willing to donate blood and that this was a situation which needed to be remedied. By all accounts he was a splendid organizer and rapidly formed what he unofficially called the Red Cross Blood Transfusion Service. After discussing the problem with local hospitals he set about the task of building up a donor panel very methodically; appealing to friends and fellow members of the local Red Cross. The blood of potential donors was grouped, free of charge, at any one of the hospitals that wanted to make use of the service. In addition, volunteers were given a brief medical examination designed pri-



Fig. 2.1 Percy Lane Oliver, 1878–1944.

marily to ensure that there was no history of transmissible disease and that their veins were accessible. A card index was created, including each donor's name, address and blood group, together with the dates and the places where donations were made. Every effort was made to use donors in strict rotation, without causing them the inconvenience of travelling great distances. Each donor was bled soon after enrolment so that his or her enthusiasm would not flag. From the very beginning Oliver insisted that under no circumstances should a donor accept money for a blood donation and anyone suspected of doing so was crossed off the donor panel. Grateful recipients were, however, encouraged to make a contribution towards the Service's expenses.

It was agreed that volunteers should only accept calls through Oliver's office so that there would be a reliable record of donation frequency and the pattern of requests. Few private homes had telephones in the early days of the Service and the police, many of whom enrolled as donors, were frequently called upon to take messages informing donors that they were needed. The public perception of blood donation as dangerous and likely to harm the donor was so prevalent that many donors had to keep their activities secret from family and friends and could only be contacted at work. Needless to say, under these circumstances, the cooperation of employers was essential.

Communication with most donors was indirect and volunteers were asked to make contact with the office, confirming receipt of a request to donate. They would be told where and by whom their services were required so that they could ask for the surgeon by name. The surgeon was expected to complete a form for the Service giving some details of the patient's problem (Fig. 2.2). In this way, Oliver hoped to accumulate statistics which could be used to maintain donor interest. However, in an unpublished report he admitted that the medical profession proved to be most uncooperative and that he frequently made numerous requests before any information was provided.²

British Red Cross Society—Blood Transfusion Service.

Telephone (night and day):
Forest Hill 2354 (3 lines). CASE 1530/2422 5, COLYTON ROAD, SE22.
The Hon. Secretary has pleasure in forwarding the following report of your 28th transfusion with the sincere acknowledgments of the Society for the service rendered.
Date of transfusion 4.5.38. Hospital Yingfa College
Ward Storka Donor Miss H.L. Jones Surgeon Dr. Conway
Sex Male Age 58 Blood Group 1 Blood drawn 550 ccs.*
Nature of disease or injury Pernicious anaemia.
Result of transfusion, so far as can be ascertained. Patient came into hospital in a very bad condition and transfusion was given on the same day.
The patient showed immediate improvement and is now reacting well to liver injections.

Form 10—5,000/2/1836

*Note.—1 pint blood = 568 ccs. or 20 ozs.

Fig. 2.2 Report on the results of a transfusion given to a patient suffering from pernicious anaemia.

FINANCING THE SERVICE

Although volunteers were not paid for their donations they were able to claim travelling expenses; Oliver was proud to record that very few actually did so. In order to minimize organizational costs the Service was run from Oliver's own home above the local Red Cross Divisional Headquarters. His family were reimbursed by the Red Cross for the cost of telephone calls and stationery, but never accepted personal remuneration even though the telephone was never left unattended by day or night. In spite of the donors' generosity and the Oliver family's economy, funding the Service undoubtedly presented problems. The money raised through gifts was never enough to cover expenses. Oliver had to swell the funds by organizing the collection and sale of tin foil. He also successfully applied for contributions from the Sunday Cinema Fund, a contemporary tax on Sunday cinema viewing which was used to help charities.

EXPANSION OF THE DONOR SERVICE

There was little demand for the Service during 1922 but after that, when more hospitals had heard of the voluntary donor panel, the number of requests for donors increased year by year. By 1924 the office was so busy that Oliver resigned his post as Honorary Secretary to the Camberwell Division of the Red Cross in order to devote all his spare time to the donor service. As a result of his resignation the family had to leave their flat over the Red Cross headquarters and eventually settled in a large house at 5 Colyton Road, SE22. By that time the Service was receiving so many calls that it was necessary to enlist part-time help. In recognition of the importance that their members attributed to the donor service the local Red Cross Division agreed to pay the assistant's wages and also contributed a guinea a week towards rent and office expenses.

When the Camberwell Red Cross could no longer meet demands for donors, Oliver set about recruiting from other organizations including the London Rover Scouts, the St John's Ambulance Brigade and the Toc H. At one point the Toc H provided almost a third of the donor panel. Many of the night calls came from the London teaching hospitals and were accepted by the central London YMCA. The Service, having extended throughout the capital, was referred to as The London Blood Transfusion Service.

On 11 November 1924, Oliver was invited to address a meeting at St Thomas's Hospital, London, in which he described the voluntary blood donor scheme to Red Cross representatives from the provinces. After the talk it was agreed to adopt the scheme as a Red Cross service throughout the

² Report on the work of the London Blood Transfusion Service. P. L. Oliver, unpublished report. Private Archives, F. Hanley.

country though, in general, expansion had a very slow start.

In 1927, Keynes assisted in the recruitment drive by broadcasting a historical account of the service on 2LO, a London radio station which could be heard nationwide. He concluded his talk with an appeal for more donors.

OFFICIAL RECOGNITION BY THE BRITISH RED CROSS

During the winter of 1925/26, when Oliver was ill, one of his assistants, F.W. Mills, realized that the Service would flounder if it were not established on a more formal basis. Mills, who became interested in blood transfusion whilst working as a field ambulance man in the First World War, appealed to the British Red Cross Headquarters for help. In reply, he was told that the London Regional Medical Committee was discussing the whole question of blood transfusion and had just invited the British Red Cross to organize the service on a permanent basis. Oliver appears to have been excluded from these discussions; a grave injustice considering that it was he who had organized the country's first donor panel without any assistance from the National Red Cross Headquarters.

Although officials were pleased to acknowledge that the donor service was an organization worthy of shelter under the Red Cross banner, they offered relatively little practical assistance. However, a committee was formed, representing hospitals, medical profession and donors. Oliver was elected Honorary Secretary and the Secretary of the British Red Cross, Brigadier-General H. B. Champaign was Chairman. Now that the organization had a more formal basis, it adopted the title of British Red Cross Blood Transfusion Service.

One of the committee's first resolutions was to invite Keynes, now Consultant Surgeon at St Bartholomew's Hospital, to join them as medical adviser. Keynes' association with the Service lasted for many years and he was a great support to Oliver both in attempting to protect donors from the more outrageous deeds of his own profession and as a propagandist for the Service.

At the first committee meeting in December 1926 the chairman reported that several letters had arrived from provincial hospitals, requesting help in setting up a blood transfusion service similar to that which had been founded in South London. He and Oliver had already accepted an invitation to visit Cardiff in order to discuss the formation of a donor panel. Throughout the following decade, Oliver was destined to spend almost all his spare time travelling around the country delivering lectures on the Society's activities. Voluntary organizations in almost all of the country's major cities invited him to speak to them, to give advice on how to open up donor services. Oliver was disappointed by the rather slow growth of provincial services and attributed it both to a lack of facilities and to a shortage of surgeons skilled in the art of

taking and giving blood. However, the scarcity of persons with his organizational ability must have been at least as important.

The transfusion service in London remained under Oliver's control but he made no attempt to administer panels which grew up elsewhere, although affiliation of provincial services to the parent body was welcome.

DONOR PROTECTION

With the help of Keynes, Oliver drew up a set of regulations with regard to the treatment of donors for doctors and institutions using the service.

Many of the regulations were self-evidently good practice; the reason for their being explicitly included was that donors were often treated shabbily either by the institutions where they gave blood or by members of the medical profession. Oliver pointed out that not only should donors be thanked for their service, they should also be given a full explanation if a transfusion were cancelled by the time they reached a hospital; after all they might have travelled some distance and at great personal inconvenience.

Hospitals were also expected to protect donors from witnessing anything which would cause them distress as this was a common cause of resignation from the Service. Oliver suggested that by the very nature of their commitment to relieve suffering, donors were a particularly sensitive group and should not be expected to give their blood in a ward full of sick patients.

Some of the Service's regulations inevitably brought it into conflict with members of the medical profession. After all, doctors argued, what right did a layman like Oliver have to dictate to professionals? They took exception to being told that needles should always be sharp; that the skin should be cleaned with ether rather than iodine as the latter caused too many allergic reactions; that they should adopt techniques which would prevent the donor from fainting whilst blood was being donated. Hospitals found the Service's regulations equally tiresome, particularly when Oliver demanded the delegation of a nurse to meet each donor on arrival at the hospital door and to accompany him or her throughout the whole procedure. When they complained about shortages of staff, officials were informed that the Service had lost many of its donors, annoyed about losing themselves in the labyrinthine corridors of large hospitals.

VENESECTION TECHNIQUES

When the Service was started up, the majority of doctors gained access to a donor's vein by exposing it through a skin incision and then, after withdrawing blood, occluding it with a ligature. That particular vein would be of no further

use and, consequently, by 1925 few of the original volunteers remained on the panel. Although the practice of cutting down on veins was henceforth forbidden by the Service, it was not eradicated until 1929 in spite of condemnation both in lectures by Keynes and in a critical article in the *Lancet* (Gibson, 1926). During his own lectures, Oliver showed a film illustrating a simple method of taking blood which would, at the same time, preserve a donor's vein for future use. A French's needle was pushed through the skin into a vein which was distended using a simple tourniquet. The needle was attached to approximately 1 foot of rubber tubing which led to a glass beaker containing sodium citrate and the blood-citrate mixture was stirred with a glass rod throughout the donation to achieve adequate anticoagulation. The film also demonstrated the importance of pressing firmly on a vein immediately after removing a needle. Several donors had withdrawn their services when large bruises appeared at venepuncture sites.

A continued distrust of citrate caused some doctors to rely exclusively on direct donation, a practice which was, however, also banned by the Service as it caused so much distress to the donors. To these doctors Oliver pointed out that a German invention 'Athrombit', in which the container was made of amber and the needle of an alloy, prevented clotting even in the absence of anticoagulant and was used with considerable success at the German Hospital in London.

PROBLEMS WITH GROUPING BLOOD AND THE USE OF UNIVERSAL DONORS

Although human blood groups had been discovered in 1900, the nomenclature had not been clearly defined (Landsteiner, 1901). A few years later, Jansky, working in Prague, had named the groups I(O), II(A), III(B) and IV(AB) but had published his work in Czech and in a journal read by few people in Western Europe or America (Jansky, 1907). Moss, of Baltimore, knowing nothing of Jansky's work, independently classified the four groups as I(AB), II(A), III(B) and IV(O) (Moss, 1910). The Moss nomenclature was widely used in the UK, but some donors were grouped according to the Jansky system. The dichotomy presented potential for some very dangerous accidents and was the reason why, when the London Service was asked for a group I donor, the practice was invariably to ask "Moss or Jansky"? The Red Cross Transfusion Service did not adopt the International ABO nomenclature until 1939 following advice given at the 1937 Congress of the International Society of Blood Transfusion held in Paris.

At the multidisciplinary Committee's second meeting in 1927, Oliver made what was to become a recurrent complaint. He pointed out that even allowing for cases at hospitals that possessed no facilities for grouping blood, the preponderance of calls for group IV, i.e. universal or group O donors, seemed to indicate that hospital authorities did not take the trouble to

group a patient's blood before applying for a donor. He told the Committee that the point was always queried when a group IV(O) donor was requested; the reply was often that "a IV(O) would do". Oliver clearly did not think that this would "do" at all. Although he had no knowledge of blood-group serology he was unable to accept that the distribution of blood groups was different amongst recipient and donor populations. He illustrated his point with the distribution of groups amongst the 99 donors who had given blood in the previous 3 months (Table 2.1). His objection to the excessive request for group IV(O) seemed to be motivated more by the wish to give all donors the same right to serve than by a belief in the need for serological purity. Unfortunately, numerous appeals for hospitals to alter their practice of requesting only group IV(O) donors were to no avail. Commercial grouping serum, purchased from Burroughs Wellcome, cost 4 s. for two capillary tubes, one containing anti-A and the other anti-B in a quantity which was sufficient only to group one sample. In the name of economy, hospitals either refused to group their patients' blood or prepared their own grouping serum using blood from staff members. In many cases the locally produced anti-sera had very low anti-A and anti-B titres and failed to agglutinate red cells using the contemporary technique of tile grouping.

The problem was brought to a head in 1929 when a donor, designated group III(B) by the Westminster Hospital, gave blood to a group III(B) patient in Queen Charlotte's Hospital. The patient collapsed and died during the transfusion whilst the donor was still on the premises. The donor's blood was regrouped immediately and shown to be group II(A). The subsequent inquiry revealed that not only had the Westminster Hospital's grouping serum deteriorated to such an extent that it was useless, but also that similar grouping errors had occurred in other hospitals.

The Committee asked Keynes, Oliver and Dr Conti, a medical practitioner affiliated to the Service, to solve the problem and they responded by appealing to the Medical Research Council (MRC) for help. The MRC suggested appointing a part-time clinical assistant who would be

Table 2.1 Blood groups of 99 donors used over a 3-month period in 1926 (in his unpublished *Report on the work of the London Blood Transfusion Service* circa 1937, Oliver documented the distribution of ABO groups in 4786 Red Cross donors as: AB – 3.5%, A – 42.6%, B – 8.6%, O – 45.3%)

Blood group		No. donors supplied	Percentage
Moss	ABO		
1	AB	3	3.3
2	A	24	26.6
3	B	10	11.1
4	O	62	68.8

responsible for donor care and blood grouping and also awarded a grant to cover his salary for the next 4 years. Keynes recommended that the post be filled by Dr H. F. Brewer, Consultant Pathologist at St Bartholomew's Hospital. His appointment in 1932 marked the continuation of a long association between Bart's and the Red Cross Transfusion Service. After Brewer's appointment the medical and scientific aspects of donor care improved enormously, with a consequent increase in morale amongst volunteers and fewer resignations from the Service.

DR BREWER'S CONTRIBUTION TO THE SERVICE

Potential donors were carefully examined and were rejected if their veins were not readily accessible. Blood tests, including haemoglobin measurement, blood grouping and serological tests to exclude syphilis were carried out, not only on enrollment but after every tenth donation. Brewer's main contribution was to negotiate with Burroughs Wellcome to supply less expensive grouping sera. The blood of all groups A and B donors who had an anti-B or anti-A titre of more than 1 in 200 was taken at St Bartholomew's Hospital where the serum was separated and sent to Burroughs Wellcome. For a small fee the company put the sera into capillary tubes and sent it to the Service Headquarters whence it was sold to affiliated hospitals at the bargain price of 6 s. for a dozen pairs of tubes; non-affiliated hospitals had to pay 12 s. Brewer expressed the hope that hospitals would purchase and use the antisera, thus saving unnecessary calls on universal donors. At about the same time he advised doctors to group the blood of pregnant women so that should a transfusion be needed to cover delivery, blood of the correct group could be given.

Unfortunately, sera stored in capillary tubes deteriorated very rapidly and even the Service's high-titre sera were responsible for the occasional misgrouping. The practice of supplying grouping sera in capillary tubes nonetheless continued until after the Second World War and complaints to the Director of Burroughs Wellcome were met only with displeasure (P. L. Mollison, pers. comm.).

ADVANTAGES OF VOLUNTARY BLOOD DONATION

The Committee had been informed already that in countries where professional donation was the rule, sometimes as many as 30% of donors had to be rejected because of ill health and in particular because of syphilis. Syphilis was very rare amongst Red Cross Service volunteers and, when it occurred, was usually of the congenital variety. No cases of syphilis were ever discovered on re-examination after 10 donations. This particular statistic was a matter of great pride to Oliver,

reinforcing his view that those people who dedicated themselves to public service were a special breed. However, like Keynes, he decried the practice of treating donors as heroes and was ever critical of panegyrics in the press, with the implication that in giving blood the donor was running a health risk.

From the early days of the Service, Oliver had been aware that the provision of unpaid voluntary donors not only minimized expense but also reduced the risk of transmitting infection. Presumably he felt that people ready to sell their blood belonged to a group whose health and hygiene were of a lower standard than normal and might not be truthful when asked their medical history. He was very critical of the professional transfusion services which grew up in cities like Manchester, Swansea, Sheffield, etc. These professional services, which took the form of a small group of people prepared to sell their blood to particular hospitals, were an impediment to anyone trying to build up a voluntary unpaid donor service in the same city. For example, the Manchester and Salford Transfusion Service, run by the Red Cross, found itself in competition for donors with a professional donor service run by the Manchester Public Health Department. The latter paid 10s. 6 d. for a donation and 5 s. to potential donors attending for a blood test. The fee was increased considerably, until in 1930, donors were being paid 3 guineas for each donation (Table 2.2).

RECOGNITION OF DONOR SERVICE AND PUBLICATION OF THE QUARTERLY CIRCULAR

Members of the Service had advised the Committee that even altruism breeds on recognition and, almost from the beginning, volunteers received a certificate of each donation. After January 1934 the practice changed to the presentation of a

Table 2.2 Fees paid to professional donors in various towns/districts in the UK between 1921 and 1938 (information supplied by Mr F. Hanley JP, President, Oliver Memorial Fund and Chairman, Greater London Red Cross Blood Transfusion Service 1962–1986)

Town or District	Year	Fee
Sheffield	1921	£5 5s.
Melton Mowbray	1928	£2 2s.
Norwich	1928	£4 4s.
Manchester	1930	£3 3s.
Glasgow	1930	£1 1s.
Essex	1931	£1 1s.
Swansea	1934	£1 1s.
Leicester	1936	£4 4s.
Nottingham	1938	£3 3s.
Kings Lynn	1938	£1 1s.

medal following the tenth donation with a bar for each subsequent 10 donations (Fig. 2-3). From October 1933, Oliver, by then retired from his post at Camberwell Town Hall, edited and published a quarterly bulletin. The *British Red Cross Blood Transfusion Service Quarterly Circular* kept panel members informed of the Service's activities and also of any advances in transfusion techniques. The first edition included case reports of several patients whose lives were saved by blood transfusion, invited donors to contribute accounts of their own transfusion experiences, listed venues and times of lectures and gave the donor statistics for the years 1931, 1932 and 1933.

The *Circular* was full of good advice to donors. For example, they were warned against giving their addresses to surgeons in order to protect themselves from exploitation and forms of moral blackmail. It was not uncommon for surgeons, discovering that a donor lived close to the hospital, to try to persuade him or her to donate without putting a call through the Service's central office. Arrangements of this type doubtless saved time in an emergency but resulted in some donors being overused and others never being called at all. As an example, Oliver cited the case of a group O donor, in a poorly organized provincial, professional service, who had been called to donate 12 times in less than 10 months by different surgeons and all because he lived close to the hospital.

The regular blood tests done on Red Cross donors led to the advice that men should donate not more than four times and women not more than three times per year.

In order to put things into perspective for his readers, Oliver pointed out that, even though the Red Cross Service was answering more and more calls, many donors continued to be found amongst family and friends of the patient.

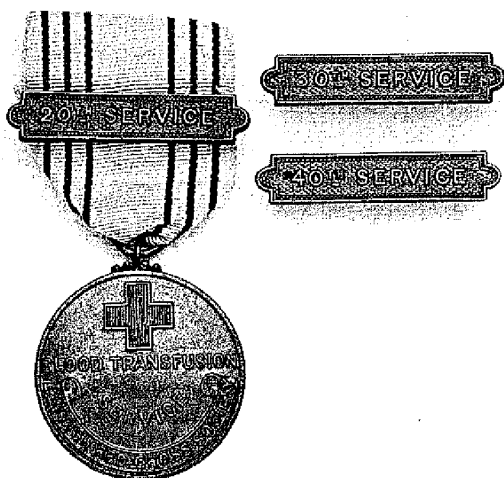


Fig. 2-3 Medal given to a donor after 10 donations together with bars for 20, 30 and 40 donations.

The July 1935 *Circular* gave details of a continuous drip transfusion technique by which it was possible to transfuse 8–10 pints of blood at a rate of 40 drops per min (Marriott & Kekwick, 1935). Oliver realized that the use of such large quantities of blood might have momentous effects on the future of blood transfusion in general, and the Red Cross Service in particular, because some patients would inevitably need several donors.

In October 1935, the *Circular* recorded that all German military personnel had their blood grouped and recorded on identity discs (an inaccurate statement: only members of the Waffen SS were grouped). Oliver and his colleagues felt that this could be useful information in wartime but there was no indication that the British government intended to emulate the Germans.

Donors were encouraged to record their experiences of blood donation in the bulletin. Complaints about treatment by hospital staff or surgeons were recorded. Although no specific hospital or surgeon was named, readers were left with the impression that a strongly worded complaint was sent, on their behalf, to anyone who harmed or offended a Red Cross donor. In fact, a decision to withdraw the Red Cross Service from recurrently offending hospitals was occasionally taken by the Committee (Minutes of BRCBTS, Hanley; private archives).

In July 1936, a donor visited the Leningrad Blood Bank during her summer holiday and a report of her impressions were published in the *Circular* of January 1937. She recorded that, as in Moscow, some of the blood for transfusion was taken from cadavers largely in order to cut down the cost of the service. In Leningrad, a city with a population of 3 million, 1640 professional donors between the ages of 19 and 50 years gave blood at intervals of 4–6 weeks; in marked contrast to the regulations concerning donation frequency in Britain. It would seem that in Russia where the lowest factory wage at the time was 180 roubles per month, some people relied upon their blood donation for a living. In Leningrad women were paid 180 roubles per donation, whereas men were paid 360 roubles. Dr E. Hesse, Director of the Leningrad Service, must have received a copy of the *Circular*; for he responded in a letter to the editor stating that in Russia the blood of women was valued every bit as highly as that of men. Men were paid more only because, being somewhat larger on the whole, they were allowed to donate 500 ml at each visit, whereas only 300 ml was taken from women. He added that all blood was taken into citrate anticoagulant and was stored for up to 15 days.

THE MEDICAL PROFESSION AND THE RED CROSS TRANSFUSION SERVICE

In spite of widespread publicity for the Red Cross Transfusion Service, the British medical profession sometimes gave the

impression that they knew nothing of its existence. In 1936, a British Medical Association member, Mr Denis Browne, presented a paper at the Association's annual meeting; in it he envisaged a Utopian situation where blood transfusion could be obtained rapidly in any part of the country. Oliver responded with an article in the *British Medical Journal* asking why an effective transfusion service should be considered Utopian; after all it had already been achieved in many cities (Oliver, 1936).

He went much further, suggesting problems which should be addressed at a national conference. These included: standardization of techniques, the value of whole vs. citrated blood, the need for cross-matching donor blood with that of recipient, the time necessary for cross-matching blood, the frequency of donation and several other donor-related matters. He placed particular emphasis on the need to establish, once and for all, whether donors should be professional or should be expected to give their services free of charge. Readers were left in no doubt about Oliver's own view on the latter point. He emphasized that paid donors should be discouraged because they were more likely to spread disease and, apart from that, he was certain that a professional service would be prohibitively expensive. Subsequent experience in the USA has proved that he was incorrect on the latter count. The American plasma industry has shown that a professional donor service can be cost-effective; fewer donors being needed because they return for payment. Voluntary, unpaid donors leave the Service if they are discontented and more have to be recruited with increased cost.

BLOOD BANKING AND THE SPANISH CIVIL WAR

The *Circular* of April 1937 contained a report by Dr F. Jorda on his experiences in blood banking. Jorda, a card-carrying communist and Republican sympathizer, had been inspired by blood-banking practices in Russia to set up a blood bank in Barcelona. His transfusion service supported both the army and civilians during the Spanish Civil War, functioning from August 1936 until January 1939; incidentally, it is worth mentioning that Jorda used grouping sera supplied by Burroughs Wellcome. He described the logistics of transporting refrigerated anticoagulated blood to the battle front and ended with an appeal to the British Red Cross for funds to purchase microscopes and centrifuges. There is neither a record of whether help was forthcoming nor a hint that anyone in his audience found the talk particularly prophetic. Letters to the *Quarterly Circular* suggest that the donors' only concern was about losing their close personal contact with hospitals if blood banking should become fashionable in Britain.

It was not only the donors who were resistant to using stored blood. A large proportion of the British medical establishment, who used blood transfusion in the care of their

patients, disliked the idea of using that which was not freshly donated. Oliver was, however, impressed by Jorda's work and staged an exhibition illustrating methods of storing blood as practised during the Spanish Civil War.

In 1937 Oliver returned from a visit to the Second Congress of the International Society of Blood Transfusion in Paris, to report that much of the discussion had been on blood banking with particular emphasis on the need to have stocks available for civilian casualties should war occur. At the conference, plans had been made to compare the value of fresh blood and stored defibrinated blood. Also, it was decided that different anticoagulants should be compared to establish how long anti-coagulated blood could be stored. The Russian and Spanish experiences in blood banking were mentioned. In Russia all large hospitals used stored blood to the exclusion of that which was freshly drawn; the donors attended a central institute for blood collection. In England this was regarded as carrying change too far. "Where voluntary service predominates, wholesale diversion of donors' services to a common supply might very well dry up the spirit of altruism" (Riddell, 1939).

Oliver realized that if the Service were to be extended to areas away from large towns, where all the donor panels were situated, some form of blood banking would be necessary. Nonetheless, he reassured Red Cross donors that their services would be needed because "English surgeons would continue to demand high-quality fresh blood for their patients." His report on the Congress concluded with the following somewhat chauvinistic statement: "British delegates (Oliver and Brewer) were of the opinion that this country has little to learn from abroad in regard to either the technique of blood transfusion or the administration of services".

The problem of whether or not to store blood was not one which would go away. By January 1938, donors themselves were asking for blood banks to be established in hospitals so that they would not be called away from work so frequently. In the next edition of the *Circular* there was a reference to an American article describing the benefits from a blood bank in Cook County Hospital, Chicago (Fantus, 1937). Yielding to pressure from volunteers, the Red Cross appointed Drs Brewer, Moore and Riddell, representing the Voluntary Blood Donors Association, to a technical sub-committee which would experiment with methods of preserving blood. It was recorded that: "A letter has also been sent to Cook County Hospital asking for details of the methods employed, but it is probable that [blood banking] will be more in the nature of a pious aspiration than an accomplished fact". Nevertheless, a mass of information was received from Chicago and the *Circular's* readers were assured that it was being digested and summarized.

In July 1938, in an article entitled *Blood transfusion in time of national emergency*, volunteers were warned that they should not expect to be informed about what happened to their blood, were it to be supplied to the armed forces. It was

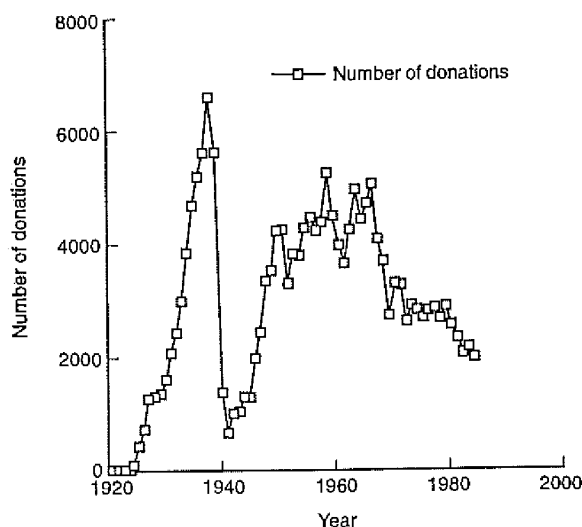


Fig. 2.4 Donations offered through the London Division of the British Red Cross Transfusion Service, 1921–1985.

suggested that in case of war a large plant would be needed to produce typing serum and that blood could be withdrawn into milk bottles or any other suitable glass vessels which were available.

In October 1938, with the threat of war looming large, the Service could no longer meet the increasing demands for typing serum. Oliver and his supporters, conceding that it would be impossible to continue with the system of summoning individual donors, set about organizing a blood depot in a disused dairy in Surrey. Although they gathered together some bottles with rubber caps and a variety of other pieces of equipment, their efforts were overtaken by events and the Red Cross Depot never became operational. Through the Circular of January 1939, Oliver informed volunteers that should the country become involved in hostilities, the London branch of the Red Cross Service would cease to function in its present form primarily because civilian patients would be transferred to hospitals outside the area. At the outbreak of war, Oliver joined Brewer when he became Medical Director of the newly formed Luton Blood Depot and worked with him for a short time organizing the donor panel. He found the work unsatisfying; feeling out of place and under appreciated he returned to London but continued his work with the Red Cross Service until his death in 1944.³

There are probably two main reasons why Oliver is not better known today. First, he died at the height of the war: there seems to have been no official obituary in the national press. Second, the very rapid changes in blood transfusion

³ The British Red Cross Transfusion Service continued to function, nationwide, throughout the war and was active in London until 1986 when immediate pre-transfusion testing for HIV infection was obligatory, making walk-in donation impractical.

technology and the increased use of transfusion in civilian practice during the war rapidly rendered the Red Cross Donor Service virtually obsolete. Stored blood was so much more convenient in emergencies. Calls for Red Cross donors steadily declined from all but those surgeons absolutely convinced of the value of fresh blood and the Service's own statistics show that it was at the height of its activity in the year before war started (Fig. 2.4).

Nonetheless, Oliver's activities did not go unrecognized in his own time. In 1934, he and his wife were invited to Buckingham Palace to describe the Service's activities to their Majesties, King George V and Queen Mary. What is more, he received international recognition. At the First Congress of the International Society of Blood Transfusion held in Rome in 1935, Dr Anet, a Belgian delegate, praised Oliver's service with these words: "It is to the Red Cross in London that the honour is due to having been the first, in 1921, to solve the problem of blood donation by organizing a transfusion service available at all hours, and able to send to any place a donor of guaranteed health, whose blood group has been duly verified. This Society, whose encouraging experiences were watched by Red Cross Societies in other nations, served both as a model and an inspiration for the organization of similar services in seven other countries" (*Quarterly Circular*, Oct. 1936: 4).

THE INTRODUCTION OF BLOOD BANKING INTO BRITAIN

During the Spanish Civil War (1936–1939) Dr Janet Vaughan (later Dame Janet) was a member of the Committee for Medical Aid to the Republican Government and knew that the Spaniards were using stored blood to treat civilian and military casualties. Through the committee she became acquainted with Duran Jorda who, when it was apparent that the Fascists would win the war, escaped to England and stayed with Janet and her husband David Gourlay. Whilst in England, Jorda worked with Vaughan in her laboratory at the Hammersmith Hospital and convinced her that it was essential to store blood rather than to rely on peripatetic donors in time of war. In the light of what was to follow, Jorda must be given some credit for introducing the use of blood banks to the UK.

Jorda's own processing and storage techniques were very complex and involved mixing several donations of the same group followed by subdivision of the mixture to make the haemoglobin level of donor units similar. Pressurized air was then introduced into the units, converting 99% of the haemoglobin into oxyhaemoglobin; a step taken in order to prevent the growth of anaerobic organisms (Jorda, 1939). Jorda's techniques were never adopted in Britain because, in spite of all the precautions taken, and probably as a result of the excessive handling, bacterial contamination was

common (Saxton, 1939). Using the much simpler technique of taking blood into sodium citrate solution, Vaughan and her colleagues at the Hammersmith Hospital set about comparing the therapeutic effects of stored and freshly donated blood.

At the time of the Munich Accord in September 1938, it was apparent that at least some members of the government had little hope that there would be "Peace in our time". In fact, the level of cynicism was such that Drs Vaughan and R. G. McFarlane were advised by the government to be prepared for about 57,000 casualties in London during the weekend after Chamberlain returned to Britain (J. Vaughan to P. L. Mollison, pers. comm.). Many donors were bled and, when the expected air-raids did not materialize, their blood was used for patients in the Hammersmith Hospital. Blood which had been stored for several days was shown to be no more likely to cause reactions than that drawn into the same anticoagulant and used immediately (Elliot *et al.*, 1939). If this appears to be an insignificant step forward it is as well to remember that the issue of fresh vs. stored blood was still very much alive (Riddell, 1939; Wain, 1984).

It was obvious that war with Germany was imminent and on 5 April 1939 an informal meeting was held in the Gourlays' flat at which a tentative scheme was drawn up to provide London with blood for civilian casualties. The scheme, involving the creation of four blood-storage depots, was submitted to Professor Topley who was responsible to the government for organizing emergency medical services. With Topley acting as intermediary, the plans were presented to the Cabinet, adopted officially on 20 April 1939 and then put into effect as soon as there had been an estimate of the cost and extent of the enterprise. It was assumed that 10% of casualties would require transfusion and that casualty-receiving stations would be too busy to group and cross-match blood and should therefore only use group O. Each depot should be able to provide a daily average of 25 bottles, to hold up to 500 in cold storage and to have a donor panel of 25,000.

THE MEDICAL RESEARCH COUNCIL (MRC) AND THE LONDON DEPOTS

The MRC agreed to administer the depots, on behalf of the MoH, through a committee chaired by Professor G. Payling Wright. The depots were sited in areas where donors were readily available, and which were as close to the main concentration of hospitals as possible yet lying outside the likely target of enemy aircraft. The South West London Depot was accommodated in an adult education school at Sutton in Surrey, the South East London Depot in two converted houses at Maidstone, the North East London Depot in a hospital at Luton and the North West London Depot in the social centre on Slough Trading Estate. Somewhat later, on

3 September 1939, the army opened its own blood depot in Southmead Hospital, Bristol, directed by Colonel L. E. H. Whitby (later Professor Sir Lionel Whitby).

The London depot directors appear to have been self-appointed. Dr J. O. Oliver (later succeeded by Dr O. M. Solandt and he in turn by Dr J. F. Loutit) assumed responsibility for the Sutton Depot, Dr M. Maizels for that at Maidstone, Dr H. F. Brewer for that at Luton and Dr J. Vaughan (succeeded in 1944 by Dr S. Shone) for that at Slough. The MRC adopted a flexible attitude towards depot activities; it was realized that, as an entirely new service was being set up, it had to get underway before details of organization could be worked out.

By July 1939, Payling Wright was able to report that stocks of equipment were ready for despatch to the depots and designated casualty-receiving centres. Meanwhile, the depot directors reported a satisfactory increase in size of their donor panels. By August 1939, all essential equipment, including large storage refrigerators, were in place and on 3 September, when war was declared, the directors received telegrams instructing them to start bleeding donors.

Unavoidably there were some setbacks. The entire Service seemed in danger of being discredited in a report that stored blood was less effective than freshly donated blood (Paterson, 1939). Consequently, on 3 November 1939, a meeting of London pathologists was convened to discuss the question of a centralized blood supply. Fortunately, by that time the London depot directors had gained considerable experience with the use of stored blood and, in letters to both the *Lancet* and *British Medical Journal*, were able to dismiss Paterson's claim. (Brewer *et al.*, 1939 a & b). Having transfused altogether 219 pints of blood which had been stored for periods between a few hours and 3 weeks, their impressions of the efficacy of stored blood were entirely favourable. There had been very few complications. Three recipients developed transient jaundice and 10 had slight rigors. The directors emphasized the importance of cleaning apparatus scrupulously, of using twice distilled water for the manufacture of anticoagulant and of applying strict surgical aseptic techniques whilst giving blood transfusions.

Further support for the use of stored blood was provided in a report from Sir John Fraser, Chairman of the Medical Advisory Committee (Scotland) and Advisor in Surgery to the MoH, to Sir Edward Mellanby, Director of the Medical Research Council (MRC Archives, Public Record Office (PRO), FD/1/5891). In October 1939 there had been an air-raid on the Firth of Forth resulting in a number of naval casualties, many of whom had been resuscitated using transfusions of blood stored for over a week. Moreover, Sir John added that from September 1939 onwards all transfusions in Edinburgh had been made with stored blood. He also recorded that, although clinicians were disappointed to find that blood transfusion neither stimulated bone marrow nor had a haemostatic effect, the benefit in cases of shock and

anaemia was incontrovertible. Unfortunately, the Scottish experience was that as many as 20% of transfusions involving stored blood had caused rigors, a figure considerably higher than when freshly drawn blood was used.

THE REGIONAL DEPOTS, 1940

During the first nine months of the war there were no air attacks on London. The four blood depots had time to perfect arrangements for bleeding donors on a large scale, for ordering and improving equipment, for distributing equipment to major casualty centres and for educating staff in transfusion techniques. Donors were recruited in a variety of ways. The depots advertised their donor sessions in libraries, shops, post offices, on street hoardings and by means of vans equipped with loud-hailers (Fig. 2.5). Representatives of voluntary organizations, including the St John's Ambulance Brigade, Guides, Scouts, Red Cross and Toc H provided refreshment and helped to care for the donors (Fig. 2.6). Blood was grouped at the donor sessions using a simple slide test and with anti-sera provided, at first by Burroughs Wellcome and later by the depots themselves (Fig. 2.7).

Very little blood was being transfused and each depot was able to bleed donors in excess of local needs in order to produce plasma (Table 2.3). The first occasion on which blood was transfused in considerable quantity was between 20 May and 4 June 1940 when about 340,000 troops were evacuated from the Dunkirk beaches. The South Coast ports were outside the orbit of the London Blood Storage Depots and blood for those casualties in greatest need had to be sent from Maidstone. The other three depots supplied blood and plasma for many more wounded men who were transferred, in convoys, to the London hospitals (MRC Archives, PRO, FD/1/5892).

Dr A. N. Drury, now in charge of the London depots, realized that the situation regarding provision of blood out-

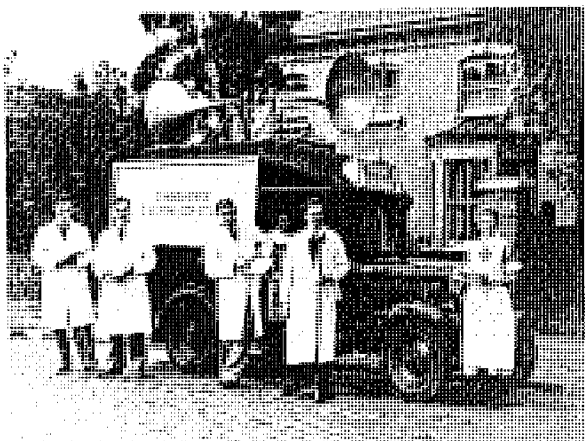


Fig. 2.5 'The Enrollment Squad'. South London Depot, c 1940 (courtesy of B. Cant).



Fig. 2.6 A Girl Guide indicating the way to a donor session. The venue is protected with sand bags (courtesy of B. Cant).

side London was most unsatisfactory and in June 1940, he and Sir Philip Panton, Consultant Advisor in Pathology to the MoH, drew up a scheme for establishing a regional transfusion service. They decided to place depots, similar to those in London, close to either teaching hospitals or large district hospitals. In addition, there would be two small sub-units to support the depots at Maidstone and Sutton. Dr T. A.



Fig. 2.7 The grouping test at a donor session (courtesy of B. Cant).

Table 2-3 Statistics from the four London depots, June 1940

Donor panels	No. of donors	Output bottles/week	Normal civilian demands/week
NE depot	12,500	400	100
SE depot	33,000	600	150
SW depot	38,000	600	150
NW depot	30,000	600	100
Totals	113,500	2200	500

Excess donations over civilian requirements; more than 1500 bottles.

Boon was appointed to direct a depot in Newcastle, Dr W. S. Stanbury in Leeds, Dr P. Kidd in Nottingham, Dr G. A. Harrison in Cambridge, Dr W. Carr in Birmingham, Dr A. G. Sanders in Oxford, Dr R. J. Drummond in Cardiff, Dr J. F. Wilkinson in Manchester and Professor T. B. Davie in Liverpool. Somewhat later a depot was established in Belfast with Professor J. H. Biggart as Director.

Starting from September 1940, London was bombed uninterruptedly for three months and, together with most of the large provincial cities, intermittently until 1942. During this period the transfusion service rapidly expanded, in order both to meet the needs of injured civilians and to provide plasma for the armed forces. Mobile transfusion teams were established in association with the Luton and Nottingham depots to support the Royal Air Force and the Army Depot extended its area of activity to include the whole of South West England.

Regular meetings were held between the directors, with Dr L. W. Proger as Chairman, representing the MoH. Vigorous and often acrimonious debates took place at these meetings and were faithfully recorded in the minutes (Maycock archives, PRO, BN/13/30). There were complaints of: inadequate funding, problems in transporting supplies particularly during air raids, poor recruitment due to inadequate publicity (the paper shortage made advertising donor sessions very difficult), and of donor sessions disrupted by bombing attacks. Reference was made to some independent blood-supply services like that of Captain Cooper in Birmingham and Mr Holland in Newcastle, which lacked professional supervision. The directors were anxious to be assured that they themselves carried no responsibility for misadventures arising within areas over which they had no jurisdiction. The MoH was reluctant to close down any of the independent services, knowing full well that the regional centres were not yet able to meet demands made on them. It was suggested instead that all blood depots outside the centrally organized Blood Transfusion Service should submit to inspection by a competent pathologist who would enforce standards governing blood grouping and the sterilization of equipment.

When bombing ceased, in late 1942, the general public no longer perceived the need for donating blood. However,

by this time doctors had started to appreciate the efficacy of blood transfusion in treating a wide variety of conditions and apart from this, the army's requirement for plasma was increasing. In order to recruit more donors, on 30 March 1943 Lt General A. Hood gave a talk on the BBC Home Service entitled *The Army Medical Services in Action* (WI, CMA, GC/107/1). He referred to blood transfusion as the greatest life-saving measure ever provided for an army and exhorted the public to continue donating regularly. He also mentioned that the enemy was envious of British dried plasma; captured German and Italian medical equipment contained only bottles of the synthetic colloid, polyvinylpyrrolidone, known commercially as Periston.

Later in 1943, the MoH published a booklet designed to encourage blood donation. It included items describing the nature of blood and blood groups and gave details of how the Transfusion Service was organized. There were stirring stories with titles like: *Ten that were snatched from death* and *From donor to Sicilian Beaches*, the latter including the homely detail that units of plasma were carried ashore protected by Bath Oliver biscuit tins.

PLANNING A POST-WAR TRANSFUSION SERVICE

By mid-1943, when it became clear that the allies would eventually win the war, the country's mood was becoming more optimistic and thoughts turned towards organizing post-war services. On 3 June, Drury, Professor Francis Fraser (CMO) and the four London directors met at the MoH to discuss the future provision of a transfusion service. Based on the personal experiences of the London depot directors, a memorandum was produced emphasizing that although the depots were set up to meet the needs of air-raid casualties, the bulk of their work had been in connection with the civilian sick (WI, CMA, GC/107/3 June 1943). The regional directors had told the same story. In short, blood transfusion had proved its worth in civilian medical care. Everybody present at the meeting realized that it would be impossible to revert to the pre-war hospital-based donor service as the volume of work would be too great for individual hospitals to accommodate. Drury reinforced this view by pointing out that the London Red Cross Blood Transfusion Service had met only 3000 calls for donors in 1938, whereas by 1943 the London depots were issuing more than 2000 bottles of blood per week.⁴ Also, he pointed out that although after the war the MRC could no longer be expected to concern itself with routine supply and organization, it had research interests in blood coagulation, plasma protein fractionation and blood-group serology. His plans for the future MRC

⁴ He had been incorrectly informed: there were about 6000 donations through the London service in 1938.

transfusion-related research units were outlined and accepted at this same meeting.

The rational solution seemed to be a nationwide transfusion service controlled centrally by the MoH with, as its major concerns; the supply of blood to hospitals, education of medical and technical staff and research into transfusion-related problems. In the final analysis the justification for forming a centrally controlled National Blood Transfusion Service was based on the fact that it was a scientific service offering potentially dangerous products responsible for a number of deaths from causes that were not fully understood. Everyone agreed that blood donors should continue to be voluntary and unpaid but that some charges might have to be made to hospitals in order to cover the costs of processing.⁵

Discussions continued throughout the next 18 months and difficult problems were thrashed out. For example, it was agreed that many of the donor panels should continue to be organized by the Red Cross and other charities, the siting and staffing of depots were defined, the provision of grouping sera to depots and hospitals was organized and the decision made to fund depots through local health authorities.

In a letter dated 11 May 1945, the Treasury accepted the principle expressed in the Health Service Bill 1945, that the MoH should take power to provide a National Blood Transfusion Service. The Service would continue to be organized on a regional basis, with 12 centres situated at Newcastle, Leeds, Sheffield (transferred from Nottingham), Cambridge, Oxford (or Southampton), Bristol, Cardiff, Birmingham, Liverpool and Manchester; the remaining centres in Luton and Sutton would serve Greater London and the South East.

A further memorandum was published defining the responsibilities of the individual transfusion centres (Table 2.4) (WI, CMA. GC/107/3. February, 1946).

The first mention of the National Blood Transfusion Service to the Red Cross was made by Dr W. d'A. Maycock during a meeting of the Voluntary Blood Donors Association on 3 July 1946. Their representatives commented first, that the Red Cross had a 1000-donor panel that wished to remain independent of a centrally organized national transfusion service; second that although they were not exactly hostile to blood banks, the latter were unpopular with members as blood banking reduced personal interest. They made a strong bid to revert to the pre-war system of providing donors, claiming that dried plasma could be used in emergencies and immediate transfusion provided by donors attending

⁵ Drury estimated that it cost 7s. 6 d. to process a bottle of blood in the London depots.

Table 2.4 Responsibilities of a Regional Blood Transfusion Centre

- 1 The enrollment and call-up of donors, including the co-ordination of local voluntary donor organizations
- 2 Grouping of new donors and making haemoglobin estimations on all donors on each occasion before taking blood; grouping and serological testing of blood drawn for storage and for immediate use
- 3 Organization of mobile bleeding teams
- 4 Maintenance and supervision of hospital blood stores
- 5 Distribution of blood products with pyrogen-free distilled water for reconstitution of the dried product
- 6 Distribution and maintenance of sterile standard transfusion apparatus
- 7 Rh typing and provision of Rh negative blood
- 8 Preparation of concentrated red-cell suspensions
- 9 Separation of sterile plasma for the processing laboratory
- 10 Assistance with investigation of transfusion reactions and consultations in difficult or atypical cases
- 11 Research into blood transfusion problems
- 12 Post-graduate instruction and dissemination of specialized knowledge of blood-transfusion therapy
- 13 Giving of transfusions. Hospital staff to give transfusions; arrangements to be made with hospitals in vicinity of Blood Transfusion Centres for the centre staff to give sufficient transfusions, within the hospital, to provide instruction and interest

hospitals. Ronald Smith, member of Parliament for South East London, was asked to plead the Red Cross cause with the MoH. He made heavy weather of the fact that a significant proportion of banked blood was not transfused, a matter of some annoyance to the donors. The Minister argued against any system involving 'walk-in' donors by pointing out that:

- new scientific developments had largely supplemented and often replaced the pioneer work of the Red Cross Blood Transfusion Service;
- stores of blood must be maintained for immediate use;
- the plasma from time-expired blood could be used to make products of therapeutic value;
- the increased use of blood during the war as a result of its ready availability meant that hospitals simply did not have enough staff to bleed the large number of donors which were needed and so preferred to use stored blood.

The Red Cross proposals were not followed up and the final transfer of responsibility for transfusion services from the MRC and the Emergency Medical Service to the Ministry of Health took place on 26 September 1946.

Chapter 3: The National Blood Transfusion Service (NBTS), 1946-1988

Once the NBTS, the name adopted by the Ministry of Health (MoH) in 1946, had been established, the Regional Blood Transfusion Officers (RBTOs) in charge of the ten Regional Transfusion Centres (RTCs) and the two London Blood Supply Depots, continued to meet regularly under the chairmanship of Dr Bill Maycock. This Committee was informal only; it was not recognized by statute and its purpose was to keep Dr Maycock, in his capacity as the Consultant Adviser in Blood Transfusion, informed on matters relating to blood-transfusion practice.

The minutes of these meetings cover a wide variety of topics, some of which would now be considered inappropriate for medical directors, e.g. the style of uniforms for drivers and donor attendants, the presentation of 'chits' for beer by service donors to NAAFI canteens where no financial provision had been made for their redemption and whether donors should be offered milk as an alternative to tea and coffee! Other topics included medical and scientific policies for the performance of the work of the RTCs. The reasons for this diversity of topics was because the RBTOs, at this time, were responsible for the entire operations of the RTC. The only other group of staff who had their duties defined in 1946 were the Donor Panel Liaison Officers (later known as Regional Donor Organizers [RDOs]). They held regular meetings until 1993. Initially these were chaired by Dr Maycock, but after 1978 the RDOs elected their own chairman.

TRANSFER OF MANAGEMENT TO REGIONAL HOSPITAL BOARDS (RHBS)

Between 1946 and 1948 the RBTOs were concerned with the implementation of the National Health Service Act. As a consequence of this Act, the MoH devolved the management of RTCs to Regional Hospital Boards (RHBs). Dr Maycock expressed the hope that, after 5 July 1948, management by RHBs would not be accompanied by a loss of uniformity in general policies relating to donors, technical procedures and apparatus.¹ It was agreed by RBTOs that the Service should retain uniform policy in such matters, although it seemed inevitable that regional differences in administrative and medical policy would occur. Indeed, differences had always existed.

Minutes of meetings of Regional Transfusion Directors, ¹28/6/48, ²26/10/49, ³26/3/52.

In 1949, RBTOs decided to change their titles to Directors of Regional Blood Transfusion Services (RTDs). At the same meeting it was suggested that the London Blood Supply Depots became RTCs; this was rejected because of the tradition and reputation they had built up over many years.² They were not renamed as RTCs until 1952 when the North London Depot became responsible for the service to the national regions 5 and 6 and South London for regions 7 and 8.³ (The country was divided into regions at the beginning of the Second World War; the numbers ran clockwise from Newcastle through to Lancashire and Westmorland.)

For a number of years the number and location of the RTCs remained the same as in 1946, but in 1955, building of the Brentwood RTC commenced. Initially, it was proposed that this became a sub-centre of the North London RTC, which was now located at Edgware. However, it was decided to confer RTC status on the Brentwood Centre (region 6) and its first Director, Dr John Jenkins, was appointed in 1955. In the North West, the Liverpool RTC supplied blood and blood products to the hospitals in North Lancashire through a depot located in the Royal Lancaster Infirmary. In 1964, two wards in the Lancaster Moor Psychiatric Hospital were converted to form the Lancaster Blood Transfusion Centre. This was managed as part of the NW RHB Transfusion Service by the Manchester RTC. A second new RTC was established at Southampton to service the Wessex Region which had been previously part of the remit of the South London Centre.

By 1970, there were 14 RTCs in England and Wales. Thirteen regions had a Transfusion Centre, the exception being SW and SE Thames which were serviced by one RTC; the former Depot in Sutton was rehoused in newly built premises in the grounds of St George's Hospital, Tooting in 1970. There was a second centre based at Hither Green Hospital, Lewisham. This was not given the status of an RTC but mobile teams were based there and grouping and processing of donations took place followed by a limited distribution service for blood products. The RTC in Cardiff was managed by the Welsh Office.

Guidance was given to RHBs in 1948 on the functions of the NBTS (RHB 48/16) but little was stated about the problems which might arise from devolvement to regions or about the principles which RHBs should apply in their relationships with RTCs. Inevitably, organizational differences between RTCs quickly emerged. Some differences were attributable to specific regional needs and some to management. Attempts were made to establish a degree of uniformity, for instance the *Memorandum on the Selection, Medical*

Examination and Care of Donors and the booklet *Notes on Transfusion* were written by the RTDs and updated regularly.

By 1970 there were 14 quasi-independent regional centres and two central laboratories. All were attempting to provide a uniformly efficient service but without central co-ordination other than the RTD Committee which had no formal authority.

ATTEMPT TO RECREATE A NATIONAL SERVICE

RTDs considered that whilst the Department of Health and Social Security (DHSS), which had succeeded the MoH, were implementing the reorganization of the NHS, some thought might be given to returning the NBTS to the centrally organized service it had been until 1948.

A discussion paper was prepared by one RTD following consultation with his colleagues. The general arguments put forward to justify a centrally managed service were:

- the NBTS was a service of considerable complexity which had grown unevenly since 1948 due to the differing responses of RHBs;
- there was no uniformity in financial management;
- although the various categories of staff in RTCs were, in general, carrying out the same duties, grading and treatment in such matters as allowances were not uniform;
- an RHB could, within its rights, make a decision concerning the administration and staffing of an RTC that could fundamentally change the character of that RTC in relation to other RTCs;
- some policy decisions, e.g. in relation to the Central Laboratories, were determined by centrally managed services. RHBs or regional committees were under no obligation to carry out such national policies.⁴

A Working Party was established to prepare a document for the Chief Medical Officer's (CMO's) consideration.

In October 1972,⁵ the DHSS responded to the RTDs' request for a centrally managed service. It was explained that the Government's White Paper on the reorganization of the NHS left the responsibility for the provision of a blood transfusion service with the newly created Regional Health Authorities (RHAs). The DHSS recognized, however, that the NBTS was unlike any other component of the NHS and that a degree of central coordination was desirable. It was the intention of the DHSS to monitor the plans of RHAs closely and, in this way, ensure that important requirements of the NBTS were not neglected.

The RTD meeting would continue to act as the co-ordinating body for the NBTS. It was stressed by the DHSS that this could not be a statutory advisory committee, but that advice given by the Committee would be considered

and appropriate weight given to it.

Despite the assurances concerning the likely effectiveness of continuing regional management following reorganization, RTDs remained sceptical. The proposals sent to CMO were revised and presented to the Standing Medical Advisory Committee of the DHSS (SMAC). At their meeting on 9 January 1973, the SMAC recommended that the DHSS set-up a small committee to look into the NBTS proposals. The DHSS responded and constituted an *ad hoc* committee under the chairmanship of a Deputy Chief Medical Officer to consider the future of the NBTS. The committee comprised representatives of the Medical Research Council, the Royal Colleges of Pathologists and Surgeons and senior representatives of the medical profession involved with blood transfusion practice. Its terms of reference were "to consider whether any change should be made in the present organization of the blood transfusion services in England and Wales and to make recommendations".

In its report of November 1973, the committee acknowledged the force of many of the reasons for advocating centralization of the administration as the best means of eradicating the present shortcomings of the NBTS. But it was not convinced that they outweighed the administrative and managerial arguments on which the basic principles of the NHS reorganization had been developed, viz. while the DHSS is responsible for the formulation of policy and the issue of guidance, the responsibility for administration and for providing services was that of RHAs.

It was recognized, however, that the NBTS required a degree of central coordination in its operation. It was proposed that a Central Committee for the NBTS should be created with the following terms of reference. "to keep under

Table 3-1 Proposed membership of the Central Committee of the NBTS, November 1973

A senior DHSS Medical Officer, Chairman
The Consultant Adviser in blood transfusion
A senior DHSS administrative officer
Two regional transfusion directors*
Two regional medical officers*
A regional scientific officer*
A representative of the MRC
An anaesthetist
A general practitioner
A nursing representative
An obstetrician
A pathologist
A physician
A surgeon
A representative of the Welsh Office

*As far as possible the two RTDs, the two regional medical officers and the regional scientific officer should come from different regions.

Minutes of meetings of Regional Transfusion Directors,
⁴16/12/70, ⁵25/10/72.

review the operation of the National Blood Transfusion Service, including the Blood Products Laboratory and Blood Group Reference Laboratory, in England and Wales and to advise the Department of Health and Social Security and the Welsh Office on the development of the Service." The recommendations for the membership of the Committee are given in Table 3.1.

It was pointed out that the DHSS had, independently of NHS reorganization, strengthened its administrative staff by appointing an officer of Principal Grade to deal exclusively with blood transfusion. Also, it was proposed that an additional medical officer at a senior level would be appointed to undertake blood transfusion duties. The periodic meetings of the RTD Committee should continue but there would be no formal arrangements for regulating the relationship between the RTDs and the Central Committee.

In the 1974 reorganization the names of most RHAs were changed to indicate the regions they served rather than the principal city in the region (Table 3.2). Also, the boundaries of some RHAs were changed from those of the RHBs they had replaced. This caused concern to RTDs, since boundary changes for blood collection could cause logistical difficulties. The size of some RTCs would have to increase and whilst others would decrease and donor panels would become unbalanced. The Central Committee, at its first meeting on 19 June 1975 recommended that these arguments should be settled locally. In the event, RTCs generally kept to their pre-1974 boundaries.

Because of its size and general terms of reference the Central Committee was unable to provide the advice on the NBTS that the DHSS needed. Some RTDs commented that it was not providing the central direction that they had hoped for, and without executive authority it was difficult for it to manage resources nationally. Other RTDs considered that the Central Committee had not been provided with sufficient data. The majority view was, however, that the arguments put forward for a centrally managed service to the DHSS *ad hoc* Committee still remained valid.⁶

The Central Committee held its last meeting in 1978 and was disbanded in 1980.

There was consternation among the RTDs when they learnt that the Scottish National Blood Transfusion Service (SNBTS) had been asked to give evidence to the Royal Commission on the NHS.⁷

Dr Maycock explained that the reason for this was that SNBTS was constituted as a national service, whereas the NBTS was not. Two members of the RTD Committee prepared a paper advocating centralized management for the NBTS, but it could not be entered as evidence to the Royal Commission.

Table 3.2 Name of Regional Health Authorities in 1974 and the location of the Regional Transfusion Centre serving them

Region	Name of RHA	Location of RTC
1	Northern	Newcastle
2	Yorkshire	Leeds
3	Trent	Sheffield
4	East Anglia	Cambridge
5	NW Thames	Edgware
6	NE Thames	Brentwood
7/8	SW Thames/SE Thames	Tooting
9	Wessex	Southampton
10	Oxford	Oxford
11	S Western	Bristol
12	W Midlands	Birmingham
13	Mersey	Liverpool
14	N Western	Manchester

FORMATION OF DIVISIONS

Dr Geoffrey Tovey, who succeeded Sir William Maycock as Consultant Adviser in Blood Transfusion in 1978 considered that there should be regional meetings of RTC medical staff which should involve all consultant medical staff. In this way the latter could be involved with decisions taken at RTD meetings. He proposed three divisions comprising the RTCs in the following regions:

- Eastern — NW Thames, NE Thames, SE/SW Thames, E. Anglia;
- Western — Oxford, S Western, Wessex, West Midlands, Wales;
- Northern — Mersey, Northern, N Western, Trent, Yorkshire.

The Divisional Chairmen were elected from the RTDs in the Divisions. It was envisaged that the agenda for the RTD meeting would be prepared one month before the meeting and that Divisions would meet during that month to discuss items on the agenda. They were encouraged to comment and put forward other matters for discussion at RTD meetings.

The Divisional meetings were welcomed by the consultant medical staff of RTCs who had been largely excluded from policy decisions in the past. Indeed, in some RTCs where there was poor internal communication the senior staff knew little of the content of the discussions at RTD meetings.

RDOs have met as a group since 1946. They were also represented on the DHSS Central Publicity Sub-committee (three RDOs and three RTDs) which allocated central funding for donor publicity. During the early 1980s, in the newly formed democracy within RTCs, other groups of managerial staff met two or three times per year, e.g. nurses, managers/

Minutes of meeting of Regional Transfusion Directors ⁶8/12/76, ⁷2/3/77.

administrators and head laboratory scientists. Such meetings had been discouraged in previous years.

The RTD Committee also formed a number of Working Groups to examine certain aspects of the work of the Service. A number of these embraced both the NBTS and the SNBTS. Attempts were made through these Working Parties to introduce some degree of standardization in the operations of the Service. Examples of notable successes on a UK basis were the uniformity in the design of machine-readable labels for blood packs, the guidance on apheresis and, in England and Wales, a uniform pack design for plasma destined for fractionation (Chapter 8).

ADVISORY COMMITTEE ON THE NBTS

Following the failure of the Central Committee to coordinate the work of the NBTS Dr Tovey proposed to the DHSS that it should be replaced by an Advisory Committee on the NBTS. The DHSS accepted this proposal and insisted that the membership should be restricted to those persons most closely concerned with the NBTS and RHAs (Table 3.3).⁸

The terms of reference of the Advisory Committee were: 'to advise the DHSS and the Welsh Office on the co-ordination of:

- i) the development and work of Regional Transfusion Centres and the Central Laboratories in England and Wales; and
- ii) as necessary, the English and Welsh Blood Transfusion Service with that of Scotland".

The Advisory Committee on the NBTS met on 14 occasions between 1 December 1980 and 8 February 1988. A number of major decisions were taken which influenced the work of the NBTS. These included the following:

- recommendations for record keeping and stock control of blood supplies at hospitals and RTCs;
- the volume of plasma required by the new BPL to provide self-sufficiency in fractionated plasma products (Chapter 8);
- the establishment of a pro-rata supply of fractionated plasma products to RTCs, determined according to the quantity of plasma sent to BPL. Certain special allocations were made to hospitals which had unusually high demands because of nationally-based activities, e.g. factor VIII for the Lord Mayor Treloar School and albumin for the Postgraduate Medical School and Northwick Park Hospital;
- a system for introducing handling charges for blood supplies to private hospitals;
- trials on inter- and intra-regional charging;

⁸ Minutes of meeting of Regional Transfusion Directors 5/6/80.

- evaluation of nurses performing blood collection.

It is worthwhile commenting further on some of the above actions.

Record keeping and stock control

An investigation by the DHSS Central Management Services revealed that, in general, record keeping and stock control were satisfactory in RTCs. Deficiencies were found in many hospitals. Guidance was issued under the aegis of the Advisory Committee.

Pro-rata supply of blood products

It will be noted later that there was a considerable variation between RTCs in the volume of plasma supplied to BPL pro-rata to their regional populations (Chapter 11). In an attempt to correct this situation, RTCs received only the quantity of products fractionated from their plasma. Whilst this decision influenced underperforming RTCs to improve plasma collection, surprisingly it did not have a major effect on supply to BPL.

Introduction of handling charges for blood supplies to private hospitals

Since 1948 the NBTS had supplied blood to private hospitals free of charge. This policy was questioned in Parliament in the late 1970s and early 1980s. The DHSS considered the levy of a handling charge, although charging for the donation itself was out of the question. RTDs were concerned that with the introduction of such charges, private institutions might recruit their own donors and carry out blood collection. There was concern, also, that certain groups of people might try to influence blood donation because of political motiva-

Table 3.3 Membership of the Advisory Committee on the NBTS, December 1980*

Deputy Chief Medical Officer, DHSS, Chairman
Consultant Advisor in Blood Transfusion
Chairmen of the three divisions of the NBTS
A regional administrator
A regional medical officer
A regional treasurer

(later a regional nurse became a member)

*Observers: The National Director, SNBTS
Representatives of the Scottish Home and Health Department; the Welsh Office and the Northern Ireland Office.

tion. For this reason some RTDs considered that it might be appropriate to introduce charges to all hospitals, anticipating in 1982 changes which were to take place in 1991.⁹ Handling charges to the private sector were introduced in 1984 and despite active correspondence with a minority of donors there were no undesirable repercussions.

Inter- and intra-regional charging

The introduction of handling charges and future proposals for cross-charging raised the question of the cost of collection and processing blood. Previously there had been no need to break down the RTC financial allocation. A small working party chaired by Mr Tom Layzell, the Wessex Regional Treasurer and member of the Advisory Committee, devised a system for apportioning costs. Trials were arranged between the North Western and Northern Regions and BPL. Intra-regional charging was piloted in Wessex, Northern and NE Thames regions.

Nurses performing blood collection

During 1984, NE Thames RTC had set up a training scheme for registered nurses to enable them to undertake blood collection on sessions without a doctor being present. There was disquiet among the majority of RTDs who were afraid of medico-legal repercussions. The Advisory Committee appointed assessors who visited several sessions conducted by nurses and compared them with those where medical officers were in charge. Their report on the nurse-managed sessions was favourable. The nurses had been well trained and they were able to consult medical officers by telephone during sessional times. Nurses now manage blood-collection sessions at several RTCs.

FURTHER ATTEMPT TO OBTAIN A CENTRALLY MANAGED SERVICE

Discussion began again, in 1984, with respect to the formation of a centrally managed NBTS. The Advisory Committee had been successful in a number of areas in achieving central co-ordination but there was still a variability in operations at RTCs. Moreover, the central laboratories were now managed by a Special Health Authority. The implementation of policies with respect to the transmission of the human immunodeficiency virus had demonstrated the need for RTCs to conform to a national policy.

Dr Harold Gunson, who had succeeded Dr Geoffrey Tovey as Consultant Adviser in 1981, was asked to prepare

a paper for consideration by Divisions and RTDs on the advantages of a centrally financed and managed service.

The Advisory Committee on the NBTS agreed, in 1986, that a team from the DHSS Central Management Services would visit RTCs, BPL, teaching and general hospitals to carry out an investigation of the organization of the NBTS. Their report was considered by a Steering Group appointed by the Advisory Committee. The conclusions of this Group were received by the DHSS early in 1988. They contained criticism of several aspects of the organization of RTCs, in particular, the lack of management information. The following recommendations were made for future management:

- to do nothing;
- to create a Special Health Authority;
- to retain management by RHAs but with formal co-ordination of the work of RTCs.

After wide consultation, DHSS accepted the third option. and the National Directorate was formed of which Dr Gunson was appointed National Director in July 1988.

STAFF IN THE NBTS

In this account of the history of the NBTS there are repeated references to RTDs and their determination of policy. One must not forget that the RTD had a changing role over the years. It has been pointed out that in the early years of the Service the RTD was in charge of all the activities of the RTC. Initially, there were relatively few consultants in the Service, other than the RTDs. Following the Platt report in 1963, more consultant posts were created. In 1978 Dr Tovey, recognizing the contribution made by these consultants, involved them directly in policy making.

RDOs have had an important role in the work of RTCs since their inception. The recruitment of blood donors had been the cornerstone of RTC activity. Simply, without blood donations the Service could not function. The status of nursing staff has increased over the years and the gradings of the senior nursing officers has, rightly, reflected the responsibility they carry for the training and supervision of up to 100 donor attendants in some of the larger centres, their involvement with plasmapheresis and organization of blood collection.

The most significant change in work patterns during the 50 years of the NBTS has been experienced by the scientific and technical staff. In 1948, blood transfusion therapy was restricted to the transfusion of whole blood, red-cell concentrates and plasma. The only microbiological test performed on donations was that for syphilis. The number of such tests has increased to four and, with the advent of plastic packs, component therapy became feasible. Moreover, in order for RTCs to obtain Manufacturer's "Specials" Licences, quality assurance has had to be formalized.

⁹ Minutes of meeting of Regional Transfusion Directors 18/2/82.

Finally, the general managers employed to implement the Griffiths report (1983) have introduced sophisticated management techniques into RTCs. These would have brought dismay to the RTC administrators of 50 years ago, whose every action had to be reported and approved by the RTD at the daily visit. The RTD was no longer the only person who made decisions at the RTC. By 1988, in the majority of RTCs there was a senior management team which discussed important RTC activities.

RESPONSIBILITIES OF RTCs

The responsibilities allocated to RTCs in 1946 were stated in Table 2.4. These were redefined in 1972 in the submission of the report to the Standing Medical Advisory Committee. At this time the original responsibilities were updated to include the testing of blood donations for infectious markers, plasmapheresis, the preparation of components, and liaison with BPL and BGRL. Also included was the involvement in national programmes, e.g. the prophylaxis of Rh haemolytic disease and the production of national standards.

Dr Gunson re-defined the responsibilities of RTCs in 1986 by dividing their activities into 'core' and 'specialist'

Table 3.4 Responsibilities of RTCs (1986)

Core activities

- Maintenance of volunteer, unpaid, donor panels
- Blood collection and blood grouping
- Testing blood donations for infectious markers
- Processing of donations into blood products:
 - platelet concentrates
 - plasma for clinical use
 - cryoprecipitate
- Distribution of products to hospitals
- Supply of plasma for fractionation to BPL including normal plasma and special antibody containing plasma
- Supply of antisera to IBGRL
- Selection of donors for the National and International panels of donors of rare types

Specialist activities

- Antenatal testing
- Reference work, both clinical and serological for transfusion problems
- Tasks undertaken on behalf of the NBTS:
 - pyrogen testing
 - frozen blood banking
 - provision of antisera prepared in animals
- Provision of a tissue-typing service
- Provision of bone marrow and HLA-typed donors
- Provision of CMV-antibody negative donors
- Training of medical, scientific and nursing personnel
- Research and development

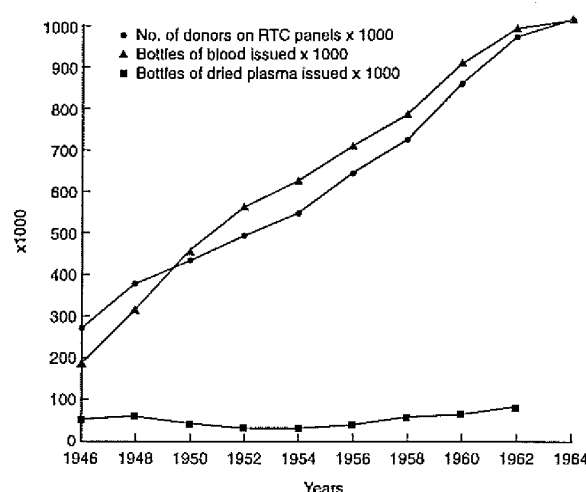


Fig. 3.1 The increase in the donor panel size from 1946 to 1963 when the 1 million level was reached and 1 million donations in a year were collected (—●— no. donors on RTC panels $\times 1000$, —▲— bottles of blood issued $\times 1000$, —■— bottles of dried plasma issued $\times 1000$).

(Table 3.4). Core activities were undertaken at all RTCs. Specialist activities were undertaken to a different extent in RTCs, often dependent upon the research interest of the Director or other members of the staff and the demands made by regional hospitals.

A number of the core activities have been described in later chapters. It is pertinent, here, to review the collection of blood donations. When the paid donors of the 1920s and 1930s were abolished, the NBTS traditionally recruited voluntary, unpaid donors. It can be seen from Fig. 3.1 that in 1946, donor panels numbered approximately 270,000 and blood collection was less than 200,000. A number of milestones have been achieved in the subsequent 35 years. Donor panels and blood collection exceeded 1 million in 1963. This prompted a message from HM the Queen (Fig. 3.2). Donor panels reached 1.5 million and blood donations exceeded 1.5 million in 1972.

The decade 1975 to 1985 was an important one for the NBTS. From Fig. 3.3 it will be seen that in 1975, 90% of blood issues comprised whole blood; in successive years the number of red-cell concentrates increased until it was 50% of blood issues in 1984. The gap between blood collected and issued narrowed after 1975. There was a 10% increase in use of red cells and whole blood between 1980 and 1985. Acid citrate dextrose (ACD) was superseded by citrate phosphate dextrose (CPD) which allowed 28-day storage of red cells. In 1983 the use of saline, adenine, glucose with mannitol (SAG-M) solution was used as an additive to concentrated red cells with CPD anticoagulant in the primary pack. This improved their flow properties and also enabled storage for 35 days (Högman *et al.*, 1983).

The 1980s was the decade in which component therapy was introduced, leading to the preparation of products in RTCs, notably platelets. National statistics for the issue of platelets were not collected until 1982. However, from the time platelet production started in the mid-1970s many RTCs experienced increases in production of several hundred per cent in the next decade. Steps were also taken to make the platelet concentrates more effective and less likely to cause febrile reactions by reducing contamination with leucocytes. Platelets from donors who had been HLA typed were requested in increasing numbers to support multi-transfused patients, those on chemotherapy or with leukaemia.

Dr Ben Bradley, Director of UK Transplant, based at the Bristol RTC, was appointed in 1980. He was anxious to provide a register of bone-marrow donors. By 1983, a panel had been established and transplant centres requiring a donor would confirm compatibility between patient and potential donor. The development of the bone-marrow donor panel was slow. RTDs were asked to cooperate in 1985 and by April 1986, the panel consisted of 10,000 donors, the majority having been contributed by the SW region. There had been 165 searches during the year and requests were increasing. The roles of UK Transplant and the independent Anthony Nolan Panel were not clear. RTDs agreed to form a steering

group for bone-marrow transplantation. Bone-marrow donors were recruited at RTCs but there was a reluctance to transfuse tissue-typed platelet donors to this panel in case external pressure was placed upon such donors to donate bone marrow for which many had not volunteered.

In 1987 two businessmen offered to finance HLA and DR typing of potential bone marrow donors to increase numbers on the panel. Several RTCs contracted to perform such tests.¹⁰ The British bone-marrow donor registry was formed which was managed by the NBTS and to which access could only be gained by NBTS Consultant staff.

Teaching has been an important activity at RTCs. Much 'in service' training has been provided for unqualified staff who needed to learn skills for important work either in the laboratory or on blood-collection sessions. Senior registrars in haematology were trained at RTCs as part of the formal rotation and centres were involved in the examination for membership of the Royal College of Pathologists. In conjunction with polytechnics and the Institute for Medical Laboratory Science, training courses were organized for the medical laboratory scientific trainees.

It was proposed in 1981 that regular scientific meetings should be held annually in order that staff in RTCs might report on research and development work they were undertaking.¹¹ From this suggestion the British Blood Transfusion Society was founded.¹²

A specialist activity which deserves particular comment is research. A very large number of scientific publications

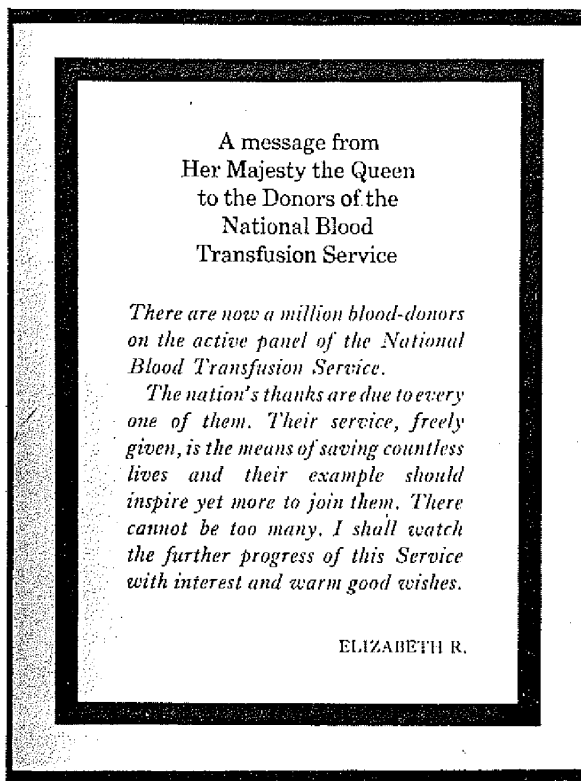


Fig. 3.2 The message from HM the Queen to blood donors, 1963.

Minutes of meeting of Regional Transfusion Directors,
¹⁰ 7/10/87, ¹¹ 19/05/81, ¹² 07/10/81.

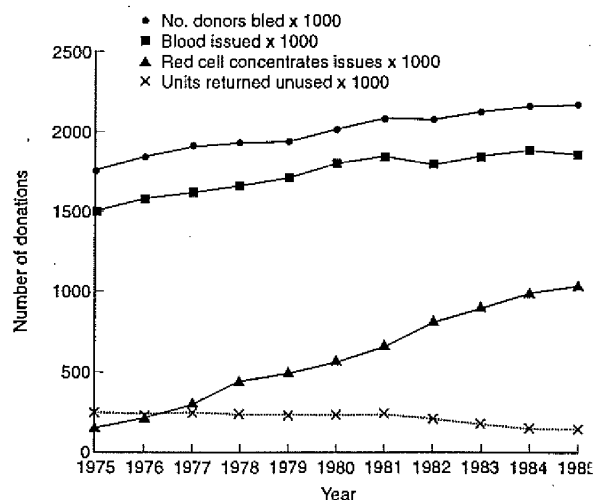


Fig. 3.3 The number of donors bled, red cells issued and time-expired blood returned 1975–1985 (—•— no. donors bled x 1000, —■— blood issued x 1000, —▲— red-cell concentrates issued x 1000, ---×--- units returned unused x 1000).

have emanated from RTCs. Whilst some fundamental research was performed, the majority of projects were developmental. During its existence, the NBTS has monitored activities such as the results of transfusing products, the testing of donations and methods of blood collection. The advent of AIDS caused a major change in the operations of the NBTS and there is no guarantee that another disruptive event will

not occur in the future; it is vitally important that research and development activities continue.

The MRC's Blood Transfusion Research Committee, which was formed in 1939, was disbanded in 1982. This severed the last formal link between the NBTS and the MRC, an organization which had played such a vital part in the early development of the NBTS.

Chapter 4: From the 'MRC Blood Transfusion Outfit' to blood components

THE MRC BLOOD TRANSFUSION KIT

In 1939 the London depot directors, in conjunction with the Medical Research Council (MRC) decided to standardize transfusion equipment (Vaughan, 1939). It was argued that, if all blood depots used similar equipment, bottles of blood distributed by any depot could be used with equal facility by hospital staff. The MRC standard transfusion kit included a modified milk bottle, slightly waisted and therefore easy to hold. The bottle was fitted with an aluminium screw cap which was lined with a rubber diaphragm and there was a metal band and a loop at the bottom of the bottle with which to hang it up. There were marks at 180 ml and 540 ml for measuring volumes of anticoagulant and blood, respectively (Fig. 4-1).

The taking and giving sets were made of rubber tubing fitted with metal needles. Filters of either glass wool, glass beads or knitted cotton (a modified gas mantle) were incorporated into the giving set or the neck of the bottle (Fig. 4-1). The gas mantle filter, naturally without its customary impregnation with thorium nitrate and collodion, was particularly successful (Maizels, 1939) and was used until plastic administration sets were introduced. The whole assembly was sterilized and the needles sharpened after each use. The same equipment remained in use, with only minor modifications,

for almost three decades and the MRC bottle was adopted for use in other countries.

THE BLOOD TRANSFUSION RESEARCH COMMITTEE

Realizing that blood transfusion would open up a large scientific field for applied and basic research, the MRC formed the Blood Transfusion Research Committee in December 1939. Membership included the four London depot directors, scientists and representatives of the armed forces and of charitable organizations like the Red Cross and Toc H. The chairman, Professor Topley, was succeeded in May 1940 by Dr Alan Drury who, at the same time, assumed overall responsibility for the London Blood Supply Depots.

At the Committee's first meeting, everyone agreed that the most pressing problems were improving red-cell preservation and developing better techniques for processing plasma. Also, the Committee decided that clinical trials were essential in order to discover whether stored blood was inferior to that which was freshly donated. Professor Topley suggested that three young medical officers attached to the Sutton Depot, A.C. Dornhorst (later Professor), P. L. Mollison, (later Director, MRC Blood Transfusion Research

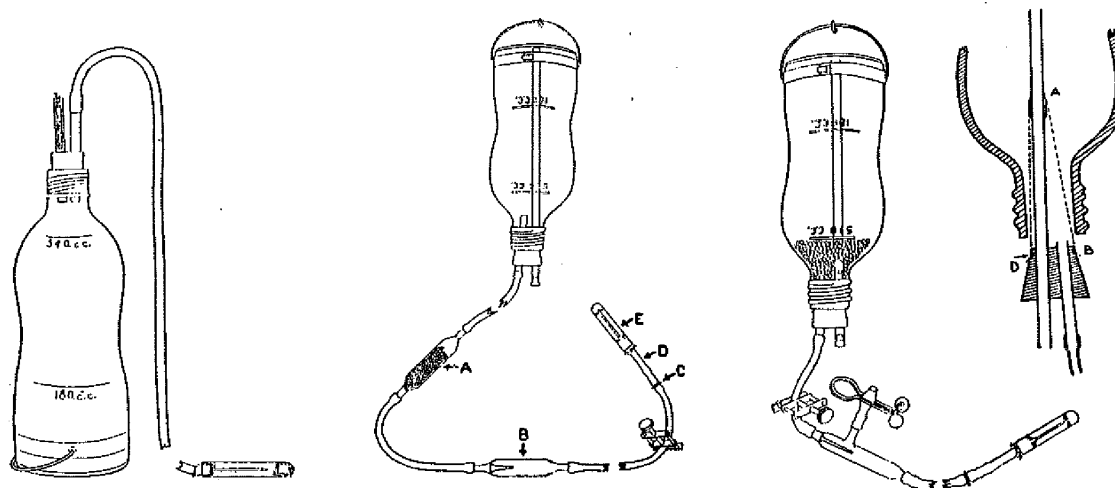


Fig. 4-1 Left: The MRC blood transfusion bottle. Centre: Inverted bottle with standard drip set and closed glass bead filter. Right: transfusion bottles with loose glass bead filter (left) and gas mantle filter (right) (From Vaughan, 1939).

Unit) and D.G. MacQuaide should undertake clinical trials on behalf of the Committee.

RED-CELL PRESERVATION

Work done at the Rockefeller Institute, New York, USA during the First World War had shown that red cells were less likely to haemolyse when stored in a sugar-citrate solution: the sugars were assumed to protect by a colloidal effect (Rous & Turner, 1916a). Rous and Turner performed all their transfusion experiments on rabbits, using cells stored in sucrose-citrate. Years later it was realized that sucrose does not cross the red-cell membrane and is relatively ineffective in preventing stored red cells from haemolysing (Mollison & Young, 1941). In retrospect, it seems likely that the Rous-Turner sucrose-citrate anticoagulant was effective only because its low pH preserved red-cell ATP.

Fortunately, Rous and Turner (1916b) were convinced of a species variation with respect to the protective effect of sugars in red-cell storage. The results of their *in vitro* studies persuaded them that, although sucrose was effective in preserving the red cells of rabbits, glucose was more effective for those of humans. Rous and Turner considered that a very large quantity of sugar was essential and recommended 500 ml glucose (5.4%) with 200 ml citrate (3.8%) to preserve 300 ml blood, diluting the plasma to such an extent that it was useless. A further problem, caramelization of glucose when the mixture was autoclaved, was avoided by sterilizing the citrate and glucose solutions separately. Nevertheless the Rous-Turner anticoagulant was an excellent red-cell preservative and was used to good effect in small blood banks on the Western Front (Robertson, 1918).

The Russians, who had started to bank cadaver blood as early as 1929, appear either to have ignored or overlooked the work of Rous and Turner. IHT, the Russian anticoagulant, contained sodium citrate, sodium and potassium chlorides and magnesium sulphate. Red cells stored for 2–3 weeks in IHT had a normal osmotic fragility and there was little *in vitro* haemolysis. There was, however, a high incidence of jaundice immediately after transfusing blood stored for more than a few days, although it had been shown to be compatible. By 1936 Duran Jorda, in Barcelona, was using a glucose-citrate anticoagulant (Jorda, 1939). Undoubtedly his reason for doing so related to improved *in vivo* red-cell viability, though neither he nor the Russians performed post-transfusion survival studies.

The London depot directors decided to use a simple citrate-saline solution because it was easy to make and to sterilize. It was, however, impossible to ignore the evidence that glucose improved red-cell preservation but the problems posed by the Rous-Turner anticoagulant proved difficult to solve. Maizels and Whittaker (1939) substituted dextrin for glucose in order to avoid the problem of over-dilution. Dextrin, being of higher molecular weight than glucose, passed more slowly

into cells and could be used in greater concentration. Before trials with dextrin were completed the problem was solved in America by Gwynn and Alsever (1939). They realized that stored red cells only haemolysed when glucose could no longer be detected in the storage medium and that much smaller quantities of glucose were needed for red-cell preservation than those used by Rous and Turner. At about the same time, work done in the UK showed that in order to prevent delayed clot formation the final citrate concentration should be 0.35%. In order to delay haemolysis the final concentration of glucose should be at least 0.1% and contrary to Jorda's view, oxygenation of stored blood was not important and that no benefit was derived from adding magnesium to the storage medium (Harrington & Miles, 1939).

In January 1940, the London depot directors agreed to use a glucose-citrate anticoagulant with a final concentration of 0.3% glucose as their standard blood preservative. Although it was shown that red cells stored for up to 3 weeks in glucose-citrate would survive in a recipient's circulation as long as freshly donated cells (Maizels & Paterson, 1940; Mollison & Young, 1940; Bushby *et al.*, 1940) the directors limited storage to 2 weeks. The Rous-Turner practice of sterilizing sugar and citrate separately was adopted to prevent caramelization of the glucose although the post-sterilization mixing of glucose and citrate solutions was occasionally responsible for bacterial contamination.

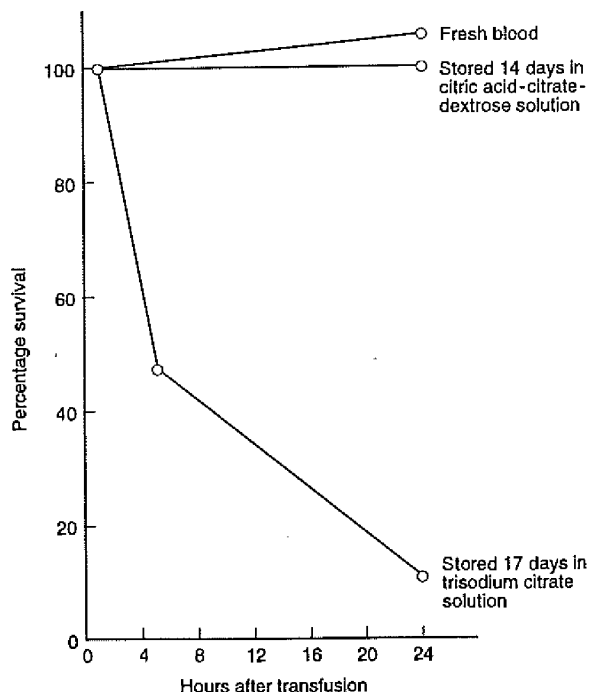


Fig. 4-2 Survival of fresh blood and of cells stored in citrate-acid-dextrose and in trisodium citrate. From *Blood Transfusion in Clinical Medicine*, 1st edn, 1951 (Data from Mollison & Young, 1941–2 and Loutit *et al.* 1943).

The long-held prejudice that *in vitro* tests were a guide to the value of stored blood was eventually dispelled. The red-cell sodium content, which increased on storage, was shown to revert to normal after transfusion (Maizels & Paterson, 1940) and osmotically fragile stored cells were shown to have a normal post-transfusion survival (Mollison & Young, 1941). Investigations designed to compare the relative merits of a variety of anticoagulants showed that, although the post-transfusion survival of cells stored in citrate and in glucose-citrate was virtually the same for the first 5 days after donation, thereafter the glucose-citrate medium conferred an enormous advantage (Mollison & Young, 1941–2) (Fig. 4.2).

Between 1942 and 1943, at the South London Blood Depot, studies on stored blood were carried further by Drs Loutit and Mollison with the assistance of a qualified scientist, Maureen Young (later Professor Young). Additionally, Miss Young supervised practical classes at Bedford College. During a class designed to investigate the properties of sugars, she noticed that glucose, heated in acid solution, did not caramelize. When her observation was applied to the glucose-citrate anticoagulant it paid off. If citric acid was substituted for some of the trisodium citrate, the pH fell from 8.5 to 5.5 and there was virtually no caramelization on autoclaving the mixture (Loutit *et al.* 1943). A further modification, substituting disodium citrate for the trisodium salt produced acid-citrate-dextrose (Loutit & Mollison, 1943) which remained the standard anticoagulant in worldwide use until the introduction of citrate-phosphate-dextrose in 1957.

THE DISCOVERY OF POLYTHENE AND ITS USE IN BLOOD TRANSFUSION

In July 1930 a research department of Imperial Chemical Industries (ICI) invested in a new programme of fundamental research. Experiments designed to study the effect of high pressure on certain reactions resulted in the conversion of gaseous ethylene into a solid white polymer (Allen, 1945). The electrical industry was quick to recognize the advantages of polythene. It was tough, light, flexible and waterproof; in every way superior to gutta-percha, the only insulating material then available.

Even before ICI had resolved its large-scale production problems the Telegraphic Construction and Maintenance Company had adapted their machinery to coat submarine cable with polythene. Also, the Post Office was interested in the product because it had outstanding properties when used to transmit high frequencies and could be used in television. ICI opened a full-scale manufacturing unit on the day that the Germans invaded Poland. The use of polythene in the UK was directed towards the war effort, in particular for radar. The Americans, wishing to use polythene for their own radar equipment, visited ICI in 1941 and were given full details of

the manufacturing process. Having rapidly appreciated the product's wider applications, they were soon using it to make intravenous cannulae.

There were no reports of polythene's clinical application in the UK until reference was made to a fine-bore plastic tube used to cannulate the umbilical vein of a neonate (Mollison, 1948). ICI identified the plastic as polythene and agreed to supply samples of 0.5 mm-bore tubing for experimental purposes. The tubing proved so successful that the Telegraphic Construction and Maintenance Company were persuaded to take over production on a commercial scale. It was, however, left to the Americans to exploit further the use of polythene in blood transfusion.

PLASTIC TRANSFUSION EQUIPMENT

Professor Cohn, working at Harvard University, needed a supply of sterile plasma for his fractionation process. With Cohn's requirements in mind, one of his surgeon colleagues, Professor Carl Walter, designed a complete set of plastic transfusion equipment. A plastic pack with an integral donor tube was used to receive the donation. Blood was transfused through a one-piece, polythene, giving set incorporating a drip chamber with a nylon filter. The whole assembly was designed to be disposable (Walter & Murphy, 1952).

Immediately, the advantages offered by plastic equipment were apparent. The bags, containing ACD, were light and took up less space than glass bottles both when empty and filled. More importantly, because the tubing was attached to the pack to give a closed system, the risk of bacterial contamination was less than with glass bottles and rubber taking sets. An additional advantage was the ease with which blood could be separated into its components by squeezing the bag after centrifugation.

The design was so successful that Walter, in conjunction with a local Boston firm, founded a company, Fenwal, to produce plastic transfusion equipment on a commercial scale. By the late 1950s most large hospitals in the USA and Canada were using plastic equipment, at least for some of their transfusion requirements.

In 1950, the British government, with a weather eye on Russia, had given instructions that any apparatus which might be used in war should be compatible with that used in the USA. Dr W. d'A. Maycock, Consultant Adviser in Blood Transfusion, had this interdiction in mind when he attended an International Transfusion Committee meeting in 1952. At the meeting, the advantages of plastic transfusion equipment were demonstrated. Maycock realized that, given the variety of equipment used throughout Europe, standardization would have to wait for universal introduction of the new technology. Britain's economy was too weak to contemplate either importing plastic transfusion equipment from the USA or manufacturing it locally (Maycock archives, Public Records Office [PRO], BN/13/20)

As the number and duration of blood transfusions increased it became apparent that rubber giving sets were associated with thrombophlebitis (Handfield-Jones & Lewis, 1952). The damage, thought to be caused by chemicals leached out of the rubber, could be lessened by boiling the tubing in alkali but this treatment made rubber so brittle that giving sets could rarely be used more than two or three times. Dr H. B. M. Lewis, Deputy Director of the Oxford Transfusion Centre, was invited to speak to the RTD meeting about post-transfusion thrombophlebitis (30 January 1952). He was aware that Fenwal plastic giving sets were in use at an American Air Force Base near Oxford and that the incidence of post-transfusion thrombophlebitis at the base was very low. In 1953, Lewis wrote to Maycock, requesting permission to purchase 200 sets for use at the Radcliffe Infirmary. The answer was a categorical no (Maycock archives, PRO): the country simply did not have enough dollars. He was, however, invited to join a sub-committee of the MRC Blood Transfusion Research Committee, set up with Mollison as Chairman, to investigate the cause of post-transfusion thrombophlebitis.

A clinical trial was designed to compare the incidence of thrombophlebitis using rubber and plastic giving sets. Plastic sets were imported initially from America but, in 1955, a plastics manufacturing company in the Midlands, Capon-Heaton, was given a licence by Fenwal to produce them in the UK. There were long and frustrating production problems. The junctions were inclined to leak and early efforts to produce a nylon mesh filter were a failure. The plastic piercing needle, suitable for use with the plastic bags used in America, would not penetrate the rubber stopper of British bottles and a metal needle had to be incorporated. What is more, Capon-Heaton was so inadequately staffed that, for the first 10 years, production always fell behind demand. In order to resolve the supply problem the MoH later negotiated with Abbott Laboratories and Ethicon as alternative sources of plastic disposable giving sets.

The MRC report (1957) was strongly in favour of using plastic giving sets but there was opposition to their nationwide introduction from some of the Regional Transfusion Directors (RTDs). From their point of view there were two quite separate problems. The first was one of staffing. The staff hired to sharpen needles and to clean and assemble rubber giving sets had never been fully employed and were used for numerous small tasks. The directors could not imagine how these 'odd' jobs would be done if the assembly staff became redundant! The second problem was more serious.

The method of financing transfusion centres, through Regional Hospital Boards (RHBs) had always been uneven. Some boards attributed relatively little importance to blood transfusion and their local centres were virtual orphans with requests for an increase in funding regularly refused. The MoH Supplies Director suggested that transfusion centre directors write to their RHBs saying that whilst plastic giving sets were more expensive, they had to be purchased. At the

same time the RHBs should be reminded that the extra funds of £4500 to £6800 per region ought to be recovered within hospital running costs (Maycock archives, PRO).

There could be no doubt that plastic giving sets were more expensive than the standard rubber ones: a rubber set cost 2 s. 6 d. to clean and assemble and could be used two or three times, whereas a plastic set cost from 3 s. to 4 s. and could be used only once. Several RHBs refused to meet the extra costs and the problem had to be resolved by the Under-secretary of State for Health in 1957. By 1962, plastic giving sets were still in short supply, though they were supposed to be used nationwide. Only in 1970 were orders for red rubber tubing finally cancelled.

Meanwhile, similar battles were being fought in an effort to substitute plastic packs for glass bottles. An Australian firm, TUTA, had sent samples of their bags to Maycock in 1959 and Baxter Corporation, which had taken over Fenwal, offered to open a factory in the UK in 1960.

Again, some RTDs raised objections. They admitted that plastic packs had an advantage over glass bottles for special purposes such as producing platelets and coagulation factor concentrates. Also, the loss of staff employed to clean and sterilize glass bottles no longer seemed to present such a problem. The directors could, however, see two major problems. Firstly, it seemed unwise to be dependent on the single Baxter factory. (At that time the alternative supplier, TUTA, was involved in a serious industrial dispute with its employees and could not reliably supply blood packs, although it subsequently became a major UK supplier of plastic transfusion equipment.) Secondly, the cost of converting from bottles to plastic bags would be of the order of £240,000 per year, or 16% of the NBTS budget. One director, Dr J. D. James of Edgware Transfusion Centre, voiced the view that the NBTS should seriously consider Baxter's offer, but he was supported by only three of his colleagues, Drs Grant (Oxford), Wiener (Birmingham) and Gordon (DoH, Scotland). The remainder felt that the advantages of the complete plastic transfusion assembly were outweighed by the expense.¹

Nonetheless, plastic bags were very slowly introduced into the Service. Some directors, notably Dr John Jenkins at Brentwood, Dr Tom Cleghorn at North London and Dr George Bird, successor to Dr Wiener at Birmingham, were more successful than others in persuading local hospital boards to fund the change to plastic. The hospitals in those particular regions quickly appreciated the advantages, particularly when platelets were needed to support patients with leukaemia or on chemotherapy and when haemophiliacs needed cryoprecipitate.

It was not until July 1975 that plastic packs were introduced throughout the country, at last putting an end to the nation's inequalities in provision of blood-component therapy.

¹ Minutes of meeting of Regional Transfusion Directors, 3/5/60.

Chapter 5: Transfusion transmitted infections, 1946–1993

In the preface to the ninth edition of the textbook *Blood Transfusion in Clinical Medicine* (Mollison *et al.*, 1993) the authors comment, "In the first edition of this book, published more than 40 years ago the emphasis was very heavily on the transfusion of red cells The only diseases known to be transmitted by transfusion were hepatitis, the infectious agents for which no tests were available, and syphilis and malaria. Only four pages were devoted to the subject in a general chapter on the ill-effects of transfusion....The longest chapter in the (present) book is now devoted to infectious agents transmitted by transfusion."

For those who have been involved with the Blood Transfusion Service during the past 30 years, the transmission of infections, arguably, has had the greatest impact on the practice of transfusion medicine. An inevitable consequence has been that Regional Transfusion Centres (RTCs) had to recruit staff skilled in microbiology and virology and develop sophisticated and sensitive techniques for the detection of markers of infectious disease. However, the most dramatic effect on the Transfusion Service has been the interest taken by the media in its activities. From being a Service which had operated in relative obscurity, it has been thrust into the public forum worldwide following the transmission of HIV, the causative agent of AIDS.

In this chapter an account will be given of the introduction of pre-transfusion tests for infectious reagents. To understand fully the reasons for the action taken it will be necessary briefly to review the scientific aspects of transfusion transmitted infections. Mention will be made of other diseases where attempts are made to exclude transmission by obtaining evidence of potential risk factors for infection from a history of the donor's health, inoculations and travelling.

A number of expert groups and committees have considered the impact of the transmission of infection following the transfusion of blood and blood products.

The Expert Advisory Group on AIDS (EAGA) was constituted in January 1985 and continues to meet. It is chaired by a Deputy Chief Medical Officer and has a membership with a wide range of experience in relation to the effects of HIV infection. Its terms of reference are "to provide advice on such matters relating to the Acquired Immune Deficiency Syndrome (AIDS) as may be referred to it by the Chief Medical Officers of the Health Departments of the United Kingdom". Blood transfusion practice is included in its remit.

The UK Advisory Committee on the Virological Safety of Blood (ACVSB) was established in April 1989. Its terms of reference were "to advise the Health Departments of the UK on measures to ensure the virological safety of blood

whilst maintaining adequate supplies of appropriate quality both for immediate use and for plasma processing". In October 1993 the terms of reference were extended to include transplantation of bone marrow and organs. The committee was renamed the Microbiological Safety of Blood and Tissues for Transplantation (MSBT).

Within the NBTS the Regional Transfusion Director's (RTD) Committee provided the forum for discussion of transfusion transmitted infections. During the 1980s *ad hoc* groups were formed to consider tests for HIV.

With the disbanding of the RTD Committee in January 1989 it was necessary to have means of considering the response of the NBTS to transfusion transmitted infections. The National Directorate of the NBTS created the UK Advisory Committee on Transfusion Transmitted Diseases (UK ACTTD). The first meeting was held in February 1989 and the aim of the Committee was to consider the implications of transfusion-transmitted infections on the Transfusion Services in the UK and to provide advice for the Departments of Health. The membership comprised persons with expertise in blood-transfusion medicine, virology and microbiology in England and Scotland. The name was changed to the UK Advisory Committee on Transfusion Transmitted Infections in 1993.

SYPHILIS

The transmission of syphilis was a serious problem with direct transfusion from donor to patient. The storage of blood at 4–6°C has largely eliminated syphilis transmission by transfusion; it has been known since 1941 that spirochaetes survive poorly at these temperatures (Bloch, 1941; Turner & Diseker, 1941).

A pre-transfusion test for syphilis has been performed routinely on each blood donation since the inception of the service. The need for such tests is a matter for debate. There is no mandatory requirement for screening in Europe (Commission of the European Communities, 1991) and certain countries, e.g. Denmark, have discontinued syphilis testing.

Nevertheless, it seems prudent to continue testing blood donations for several reasons which are summarized by Mollison *et al.* (1993). The two most compelling reasons are the increasing use of blood products, notably platelets, stored at 22°C and that screening for syphilis may be useful as a life-style marker to exclude those persons who may be at increased risk of acquiring other sexually transmitted infections, e.g. HIV and HBV.

In the early days, testing for syphilis was not entirely satisfactory. The one-tube Kahn test and the Price Precipitation reaction (PPR) suffered from the disadvantage that false-negatives occurred because of a prozone phenomenon. Testing using several dilutions of serum could overcome this problem. The Berger-Kahn slide test, not affected by pro-zoning, was so sensitive that many false-positives were found.

Procedures had to be revised when a donor requested compensation for mental stress and loss of wages following investigations at a Special Clinic after three false-positive reactions.¹ Attention was given to the wording of the standard letter sent to donors' general practitioners. It was agreed, however, that follow-up of false-positives was justified because such reactions may herald the onset of serious disease, e.g. disseminated lupus erythematosus.

These problems were still not entirely resolved some years later. Dr A. J. King, Consultant Adviser in Venereology and Dr A. E. Wilkinson from the VD Reference Laboratory at the London Hospital, advised the Regional Transfusion Directors (RTDs) that, following the finding of a positive reaction, repeat tests on the same specimen should be performed. These should include a battery of tests which, if available, should include the *Treponema pallidum* immobilization (TPI) test.² Several RTCs already had reference centres who performed this test.³

A further detailed review of syphilis testing was carried out in 1969 following an incident at an RTC where investigations had revealed inadequacy of syphilis testing leading to a false-negative result on a donor who was subsequently shown to be suffering from tertiary syphilis.⁴ The use of the cardiolipin antigen in the Wasserman Reaction (WR) was recommended since it was chemically refined and more specific than other antigens. The other test which was in use was the venereal disease research laboratory slide technique (VDRL).

Based on the number of confirmations by TPI and the fluorescent treponemal antibody absorption test (FTA), use of the VDRL seemed to be as efficient as the use of both WR and VDRL and a better screening test than WR alone. This advice followed the report of an investigation by Dr A. E. Wilkinson who had performed tests on positively reacting sera from nine RTCs in the period February to April 1970.⁵ The VDRL test has continued to be used as the initial screening test at a number of RTCs.

Attempts were made to automate the testing for syphilis in 1970 using an automated reagin test (ART) based on the use of a VDRL carbon particle method.⁶ These early automated methods were not particularly successful and progress in syphilis testing was not made until the use of the *Treponema pallidum* haemagglutination assay (TPHA) which was more sensitive and specific than other assays (Barbara *et al.*,

1982). More recently an enzyme-linked immunoabsorbent assay (ELISA) has been developed which is even more specific and sensitive, and can be fully automated.

HEPATITIS

Homologous serum jaundice has been recognized as a trans-fusion-transmissible form of hepatitis since the 1940s. It was particularly common when large pools were used as the starting material for dried plasma. As a result, pools of plasma were limited to 10 donations (Chapter 7), reducing the incidence of hepatitis transmission by approximately 10-fold. Later the term 'serum hepatitis' replaced homologous serum jaundice to distinguish it from infectious hepatitis (now known as HAV) which is transmitted almost entirely by the oro-faecal route.

The existence of 'syringe' jaundice due to imperfect sterilization of syringes and needles was also a recognized phenomenon. In 1960, it was stated in the monthly bulletin of the Ministry of Health that the forthcoming MRC memorandum on Sterilization, Use and Care of Syringes would recommend that a separate syringe and needle should be used for each person injected. It was agreed that the NBTS should implement this recommendation for administration of local anaesthetic to blood donors.⁷

Without a definitive test, the only measure that could be taken to limit the transmission of serum hepatitis was to remove donors from the panel when a patient developed hepatitis following a transfusion of their blood. During the 1960s hepatitis became a notifiable disease in many regions of the country. RTDs were notified of outbreaks in their area and this led to indecision with respect to the issue of blood from collection sessions in the area of the outbreak. Experience showed that there was little transmission of hepatitis from such blood. It is likely that the majority of these cases were hepatitis A.

Hepatitis B (HBV)

A major advance occurred when an antigen, thought initially to be linked with leukaemia (Blumberg *et al.*, 1965), but later shown to be associated with hepatitis, was found in the serum of an Australian aborigine (Blumberg *et al.*, 1968; Prince, 1968). By March 1970, it was estimated that by screening donations for the Australia antigen (now known as the hepatitis B surface antigen or HBsAg), the incidence of transfusion transmitted hepatitis could be significantly reduced. However, the major problem was the lack of suitable antisera.

It was agreed by the RTDs that when routine screening for HBsAg was introduced it should be on a nationwide basis. The testing of blood donations was approved in July

Minutes of meetings of Regional Transfusion Directors,

¹ 20/1/54, ² 26/10/60, ³ 29/6/60, ⁴ 17/12/69, ⁵ 21/10/70, ⁶ 16/12/70.

⁷ Minutes of meeting of Regional Transfusion Directors 4/5/60.

1971 following a recommendation by the DHSS Advisory Group on Testing for the presence of the hepatitis-associated antigen. It was not possible to introduce the test simultaneously in each RTC for the routine screening of donations. Preference was given initially to testing donations used for renal dialysis, and BPL established a panel of tested donors to supply plasma for the preparation of fibrinogen. Tests were introduced in all RTCs during 1972 and by December all donations were being tested.⁵

Initially, screening tests were performed using immunodiffusion and counter immuno-electrophoresis (IEOP). These techniques were not particularly sensitive and the results of tests during the first 4–6 months showed that about 1 in 1500 donations was positive. The sensitivity of the tests improved with the introduction, in 1975, of the reverse passive haemagglutination assay (RPHA).

In 1978, a source of high-titre anti-HBs, raised in two horses and eight goats, became available to Dr Tom Cleghorn, Director of the North London RTC. Dr David Dane, Consultant Virologist at the Middlesex Hospital, Dr Richard Lane, Director of BPL and Dr Cleghorn decided that these antisera could form the basis of a radioimmune assay for the NBTS. To produce this assay there was collaboration between John Barbara and David Howell at North London RTC and Colin Cameron at the Middlesex Hospital. Purified HBsAg from the plasma of blood donors was used to boost the antibody response in the animals; the resulting antisera were frozen and stored, and were available for many years. Finally, in this first class cooperative effort, Brian Combridge at BPL was responsible for the bulk production of the RIA test. By 1983, it was being used at all RTCs in England and Wales, several RTCs in Scotland, some PHLS Laboratories and the Army Blood Supply Depot.

There were two significant sequelae to the BPL RIA test. Firstly, it established a low-cost assay for many years and secondly, it led to increased coordination of transfusion microbiology in the NBTS. The first issue of Transfusion Microbiology Newsletter was published in 1981 and, following the founding of the British Blood Transfusion Society in 1982, Transfusion Microbiology became the first Special Interest Group to meet under the aegis of the Society.

The RIA test proved highly successful and was used in combination with RPHA until 1991 when it was phased out. By that time tests were being performed for HIV and HCV antibodies in addition to HBsAg and the need to automate was paramount. Also, the ELISA test, which replaced the RIA, avoided the restrictions placed on producing and performing assays using radioactive substances.

In 1980, a British Standard for HBsAg was issued by the National Institute for Biological Standards and Control (NIBSC). It was designated to contain 100 British units per ampoule. Later this was adopted as a WHO standard and the

British units became international units (iu). The Department of Health and Social Security (DHSS) were able to set a requirement that assays for HBsAg had to be able to detect at least two British units. In 1993, a working standard for HBsAg was developed by NIBSC which contained 0.5 iu per ml (Ferguson *et al.*, 1993). This preparation is used as a 'go/no go' standard with each batch of tests which now have the sensitivity to detect this quantity amount of antigen (Barbara, 1993).

Steps were taken to withdraw all donors who were confirmed HBsAg-positive. Such donors were informed of the result, mostly by letter, but in some RTCs, notably North London, by interview. In a number of regions one or more consultant physicians undertook to see HBsAg donors and advise them on their future health. Advice was given to RTDs by the DHSS that both negative and positive results should be recorded. This marked the first step in improving record keeping although the advice had been given for medico-legal reasons.

Non-A, non-B hepatitis (NANBH) and hepatitis C (HCV)

Despite the introduction of donor screening for HBsAg, transfusion-transmitted hepatitis continued to occur. For the want of a better term this parenteral hepatitis was called non-A, non-B (NANBH). Transfusion-transmitted NANBH is usually a mild illness and many instances are sub-clinical. There is, however, a tendency for the disease to lead to chronic liver damage which may vary from a mild persistent abnormality of liver function and chronic hepatitis to cirrhosis and occasionally to hepato-cellular carcinoma (Kozioł *et al.*, 1986).

Independent studies have suggested that there is a relationship between parenteral NANBH and both raised levels of alanine amino-transferase (ALT) and also the presence of anti-HBc (Aach *et al.*, 1981; Alter *et al.*, 1981; Kozioł *et al.*, 1986). In 1981 the National Institutes for Health, USA, introduced ALT testing and excluded blood donations with an abnormal ALT. The incidence of transfusion-transmitted NANB did not change in the subsequent 3 years compared to the 2 years prior to the testing (Alter, 1985). Despite these findings the American Association of Blood Banks (AABB) introduced screening for both ALT and anti-HBc; similar action was taken by the American Red Cross. Neither of these tests has been introduced in the UK.

In 1988, the DHSS commissioned an investigation of ALT and anti-HBc tests on a sample of the current UK donor population. The results confirmed previous studies that the majority of persons with a raised ALT had increased alcohol intake or were obese (Alter, 1984). It was concluded that the only way to evaluate the use of ALT and anti-HBc as non-specific markers for NANB was to carry out a prospective randomized trial.

During the course of the above investigation a virus was identified by cloning nucleic acid from plasma of chimpanzee

⁵ Minutes of meeting of Regional Transfusion Directors, 10/1/73.

anzenes infected with NANB (Choo *et al.*, 1989). Chiron, the manufacturers of the genome, produced a diagnostic reagent in late 1990. Two companies were licensed to market test kits. The assay produced non-specific positive results which were excluded to some extent by the later introduction of RIBA-2, an improved immunoblot assay. This contained recombinant antigens to the core region and the NS-3 in addition to the NS-4 region of the genome (Follet, 1995).

The first generation of tests for anti-HCV included recombinant antigen to only one region of the genome (NS 4), but as two components, 5-1-1 and c100. In the autumn of 1990 a multi-centre trial was carried out to compare the assays from the two manufacturers on the same donor samples at three RTCs. Approximately 3500 tests were performed at each RTC and the repeatedly positive rate with both tests was between 0.4% and 0.5%. Interestingly, only one third to one-half of the sera were repeatedly positive with both test kits. The remainder were positive with one or other test.

A second-generation test containing, in addition, the c22 and c33 antigens was introduced early in 1991 by the companies which had marketed the first generation tests. Other manufacturers had independently cloned HCV, one from known carriers of transfusion-transmitted NANBH in London (Glazebrook *et al.*, 1992). It was considered prudent to evaluate all the second-generation tests available prior to introducing the test as a routine.

The second study was carried out at the same three RTCs. The test kits from the two original manufacturers gave fewer positives than with their first-generation tests. Of the two other manufacturers one gave a higher positivity rate and the other a lower one. Significantly, of the six samples thought to be truly positive by confirmation with RIBA-2 and polymerase chain reaction (PCR), all were detected by three test kits. The fourth failed to react with two of these samples.

Testing of blood and plasma donations commenced in all UK RTCs on 1 September 1991. An action chart was

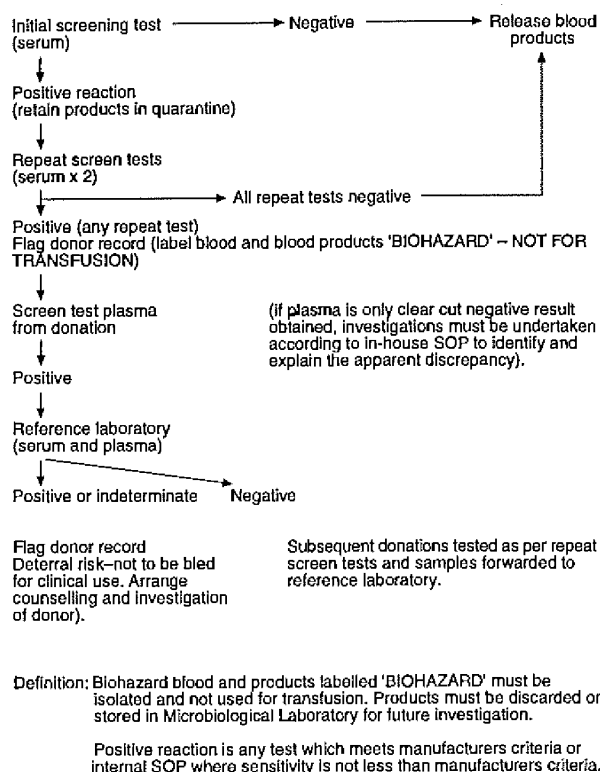


Fig. 5.1 Action chart — anti-HCV testing.

published illustrating the procedure to be taken when a positive result was found (Fig. 5.1). Donors can now be readmitted to the panel when falsely positive for any marker if the Reference Laboratory obtains a negative result or if the subsequent donation after 6 months is negative using an assay of equal sensitivity.

Table 5.1 Results of testing all donations and first-time donors with anti-HCV and RIBA-2 tests on the repeatedly positive donations

Year	Anti-HCV tests		RIBA-2 tests		
	No. tested × 10 ⁶	RP* %	Positive %	Indeterminant %	Negative %
All donations					
1/9/91–31/12/91	1.2	0.39	17.6	26.1	56.3
1992	2.9	0.26	12.9	31.7	55.4
1993	2.9	0.16	11.3	34.7	54.0
First-time donors					
1/9/91–31/12/91	0.12	0.5			
1992	0.35	0.38			
1993	0.33	0.36			

* RP = repeatedly positive.

Repeatedly positive sera at RTCs were tested with RIBA-2. Statistics for the period 1 September 1991 to 31 December 1991 and for January to December for the years 1992 and 1993 are shown in Table 5.1 (compiled by Miss V. I. Rawlinson, Manchester RTC). It can be seen that the percentage of repeatedly positive results for all donations has fallen during the period of just over 2 years. This was not surprising as donors whose sera were confirmed positive were withdrawn from the panel. Neither was it surprising that the positive rate was higher in new donors. What was of concern was the relatively high percentage of indeterminate results with RIBA-2. Explaining such a result to a donor presents difficulties, Follet (1995) considers the majority of RIBA-2 indeterminates are false-positives. Perhaps the introduction of the further improved RIBA-3 will assist in this dilemma.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Following the initial reports on the AIDS syndrome it was not immediately obvious that this illness could be transmitted by the transfusion of blood and blood products. The first account of AIDS in three haemophiliacs was reported in 1982 (Centers for Disease Control). In 1983, Amman *et al.* reported that an infant who had received several infusions of blood and blood products had developed AIDS and that one of the donors subsequently manifested symptoms of the disease.

The RTDs agreed that an information leaflet on AIDS should be prepared for distribution to donors. The leaflet was issued on 1 September 1983.⁹ It was stressed in the leaflet that AIDS was a serious but rare disease, probably caused by a virus and that the following groups of persons appeared to be particularly susceptible:

- homosexual men who have many different partners;
- drug addicts, male and female, using injections;
- sexual contacts of people suffering from AIDS.

As no screening test was available, persons were requested not to give blood if they thought they may have the disease or be at risk of contracting it. It was stressed that donors would not be questioned on sexual matters when they attended to give blood.

The leaflet was distributed to donors either by sending it to them with the call-up card, by handing it to them or by making it available on blood-collection sessions. When the chosen method for distribution was availability at sessions, the take-up rate was low. To ensure that future leaflets would be seen by all donors, the DHSS issued a Health Circular in 1985 (HC(85)3) in which RHAs were asked to distribute leaflets to each donor with the call-up card or letter. In addition to distributing leaflets, a number of RTCs contacted local homosexual societies to enlist their assistance.

⁹ Minutes of meeting of Regional Transfusion Directors, 18/5/83

In July 1984 the North London RTC introduced a questionnaire for donors attending their permanent blood-collection centre in London, in an attempt to reduce the number of donors at risk of HIV infection. After a successful trial its use was extended to a second permanent centre in April 1985 and on the mobile blood-collection teams from June/July 1985. The reason for the use of this questionnaire was a suspicion that the North London RTC might be liable to have more donors at risk than RTCs in other regions in view of the number of homosexuals found to have HBV infection in North London (Jeffries *et al.*, 1973).

Thirty-eight of approximately 5000 donors admitted to homosexual behaviour, although none had detectable infectious markers for hepatitis B, *Treponema* or HIV (Contreras *et al.*, 1985). However, several seroconverted for HIV on follow up (J. A. J. Barbara, pers. comm.). Many of the homosexual donors stated that they had continued to donate blood because they considered that those with stable partnerships were still eligible.

Even though it was possible to test for anti-HIV from 1985, six leaflets were issued between January 1985 and February 1993 as there was a chance that a donation might be collected following infection but before antibody could be detected. The earlier leaflets were intended to discourage homosexuals, those who injected drugs and their sexual partners from donating blood. The leaflet issued in 1986 included 'since 1978' for high-risk behaviour as tests on stored haemophiliac samples had shown that the first cases of HIV infection had occurred during that year (Evatt *et al.*, 1983; Machin *et al.*, 1985). The year was changed to 1977 subsequently to achieve uniformity with leaflets from other countries, but it was omitted from the 1993 leaflet as many donors who were anti-HCV positive were homosexuals who had experienced sexual activity prior to this date (Barbara & Contreras, 1991).

It was difficult to assess how the use of the above leaflets improved the safety of the blood supply. It could be argued that some donors would not be able to read the leaflets, or could not understand the contents sufficiently to self-exclude. Circumstantial evidence that the leaflets had a beneficial effect can be obtained by examining the rates for HBsAg positive donors, because HBV is also a sexually transmitted disease.

Table 5.2 shows that the rate in new donors was about 1 in 1000 in 1979 and 1980. There was a reduction in the next 2 years, probably as a result of discontinuing blood collection from prisoners in HM prisons. However, there was a considerable reduction in 1985 and 1986 which coincided with the release of the early leaflets, together with advice in the media. The variable incidence in 1987 and 1988 is difficult to explain: perhaps the contents of the leaflets had become too familiar and new methods should have been employed to ensure that potential donors were aware of the risk factors for AIDS.

Table 5.2 Results of testing first-time donors for HBsAg: number of confirmed positives (DHSS statistics on NBTS activities)

Year	No. first-time donors tested × 10 ³	No. found HBsAg-positive	HBsAg positivity rate
1979	168	165	1 in 1020
1980	166	165	1 in 1009
1981	177	137	1 in 1295
1982	211	160	1 in 1320
1983	208	172	1 in 1207
1984	209	133	1 in 1568
1985	278	126	1 in 2211
1986	284	91	1 in 3120
1987	277	160	1 in 1728
1988	298	131	1 in 2270

Tests for HIV

During 1984, the causative virus for AIDS was recognized as a retrovirus. It was called lymphadenopathy-associated virus (LAV) by Barre-Sinoussi *et al.*, (1983) and human T-cell Lymphotropic virus, (HTLV-III) by Popovic *et al.* (1984). In this account the current term HIV will be used.

The development of tests to detect anti-HIV was carried out initially in the USA, although a successful competitive RIA assay was prepared in the UK and subsequently changed to an ELISA technique (Chien-song-Popov *et al.*, 1984). The first tests were licensed by the Food and Drug Administration (FDA) in March 1985. It would have been reasonable to expect that when a test for the detection of anti-HIV was available, problems for the transfusion services throughout the world would be greatly reduced. In the event the intro-

duction of screening tests raised new problems of a practical and ethical nature.

Budiansky (1984) reported that five US companies had been given 3000 samples from plasma and 3000 samples from whole-blood donations to evaluate the tests they were each licensed to develop. Positive results had been obtained on a widely varying number of samples varying from five to 100, when some 20 positives could have been expected. Strict comparability could not be achieved since the companies did not receive aliquots of the same samples. Nevertheless, Western Blot assays suggested that a false-positive rate of one out of 10 positive with the ELISA test.

In a further article in 1985, Budiansky expressed concern about the significance of a positive result. The recommendation of the AABB to its members noted that "only after several years of experience along with appropriate epidemiological studies will there be sufficient information to assess the meaning of a positive test for antibodies to HTLV-III".

During the period March to October 1985 successive events took place in the UK which were essential before the introduction of screening tests for anti-HIV (Gunson, 1986):

- an evaluation of the available test systems for anti-HIV by the Central Laboratory of the Public Health Laboratory Service (PHLS). From this evaluation, three tests emerged as the most suitable for screening blood donations (Mortimer *et al.*, 1985);
- of these three, two assays were investigated in two RTCs to assess how they could be incorporated most effectively into the work schedules of the Centre;
- arrangements were made with the PHLS to carry out confirmatory tests on repeatedly positive sera found at RTCs;
- it was agreed that the initial counselling of blood donors whose confirmatory tests were positive would be carried

Table 5.3 Number of confirmed positives for anti-HIV for all donations and first-time donors, 1985/6–1993

Year	Donations tested × 10 ⁶	Positive			No. tested × 10 ³	Positive		
		Total	Male	Female		Total	Male	Female
All donations*					First-time donors*			
1985	0.6	15	15	0				
1986	2.8	54	45	9	342	20	17	3
1987	2.7	26	21	5	359	13	11	2
1988	2.8	25	20	5	371	9	6	3
1989	2.9	41	28	13	391	20	13	7
1990	3.0	35	23	12	373	18	13	5†
1991	3.1	32	24	8	463	16	12	4
1992	3.1	29	18	11	368	13	5	8
1993	3.1	23	19	4	353	11	7	4

* Includes UK, Ireland, Isle of Man and States of Jersey.

† Includes one anti-HIV 2 positive.

out by senior medical staff at RTCs. The persons involved attended training courses at St Mary's Hospital;

- alternative sites for HIV antibody testing were established by Regional Health Authorities in order that those persons who wished to have an anti-HIV test need not enrol as a blood donor for this purpose;
- a training programme for scientific staff was commenced since ELISA techniques, at that time, were novel in most RTCs.

Routine screening of blood and plasma donations commenced simultaneously in all RTCs in the UK on 14 October 1985. In addition to testing the incoming donations, all stocks of blood and plasma held in RTCs were tested so that from this date no untested blood or plasma was issued.

With the cooperation of RTDs, Miss V. I. Rawlinson analysed data on a monthly basis to provide information on the quality control of each batch of assays and the initial and repeatedly positive results on blood donations. A monthly report was sent to each RTC in the UK and the service was extended to include Ireland, The Isle of Man and The States of Jersey. The early results of this work was published in 1988 (Gunson & Rawlinson). Table 5.3 shows a summary of the number of positives found in all blood and plasma donations and in new donors from 1985 to 1993. This is a prime example of a national collation of microbiological data which has served as a model for further coordinated quality monitoring (see below).

Other retroviruses

Anti-HTLV I has been associated with tropical spastic paraparesis after the transfusion of infected blood. Following a study of donors in North London it was decided not to

introduce routine screening for this virus (Brennan *et al.*, 1993).

Cytomegalovirus (CMV)

Certain groups of patients are unduly susceptible to transfusion-transmitted infection with CMV. These include newborn infants, particularly when premature, and patients whose immune system is suppressed. Foremost amongst this group are patients undergoing transplantation. Screening of approximately 10% of the donor panel is usually sufficient to provide CMV antibody negative blood for such patients who are anti-CMV negative. Once such a CMV antibody negative panel has been established relatively little additional screening to augment the panel is required as the conversion rate for CMV in established adult donors is only about 1.5% per annum (H. H. Gunson, pers. observ.).

The development of modern filtration systems may serve to reduce the extent of screening. However, when a panel of sero negatives has been established it is probably cost-effective to maintain this compared with the use of filters.

Malaria

It has been known for many years that malarial parasites will survive in stored blood (Hutton & Shute, 1939). Episodes of transfusion transmitted malaria have occurred in recent years (De Silva *et al.* 1988). During the 1960s and 1970s donations from persons who had lived in or travelled to malarial areas were collected for plasma, as the parasite is intracellular. This is still an option, as the action chart shown in Fig. 5.2 demonstrates. Donors can be returned to the panel

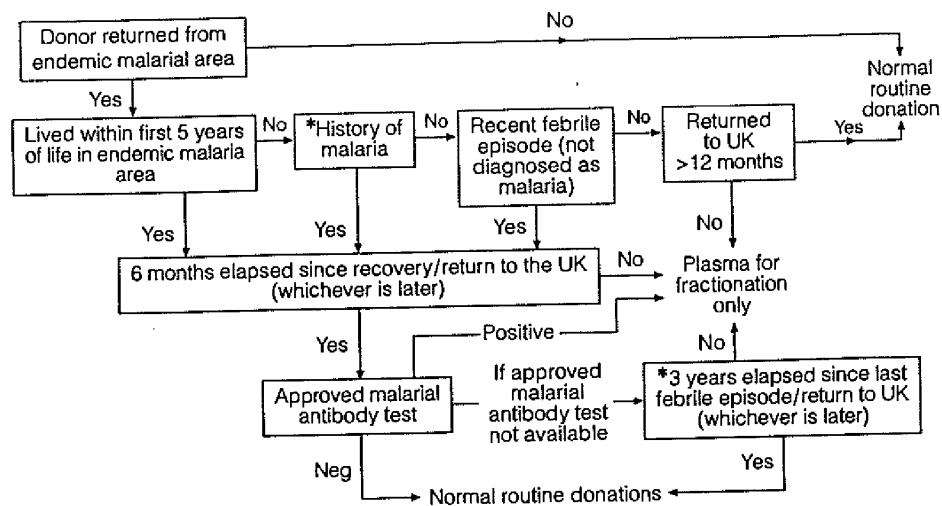


Fig. 5.2 Action chart for donors returning from malarial areas.

SESSION.....DATE

PLEASE READ THIS FORM CAREFULLY BEFORE YOU SIGN

DECLARATION BY DONORS

I agree to tell the doctor or nurse in charge:

1. If I have had an infectious disease in the last two years, or if I have been in contact with an infectious disease in the last 6 months.
2. If I have been or lived abroad other than in Europe.
3. If I have received any inoculations or vaccinations in the last 6 months or ever been treated with human growth hormone.
4. If I have had any of the following: ANAEMIA; ASTHMA; BRUCELLOSIS (Undulant Fever); CANCER; DIABETES; EPILEPSY (FITS); GLANDULAR FEVER; HAY FEVER; HEART DISEASE; HIGH BLOOD PRESSURE; HOSPITAL ADMISSION; JAUNDICE (including contact with a case during the past six months); KIDNEY DISEASE; MALARIA; STROKE; TUBERCULOSIS; VITILIGO
5. I confirm that I have read the AIDS leaflet and I am not at risk.
6. I agree that my donation can be tested for AIDS antibody and other infections.

Fig. 5.3 Abbreviated questionnaire used on blood-collection sessions (NBTS 110).

after 6 months instead of 3 years by performing an antibody test, as it has been shown that persons negative for malarial antibodies do not carry the parasites.

Bacterial infections

A report of transmission of *Yersinia enterocolitica* (Smillie & Ala, 1991) and of post-transfusion septicaemia (Puckett *et al.*, 1992) prompted the UK ACTTD to carry out a survey of bacterial contamination of blood products in the 5-year period 1986 to 1990 (Mitchell & Barr, 1992). With respect to whole blood, red-cell and platelet concentrates the reported incidence of bacterial contamination was approximately 1 in 1 million. None was reported in donations of fresh frozen plasma or cryoprecipitate. The most common organisms involved were *Yersinia enterocolitica* and *Pseudomonas fluorescens*. Because it is impractical to culture each donation before issue, guidelines are being produced for RTCs to ensure that this situation is monitored closely.

Other infections and illnesses

The medical assessment of donors is designed to detect two conditions, viz; those medical conditions and activities where blood donation may adversely affect the donors' health and those which may cause patients harm following transfusion.

Whilst it has been decided to perform virological tests on donations for certain transmissible infectious agents, in other instances this is neither feasible nor practical. In order to ensure maximum safety of the blood supply it is important

to obtain an accurate medical history from the donors, together with an assessment of their health. This is to exclude infections that may be obvious and to decide whether the donors' behaviour puts them at risk of contracting an asymptomatic, long incubation infection or develop carrier status.

In some RTCs a detailed questionnaire was given to the donor to complete before donation which allowed a donor to state "don't use my blood" without embarrassment. However, in the majority of RTCs the donor was asked to read a series of questions which were supplemented by several verbal questions. A typical proforma (coded NBTS 110) used in the Manchester RTC is shown in Fig. 5.3.

In 1993 pilot trials were begun in two RTCs to change the system of medical assessment of donors to a confidential interview, based on the work of Mayo *et al.* (1991). Also, comprehensive guidelines were distributed to each RTC to be used as a controlled document so that progress could be made to establish a standardized method of assessing donors' health and the decision whether to accept a donation.

Recently, in the UK an initiative has been undertaken to report all serious hazards of transfusions (SHOT) including infections. This national monitoring can give estimates of risk and forms, therefore, a sound basis for future policy decisions (J. A. J. Barbara, pers. comm.).

One cannot attach too much importance to the control of the medical selection of donors since the quality of the blood supply is dependent on this procedure being performed with care and accuracy. Also, the continuing supply of blood depends on this task being carried out with sensitivity so that donors will not be offended and will return on future occasions. This requires highly trained and motivated staff.

Chapter 6: The drying and fractionation of plasma, 1935–1955

During the mid-1930s it was found that therapeutic antisera could be preserved by drying without losing their specific activity. This observation, and the fact that the potency of antisera deteriorated rapidly under normal storage conditions, encouraged Dr R. I. N. Greaves and his colleagues at the Department of Pathology, Cambridge, to freeze-dry animal antisera. Greaves installed a pilot plant for this purpose at Cambridge in 1936 (Greaves, 1946).

Although it was designed originally to prepare freeze-dried tetanus antitoxin, experimental batches of human serum and plasma were dried in the plant. In 1939 these were shown to be safe when transfused to patients.

This was the beginning of a period of intense activity. Methods of preparing serum and plasma were developed and later, plasma fractions to meet the needs of war-time casualties. This work was centred principally in Cambridge, the London County Council Serum Institute at Carshalton, Surrey, and later at the Lister Institute at Chelsea Bridge.

Dr Alan Drury, Chairman of the Medical Research Council's (MRC's) Blood Transfusion Research Committee, founded in 1939, persuaded the MRC to establish a drying unit for serum and plasma at Cambridge with Greaves as Director (Kekwick, 1981).

In December 1939, information from the USA indicated that unfiltered liquid plasma was a useful substitute for whole blood. This product had been used successfully at the time of the Dunkirk emergency and during the Desert campaign. Indeed a great deal of ingenuity was used to collect plasma as the following description from Ellis (1942) indicates. "In view of the lack of glassware, etc. from the UK for bottling blood or blood products, blood bottles were made locally but plasma, in the experimental phase which lasted until after the battle of El Alamein, was bottled at first in whisky bottles obtained from the barman at the Union Club." Figure 6-1 shows plasma in a half-bottle which had contained Johnny Walker whisky. Dr Ellis continues, "As the clinical usefulness of unfiltered plasma became apparent and the Blood Bank increased in size, Gordon's gin bottles, which held about 600 ml of undiluted plasma, were used. At the time of the battle of El Alamein nearly 1300 of these units, which had been stored frozen in the Royal Army Service Corp's meat safe in downtown Alexandria, were used in the resuscitation of casualties without any immediate toxic effects, although the very real possibility that some of these patients developed hepatitis cannot be ignored, as this infection was rife in the 8th Army at that time."

There were serious doubts raised by the use of unfiltered plasma because the inherent opalescence prevented the detec-

tion of contamination by visual inspection (Medical Research in War, 1947). Therefore, it was decided that products issued for transfusion should be subjected to bacteriological filtration. Unfortunately, when plasma was Seitz filtered the coagulation process was initiated. Various procedures were adopted to solve this problem, e.g. addition of calcium chloride (Clegg & Dible, 1940), recalcification and the addition of serum (Maizels, 1941), altering the pH to 10.6 (Bushby & Whitby, 1942) and preliminary adsorption of fibrinogen with kaolin (Maizels, 1944). None was entirely satisfactory. Although clotting during filtration was prevented, a precipitate formed on storage, particularly in the tropics, which was indistinguishable from bacterial contamination (see above).

Also, filtration did not always prevent bacterial contamination. The USA responded to a request for supplementary

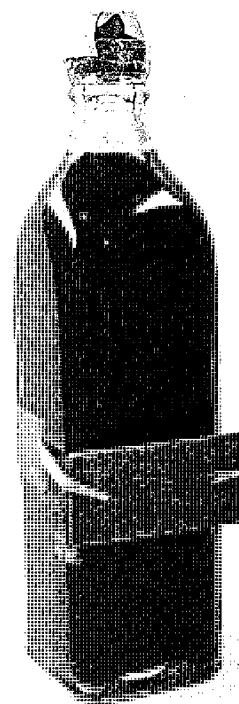


Fig. 6-1 Unfiltered wet plasma decanted in 1941 from bottles of blood which were more than 4 days old and stored at room temperature with sulphanilamide 1/1000 at the Blood Transfusion Unit. Three similar bottles were lodged with Dr W. d'A. Maycock for relevant laboratory investigations (Courtesy of E. D. Wesley).

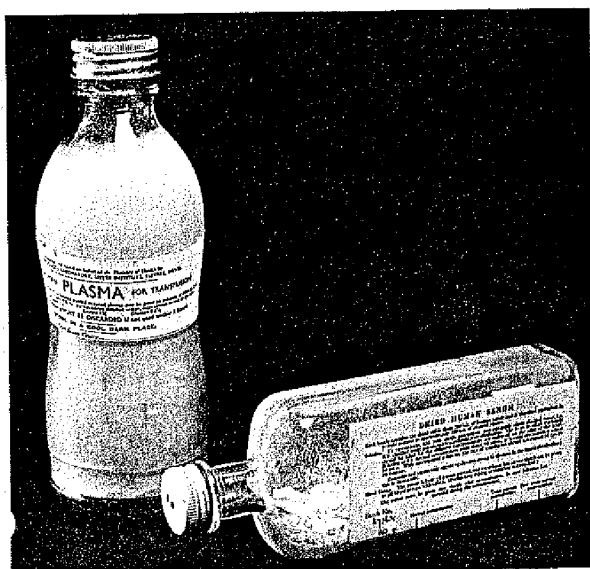


Fig. 6-2 The 400-ml MRC bottle, *left*, and the 12-oz medical flat bottle, *right* (Courtesy of E. D. Wesley).

supplies of plasma by sending about 5500 litres of filtered plasma to the UK between August 1940 and February 1941. By the time the plasma had crossed the Atlantic, many of the batches were infected (Drew *et al.*, 1941).

Initially, the Cambridge drying plant handled serum which was supplied from the London blood depots in the form of group AB clotted blood. The serum was separated, filtered, dried and returned to the London depots for clinical trial. Before drying, the serum was wedge frozen in 12 oz medical flats in 200 ml quantities (Fig. 6-2). Distilled water for reconstitution of the dried serum was dispensed in MRC transfusion bottles so that the reconstituted serum could be transfused using the standard giving sets (Greaves, 1946).

At first, drying was carried out in the pilot plant originally developed for anti-toxic animal sera (Fig. 6-3), but in December 1939 it was decided to increase the scale of production. The so-called 'final plant' came into operation in June 1940 and operated continuously until February 1943. The serum was separated at the London depots using group A and B in addition to group AB donations. The output to February 1943 is shown in Table 6-1. In addition, the Wellcome Foundation constructed a plant at Beckenham similar to that of the 'final plant' (Greaves, 1946).

The main demand for dried serum at this time was for the Armed Forces overseas, although civilian requirements increased following the bombing of British cities. In January 1941 the Army Blood Transfusion Service decided to build their own drying plant at Chilton Polden in Somerset using funds donated to the war effort by the Needle Women of India. Captain E. C. G. Lanyon, RAMC, an experienced refrigeration engineer from J. & E. Hall Ltd, leading manufacturers of refrigeration plant, devised a method of using

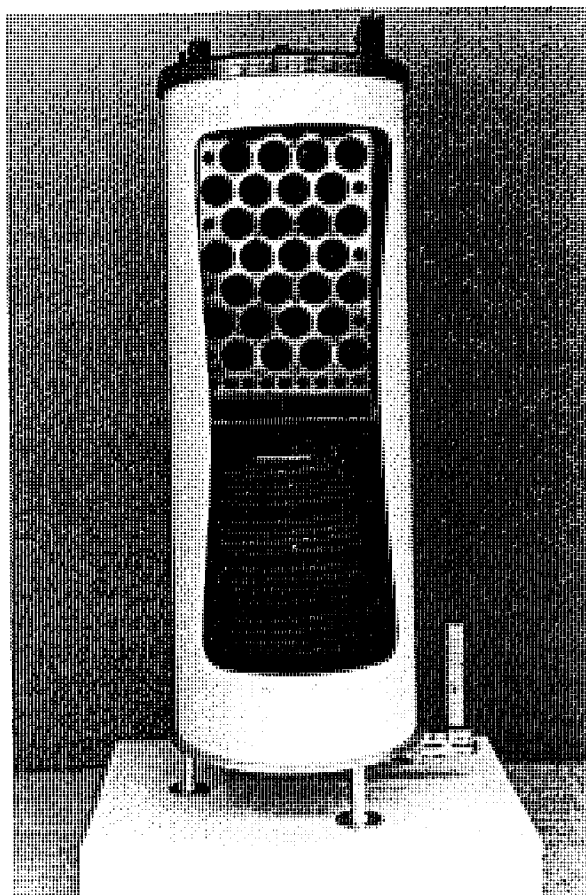


Fig. 6-3 Freeze Dryer, 1939, similar to that used by Greaves (Courtesy of the Royal Scottish Museum).

MRC transfusion bottles for drying serum (Lanyon, 1941). The initial installation of two drying units gave a weekly output of 280 litres (700 bottles). The output was doubled following the installation of two further units.

The insistence of the Army Blood Transfusion Service on drying serum in the more acceptable MRC transfusion bottles persuaded the MRC Unit at Cambridge to change to this bottle from the medical-flat (Fig. 6-2). Lanyon had intro-

Table 6-1 The distribution of freeze-dried serum from the 'final' drying plant, Cambridge, in 12-oz medical flat bottles and MRC transfusion bottles*

Destination	To June 1941	June 1941–Feb. 1943
	No. 12 oz/200 ml medical-flats	No. 400 ml MRC bottles
London Area Depots	5344	
Armed Services	13,386	13,760

* modified from MRC Special Report Series, No. 258.

Table 6.2 The distribution of MRC transfusion bottles containing 400 ml dried serum and plasma from the 'large' drying plant, Cambridge from February 1943 to September 1945*

Destination	No. 400 ml MRC bottles
Royal Navy	82,616
Army	63,943
London	62,032
Newcastle	5483
Leeds	14,461
Nottingham	11,793
Cambridge	10,832
Cardiff	7959
Birmingham	23,957
Liverpool	14,147
Manchester	7850
Polish Red Cross	2016
Miscellaneous	1553
Reserve Store	10,058
Total	318,700

* Modified from MRC Special Report Series, No. 258.

duced a method of shell freezing by rotating the MRC transfusion bottle at an acute angle from the horizontal in a current of cold air at -20°C . Fast freezing by this method formed a smaller crystal structure in the frozen plasma and resulted in a more readily soluble product. However, Greaves found this technique unsuitable for routine work and introduced the high-speed vertical spin-freezing method which was simpler in operation (Greaves, 1941).

By the early months of 1942, difficulties were encountered in the issues of liquid serum and plasma due to the development of haziness on storage referred to earlier. This resulted in considerable wastage and consequently there was an increased demand for dried products. The MRC, following a gift from the Wellcome Trustees of £20,000, constructed the 'large' drying plant at Cambridge to meet the country-wide demands, estimated at 2500 bottles per week with a potential increase to double that quantity (Greaves, 1946). This plant began routine drying on 1 February 1943 and was in operation until September 1945 when it was closed. The output from 1943 to 1945 is given in Table 6.2.

Meanwhile, developments were occurring at the Lister Institute which were to have a significant effect on the fractionation of plasma. In 1935, Arthur McFarlane, a graduate in medicine and physics at Glasgow University, joined the staff at the Lister Institute working in the Department of Bacteriology. He had spent a year in Professor Svedberg's Institute at the University of Uppsala, Sweden, where he learned to analyse the sedimentation charac-

teristics of macromolecules, including plasma proteins, by ultracentrifugation. The Rockefeller Foundation provided a grant to the Lister Institute towards the cost of purchasing the Svedberg oil-turbine ultracentrifuge. This centrifuge was accommodated in the new Biophysics Building at Chelsea Bridge, together with Tiselius's apparatus for electrophoresis in which proteins and other charged macromolecules could be separated and observed analytically in a U-tube of unique design (Chick *et al.*, 1971).

These two basic instruments for examining the physico-chemical properties of proteins were used initially for the study of micro-organisms. In 1937 Ralph Kekwick, having received a grant from the MRC, was appointed to the Biophysics Department at the Lister Institute and was joined in 1938 by Basil Record. McFarlane, Kekwick and Record carried out investigations on freeze-drying of vaccinia virus, the physico-chemical nature of diphtheria antitoxin and the ultracentrifugal and electrophoretic analysis of normal and pathological sera (Kekwick, 1993).

The scene was set for the major contribution these workers made in the fractionation of plasma. Dr (later Sir) Percival Hartley, head of the MRC Biological Standards Division, Hampstead, who had been closely involved with the establishment of the freeze-drying unit at Cambridge, discussed the development of the haze in stored plasma with McFarlane and Kekwick. It was found that this was due to the liberation of lipid from unstable lipoproteins (Francis *et al.*, 1944). Initially, McFarlane tried to remove these lipids by using ether in a Kossel-Kutscher extractor but an intractable foam developed. However, simply shaking with excess of ether, combined with freezing to -25°C followed by thawing, proved sufficient to remove the lipid in the ether layer. When citrated plasma was mixed with ether, fibrinogen was removed in addition to lipid leaving a supernatant that could be sterilized by filtration and remained clear on storage (McFarlane, 1942).

Following the cooperation with Hartley, McFarlane became interested in freeze-drying human plasma under aseptic conditions. As there was no space to develop such a plant in the building at Chelsea Bridge, McFarlane and Kekwick moved to the London County Council Serum Institute at Carshalton, Surrey, in 1941. Record left the Institute to join, as a civilian, the Army Operational Research Group to work on an application of radar as a method of operating light anti-aircraft guns at night (L. Vallet, pers. comm.).

At Carshalton, the freeze-drying plant was used to dry ether treated human plasma from the Sutton and Slough Blood Transfusion Depots. First, the ether was removed by directing streams of sterile air on to shallow pans containing the plasma. During 1942–3, 1000 litres of serum and 2500 litres of plasma were processed. The products were successfully used by Drs Loutit and Vaughan.¹

¹ Lister Institute of Preventive Medicine, Report of the Governing Body, 1943.

The control of sterility was supervised by Margaret Mackay who had developed methods of bacteriological control of production at Greave's unit in Cambridge. She joined the Lister Institute as a member of the external MRC staff at Carshalton in 1942, where she continued this work and also contributed to processing methods.

Plasma drying was discontinued at Carshalton in 1943 and Kekwick and Mackay were recalled to the Lister Institute at Chelsea Bridge to establish a plasma filtration and drying unit. In 1944, this became the MRC unit for Research into Filtration of Blood Plasma and Serum for Transfusion and it was supervised by Margaret Mackay with Alan Drury, the Director of the Lister Institute (Kekwick, 1993).

The filtration unit received plasma which had been treated with kaolin according to the method devised by Maizels (1944). Kaolin removed the fibrinogen and prothrombin allowing the treated plasma to be sterilized by filtration in pools of 500–1000 donations. In the 1944 Report of the Governing Body of the Lister Institute it is recorded that the Unit had successfully filtered the entire output of the London blood-transfusion depots prior to despatch of the filtered plasma to Cambridge for freeze-drying. As a result of the high incidence of transfusion-transmitted homologous serum jaundice, now known to be caused by the contamination of plasma with hepatitis B virus, the MRC decided in June 1945 that, in future, plasma would be processed from pools of only 10 donors and handled aseptically without filtration (Medical Research in War, 1947). Kaolin treatment was abandoned.

During 1944, the MRC received confidential reports from the USA describing Cohn's procedure for fractionating plasma using ethanol. This enabled a relatively pure albumin preparation to be fractionated from human plasma which could be concentrated and stored for long periods even in the tropics. Other useful fractions, i.e. gammaglobulin, thrombin and fibrinogen were also prepared by ethanol treatment. Small quantities of these products were sent to the UK for clinical trial and the users reported favourably (Chick *et al.*, 1971).

The MRC's Blood Transfusion Research Committee, and in particular its Chairman, Alan Drury, decided that fractionated plasma products should be made available in the UK. There was a need by the Armed Forces for supplies of fibrinogen with thrombin, useful as an adhesive when grafting skin and suturing nerves and fibrin foam which was effective in controlling haemorrhage during cranial surgery.

Basil Record was recalled to work on this project with Kekwick and Mackay. Unfortunately, the equipment needed for Cohn fractionation was not available in Britain and ether was more easily obtainable than alcohol which was needed for nitroglycerine production (Kekwick *et al.*, 1946). Preparation of these products fell to the Lister Institute because it was the only organization in the country with equipment available to monitor fractionation processes.

Having shown that both fibrinogen and prothrombin could be precipitated from plasma with ether, an aseptically operated closed plant (essential with the use of ether) was designed to prepare fibrinogen (85% pure) and a prothrombin concentrate (later converted to thrombin). These products were Seitz-filtered and freeze-dried. From them, fibrin foam was prepared. This remarkable development had taken less than 1 year (Kekwick, *et al.*, 1946).

In 1946, following the closure of the Army Blood Transfusion Service Drying Plant at Chilton Polden, two of the drying units were presented on extended loan to the Lister Institute because, having been a gift to the RAMC, they could not be sold. They were installed at Chelsea Bridge by Basil Record and Arthur Jackson, a refrigeration engineer, who had worked with Captain Lanyon at Chilton Polden. Arthur Jackson used this equipment to provide freeze-dried plasma for civilian use. The other two units were installed later at the Lister Institute's laboratories at Elstree (L. Vallet, pers. comm.).

The MRC Filtration Unit was renamed the MRC Blood Products Research Unit in 1947. Additional steps were added to the ether method of fractionation of plasma to provide gammaglobulin (90–95% pure). Although ethanol-prepared gammaglobulin had been shown to be a safe and reliable agent for passive immunization of measles contacts, clinical trials were started at Colindale on the use of the ether extracted gammaglobulin. It was used first on a small group of children in day and residential nurseries (Cockburn *et al.*, 1950). It is interesting to note that Cockburn *et al.*, 1951, reported seven cases of hepatitis, three fatal, in 10 children given serum or plasma prophylactically whereas with gammaglobulin there was only one mild case. This was the first report of the later well-established safety of intramuscularly administered immunoglobulin prepared by ether or alcohol extraction.

Between 1948 and 1953, the production of plasma fractions and freeze dried plasma continued as shown in Table 6.3. A further extension of the ether fractionation method involving the addition of ethanol led, in 1950, to the recovery of a fraction rich in albumin which was heated at 60°C for 10 h to prevent transmission of hepatitis. By 1952, this albumin preparation was available for clinical trials which were carried out by Dr N. H. Martin at St George's Hospital (Kekwick & Mackay, 1954).

By 1950, it was recognized that the increasing demand for dried plasma and plasma fractions could no longer be met with the existing arrangements at the Lister Institute and that a separate Blood Products Laboratory (BPL) was required. The building with its equipment, financed by the MRC as agents for the Ministry of Health (MoH) was erected on a site leased from the Lister Institute at Elstree. Running costs, including staff salaries, were funded by the MoH through the MRC. However, BPL operated as a department of the Lister Institute which employed the staff (Vallet, 1993).

Table 6.3 Production data, 1948–1953, Blood Products Research Unit, Lister Institute

Year	Bottles			Ampoules	
	Dried plasma	Fibrinogen*	Fibrin foam	Thrombin	Gamma globulin
1948	20,000	2400	5000	5000	
1949					2500
1950	18,500	900	3300	3800	3700
1952	29,854				
1953	28,610				

* Small bottles with screw caps which were replaced by ampoules. They should not be confused with MRC bottles.

Sir Alan Drury established the post of Superintendent of the Elstree laboratories and in 1949 invited Dr William A. Maycock to take this appointment. Dr Maycock had been in command of a mobile transfusion unit in France in 1940. After his return to England he joined Colonel (later Sir) Lionel Whitby at the Army Blood Transfusion Service, Southmead Hospital, Bristol. As Colonel, RAMC, he directed the Depot during its last year and joined the Lister Institute after the war (see Chapter 10). He was Consultant Adviser in blood transfusion to the Chief Medical Officer, MoH, and chaired the newly formed Regional Blood Transfusion Officers' Committee. He became Head of BPL and later its Director (Kekwick, 1981).

BPL was designed, primarily, to house facilities for the production of freeze-dried ultra-violet light (UVL) irradiated large-pool plasma. Leon Vallet had been employed by the Lister Institute in 1949 to investigate the possible inactivation of the viral infectious agent which caused the transmission of hepatitis using UVL irradiation. Routine production of UVL irradiated large-pool plasma commenced in 1950 but, following trials, the failure of the technique became



Fig. 6.4 The Blood Products Laboratory, 1954 (Courtesy of L. Vallet).

evident. It was abandoned during the construction of BPL in favour of a return to freeze-dried 10-donor small-pool plasma (L. Vallet, pers. comm.).

The potential advantage of the use of plasma fractions was not appreciated at this time and accommodation for this development was added as an afterthought. In 1952, working with R. A. Kekwick and APV Company Ltd, Wandsworth Park, London, Vallet designed a stainless steel vessel for the large-scale ether fractionation of human plasma proteins. This was to allow for increased production of plasma fractions from the current weekly 10 litres of plasma to, at first, 60 litres with provision for larger plasma volumes in the future (Vallet, 1993).

By 1954 Vallet was in charge of production at the Lister Institute and he finally moved to Elstree to supervise the installation of eight plasma dryers and the new plant for fractionation. These were housed in a single-storey building (Fig. 6.4).

At a meeting in March 1954 of the Regional Transfusion Directors (RTDs), formerly the Regional Blood Transfusion Officers, Dr Maycock asked for increased plasma supplies according to targets which he had set. By October 1955, only two Regional Transfusion Centres (RTCs) had reached their target due to difficulties in recruiting staff and providing facilities for the separation of plasma.

In 1954 and 1955, the staff at BPL were engaged in commissioning the new laboratory. During this period of transition the supply of dried plasma was maintained but the production of plasma fractions declined. By the end of 1955, the transfer of staff from the Lister Institute had been completed, but because of a combination of a deficiency in the plasma supply, difficulties with equipment and problems of scaling up the process from the pilot plant at the Lister Institute, the laboratory was not ready to work at full capacity. This situation was corrected during the next few years.²

² Lister Institute of Preventive Medicine. Reports of the Governing Body 1955 and 1956.

Chapter 7: The drying and fractionation of plasma, 1955–1978

FREEZE-DRIED PLASMA

This product was in use from the 1950s to the 1970s. It was still being manufactured at the Blood Products Laboratory (BPL) in small quantities (10,000 × 400 ml bottles) in 1978. This was due to its preference under certain circumstances by the Armed Forces and in some burns units where it was claimed that treatment could be accomplished using a smaller total volume than when plasma protein fraction (PPF, a 4.5% solution containing at least 90% albumin) was used.

Plasma for freeze-drying was aspirated from outdated blood donations at Regional Transfusion Centres (RTCs) and despatched to BPL in small pools (Fig. 7.1). In order largely to neutralize anti-A and anti-B, the 10-donor pool consisted of four group O, four group A and two group B or group AB donations. The resulting approximately two litres of plasma was stored at +4°C in sterile Winchesters before despatch to BPL.

Prior to drying, the first sterility test was performed at BPL on a sample of plasma from the Winchester. If the culture remained sterile the contents of the Winchester were dispensed in 400 ml quantities into usually four, but occasionally five transfusion bottles, initially the Medical Research Council (MRC) bottle and later the straight-sided neutral glass bottle. The residual plasma in the Winchester was cultured. The plasma was spun-frozen and stored at –25°C and if the second sterility test was satisfactory, freeze-drying took place. When this had been completed, the drying caps which allowed the escape of water vapour from the bottles were replaced with rubber closures and aluminium caps (Fig. 7.2). Finally, air

was withdrawn from the bottles and replaced with ‘oxygen-free’ nitrogen (E. D. Wesley, pers. comm.).

The maintenance of sterility at the RTCs was a major problem and a significant number of Winchesters held contaminated plasma detected on the first sterility test. As early as 1949¹ it was suggested that staff in RTCs carried out a minute overhaul of the syphoning technique, treat the floors of the plasma laboratory with spindle oil every 3 months and consider installing ventilation with sterile air. It was noted that a suitable ventilator built to MRC specifications was supplied by Air Control Installations Ltd, Ruislip, Middlesex.

A total of eight drying plants were installed. Initially, technical difficulties with both vacuum and refrigeration systems made it difficult to maintain a dependable drying operation. Each drying chamber held 152 transfusion bottles

¹ Minutes of meeting of Regional Transfusion Directors, 23/2/49.

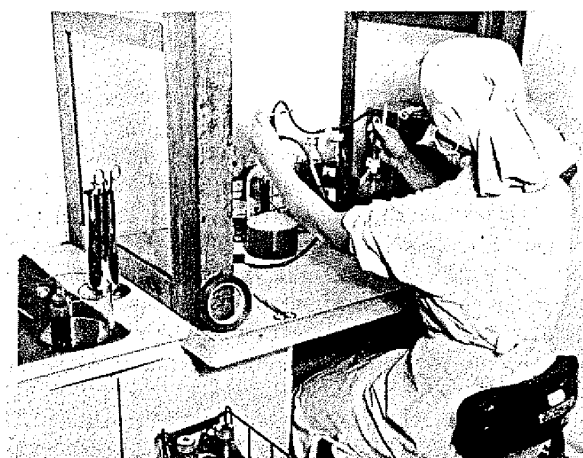


Fig. 7.1 Aspirating plasma into a Winchester (Courtesy of J. F. Harrison).



Fig. 7.2 Dried plasma in transfusion bottles. The two bottles in the foreground are fitted with drying caps. Note that the dried plasma has retained its frozen shape (Courtesy of L. Vallet).

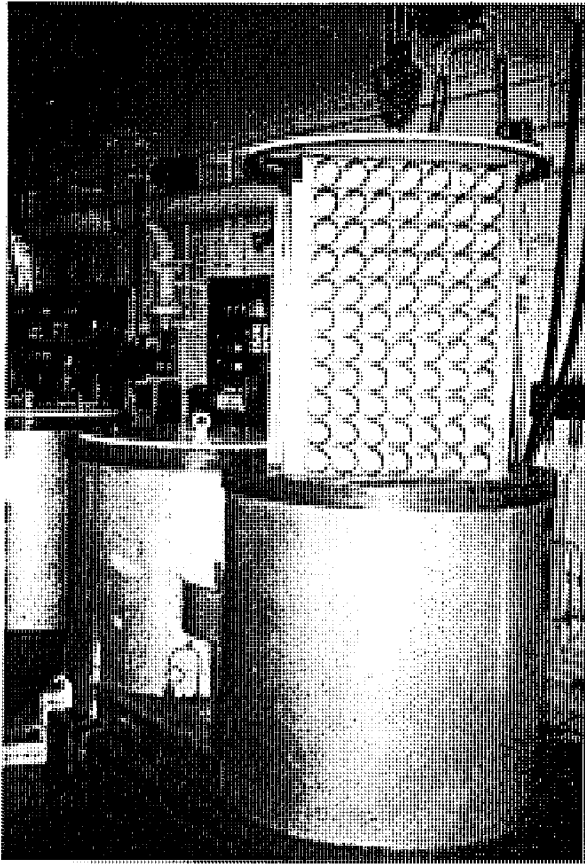


Fig. 7-3 Primary desiccator ready for unloading after a drying run. (Courtesy of L. Vallet).

(Fig. 7-3) and with two loads each week there was a potential for drying almost 120,000 bottles per year. In practice the average yearly output totalled 90,000 bottles. This quantity was achieved during the 1960s and continued until 1973 when the number declined with the increasing use of PPF (Table 7-1).

Accommodation for work on plasma preparatory to freeze-drying was increased in 1962. This was achieved by moving bacteriology and enlarging the small-pool plasma laboratory. Also, the plasma drying plant was refitted with large capacity single-stage vacuum pumps and refrigerator compressors of more advanced design. These gave lower condenser temperatures and made it possible to shorten the plasma-drying time. To achieve this it was necessary to devise a method for regulation of both temperature and duration of the heating during the later stages of drying.²

PLASMA FRACTIONS

It was noted at the end of the last chapter that the production of plasma fractions declined following the transfer of the

Table 7-1 Issues of freeze-dried plasma 1973–1978

Year	No. containers 400 ml freeze-dried plasma
1973	91,527
1974	68,640
1975	8210
1976	8724
1977	16,746
1978	13,893

technology to Elstree in part due to the problems encountered in scaling up the fractionation process from the pilot plant. A major factor was the delay which resulted from the carry-over of ether from the final precipitates of the fractions. Being oil-soluble, ether contaminated the oil of the vacuum pumps and this had to be changed before the pumps could achieve an adequate degree of vacuum for drying to proceed. The addition of a liquid nitrogen trap to condense the ether improved matters, but, later, a new design of pump unaffected by ether became available.

Also, it was necessary to improve the separation of protein precipitates in large-scale fractionation. Vallet achieved this by employing continuous flow centrifugation following resuspension of the precipitates without preliminary removal from the centrifuge bowl (L. Vallet, pers. comm.).

Using the ether fractionation process for a period up to the early 1960s, fibrinogen, thrombin, gammaglobulin (immunoglobulin) and albumin were prepared. In 1956, the ether fractionation of anti-haemophilic factor (AHF) from the fibrinogen fraction was adapted to allow a medium-scale operation to proceed (Kekwick & Wolf, 1957).

By 1963 it became evident that a much larger plant was required and planning commenced for a significant extension. Primarily the extension was to provide more normal immunoglobulin since there was an increasing demand for this product for the prevention of rubella during pregnancy. The steep rise in demand for AHF concentrates was not foreseen at the time and the plans had to be modified later to accommodate this. Later still, it was recognized that all plasma would have to be fractionated and that the freeze-dried small pool plasma would be replaced by albumin and PPF.

Another major decision taken in 1963 was to change from ether to ethanol fractionation. The explosion hazard with ether was an ever-present potential danger. The electrical equipment had to be a 'flameproof' grade similar to that used in coal mines. Antistatic rubber was required for tubing and boots and antistatic cotton for laboratory coats. Anaesthesia was another hazard and more than one member of the staff

² The Lister Institute of Preventive Medicine. Report of the Governing Body, 1963.

had to be assisted into the fresh air to recover. In particular, a near victim was a laboratory assistant, an old soldier, who had no sense of smell and delivered the ether to the laboratory from the outside 'inflammable' store! (L. Vallet, pers. comm.)

Also, to avoid unwanted contamination of the product, the grade of ether had to be free from stabilizers which are added to ether to prevent the formation of organic peroxides. Unfortunately, these peroxides which formed on storage inactivated factor VIII. This led to large quantities of ether being rejected and returned to the manufacturer. Vallet and David Wesley, a Nottingham graduate in pharmacy with industrial experience, carried out experiments on small-scale fractionation of plasma using ethanol. In September 1963, an experimental cold laboratory equipped to fractionate 60-litre pools of plasma was commissioned.³

Plans for the new building were finalized in 1965, it was taken over in February 1972 and processing was commissioned during the following months. It became possible to prepare plasma fractions by the end of that year which reached their planned levels by the end of 1973.⁴ Unfortunately, a major defect in the floors of the sub-zero temperature laboratory, first noted in 1973, proved to be extensive. This defect did not affect production in 1974, which was determined by the volume of plasma supplied from the RTCs. During the first half of 1976 the floors in this laboratory and the adjoining rooms had to be replaced, together with the insulation of the -25°C cold rooms. This caused considerable disruption to production. However, when this corrective work was completed during the second half of 1976, batches of plasma of 1500 litres were successfully fractionated.⁵ By this means, much of the shortfall was recovered. Albumin was heated in ovens rather than water baths and a cost-effective low-pressure distillation was used to remove ethanol. Also, in 1976, parts of the original building were adapted for the projected increase in AHF concentrate in accordance with the plans of the Department of Health and Social Security (DHSS).⁶ This conversion was completed early in 1977.

Following the opening of the extension in 1972/73, BPL operated three distinct fractionation plants:

- *coagulation fractions*, using fresh frozen plasma for the preparation of factor VIII, factor IX and fibrinogen;
- *'large' fractions*, using time-expired plasma, depleted plasma from the coagulation fractions and supernatants from specific antibody plasma fractionation to prepare normal immunoglobulin and PPF or albumin;
- *specific immunoglobulins*, using high-titre antibody plasmas.

It is pertinent to consider in more detail the production and use of these plasma fractions.

Lister Institute of Preventive Medicine. Reports of the Governing Body, ³ 1964, ⁴ 1973, ⁵ 1976, ⁶ 1977.

Coagulation fractions

Anti-Haemophilic Factor (AHF, factor VIII) As early as 1950, the MoH were informed that the medical and social needs of haemophilia patients were not being met adequately in the UK. At a meeting convened by the MoH it was suggested that certain measures should be taken to correct this deficiency. These included the compilation of a national register of haemophiliacs to determine the magnitude of the problem, the need for diagnostic criteria, the recognition of treatment centres, the involvement of almoners, schooling and employment and the education of the medical profession.

Dr R. G. Macfarlane agreed to contact interested parties. Later in 1950, Dr Maycock suggested that haemophiliacs should carry cards stating their blood group and treatment centre.

The treatment of haemophilic haemorrhage at this time consisted of transfusion with freshly collected whole blood. It was known that the fibrinogen fraction precipitated by the ether treatment of plasma contained AHF. Studies were commenced at the Lister Institute to isolate this component and by 1954 small amounts were available (Kekwick & Wolf, 1957). Although clinical trials had not been carried out, the AHF was used at least on one occasion to treat a gravely ill patient (L. Vallet, pers. comm.). It was not until 1956 that it was possible to obtain several batches of AHF from this source. It was shown to be successful in controlling bleeding during various surgical and dental operations on haemophilic patients. In the 1957 Report of the Governing Body of the Lister Institute it was commented that "the preparation of large quantities of AHF presents many difficulties and it is unlikely that more than very small amounts can be made available for some time to come." The MRC Haemophilia Committee, formed in 1954 to investigate haemophilia and its treatment, was given the responsibility for allocating available supplies of AHF.

To supplement the supply, the MRC recommended that bovine (Maw and Son) and porcine (Crookes) AHF be made available to Haemophilia Centres. The supply was inadequate to meet demand and the cost was 10 d. per ampoule.

Production of relatively small quantities of AHF was maintained during the next few years. The product was largely distributed to three hospitals; the Lewisham and Hammer-smith Hospitals in London and the Radcliffe Infirmary in Oxford. By 1959, 75 haemophiliacs had been treated. Batch to batch variation of potency was a problem.⁷

A clinical trial of AHF prepared by BPL was initiated in 1960 by an MRC Working Party. The subjects chosen for the trial were haemophiliacs undergoing dental surgery. It was hoped to devise a scheme of dosage of AHF related to the clinical severity of the disease and the scope of the surgical

⁷ Lister Institute of Preventive Medicine. Reports of the Governing Body 1959

intervention proposed. It was also hoped to investigate the reactions which occurred after the administration of certain batches of AHF.⁸

However, there was a problem in the assay of AHF as none of the available methods was entirely satisfactory; the methods required haemophilic plasma which was difficult to obtain and the standard against which the AHF was assayed was normal human plasma, the AHF content of which varied from person to person and possibly within the same person at different times.⁸ Although attempts were made to find batches of AHF which could be used as standards, the problem was not solved until the late 1970s.

Investigations during 1964 revealed that human AHF was dependent upon pH, with greatest stability at pH 7.1–7.2. Below pH 6.5 and above 7.5 the rate of loss of activity increased rapidly. Acid citrate dextrose (ACD), the standard anticoagulant in use at that time has a pH of 5.0 rising to about 6.8 on the addition of blood. Trisodium citrate anticoagulant, which has a pH of 7.5 to 7.6 tends to become more alkaline through loss of carbon dioxide following blood storage. Neither is optimal for obtaining plasma with as high a content of AHF as possible.

In vitro experiments performed by Kekwick and Goldsmith on the stability of AHF and red-cell fragility on a phosphate-buffered citrate anticoagulant solution (CPD) in which the pH was stabilized at 7.1 to 7.2 were encouraging.⁹ CPD later became the standard anticoagulant for blood collection.

During 1967 a Haemophilia Centre was established at the Churchill Hospital, Oxford, in succession to the MRC Coagulation Research Laboratory. It comprised a clinical section, a coagulation research laboratory and a plasma fractionation laboratory. Following discussions between the Ministry of Health, the MRC and the Board of Governors of the United Oxford Hospitals, the Lister Institute agreed to administer the Plasma Fractionation Laboratory (PFL) together with BPL because of the similarity of the work of the two organizations and the benefits which would accrue from their close association. The work of PFL was to be concerned with the separation and purification of coagulation factors for clinical use.¹⁰ PFL became operational in mid-1968 with Dr Ethel Bidwell as Head of the laboratory.

During the next few years there were significant developments with respect to the provision of therapeutic concentrates of factor VIII (a term now more commonly used than AHF). Preparations based on the method of Blomback (1958) were manufactured at BPL and PFL between 1968 and 1972, but were poorly soluble and of low potency and specific activity. Establishment of the method of Newman *et al.* (1971) at PFL from 1970, and subsequently at BPL, allowed intermediate and highly specific activity preparations to be made available. The improved solubility of these preparations made

possible self-administration and home therapy. An improved intermediate specific activity factor VIII concentrate became available at PFL and BPL laboratories during 1978. With higher potency (about 12 iu/ml), the product was suitable for injection by syringe. This product remained in use until 1985 when it was replaced by a direct variant (coded 8Y) which incorporated terminal dry heating (T. J. Snape, pers. comm.). This product will be considered in more detail in Chapter 8.

In 1969, Dr Drummond Ellis, who had worked with Cohn at Harvard and had established the Plasma Fractionation Centre in Edinburgh, joined BPL. He worked on the stability of AHF extracted from plasma with ethanol instead of ether and, significantly, with Ethel Bidwell investigated the sequential recovery of additional coagulation factors (i.e. fibrinogen and factor IX) from the supernatant following the cryoprecipitation of factor VIII.¹¹

This significant discovery by Pool (1970) was a landmark in the preparation of factor VIII concentrates. Factor VIII prepared by the ether technique of Kekwick and Wolf or by the Blomback method depended on liquid plasma as the starting material. A practical advantage from the use of frozen instead of liquid plasma was that it was possible for all RTCs to contribute plasma for factor VIII production whereas the supply of liquid plasma could be obtained only from early blood-collection sessions at RTCs near to Elstree and Oxford.

Also, once the extended plant had been completed at BPL, it was necessary to replace the small-pool liquid plasma in Winchester. Consequently, 25–30 donations of plasma were aspirated into a 5-litre polythene pack, commonly known throughout the Transfusion Service as the 'Vallet' pack (Fig. 7.4). Two packs were frozen simultaneously to –25°C in a freezer manufactured by Grant from a prototype designed and built at BPL (Fig. 7.5).

Its uniform rectangular shape when frozen allowed large quantities to be stored with great efficiency. It was intended for outdated plasma, which could be thawed easily by placing the packs on heated shelves and allowing the thawed plasma to drain into process vessels. The system could be adapted readily for the freezing of plasma within 18 h of collection in order to increase the yield of factor VIII following fractionation. The collection of fresh plasma was facilitated by the use of plastic blood-collection packs which were generally in use by 1972. The cost of the plasma pack was 18p and the cardboard box for transportation was 3p.

Factor VIII production in the early 1970s failed to meet the increasing clinical demand. Figure 7.6 shows that the principal product used to treat haemophilia was cryoprecipitate prepared in RTCs. By 1973 commercial factor VIII concentrate was purchased by Regional Health Authorities (RHAs) to supplement the BPL product.

Lister Institute of Preventive Medicine. Report of the Governing Body, ⁸ 1960, ⁹ 1964, ¹⁰ 1968.

¹¹ Lister Institute of Preventive Medicine. Report of the Governing Body 1970.



Fig. 7-4 Plasma pack for 25–30 donations frozen at -25°C . (Courtesy of L. Vallet)

In December 1974, the Department of Health and Social Security (DHSS) proposed to increase factor VIII production with the intention of developing self-sufficiency in this product within 2–3 years. For this purpose, the cost of providing the necessary facilities could amount to £0.5 million with a recurring expenditure of up to £1.0 to £1.5 million.¹²

During 1974, 11,678 litres of fresh plasma were sent to BPL from nine of the fourteen RTCs in England and Wales. Almost half this quantity was collected at the Oxford Centre. Plans were made to increase the total of fresh plasma sent to BPL to 49,500 litres from 275,000 donations of blood in 1975. This target was achieved and resulted in a significant increase in the availability of factor VIII and, in 1977 and 1978, there were further increases in production. It can be seen from Fig. 7-6, however, that demand had continued to escalate and increasing quantities of factor VIII were purchased from commercial sources. Self-sufficiency had not been achieved.

Factor IX During the 1970s, the development of factor IX production was undertaken at PFL, Oxford. In 1969 it was

¹² Letter from DHSS to Regional Administrators, December, 1974.

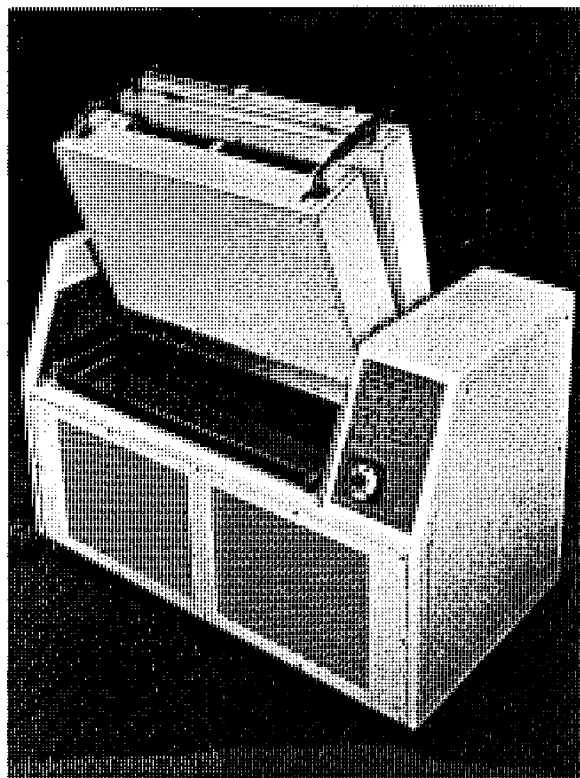


Fig. 7-5 Grant's freezer for the simultaneous freezing of two plasma packs (Courtesy of L. Vallet).

found that a clinically useful factor IX could be obtained from the cryosupernatant after extraction of factor VIII.¹³ The use of adsorption on DEAE cellulose led to the preparation of a more stable and highly purified factor IX preparation which was more concentrated than earlier preparations.¹⁴ Factor IX concentrates were, in practice, a mixture of coagulation factors II, IX and X (Dike *et al.*, 1972).

Lister Institute of Preventive Medicine. Reports of the Governing Body, ¹³ 1969, ¹⁴ 1970.

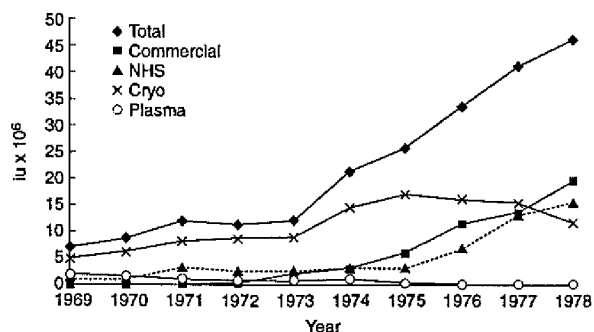


Fig. 7-6 Issues of factor VIII, 1969–1978.

By 1973, the production of factor IX complex at PFL was sufficient in quantity to treat all the cases of Christmas Disease (haemophilia B) in England and Wales and this self-sufficiency was maintained for many years.

Other coagulation factor products

Factor VII Ross Dike and his colleagues at PFL (1977) prepared factor VII concentrate from the cryosupernatant, after removal of factors II, IX and X by adsorption on DEAE-sepharose. By 1978, this product was being used to treat two patients congenitally deficient in factor VII, one on a regular basis and the other prior to tooth extraction. The DEAE-sepharose treatment did not affect the subsequent sequential fractionation of immunoglobulin (IgG) and albumin.

Factor XIII and Antithrombin III concentrate Both of these products were developed at PFL, Oxford in 1978/79.

LARGE FRACTIONS

Plasma protein fraction

At a meeting of the Regional Transfusion Directors on 28 October 1964, Dr Maycock informed those present that BPL proposed to prepare a stable plasma protein solution (later called plasma protein fraction, PPF) instead of dried small-pool plasma. Dried plasma carried the risk of transmitting hepatitis and was tedious to prepare as it involved multiple sterility tests. PPF which could be rendered non-infectious by heating at 60°C for 10 h was replacing dried plasma in many countries. It contained at least 90% albumin (see Chapter 8), no fibrinogen or gammaglobulin and little potassium. The colloid osmotic activity was equivalent to that of dried plasma and its life, when stored at room temperature, was 2–3 years.

For nearly a decade, PPF was prepared only in pilot-scale quantities. A significant increase in production became possible with the commissioning of the new plant at BPL in 1972/73 and the quantities prepared increased during the mid-1970s (Fig. 7.7). In addition to the 400 ml × 4.5%, a bottle containing 100 ml × 4.5% PPF was prepared from 1977. Dried salt-poor albumin was produced in 25-g quantities but was phased out in 1980. This had been replaced by a 100 ml × 20 g albumin solution in 1976.

Normal immunoglobulin

During 1956, the MRC set up a sub-committee to arrange for the collection of information on patients with hypogammaglobulinaemia with a view to establishing the authenticity of reported cases and to organize a clinical trial of prophylactic gammaglobulin. Kekwick and later Vallet under-

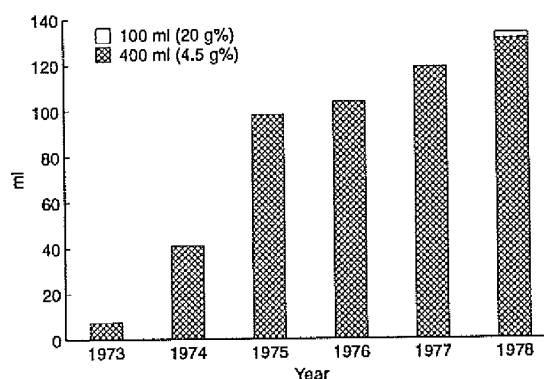


Fig. 7.7 Issues of PPF, 1973–1978.

took to estimate electrophoretically, the gammaglobulin (now known as immunoglobulin) content of serum samples from suspected cases.¹⁵

This began a long association between BPL and the MRC Working Party on Hypogammaglobulinaemia. The clinical trial lasted 12 years and the normal immunoglobulin for the trial was prepared at BPL. Following the conclusion of the trial, BPL, in association with Assistant Secretary of the Working Party, were responsible for the calculation and preparation of the doses of immunoglobulin for affected patients.

Once again, normal immunoglobulin could not be produced in sufficient quantities until the 1972 expansion. Thereafter, production of the 250-mg and 750-mg doses increased significantly. The 15-mg dose for use with measles vaccine was introduced in 1976 (Fig. 7.8).

Specific immunoglobulins

Of all the immunoglobulins produced during this period, anti-D immunoglobulin proved to be the most exciting and, arguably, led to one of the most significant immunological developments during the 1960s.

In 1964 BPL were invited to collaborate with Professor (later Sir) Cyril Clarke in the Department of Medicine at Liverpool University and Dermot Lehané at the Liverpool RTC to prepare anti-D immunoglobulin for clinical trials to assess its value in preventing haemolytic disease of the newborn. Results of the trials showed that if the immunoglobulin was administered within 36–48 h of delivery, Rh-positive cells from the infant were removed from the maternal circulation and maternal Rh allo-immunization was prevented (Combined study, 1966).

During the next few years a method for preparing anti-D immunoglobulin was developed at BPL (Maycock *et al.*,

¹⁵ Lister Institute of Preventive Medicine. Report of the Governing Body, 1957.

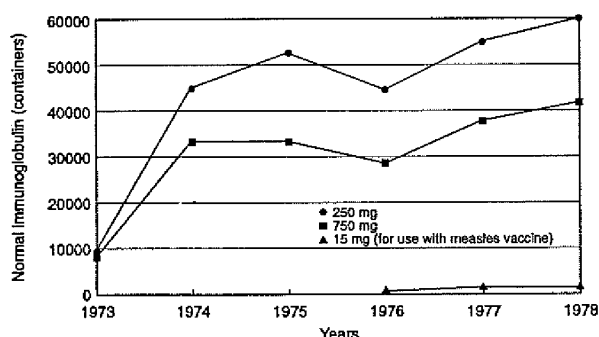


Fig. 7-8 Issues of normal immunoglobulin, 1973–1978.

1970). Following the successful outcome of the trials in Liverpool and elsewhere, there was a demand nationwide for the product for use in the prevention of haemolytic disease of the newborn. However, the optimum dosage had not been determined in the early trials and the MRC Working Party on the use of anti-D immunoglobulin looked into this aspect.

It was proposed that, initially, treatment should be given to Rh-negative primiparae and women with no living children who gave birth to ABO compatible Rh-positive children. It was calculated, based on births in 1964, that 24,000 women would require immunoglobulin annually. Based on 1 ml of a 10 g/% solution, the dosage used until mid-1967, some 750 litres of anti-D plasma or about 3000 donations would be required.

The main source of this plasma was females who had been immunized as a result of Rh-incompatible pregnancy or transfusion. Deliberate immunization of Rh-negative male volunteers at this time was discouraged until the success of the therapy had been clearly established by observations in second pregnancies. The 'boosting' of anti-D levels in post-menopausal immunized women was considered to be justified. The ABO compatible Rh-positive cells used were obtained from donors without a history of hepatitis, at least five of whose previous donations had been shown, by direct follow-up of the recipients, not to have been associated with hepatitis. The use of plasmapheresis to increase the yield of plasma was considered.¹⁶

Later, in 1966, it was agreed that three RTCs, Newcastle, Sheffield, and Cardiff would undertake the 'boosting' of already immunized men of any age and post-menopausal women. There should be expansion of plasmapheresis at Liverpool and Edgware in order to obtain wider experience of this procedure. Other RTCs would concentrate their efforts on collecting normal donations from immunized individuals with acceptable anti-D titres, i.e. greater than 1 in 8 at that time. The MoH undertook to investigate the provision of finance for the extra staff required. The problems of distribution and ethical aspects required consideration.¹⁷

The quantity of anti-D plasma sent to BPL from the RTCs gradually increased. However, the antibody content was

generally disappointing. The discovery by Hughes-Jones and Stevenson (1968) of the radioisotope technique for assaying anti-D led to the use of a dose of 200 µg anti-D. An additional criterion for treatment was introduced by the finding of fetal cells in 50 fields in the Kleihauer test.¹⁸

Incoming plasma still had to be expressed in albumin titres as the Hughes-Jones technique was not suitable for large numbers of assays at RTCs. Gradually the minimum acceptable anti-D titre for plasma donations rose to 1 in 64 and then to 1 in 128 since by 1970 the fractionating capacity at BPL was reached and the only way to increase the number of treatment doses was to increase the potency of the incoming plasma.¹⁹ Even this did not significantly increase the anti-D content of the plasma pools which, on average, contained between 15 and 20 µg/ml of anti-D with an occasional pool exceeding 20 µg/ml.

There was pressure on the DHSS to increase the categories of mothers who could be treated with anti-D immunoglobulin.¹⁹ During the early 1970s, increasing numbers of male volunteers were immunized with D-positive cells and this helped to increase anti-D levels in plasma. However, clinical trials in 1972 carried out by the MRC Working Party on the use of anti-D immunoglobulin demonstrated that, in the great majority of fetal transplacental haemorrhages following delivery, a 100-µg dose was as effective as one of 200 µg, but a definite conclusion could not be reached until a comparison could be made of the incidence of sensitization in the next pregnancies (MRC Report, 1974).

Adopting the 100 µg dose doubled the available quantity of anti-D immunoglobulin. Additionally a 50 µg dose was used for early terminations of pregnancy. During the late 1960s approximately 20,000 to 30,000 doses of anti-D immunoglobulin were produced annually. By 1973 this had risen to almost 73,000 × 100-µg doses and a level of 60,000–70,000 was maintained during the remainder of the decade. (Fig. 7-9). This quantity enabled self-sufficiency to be achieved and maintained.

Minutes of meeting of Regional Transfusion Directors, ¹⁶ 22/6/66, ¹⁷ 22/10/66, ¹⁸ 02/10/68, ¹⁹ 22/07/70.

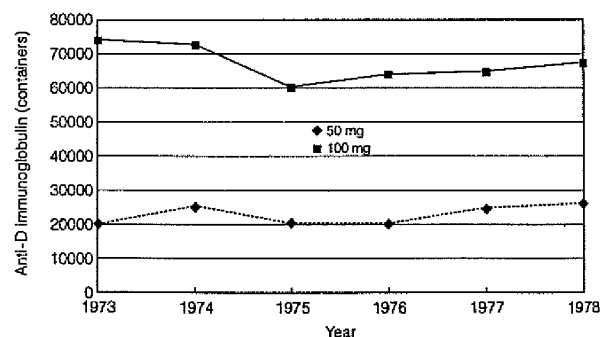


Fig. 7-9 Issues of anti-D immunoglobulin, 1973–1978.

Other specific immunoglobulins

Relatively small quantities of anti-tetanus and anti-HBs were produced (although there was a significant increase in the latter immunoglobulin from about 600 ampoules to 1400 ampoules per year between 1974 to 1975). Anti chicken-pox/varicella was prepared in increasing quantities during the 1970s. By far the greatest problem in the preparation of these specific immunoglobulins was the collection, by the RTCs, of convalescent plasma with adequate potency. The production of anti-rabies immunoglobulin from plasma from immunized individuals commenced in 1977.

The end of an era at BPL was marked in 1978 because it coincided with the closure of the Lister Institute at Elstree and the retirement of the first Director, Dr W. d'A Maycock (3, 7-10).

The authors are indebted to Mr Leon Vallet who became Deputy Director to Dr Maycock in 1954 for the following appreciation of BPL's first Director.

"In 1954, we had moved into the new Blood Products Laboratory where he had fought hard to get a good standard of building in the times of post-war shortage. He had secured plastered walls rather than painted brick but the floors were plain granolithic. One of the first tasks was to have them treated to control the dust that came off them.

"Every Wednesday he would be at the Ministry of Health. Though the name and location changed, it remained Wednesday until his retirement, although latterly this work took up more of his time. During the rest of the week he would spend some of his time in his laboratory where he had a full-time physiologist to assist him in his research on the metabolic fate of injected dextran. He went on to investigate immunological responses to dextran in collaboration with John Humphries who was working at the MRC laboratories at Mill Hill. Those studies are well remembered by a few of us for the sore arms following injections.

"Later, when Margaret Mackay joined us from Chelsea, they moved on to pharmacological studies on plasma proteins, especially those associated with kinin activity. His laboratory assistant for all this period was a young Brian Combridge who was to go on to show remarkable skill and ingenuity in many fields, notably when he took on the fickle, early assay methods for factor VIII, then going on to methods for testing for HBsAg which culminated in the BPL radio-immune assay (Chapter 5).

"For Bill Maycock, perhaps those were idyllic years following the diversity of problems which go with starting up a new laboratory in which there was novel equipment and considerable increase in scale of operations. Though many of the technical difficulties were not in his field he would quickly grasp their essentials and, more importantly, see their implications and help us in obtaining the best advice and course of action. Looking back we were rather disciplined unit in a military sense. I think the time in the RAMC

had left its mark and many of our staff had been in one or other of the services, so perhaps this was not surprising.

"By the time we were approaching the 1960s it was becoming clear that an appreciable increase in the scale of fractionation was required, primarily at the time to provide more immunoglobulin including a new requirement for maintenance doses for patients with hypogammaglobulinaemia. Before plans for that scale of increase were completed a decision was made to fractionate all our plasma intake and discontinue dried plasma so that it could be replaced by a heat-treated albumin fraction which would not transmit hepatitis. This proposal was finally approved by DHSS but, when it came to detailed planning for costing and placing of contracts, the MRC decided to discontinue its by then thoroughly established role as an agent for DHSS. At that time they had a major project of their own underway, the Clinical Research Centre at Northwick Park. The outcome for us was that the (Lister) Institute was asked to act as an agent of the Department on BPL matters.



Fig. 7-10 William d'Auverne Maycock, Kt, CBE, MVO, MD(McGill), FRCP, FRCPath. 1911–1987 (courtesy of M. Contreras)

"It was unfortunate that the last years before his retirement were such demanding ones for BPL. By then the Medicines Inspectorate had us in its sights and we were due for their visits. As things turned out it was no great surprise that the old buildings would not qualify for a manufacturing licence; BPL was stretched to its limit as a Production Unit. Finally, the news came that the Lister Institute was closing its Elstree laboratories. This caused a mass of work concerning the conditions for terminating our link with the Institute and the provision for the continuation of BPL within the NHS.

"Sir William d'A. Maycock retired, not in good health, at the age of 67 years on 1 October 1978 on the day of the management transfer of BPL, as a provisional arrangement, to the North West Thames Regional Health Authority."

Bill Maycock died on 19 February 1987 at the age of 76. In his obituary in the *Lancet* on 4 April 1987, Professor P. L. Mollison commented "he was a wonderful ambassador for this country, invariably considerate and courteous, able to substantiate with detailed information any suggestions which he made; totally free from intrigue or plans for self-advancement and always willing to take on work for others."

Chapter 8: The fractionation of plasma, 1979–1993

In his final report in 1978, Dr Maycock commented that the estimates for factor VIII concentrates and albumin production on which the 1965 plans were based had been inadequate.¹ In an attempt to remedy this situation, albeit partially, a 'stop-gap' policy was introduced. This was conceived as a two-phase increase in production of factor VIII from 12 million units each year to 24 million and of PPF and albumin from 135,000 × 400 ml bottles to 180,000. The aim was to achieve these targets in about 4 years. 'Stop-gap' was approved by the Department of Health and Social Security (DHSS) and commenced in June 1978.

Whilst, in general, targets were met in 1979, it can be seen from Fig. 8-1 that the demand for factor VIII was more than double that produced by the NHS in the form of concentrate and cryoprecipitate. The difference was made up by the purchase of imported commercial product by Regional Health Authorities (RHAs). Both Dr Maycock and Dr Richard Lane, the Director-designate of the Blood Products Laboratory (BPL), appointed on 14 April 1977, pointed out that there was an urgent need to commence planning for the future provision of plasma products for England and Wales. They were faced with a dilemma. Upgrading the existing buildings to meet the projected requirements would take at least 5 years and continued production would be compromised. Also, the core buildings would be effectively 18 years old. The time from concept, through detailed design, to building and commissioning of a new purpose-built factory would be longer still. However, some production could continue whilst building took place.

There was little choice, as matters concerning the upgrading of BPL were hastened by an adverse report on their quality assurance by the Medicines Inspectors following a visit in September 1979. The Director commented in his

report, dated 1981, that there was little or no demarcation of laboratory, processing and aseptic areas. Because the design and constructional standards for the facility pre-dated Good Manufacturing Practice, there was not much scope for corrective action.²

Nevertheless, a Medicines Act Remedial Programme (MARPO1) was implemented in 1981 and 1982 in an attempt to correct at least some of the deficiencies noted by the Medicines Inspectors. The principal remedial action was concerned with the production of coagulation factors and albumin. However, other capital projects were undertaken including improvements to the virology laboratory, to the microbiology department based in the Lister Institute bacterial vaccines laboratory and the sterile suite. An additional freeze-drying machine was installed.

From 1978, following the closure of the Lister Institute on the Elstree site, BPL and the Blood Group Reference Laboratory (BGRL) were managed by the NW Thames RHA through a Joint Management Committee (JMC) with DHSS.

The remedial work, detailed above, was regarded as a temporary solution only. The Policy Steering Group of the JMC, with advice from the Advisory Committee on the NBTS on plasma throughput, recommended the construction of a new BPL large enough to make England and Wales self-sufficient in blood products. Self-sufficiency was based on an annual quantity of plasma of 400,000 to 450,000 kg in order to produce 2 iu factor VIII and 200 kg albumin per million of the population (Gunson, 1984). A second feature of the new BPL was that it should be capable of extracting all therapeutic products from plasma.

On 1 December 1982, the DHSS created the Central Blood Laboratories Authority (CBLA). The CBLA, a Special Health Authority, was expected to provide effective management for the central laboratories and to maintain a strong working relationship with the Regional Transfusion Centres (RTCs). To recognize the role of BPL as a large-scale manufacturing plant, the membership of CBLA included, in addition to the Chairman, Mr David Smart, two persons with long experience in the pharmaceutical industry (Table 8-1).

At this time the main tasks of BPL and PFL were defined thus:

- “(i) to prepare plasma fractions for therapeutic, diagnostic and other use in accordance with the requirements of

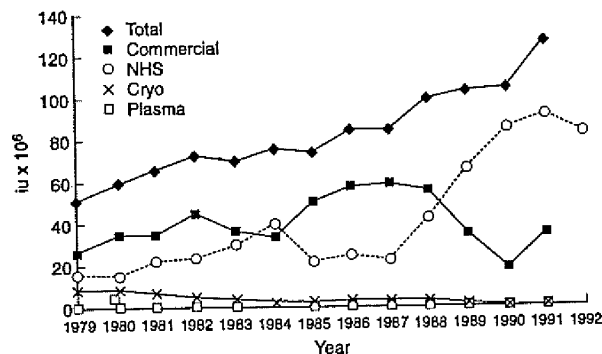


Fig. 8-1 Issues of factor VIII, 1979–1991 (—◆— total, —■— commercial, —○— NHS, —□— plasma, —×— cryoprecipitate).

¹ Report to the Advisory Sub-committee on Blood Products of the Central Committee of the NBTS, year ending March 1978.

² Blood Products Laboratory. A summary of performance since September 1979, Report by the Director, 1981.

Table 8-1 Inaugural members of the Central Blood Laboratories Authority.

Chairman:	Mr R. D. Smart*
Members:	Professor A. L. Bloom
	Dame Phyllis Friend
	Dr H. H. Gunson
	Dr E. L. Harris
	Mr A. S. Jerwood*
	Dr G. A. Stewart*
	Mr M. G. Storey
	Dr D. P. Thomas

* Members with experience in the pharmaceutical industry.

- Good Manufacturing Practice and in the quantities that management shall from time to time determine;
- (ii) to undertake research and development in plasma protein fractionation and related fields, production technology and plant design;
 - (iii) to undertake other activities, including collaboration with industry, as can in the Secretary of State's opinion conveniently be carried out in conjunction with the foregoing".³

BGRL's tasks were defined at the same time and will be included in Chapter 9.

During the 1980s there was considerable activity at BPL. The construction of a new building on a 'fast track' basis,

³ Annex to a letter from the Secretary of State for Social Services to Mr R.D. Smart, Chairman CBLA, 17 November 1982.

i.e. planning and building undertaken concurrently, had to be monitored closely whilst manufacturing plasma products in the old building. Other matters which had a major influence on these activities were the AIDS crisis, the introduction of charges for BPL products and the withdrawal of Crown Immunity in the National Health Service and Community Care Act (1990), which meant that both plant and products had to be licensed.

Building commenced in April 1983, but was not completed as scheduled in 1986. However, it was sufficiently close to completion to arrange an official opening by HRH The Duchess of Gloucester at the end of April 1987 (Fig. 8-2). Commissioning of the new facility and transfer of processing from the old buildings were managed in overlapping phases. The manufacture of factor VIII was given priority and was transferred, commissioned and scaled up in a programme beginning in November 1987. Supernatant from factor VIII production was returned to the old plant for the recovery of albumin and immunoglobulin by ethanol fractionation. The latter process was transferred to the new factory in late 1988 when commissioning problems had been overcome. Simultaneous operations in both buildings meant that at no stage was throughput interrupted; the cost was the delay in full commissioning of the new facility.

Manufacturer's Ordinary and "Specials" Licences and a Wholesale Dealer's Licence were granted in January, March and July of 1991, respectively. Product licences for factor VIII (type 8Y), 4.5% and 20% human albumin solutions and normal intramuscular immunoglobulin were also granted in the first quarter of 1991. The manufacture of other



Fig. 8-2 The new BPL, 1987.



Fig. 8.3 BPL products, 1995.

products continued by licences granted under transitional arrangements pending reviews of product licence submissions by the Medicines Control Agency (MCA). BPL now have a wide range of plasma products; of those shown in Fig. 8.3 only anti-D immunoglobulin has a transitional licence.

A new building for research and development (R&D) was completed in 1992 and was staffed by persons working at Elstree and PFL. The staff working at PFL had a distinguished record in R&D during the 1980s, as will be noted later. Dr Bidwell retired in 1981 and PFL continued under the direction of Dr Jim Smith until its closure in March 1992.

Prior to 1990, RTCs had acted on behalf of the hospitals for receipt of BPL's products which were free of charge. In line with other changes in the NHS, from that date BPL was required to charge for its products. Initially, the majority of contracts were between BPL and RTCs (in effect RHAs). However, over a period of time the number of regional contracts declined and BPL dealt directly with their customers. In order to carry out this work effectively, a commercial department was created. BPL representatives travelled

throughout England and Wales and attended national scientific meetings to advertise its products. Only in this manner could BPL compete with commercial product sales.

Mr R. W. (Ron) Wing succeeded Mr Smart as Chairman of CBLA on 1 December 1988. Mr Wing, like his predecessor, had many years' experience in the pharmaceutical industry. He chaired CBLA until it was superseded by the National Blood Authority on 1 April 1993. The name Bio Products Laboratory replaced Blood Products Laboratory in 1990.

The first Chief Executive, Mr Bernard Crowley, was appointed in December 1987. He was succeeded on his retirement in 1992 by Mr Richard Walker. Dr Lane left BPL in 1993.

THE PLASMA SUPPLY

It is pertinent to consider how the RTCs responded to the commissioning of the new BPL by increasing the plasma

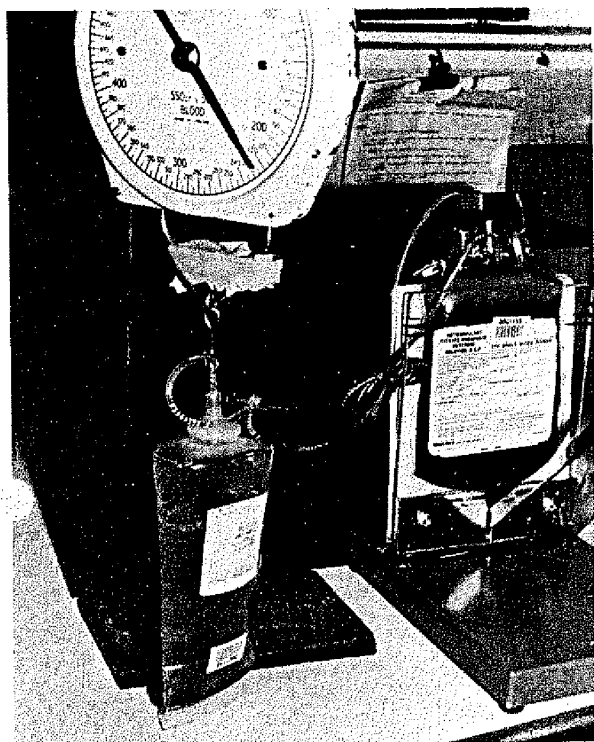


Fig. 8.4 The single, 'wedge', plasma pack (Courtesy of J. F. Harrison).

supply. Between 1979 and 1993, the product which determined the volume of plasma needed was factor VIII. If demand could be satisfied for this product, sufficient supernatant from cryoprecipitation was available for the preparation, in adequate quantities, of other coagulation factors, IgG and albumin.

The plasma sent to BPL in 1979 was pooled into 5-litre packs as previously described (Chapter 7). At the RTC, the connecting line of individual transfer packs had to be opened so that plasma could be expressed into the pool. This constituted an 'open' system and was criticized by the Medicines Inspectorate as an undesirable procedure to be carried out in general laboratories. Measurement of total viable bacterial counts indicated that, for plasma at least, the risks were largely theoretical. However, concern remained that the cellular components might be compromised by such open processing. Another disadvantage of the 5-litre pack was that if plasma was pooled prior to completion of the microbiological assays, the finding of a positive donation meant that 25–30 donations were wasted.

A working party of the Regional Transfusion Directors (RTDs) together with the Director of BPL conceived the idea of a dedicated plasma pack (Fig. 8.4). Plasma from the primary pack, after centrifugation to separate the red cells, could be expressed into the plasma pack in a 'closed' system and, therefore, carried out without any special environmental

conditions other than Good Manufacturing Practice. Baxter Corporation, now Baxter Healthcare, developed this single plasma pack (SPP), known throughout the Service as the 'wedge' pack. It had to be frozen in an upright position in order that there was an air space at the top of the pack. Baxter designed a machine which sliced the top of the pack through the air space. The wedge shape of the pack allowed the frozen plasma to be expressed into a suitable container.

The use of this pack commenced in 1981 and has continued, with several improvements in design, until the present day. It has maintained a high quality of plasma for fractionation, particularly for coagulation factors and has shown itself to be well suited to large-scale operation. RTDs have criticized its lack of flexibility, because without an administration port, it could not be used for transfused products.

A problem which BPL has had to contend with throughout its history is that it has never been in control of its plasma supply, with the exception of 1975 when the DHSS financed an increase. The only argument which could be used with the RTCs was persuasion. When the building of the new BPL started in 1983 it was estimated that RTCs needed to provide 450 tonnes (450,000 litres) of fresh frozen plasma by 1986. It can be seen from Fig. 8.5 that this quantity was not reached until 1990. In the event, the provision of less than 300 tonnes during 1986 was not responsible for a failure to meet production targets as the new factory was not fractionating effectively until 1988. This delay allowed stocks of fresh frozen plasma to accumulate and in the year ending March 1989, 470 tonnes of plasma were processed.

A major development which allowed an increase in the plasma supply was the introduction, in 1983, of saline, adenine, glucose with mannitol (SAG-M) as an additive solution for concentrated red cells (Höglman *et al.*, 1983). This system allowed the removal of 275–300 ml of plasma from each donation of whole blood compared with 180–220 ml when Citrate Phosphate Dextrose anticoagulant was used alone. By 1989, 73% of the volume of plasma came from SAG-M donations; plasmapheresis accounted for 13% and it was surprising that 9% of the plasma input was still in 5-litre packs, largely, but not entirely from donations which had time-expired.

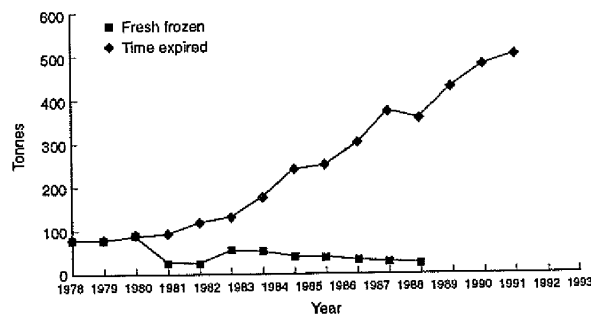


Fig. 8.5 The plasma supply, 1979–1992 (—◆— fresh frozen, —■— time expired).

COAGULATION FACTORS

Factor VIII

By 1979, the use of fresh frozen plasma for the treatment of haemophilia had been superseded by the use of cryoprecipitate prepared at RTCs and by purified factor VIII from BPL and imported commercial product. The advent of home therapy, and later prophylactic treatment, meant that purified factor VIII preparations were increasingly in demand. It can be seen from Fig. 8.1 that NHS factor VIII was available in smaller quantities than commercial concentrates except in 1984.

During 1984, steps had to be taken to eliminate the transmission of human immunodeficiency virus (HIV). At that time the recommended method was to heat the factor VIII to render it safe. Although the BPL product was a concentrate,

it contained a significant proportion of contaminating proteins and as a result could be defined as a product of intermediate purity. A procedure had been developed at PFL (Oxford) for the inactivation of viruses in freeze-dried concentrates by heating finished product in vials at 80°C for 72 h. Although the target was the inactivation of non-A, non-B hepatitis, the process was equally effective against HIV (Colvin *et al.*, 1988). In order to achieve sufficient virus kill, whilst leaving other product characteristics (active factor content, solubility, protein antigens) relatively unchanged, product formulation had to be tailored with terminal heating in mind (Smith, 1988). This process change was successfully applied to factor VIII (type 8Y), factor IX (type 9A) and a range of special products, anti-thrombin III, factor VII, factor XI and factor XIII.

Factor 8Y proved to be an excellent product and was used extensively for the treatment of haemophilia for 10 years. Clinical demand for products of even higher purity led to the decision to licence commercial technology to offer customers a choice. The new product, 'Replenate', was prepared in doses of 250 iu, 500 iu and 1000 iu and was virally inactivated by solvent detergent rather than dry-heating (Horowitz *et al.*, 1988). This product has the higher purity sought by some physicians, but unlike factor VIII (type 8Y), cannot be used for replacement therapy in the treatment of von Willebrand's disease.

Factor IX

Factor IX concentrate was manufactured at PFL (Oxford) in sufficient quantities for the needs of patients in England and Wales until 1984. During that year the need to develop a product which could be heat treated, led to the purchase of commercial product. Also, the latter product filled the void in 1985 when there was a delay in issuing the PFL factor IX whilst steps were taken to ensure that the heat treatment had not led to increased thrombogenicity. During 1986,

approximately 27,000 vials of 600 iu (16.2 million iu) of the new product, factor 9A, were issued. As usage had been in the order of 13.5 million iu, self-sufficiency had been regained.⁴

BPL's factor IX concentrates were developed at PFL (Oxford) and were manufactured there until transfer to BPL in 1991. These preparations included two generations of products, types 9D and 9A (unheated and heated prothrombin complexes) and a high-purity concentrate, type 9MC, now licensed as 'Replinine'.

Other Coagulation Factors

The early factor IX preparations contained contaminating coagulation factors, e.g. factor VII, and were used to treat patients with these deficiencies. Later, small quantities of purified factors VII, XI, and XIII concentrates were manufactured. They were used to treat the few patients who suffered from these isolated deficiencies. In particular, there was interest in the USA for supplies of factor XI concentrate prepared by a variant of the anti-thrombin process. All four concentrates, factors VII, XI, XIII and anti-thrombin III include virus inactivation by terminal dry-heating. The factor VII and anti-thrombin III manufacturing processes retain the pasteurization step introduced during developmental work.

BPL is one of the few fractionation centres to respond to requests by clinicians for orphan products such as those mentioned above in order that specific treatment can be given to rarely found coagulation factor deficiencies.

LARGE FRACTIONS

Plasma Protein Fraction (PPF) and albumin

It will have been noted in Chapter 7 that 90% was adopted at BPL as the lower limit of albumin concentration in PPF, while for salt-poor albumin there was a statutory limit of 95% [British Pharmacopoeia (BP), 1973]. The limit for PPF of 'not less than 90% albumin by electrophoresis' appeared in the BP in 1980.

The first European Pharmacopoeial (EP) monograph was in 1986 when a lower limit of 85% was stated. This, at the time, matched the level in the product approved by the FDA in the USA. In order to minimize undesirable side-effects, possibly caused by globulin contaminants, a decision was made to increase the concentration of albumin in the 4.5% product. By 1986, it contained more than 95% albumin. Consequently, to anticipate the forthcoming monographs, the term PPF was discontinued and the product named albumin.

⁴ Returns from the Haemophilia Centre Directors, 1987.

The principal albumin products between 1979 and 1988 were 400 ml \times 4.5% and 100 ml \times 20%. It can be seen from Fig. 8.6 that issues of the 400 ml container increased between 1982 and 1985. Thereafter they declined quite dramatically. The delay in transferring production to the new factory played a part in this reduction. It was affected also by a precautionary recall following reports of adverse effects in several patients undergoing therapeutic plasmapheresis with concomitant infusion of albumin at high rates in large volumes. This event and a fire in the old plant hastened its closure.

Production of the 400 ml \times 4.5% albumin was discontinued in 1988. The first product prepared in the new plant was a 250 ml \times 4.5%, followed in 1989 by the preferred 500 ml \times 4.5% (Fig. 8.6).

Increasing quantities of the 100 ml \times 20% were produced to satisfy demand. More than 90% of the albumin products used in England and Wales come from plasma fractionated at BPL.

Normal immunoglobulin (IgG)

There was a gradual but steady increase in issue of the 250 mg dose of normal IgG between 1979 and 1992. This was due, probably, to increased travel and its use for prophylaxis against hepatitis A (Fig. 8.7).

In contrast, issues of the 750 mg dose remained constant. During the 1980s there was increasing demand for an intravenous product. As early as 1982/3 BPL prepared a normal IgG for intravenous use, intended primarily for a clinical trial in patients suffering from hypogammaglobulinaemia, although it was used selectively for other patients. The product was an unmodified IgG preparation in which the level of aggregates, anti-complementary activity, pre-kallikrein activator and kallikrein were all very low. It was freeze-dried in a solution containing 10 g/% added maltose (Lane *et al.*, 1983). Unfortunately, each hypogammaglobulinaemic patient developed non-A, non-B, hepatitis and the product was withdrawn (Lane, 1983).

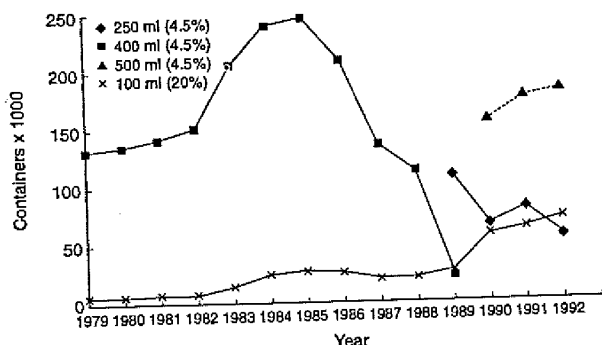


Fig. 8.6 Issues of albumin products, 1979-1992 (—◆— 250 ml \times 4.5%, —■— 100 ml \times 20%, —▲— 400 ml \times 4.5%, —×— 500 ml \times 4.5%).

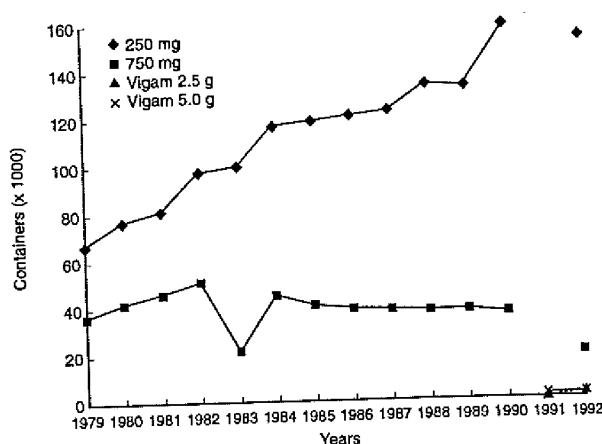


Fig. 8.7 Issues of normal immunoglobulin, 1979-1992 (—◆— 250 mg, —■— 750 mg, —×— Vigam 5 g, —▲— Vigam 2.5 g)

The safety of intramuscular IgG had been recognized for three decades (Cockburn *et al.*, 1951). In order to process the intermediate product for the intravenous preparation, a minor modification of the post-fractionation procedure for the intramuscular product had to be made; this may have permitted virus to remain (Lane, 1983).

A successful production of the intravenous IgG licensed by the Scottish Blood Transfusion Service (SNBTS) was achieved in 1988. However, progress was halted by a report of non-A, non-B, hepatitis transmission by the SNBTS product (Williams *et al.*, 1988).

Earlier, during 1986, a collaborative venture began with Kabi Pharmacia, Sweden. Arrangements were made to licence their technology for an intravenous IgG and to receive, initially, product manufactured by Kabi from BPL plasma. After initial difficulties in obtaining a suitable product which would dissolve readily, the intravenous IgG, called 'Vigam', became available for trial in 1992. Manufacture commenced at BPL in 1993. The original product was reformulated and renamed Vigam-S and was fully licensed in January 1996.

SPECIFIC IMMUNOGLOBULINS

Anti-D immunoglobulin

Production of anti-D IgG during the early 1980s continued at the same rate as that for most of the 1970s. However, reduced supplies of plasma suitable for fractionation led to demand exceeding supply in 1987. The situation was corrected by the central purchase of a commercial product. Efforts to increase the plasma supply were successful but it was not until 1990 that the situation improved significantly. The advent of antenatal prophylaxis for Rh haemolytic disease,

the reluctance to immunize male volunteers because of the potential danger of transmitting infection and the ageing population of allo-immunized female donors had made the supply of anti-D plasma difficult to maintain. In addition, there had been strong commercial competition with some customers preferring the increased anti-D content per dose in the commercial product.

In the early 1980s experimental work indicated that it might be possible to produce a prophylactic human monoclonal anti-D to replace the existing polyclonal product for the prevention of haemolytic disease of the newborn. With this in mind, by 1987 the CBLA was funding work carried out by Professor Nevin Hughes-Jones in Cambridge and by Professor Ben Bradley in Bristol. In 1990, antibodies produced by these research groups were used to show that human monoclonal anti-Ds were effective in clearing D-positive red cells from the circulation of volunteers (Thompson *et al.*, 1990). Subsequent work carried out at BPL, IBGRL and the Bristol Transfusion Centre has established that human monoclonal anti-Ds cause suppression of immunization to the D antigen in D-negative volunteers (Kumpel *et al.*, 1995). Multi-centre trials are now underway and it is hoped that an effective therapeutic product can be developed.

Other specific immunoglobulins

Approximately 6–10 tonnes of plasma have been used annually to prepare a variety of specific IgGs. From time to time during the 1980s, shortages occurred due to an insufficient supply of acceptable plasma from RTCs. The National Directorate liaised with senior staff at BPL to rationalize plasma collection for the preparation of specific IgGs. Targets were set and agreed with RTCs and, in general, between 1988 and 1993 the supply situation improved.

BPL DIAGNOSTICS

The activities of this Department of BPL will be considered in Chapter 9 on the International Blood Group Reference Laboratory.

SELF-SUFFICIENCY

When the clinical needs of individuals within a given population are satisfied by human blood and medicinal products derived from blood and plasma from that population, taking into account the therapeutic regimens applied within it, then it is considered that self-sufficiency has been achieved.⁵

Since 1976, there has been a commitment to provide an adequate supply of blood and plasma to ensure self-sufficiency in blood and blood products for England and Wales.

With respect to the provision of cellular products and fresh frozen plasma for clinical use this has been achieved, apart from an occasional import of red cells from SNBTS to correct a temporary shortage.

It has been noted earlier that if adequate supplies of factor VIII are available to meet clinical demand, sufficient quantities of other products can be made available by sequential fractionation of the cryo-supernatant. It can be seen in Figs 7.6 and 8.1 that, since the purchase of commercial factor VIII began in 1973, it has contributed significantly to the total quantity of factor VIII used. Indeed until 1989, the amount of commercial material exceeded that issued from BPL except in 1984. In 1990 and 1991 when BPL increased production and sales they contributed 80% and 70%, respectively to the total annual consumption.

In June 1989, in the framework of the single market, the Council of the European Communities unanimously adopted Directive 89/381/EEC. This Directive extended the existing pharmaceutical legislation to include medicinal products derived from human blood or plasma and prepared by an industrial process. It did not apply to whole blood, plasma or blood cells of human origin.

In addition to the introduction of measures to ensure maximum quality, safety and efficacy of these products, the Directive contained the aim, also, of promoting self-sufficiency in human blood and human plasma in the European Community.

Article 3, paragraph 4 of the Directive states: "Member States shall take the necessary measures to promote Community self-sufficiency in human blood and human plasma. For this purpose, they shall encourage the necessary measures to develop the production and use of products from human blood and human plasma coming from voluntary, unpaid donors. They shall notify the Commission of such measures."

With respect to the collection of blood and plasma from voluntary, unpaid donors the NBTS complies with the definition agreed by the Committee of Experts in Blood Transfusion and Immunohaematology of the Council of Europe. This states that a donation is considered voluntary and unpaid if the person gives blood, plasma or cellular components of his/her own free will without receiving payment, either in the form of cash or in kind which could be considered a substitute for money. This would include time off work other than that for the donation and travel. Small tokens, refreshments and reimbursement of travel costs are compatible with unpaid donations.

It will be noted that the statement on self-sufficiency in Directive 89/389/EEC was written in the imperative. As such it required a response from the UK Government. Self-sufficiency was defined by the Chief Medical Officer, DoH as follows.

"Since 1976, it has been government policy that the UK with its long tradition of voluntary blood donation should be

⁵ Blood self-sufficiency in the European Community on the basis of voluntary, unpaid donations, 12/11/92.

self-sufficient in blood products. This position is entirely consistent with the more recent decision of the EC to promote a policy of Community self-sufficiency based on voluntary blood donation.

"At the same time, Ministers accord great importance to the principle of clinical freedom. When therefore a doctor decides, in the light of available clinical information, that a particular product is indicated for a particular patient, we believe that the decision should be respected even if that product has to be imported from outside the EC. The principle of self-sufficiency, therefore, means that the supplies of domestically sourced blood products should be sufficient, both in range and quantity, to meet the needs of all patients whose clinicians prefer these to other available products."⁶

England and Wales are self-sufficient for the majority of plasma products. For a number of years, for reasons which are apparent from the contents of Chapters 7 and 8, demand for factor VIII was greater than could be met from the fractionation of domestically sourced plasma. Quite legitimate clinical demands for products which did not transmit HIV and for high-purity concentrates have had an effect on the supply of coagulation factors from BPL. Until recently, the lack of an intravenous IgG has led to imports of this product. It could be argued that the events which have taken place are within the definition of self-sufficiency by the Chief Medical Officer.

⁶ Supply of blood products, The UK view, DH, 1990.

Chapter 9: The International Blood Group Reference Laboratory

The Blood Group Reference Laboratory (BGRL) was established in 1946. The word 'International' was added to its title in 1990 to recognize, rightly, the status this organization had enjoyed for several decades. To simplify the text the term IBGRL will be used throughout.

IBGRL was funded and managed, initially, by the MoH, but soon the management was transferred to the MRC, an arrangement which continued until 1975. At first IBGRL occupied three rooms on the ground floor of the Lister Institute at Chelsea Bridge. Its terms of reference were:

- the supply of standard A, B, O and Rh blood-grouping sera;
- the preparation and supply of the rarer type of sera for blood-grouping work;
- the investigation of difficult serological cases;
- cooperation with MRC's Blood Group Research Unit.¹

Independent research activities were undertaken, and IBGRL also played an important role in the teaching of blood group serology both in the UK and overseas.

Dr Otto Hartman, Director of the Serodiagnostic Department of the Stattens Institute for Fokohelse, Oslo, proposed to the Board of Councillors of the International Society of Haematology that IBGRL should be given the status of a Central Reference Laboratory for maintaining standards of blood-grouping sera and preferably recognized by the World Health Organisation (WHO). The proposal was supported by Dr W. d'A. Maycock in his capacity of Consultant Adviser in Blood Transfusion to the Chief Medical Officer, MoH and Professor (later Sir) Ashley Miles, a member of Biological Standards Committee of WHO.

The ISH Board of Councillors approved this change in status on 21 August 1950. It is interesting to note that the Councillors, under the Chairmanship of Sir Lionel Whitby, included such internationally recognized workers in blood transfusion as W. Dameshek (USA, Vice-President), S. Haberman (USA, Secretary-General), E. Witebsky (USA) and Janet Vaughan (UK). WHO recognized IBGRL as a collaborating Centre for Reference and Research in Blood Grouping in 1952. This recognition placed an international dimension on the activities of IBGRL and their WHO status has remained until the present. The most recent renewal (for a period for 4 years) from 1993 WHO gives the terms of reference as:

- to serve as a referral centre for investigation of blood grouping and cross-matching problems and for identi-

fication of blood-group antibodies;

- to assay preparations of anti-D;
- to organize and/or participate in studies for standardization of blood-grouping reagents;
- to supply blood-grouping reagents to workers in developing countries, including training, advice and guidance on their use and standardization;
- to maintain an International Panel of Rare Blood Types.²

After the MRC relinquished its managerial role in 1975 the administration of IBGRL was transferred to the Lister Institute until 1978. Thereafter, IBGRL was managed by the NW Thames Regional Health Authority, together with the Blood Products Laboratory (BPL).

The Central Blood Laboratories Authority (CBLA) was created to manage both BPL and IBGRL in December 1982. The main tasks assigned to IBGRL were:

- "to manufacture blood-grouping and related reagents for use in the NHS where such manufacture can be justified on cost or other grounds;
- to carry out reference functions in respect of:
 - (i) the National External Quality Assessment scheme of blood-group serology;
 - (ii) blood cells and related serology for clinical purposes;
 - (iii) reagent evaluation on behalf of the DHSS or in collaboration with industry;
 - (iv) World Health Organisation activity;
 - (v) to undertake such other activities, including collaboration with industry, as can, in the Secretary of State's opinion, conveniently be carried out in conjunction with the foregoing."

At the beginning of 1986 the production of blood-grouping reagents was transferred from IBGRL to BPL as this was now regarded more as an industrial process. A new division, BPL Diagnostics, was created (Scott, 1991).

IBGRL's first Director was Dr Arthur Mourant (Fig. 9-1). He joined the staff of the North London Blood Supply Depot in 1944. It was here that he became interested in blood groups and in 1945 he joined Robert Race at the Galton Serum Laboratory and discovered the antibody to the e antigen of the Rhesus system (Mourant, 1945). In 1946 both Race and Mourant moved to the Lister Institute of Preventive Medicine; Race became Director of the MRC's Blood Group Research Unit, and Mourant Director of IBGRL (Anstee, 1995).

¹ Lister Institute of Preventive Medicine. Report to the Governing Body, 1947.

² Letter from Director-General, WHO, to Secretary of State for Health, 1/7/93. ³ Annex to a letter from Secretary of State for Social Services to Mr R. D. Smart, Chairman, CBLA, 17/11/82.



Fig. 9-1 Dr Arthur Mourant FRS, 1904–1994 (Courtesy of D. J. Anstee).

Arthur Mourant was responsible for the early international recognition achieved by IBGRL and was a distinguished research worker into the distribution of the human blood groups worldwide (Mourant, 1954; Mourant, *et al.*, 1976). He resigned from IBGRL in June 1965 to become the Director of the MRC's Serological Population Genetics Laboratory at St Bartholomew's Hospital, a post which he held until his retirement in 1976. He died in 1994, aged 90 years.

He was succeeded as Director by Dr Kenneth Goldsmith whose interest was in the detection of platelet and leucocyte antigens and antibodies. From his research in this field a routine reference service has been developed. During his directorship, MRC requested IBGRL to act as the WHO Collaborating Centre for anti-D quantitation, a function previously carried out by Professor Nevin Hughes-Jones at St Mary's Hospital, London (Scott, 1991). Following Kenneth Goldsmith's untimely death in July 1975, Dr Carolyn Giles, a senior scientist at IBGRL, became Acting Director until the appointment of Dr A. M. (Sandy) Holburn as Director on 1 February 1978. He will be remembered for the development of proficiency testing in blood-group serology and the introduction of the National External Quality Assessment Scheme (NEQAS) in Blood Group Serology (Holburn and Prior, 1987), which will be reviewed later in the chapter. Dr George Bird was Director of IBGRL in 1986 following his retirement as Director of the West Midlands RTC.

The present Director, appointed in 1987, is Dr David Anstee. He has had a long experience in research on blood-group antigens on the red-cell surface at the molecular level. He has been able to bring this expertise to IBGRL and, with the transfer of reagent production to BPL, has expanded both the reference and research functions.

In February 1964, IBGRL moved out of the main building of the Lister Institute into purpose-built accommodation on the 'tennis court' north of the Biophysics Department. This was officially opened on 7 May 1964 by Lord Newton, Joint Parliamentary Secretary for Health. Plans to extend this building were put forward in 1969 but were not implemented.

After consideration of various options for providing more space for IBGRL, including building on the Elstree site, accommodation was found, in 1982, on two floors of the Harkness Building at the Radcliffe Infirmary, Oxford. Following the reorganization in 1986 both IBGRL and BPL(D) occupied this site.

In January 1990, the Laboratory was transferred to refurbished accommodation at the SW Regional Transfusion Centre, Bristol. BPL(D) moved to Elstree into laboratories vacated following occupation of the new processing factory.

FUNCTIONS OF IBGRL

Supply of blood-grouping and serological reagents

IBGRL, like BPL, never had control of supplies of raw material. Dr Mourant, and his successors, complained on several occasions that supplies of anti-A, anti-B and anti-Rh(D) were inadequate to meet IBGRL's requirements. Originally, it was planned that IBGRL would process and supply blood-grouping reagents for the NBTS. However, the majority of RTCs prepared their own reagents and, in some instances, supplied the hospitals within their region. Only surplus antisera were sent to IBGRL.

During 1947, IBGRL examined 8700 tubes and 3500 bottles of serum for suitability for blood-grouping serum and 75 litres were issued. Over 1000 serum specimens were tested for anti-Rh(D) and supplies of anti-D and other special grouping sera were obtained from human donors and from immunized rabbits. One litre of anti-D serum was distributed.⁴

During the next decade, however, it was possible to increase supplies of grouping serum and a national reserve was created in case of an emergency. This was dispersed for storage at various RTCs. By 1962, Dr Mourant was able to announce that there was no shortage of anti-A and anti-B.⁵ Most of the commoner Rh antisera were being prepared and issued by RTCs. IBGRL was supplying certain research workers in London, the Armed Forces and British territories overseas. It was agreed that sera containing antibodies of rare blood types should be sent to IBGRL so that a central registry could be compiled and they could be distributed to best advantage.

⁴ Lister Institute of Preventive Medicine. Report to the Governing Body, 1948. ⁵ Minutes of meeting of Regional Transfusion Directors, 28/2/62.

Table 9-1 Issues of human ABO blood grouping sera from IBGRL

Year	Volume issued (litres)
1947	75
1958	306
1968	806
1972	1000
1975	1100
1978	1100
1983	1100
1986	750
1987	280
1988	140
1989	3.5

For a number of years, IBGRL assisted laboratories overseas to carry out serological investigations by providing an initial supply of reagents and by blood typing their staff so that test cells could be made available. This work was made easier after 1962 when, through the initiative of WHO, national blood-group reference laboratories were designated in a number of countries.⁶ In 1969, IBGRL launched a scheme, on behalf of WHO, for the international exchange of grouping reagents. The scheme met with initial success with sera being exchanged between laboratories in Europe, USA and Australia; it was also of benefit to serologists in developing countries.⁷

IBGRL was committed to the production of anti-human globulin (AHG) reagents. These were obtained largely from rabbits, although later goats were used. The rabbit house was built in close proximity to the Westminster City Council's Refuse Department. Coccidiosis and other infections were contracted by the rabbits and valuable stock was lost. (K. L. G. Goldsmith, unpubl. observ.). In 1969 the MRC agreed to build a new rabbit house and an animal laboratory with a sterile area. As with blood-grouping reagents, RTCs manufactured their own AHG reagents and supplied hospitals in their regions. However, difficulties in producing high-quality AHG reagents with activity for both anti-IgG and anti-non-gammaglobulin (now known to be anti-complement) caused a number of hospitals to purchase commercial reagents. Use of IBGRL's polyspecific reagent increased from 4% in 1980 to almost 30% in 1983, an important factor being the introduction of a coloured reagent. Monospecific AHG reagents were added to the range of products following the move to Oxford.

Issues of ABO grouping sera continued to increase until the 1970s when they remained relatively constant during the next decade (Table 9-1). The volume of 1100 ml per year

represents approximately 80% of the quantity required by the hospitals. In contrast, less than 200 litres of anti-D were issued in 1983; the major product being an 'albumin' anti-D which had the disadvantage that its performance may be affected by the albumin preparation which was essential for the reaction (Jones *et al.*, 1969). There was competition with commercial suppliers who introduced a 'rapid' reagent; IBGRL began to produce a similar reagent but was dependent on adequate supplies of potent anti-D plasma from RTCs. Both these reagents required a control as false-positive results were not uncommon.

By 1983, monoclonal reagents were being prepared. The use of monoclonal anti-D and anti-B during the next 4 years led to the replacement of the human-based reagents.

BPL DIAGNOSTICS

This Division of BPL was created at a watershed in the supply of blood-grouping and other serological reagents. The development of monoclonal reagents which had to be purchased could only be supplied to RTCs and hospitals by charging for them. This placed BPL in direct competition with commercial organizations whose resources were greater.

As part of their research and development activities, IBGRL commissioned the development of several monoclonal antibodies. These included anti-Ds with Professor Hughes-Jones at Babraham, Cambridge, Dr Melamed at the NE London Polytechnic and Dr Bradley at UK Transplant, Bristol. A unit for bulk production of monoclonal blood-typing reagents was established at SW Regional RTC in conjunction with Bristol Polytechnic for the production of anti-A and anti-B monoclonal antibodies in 50-litre volumes. CBLA funded several external posts and IBGRL contributed significantly to the total quantity of blood-grouping reagents (Fig. 9-2).

This work was continued at BPL(D) where a monoclonal production unit was commissioned in 1990. The 75-litre fermenter was used to produce IgM anti-D and anti-A. By

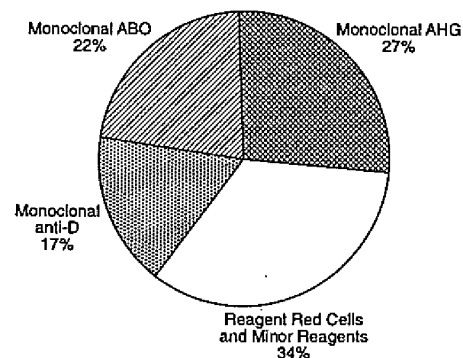


Fig. 9-2 BPL diagnostic sales, 1992, % volume based on IBGRL R&D.

Lister Institute of Preventive Medicine. Reports to the Governing Body, ⁶ 1962, ⁷ 1969.

this time, as a result of the development work at IBGRL, the CBLA owned 11 cell lines, one IgM anti-D, three IgG anti-Ds, two anti-As, two anti-C3Ds (developed from the highly successful BRIC-8 line) one anti-B, an anti-M and an anti-N. Licences were granted to Biotest and Celltech for certain cell lines. In addition to the above, an anti-IgG AHG reagent was developed in rabbits in conjunction with IBGRL to replace the sheep reagent.

Unfortunately, in 1992, price competition was strong and a number of products did not meet customer requirements as new technologies were being developed by industry. The NBA was faced with a decision on how best to ensure the future of BPL(D) as there was evidence that its existence held down the price of certain commercial products. BPL(D) has continued to manufacture reagents and no doubt this policy will continue as long as this situation exists.

Preparation of international and national standards

International Standards were established and distributed by WHO; the distribution of national standards was the responsibility of the national biological standards laboratory. In the UK this was located at the National Institute for Medical Research, Mill Hill. This is now known as the National Institute for Biological Standards and Control (NIBSC) and is based at Potter's Bar.

In 1950, IBGRL, with the cooperation of RTCs who supplied the sera, developed international standards for anti-A and anti-B. National standards for anti-C, anti-D and anti-E were prepared and in 1965 an international standard (incomplete) anti-D serum was developed by IBGRL and accepted by WHO. A case had been made out for the need to use units rather than the notoriously inaccurate titres. The WHO anti-D standard was expressed as units which were determined as the reciprocal of the median titre of the pool of anti-D sera contributing to the standard (Goldsmith *et al.*, 1967). Later its potency was determined in µg/ml by radio-immune assay (Hughes-Jones & Stevenson, 1968).

More recently, Dr Marion Scott has been involved in developing certified reference materials for anti-A, anti-B and anti-D for the European Union. These reagents will be classified under Annex 2 of the EC *in vitro* Medical Devices Directive for implementation in 1997. This work has been undertaken under the aegis of a joint working party of the International Society of Blood Transfusion and International Council for Standardization in Haematology (ISBT/ICSH) on the Standardization of Blood-Grouping Reagents. It is important that uniform standards are applied in Europe for the regulation of grouping sera.

National and international panels of donors of rare types

The creation of a national panel of donors of rare blood types was suggested by Dr Mourant to the RTDs at their

meeting on 6 December 1950. It was agreed that the panel of donors would be maintained by IBGRL and lists provided for RTCs. The objective of this panel was to provide donors for patients with multiple antibodies or for those with a requirement for an uncommon blood type, e.g. R₄R₂, R'R', R''R''. This panel exists today and has been updated regularly.

In 1965, ISBT invited Dr Mourant to present a paper on the establishment of an international panel of blood donors of rare types (Mourant, 1965). In 1966, the Society established an Advisory Committee for the International Panel of Donors of Rare Types, chaired by Dr Mourant. It was agreed that IBGRL would act as the central reference laboratory.

The scheme was based on the British National Donor Panel with the donors divided into two classes; firstly, those persons whose red cells lacked antigens to a range of blood-group antibodies commonly encountered and whose blood could be used for patients whose serum contained multiple antibodies. It was suggested that each participating country should build up a list of 20–100 such persons; they should be group O and mainly K-negative, Fy^a-negative and Jk^a-negative.

The second class would be those donors known to lack single very common antigens. These would include Ss negative, the 'Bombay' type, p, Rh 'deletions', Lu(a+b-), Lu(a-b-) kk, Kp^b negative, Vel-negative, Lan-negative, Yt^a-negative, Sm-negative and I negative.⁸ It was stressed that before using the panel, every effort should be made to locate a donor nationally.

The first donor list was issued in March 1968 and contained nearly 300 donors. Copies were issued to all WHO National Blood Group Reference Laboratories and to others who had assisted in establishing the panel. Regular updating occurred and by 1985 over 1500 donors were listed. This was the first panel to be compiled on a computer, but paper copies were sent to 110 centres throughout the world.

Initially the Director of IBGRL liaised with the centre which had listed the donor to obtain blood for the patient. The 1985 panel contained a list of contributors so that those wishing to obtain blood could contact the appropriate centre directly. Whilst this procedure saved time, it had the disadvantage that IBGRL were unable to monitor demand or assess usefulness of the panel (Poole, 1990).

At the present time all contributing centres have instructions for modem access to the panel, although the most popular route is still by fax or telephone. Security is established by releasing the modem telephone number only to contributing centres, together with the allocation of a unique code and password. The names of donors are not available; they are identified only by an identification number, and/or an IBGRL code number and their contributing centre. Back-up tapes are stored in several different places (J. Poole, pers. comm.).

⁸Minutes of the ISBT Advisory Committee for the International Panel of Donors of Rare Types, 9 February 1996.

In 1988, ISBT established a Working Party for Rare Donors. This has been chaired by Ms Delores Mallory, American Red Cross Blood Services National Headquarters until 1995 when she was succeeded by Dr Graeme Woodfield, Auckland Hospital, New Zealand. This Working Party has established guidelines for the transportation of donations of rare blood and has developed a formal liaison with IBGRL.

Reference activities

For a number of years the reference work carried out by IBGRL related to the serological investigations of antibodies referred from the RTCs in the UK and, increasingly, from laboratories overseas. These investigations led to the discovery of hitherto unrecognized antibodies.

Following the appointment of Dr Anstee as Director and the transfer of reagent production to BPL(D) the reference activities were organized in five sections, viz:

- (i) *Serological reference* — Miss J. Poole. The number of samples referred was in the order of 650–700 per year and this has remained reasonably constant since 1985 with 30–50% of specimens referred from overseas, largely from Asia.
- (ii) *Biochemical reference* — Dr Marion Reid (now Dr May-Jean King). Initially, this section was established to apply immunochemical and biochemical techniques to the characterization of blood-group antigens and antibodies. This was followed by application of the polymerase chain reaction (PCR) to study blood group antigen polymorphism on glycoprotein C. Analysis of the membrane proteins in the red cells was introduced in 1990. The requests for membrane analysis fall into one of five categories (King, 1994):

- differential diagnosis for a haemolysing condition;
- identification of the cause of mild, chronic haemolytic anaemia;
- preparation for neonatal management of a second newborn when the first has been transfusion dependent for the first few months for a haemolytic anaemia of unknown cause;
- confirmation of clinical diagnosis for hereditary spherocytosis, hereditary elliptocytosis or hereditary pyropoikilocytosis where defects in cytoskeletal proteins or spectrin may occur (Palek & Sakr, 1992);
- determination of the underlying genetic defects when the clinical presentation is not fully compatible with the primary disease.

Membrane analysis has increased more than 3-fold between 1991 and 1994 and now accounts for 92% of the samples received by the biochemical reference section. Approximately 50% of samples are from children under 10 years.

(iii) *Platelet and granulocyte reference service* — Dr Marion Reid (now Dr Geoff Lucas). This section is now well established. Antibodies are detected by chemilumi-

nescence which measures their functional activity. Several national and international trials have been organized to assess the performance of different methods for detecting platelet and granulocyte antibodies (M. L. Scott, pers. comm.).

(iv) *Quantitative immunohaematology* — Mr Barry Dawes. As a WHO collaborating centre, IBGRL is requested to assay anti-D from samples submitted from international sources together with assays on behalf of UK Laboratories and BPL.

(v) *Product development* — Dr Marion Scott. Several projects have been investigated during the past few years, e.g. formulation for the freeze-dried international reference preparation of papain and bromelain in collaboration with Dr Douglas Voak (Cambridge) under the aegis of ISBT/ICSH Enzyme Working Party (Scott *et al.*, 1994), solid and liquid-phase microplate technology and monoclonal antibody development.

An additional reference service, which was introduced in 1994, was the phenotyping of fetal cells for platelet and red-cell antigens implicated in alloimmune thrombocytopenia and haemolytic disease of the newborn. The typing for the platelet antigens HPA-1-2-3 is performed by using restriction enzymes to digest PCR-amplified foetal DNA obtained from amniotic fluid (Simsek *et al.*, 1993). Red-cell antigens for which genotyping is available, again from amniotic fluid, include Rh(D), Kell and Duffy. PCR is used to amplify exon 10 of the D gene, backed up by the simultaneous amplification of a region of intron 4, also unique to D-positive individuals (Simsek *et al.*, 1994). Kell and Duffy genotyping is performed by analysis of PCR-amplified fetal DNA after digestion by restriction enzymes (Lee *et al.*, 1994; Mallinson *et al.*, 1994).

National External Quality Assurance Scheme (NEQAS) in blood-group serology

Quality assessment schemes in biochemistry and haematology have been in existence since the 1960s. The first suggestion that a scheme should be introduced in blood-group serology was made in March 1973 by a Working Party of the British Committee for Standards in Haematology.

A pilot study was organized by Dr Goldsmith in 1973 in which seven RTCs agreed to take part. The sera used in the trial had been prepared locally and sent to IBGRL for verification of antibody content prior to issue to the hospitals.⁹ There were a large number of variables, not the least being that each region issued different sera. It was agreed that a second trial would take place organized by IBGRL and a Working Group was asked to consider the elimination of as many variables as possible.¹⁰ Their proposals were sent to the DHSS Laboratory Development Advisory Group (LDAG)

Minutes of meetings of Regional Transfusion Directors, ⁹ 26/9/73, ¹⁰ 28/11/73.

who were considering proficiency testing in a number of specialities.

Regional schemes were eventually established with sera from IBGRL distributed by RTCs. Additionally, proficiency testing of RTCs was carried out by IBGRL. This arrangement persisted until 1978 when Dr Holburn introduced a national scheme organized by IBGRL, although RTCs were still involved in the assessment of results (Holburn & Prior, 1987).

As early as 1975, DHSS had established professional national advisory panels for monitoring NEQAS and for contacting persistently poor performers. The Advisory Panel in Haematology was nominated to handle NEQAS in Blood Group Serology. Satisfactory arrangements were negotiated for representation of RTDs and the scheme organizer, the Director of IBGRL.

Following the resignation of Dr Holburn, the DHSS decided that the organization of NEQAS should be independent of reagent production. Dr Ian Fraser, RTD, Bristol RTC, became the scheme organizer and the preparation of the serological exercises was transferred to Dr Peter Phillips, NIBSC, in October 1987.

Teaching

On innumerable occasions, IBGRL have entertained workers from the UK, Europe and beyond for informal training pro-

grammes. Additionally they have arranged formal courses, such as the First European Blood Transfusion Course for the Council of Europe when 12 persons from 12 different countries attended a 2-week course, and more recently two WHO courses for training in the standardization, quality control and use of ABO and Rh monoclonal reagents. After returning to their own countries the delegates received concentrated monoclonal reagents which they had to dilute, quality control and assess their usefulness.

Research

Although this is the last of the functions to be reviewed it is, arguably, the most effective at IBGRL. The laboratory provides an excellent routine service for the NBTS and laboratories overseas, but throughout its history it has provided the Transfusion Service with one of the few centres where basic research is carried out on aspects of blood transfusion. Mention has been made of the work of Mourant on blood group anthropology in which he became an international expert. It is not possible to describe all the research activities but perhaps an indication of the extent of these activities is that since Dr Anstee became the Director in 1987 the laboratory has published almost 200 scientific papers and letters.

Chapter 10: The Army Blood Supply Depot

For the greater part of the First World War, the static nature of trench warfare made it possible to establish hospitals near to the front line. In Chapter 2 there is a brief description of blood transfusion during the First World War when several transfusion techniques were practised (Keynes, 1983). When required, a direct donor to patient transfusion could be performed in a hospital setting. Army surgical manuals of that era gave diagrams showing every possible combination of sites of access to be used for both patient and donor. However, citrated blood was introduced into British Army Medical Service by an American surgeon who was also credited with establishing the first blood bank (Robertson, 1918).

The advent of the tank brought mobility to the battlefield and transformed the way in which wars were fought. The concept of a major static hospital, close to the front line, with a plentiful supply of rear echelon troops to act as donors, was no longer tenable. The method of bringing the donor to the patient had to be replaced and the invention of the vacuum bottle (Fig. 10-1) was to revolutionize the way in which blood transfusion was to develop. This closed sterile method of blood collection, coupled with the earlier discovery of citrate anti-coagulation by Hustin (1914), Agote (1915) and Lewisohn (1915), allowed blood to be donated in one location, to be stored and then transported to a distant hospital, possibly hundreds of miles away, where the blood was then transfused to the wounded soldier. The physical link of having the donor and recipient in close proximity had been broken and the stage was set for a massive increase in the use of blood transfusion. This is illustrated by the fact that in 1939, the last complete year before the Second World War, the Greater London Red Cross donor panel, founded by Percy Lane Oliver in 1921, arranged for 5638 donations (Fig. 2-4, Chapter 2), whereas in 1940, the first complete year of the

war, the Army Blood Transfusion Service (ABTS) collected 33,865 units of blood.

How did this transition take place? In the autumn of 1938 the War Office, as the Army's section of the Ministry of Defence (MoD) was then called, convened a meeting at the Royal College of Surgeons (RCS) at which the President, Sir Hugh Lett, and the Director General of Army Medical Services, Lieutenant General Sir William Macarthur, were present. A committee was set up to consider how, in the event of war, blood-transfusion support could be provided to military hospitals. One of the members of this committee was Dr (later Sir) Lionel Whitby who was a lecturer in microbiology at the Middlesex Hospital. He had served in the First World War as a machine-gunner with the Royal West Kent Regiment, in both France and Salonika, before he was wounded near Péronne. As a result of this wound he had an above the knee amputation of his leg; the blood transfusion he received may well have saved his life. He was nominated to command the ABTS and during the ensuing 12 months set up a shadow unit based at Southmead Hospital in Bristol. So good was his organization that the unit was able to officially open on the day of the outbreak of the Second World War, Sunday 3 September 1939.

The Committee considered two options for the provision of a transfusion service. The first was to blood group every member of HM Forces and issue all medical units with the equipment required to run a donor session, so that blood could be obtained where it was needed with the minimum delay. The other option was to set up an ABTS, based on an elaborately equipped Army Blood Supply Depot (ABSD) in the UK, from which supplies could be sent to forward transfusion units close to the front. Coupled with this was the concept of the specialist Transfusion Officer, who, because of his training and wide experience, would be able to select suitable cases for transfusion and provide them with the most appropriate mix of transfusion fluids on an individual basis.

The Committee decided to follow the second option and, in the light of the subsequent developments in transfusion medicine, no one would now question this decision. The British Army was, therefore, the only army, allied or enemy, with a transfusion service capable of providing its own blood, fluid or dried substitutes, grouping sera and crystalloids suitable for use in any type of operation anywhere in the world. Experience gained during the war, and from subsequent campaigns, has shown that, except in exceptional circumstances, it is virtually impossible to find the time or personnel, at the height of a heavy battle, to set up a donor session. During the war, the German medical services, which

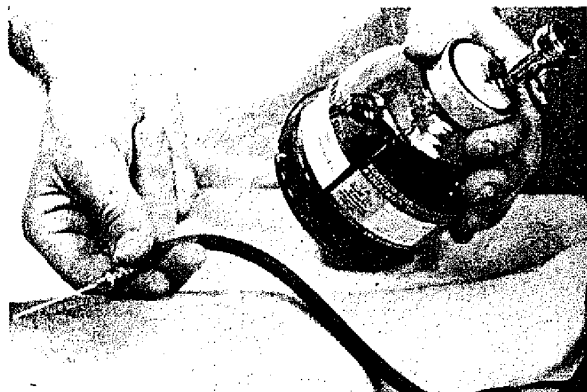


Fig. 10-1 A vacuum bottle for the collection of blood.



Fig. 10-2 An ABTS donor recruiting van in Bristol.

GUY GIBSON, V.C., GIVES BLOOD

BIG SEND-OFF FOR CITY'S CAMPAIGN

What Less Can You Do?

"MONTY'S" TARGET

WING-COMMANDER Guy Gibson V.C., D.S.O., D.F.C., opened Bristol's campaign for blood donors on Saturday with a pint of his own "dam-busting" blood.

He told a huge audience at the Colston Hall that the least the city could do to back the soldiers on the Second Front was to give liberally of its blood.

"The casualties are bound to be heavy," he said, "and blood transfusions can save thousands of our fighting men's lives. I say, and I think that if General Montgomery and Prime Minister Churchill were with me they would say, too."

THE FIRST DONOR during the Bristol Blood Transfusion Campaign, which opened on Saturday, was Wing-Commander Guy Gibson, V.C., D.S.O., D.F.C., who spoke at the opening. Watching is the Sheriff of Bristol.

Fig. 10-3 Wing Commander Guy Gibson VC, of dam-busters fame, donates a pint of blood to the ABSD.

had adopted the policy of 'bleeding on the hoof', were constantly short of blood. This applied also to the Americans, until they abandoned this practice and set up a central blood-collection depot in the UK, firstly to bleed their troops stationed in England, and subsequently to act as a distribution centre for blood delivered from the USA.

How was this concept transformed into reality? Firstly it was decided to set up the ABSD in an area where its blood-collection duties would be unlikely to be disturbed by enemy attack. The South West of England was thought to be a safe area, but close enough to the continent to allow air supply to be easily undertaken. Southmead Hospital in Bristol was chosen as the site and two maternity wards were earmarked for conversion on the outbreak of war.

The heavy bombing of Bristol in September 1940 proved how wrong one could be when trying to gauge areas that enemy were unlikely to attack and led to the subsequent splitting of the ABSD, part going to Chilton Polden. Blood was collected in the MoH Region 11, i.e. the counties of Cornwall, Devon, Somerset, Gloucester, Wiltshire and Dorset. The War Office agreed to supply all the civilian hospitals in that area with their blood requirements in addition to supplying the army's needs. This allocation, especially in the light of the civilian casualties sustained in Region 11 and the increased military requirements, proved to be inadequate. In May 1942, the MoH agreed to give the ABSD access to the donors in Regions 9 and 10, Hampshire, Oxford and Buckingham, without having to supply their civilian needs. The civilian requirements were met by donations from other regions.

The staff of the ABSD were initially drawn from the laboratories of the Middlesex Hospital and the Royal College of Surgeons, who made their way to Southmead Hospital, by various ingenious means, on Sunday 3 September 1939. There they were met by a scene of chaos with engineers, electricians and carpenters working around the clock to convert the maternity block into a laboratory. Contemporaneous reports were full of praise for the generosity and willingness of the staff of Southmead Hospital who found food and beds at short notice for the new recruits, many of whom had walked the 5 miles from the station. It is a tribute to the spirit of all, at that time, that the first blood donations had been collected and processed within 48 h of war being declared.

The initial brief for the unit was to supply 100 units of blood per day, but, by the end of the war this had increased to 1300 units, with the maximum output for one day being 1657. To enable these targets to be met, a sophisticated donor call-up and re-call system had to be set up, which differed very little from that practised within the National Blood Service today. A donor panel of some 5000 had been recruited before the outbreak of hostilities, but this soon increased to 100,000, was over 230,000 by the end of 1942 and exceeded half a million by the end of the war. This could

not be done without publicity (Fig. 10-2) and many of the recruitment tactics we use today were exploited by the ABSD. Celebrities were asked to donate (Fig. 10-3), endorsements were obtained from the war leaders (Fig. 10-4) and the donor certificate (Fig. 10-5), bearing the quotation from Shakespeare's Henry Vth 'For he today that sheds his blood with me shall be my brother', was designed to engender a spirit of camaraderie. In all 756,046 donors were bled during the war.

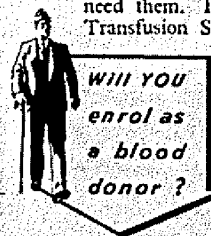
In addition to the provision of fresh blood, the ABSD supplied liquid plasma for temperate climates and dried plasma for the tropics. Dried plasma was sent to the tropics because there were worries over the stability of liquid plasma at high degrees of temperature and humidity. Much of the research into both the use of glucose-citrate as an anti-coagulant (Bushby *et al.*, 1940) and the alkalized-plasma technique for the prevention of clotting during filtration (Bushby & Whitby, 1942) was undertaken by the staff of the ABSD. Initially plasma was dried at the MRC plant in Cambridge, but in 1941 the Silver Thimble Fund of the Women of India provided funds for the purchase of a spin-

THE PRIME MINISTER
HAS SAID: (Nov. 9, 1943)

**"The
Hazards
of Great
Battles lie
before us"**



Here is a warning all must heed. Adequate reserves of fresh blood, plasma and serum, *must* be available for giving transfusions to all 1944 battle casualties that need them. For this reason the Army Blood



Transfusion Service calls for many thousands more blood donors of all groups. Will you help by giving a little of your blood? It is simple, painless and harmless, but the lives of our wounded depend upon it and thousands more blood donors are wanted.

**BRISTOL'S
BLOOD TRANSFUSION CAMPAIGN**

Feb. 12th to 26th

A.R.P. HEADQUARTERS, 55 BROADMEAD

ARMY BLOOD TRANSFUSION SERVICE

Fig. 10-4 Winston Churchill urges the citizens of Bristol to support the ABSD.

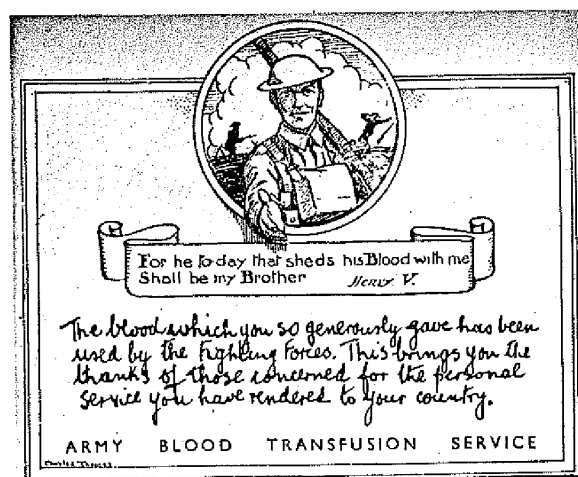


Fig. 10-5 The ABTS Second World War donor certificate.

drying plant for the ABSD (Fig. 10-6), which had a capacity of over 1400 bottles per week. During the course of the war 116,804 bottles of liquid plasma and 325,576 bottles of dried plasma were issued to the British and allied medical services and to civilian hospitals.

As well as the general administration of the ABTS, the ABSD trained medical officers and other ranks in blood transfusion practice, produced crystalloid solutions and manufactured all the grouping antisera and the transfusion equipment for the Forces. The latter involved the production of donation and transfusion sets (Fig. 10-7) and the employment of specialist glass-blowers (Fig. 10-8) and needle-sharpeners (Fig. 10-9).

The first overseas unit was the Blood Transfusion and Surgical Research Laboratory (BTSR). This was deployed, under the command of Captain W. d'A. Maycock, with the British Expeditionary Force (BEF) in October 1939 and received its first supplies of blood on the 6 October. It was to act as the distribution chain for blood sent from the UK, to manufacture crystalloids, and to salvage and re-assemble transfusion equipment. Additionally, the unit conducted research into the effects of injury, the treatment of battle casualties, wound infection and chemotherapy. Although the staff of the BTSR performed heroically during the subsequent campaign, the unit was too large and unwieldy and was disbanded after its fragmentary evacuation, with the rest of the BEF, through Dunkirk and St Nazaire.

The BTSR was replaced by Blood Transfusion Units (BTUs), which were deployed in the base areas, and distributed supplies from the ABSD, locally manufactured crystalloids and, later in the war, penicillin. They also undertook training and, when the field of operations was too far distant for air supply of blood from UK, conducted local donor sessions. Further forward were Field Transfusion Units

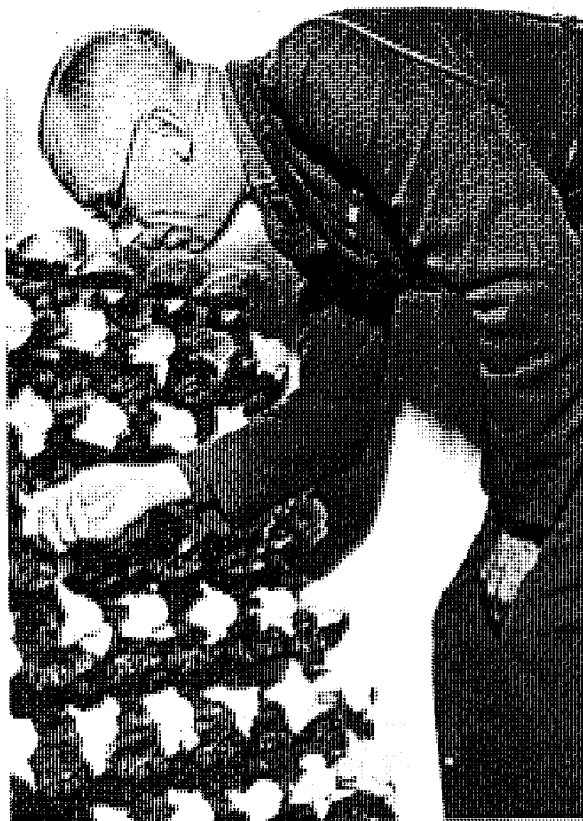


Fig. 10-6 The plasma-drying plant.

(FTUs) and Advanced Blood Banks (ABBs) which were equipped with mobile refrigerators (Fig. 10-10) capable of holding 100 pints. The FTUs and ABBs were responsible for the delivery of blood (Fig. 10-11) to the Casualty Clearing Stations and Field Ambulances to which they were attached.

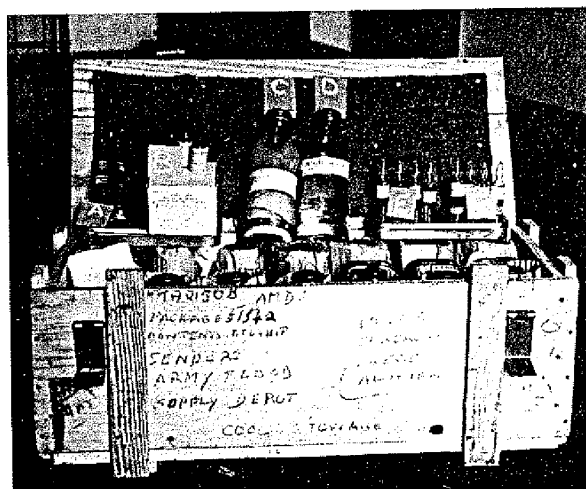


Fig. 10-7 A transfusion set boxed ready for despatch.

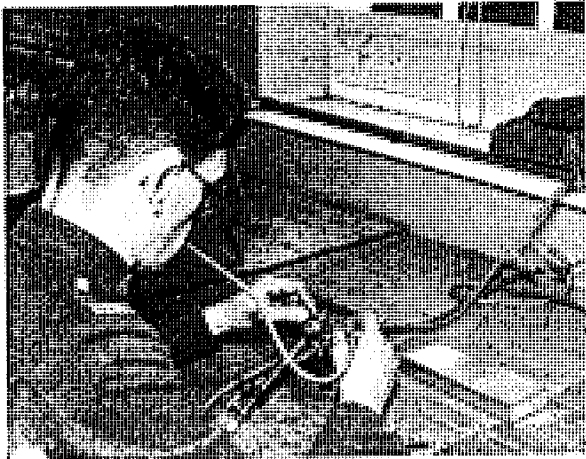


Fig. 10-8 An RAMC glass-blowing technician producing transfusion equipment.

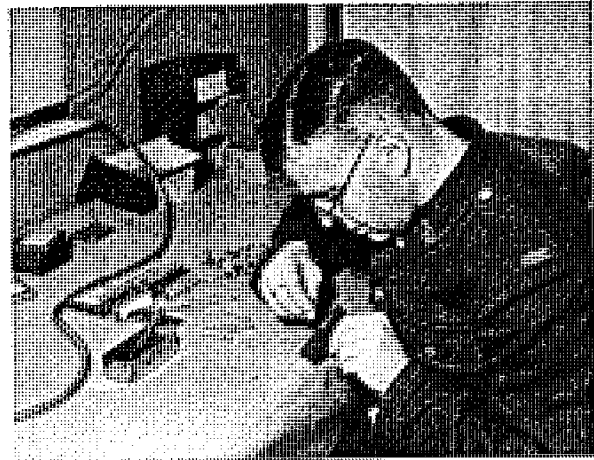


Fig. 10-9 An RAMC technician sharpening donation needles.

The FTUs were often very close to the front as is illustrated by the fact that five were deployed with the assault troops on D-Day and had to provide all the blood that was needed that day, until the first supplies came in from the ABSD on D+1. During the last year of the war, the 21st Army Group sustained 144,640 killed and wounded of whom 12% were transfused with an average of 4.3 pints of blood and plasma. Over 178,000 pints of blood and plasma were transfused and over 200,000 pints of crystalloids were manufactured. In all five BTUs and 41 FTUs were deployed during the war.

At the end of the war the ABTS, as an integral service, was disbanded. The ABSD was taken over by the MoH in January 1946. At this time all transfusion centres were called Blood Supply Depots, but, whilst the National Blood Transfusion Service (NBTS) later changed the name of their centres to Regional Blood Transfusion Centres the army has

retained the old title until the present day. UK military hospitals had their blood provided by the civilian service whilst, overseas, each individual military hospital set up a local donor panel to provide blood to cover its own transfusion requirements. In some instances, such as Singapore, where there were five hospitals with a combined capacity of over 800 beds, the requirements were relatively large, whilst in others, such as the British Military Hospital, Benghazi, very little blood was required.

The vast majority of the medical officers, who had served in the RAMC, were demobilized and returned to civilian practice. Some like William Walker and Lionel Whitby, left the field of blood transfusion, the latter becoming the Regius Professor of Physic, Master of Downing College and Vice-Chancellor of Cambridge University, before dying tragically in 1956 at the age of 61 years. Dr Maycock, in charge of ABTS during its last year, played an important part in

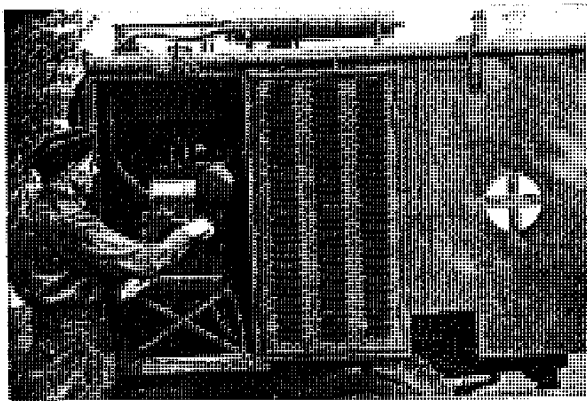


Fig. 10-10 A 100-pint mobile blood bank refrigerator, which was the standard equipment for a Forward Transfusion Unit.



Fig. 10-11 A motor-cyclist delivers blood from an Advanced Blood Bank at the battle of El Alamein.

founding the National Blood Transfusion Service (NBTS).

In 1961 the ABSD was reformed at Parsons Barracks in Aldershot to take over the blood supply to the Cambridge, Queen Alexandra and Royal Herbert Military Hospitals. Since the end of the war, these hospitals, located in Aldershot, Millbank and Woolwich, had been supplied by the South London Depot at Sutton. The administrative offices and laboratories were located in one of the old dormitory blocks and the mess hall and kitchens were later converted into the research and cryopreservation laboratories and stores.

With the advent of the Cold War and the Berlin airlift came the realization that, whilst it was perfectly possible to stockpile virtually every item of military and medical supply, this was not true in the case of blood which, at this time, had a shelf-life of only 3 weeks.

Over the previous few years there had been a steadily increasing interest in the cryopreservation of red cells. In 1949, Polge *et al.* described the use of glycerol as a cryoprotectant, whilst successfully freezing spermatozoa, and then in the following year Smith (1950), another member of Parkes' group, reported the successful cryopreservation of red cells using glycerol. In 1962 the MoD set up the Blinde project in conjunction with the US Office of Naval Research. The initial aim was to use polyvinylpyrrolidone (PVP) as a cryoprotectant and among the members of the Steering Committee were Professors Greaves and Mollison, Dr Maycock and Colonel Harold Witcher.

The project was first located at the Royal Army Medical College but, in 1964, was moved to the ABSD. PVP was found to be unsuitable and so in 1966 trials were made using the Huggins cytoagglutinator using glycerol as a cryoprotectant. This was later abandoned in favour of the method of Krijnen and Rowe (Krijnen *et al.*, 1970) and stocks of glycerolized red cells were laid down in Germany and at the ABSD. These stockpiles would be available to provide blood for transfusion until such time as supplies of liquid blood could be brought from the UK. Unfortunately it proved impossible to develop a satisfactory field processing machine and the need for washing the red cells prior to transfusion imposed an unacceptable time penalty.

In 1969 work was started on an alternative cryoprotectant, hydroxy-ethyl starch (HES). This, like PVP, is an external cryoprotectant and, as it is a widely used artificial plasma expander, does not require removal from the red cells prior to transfusion. In the early 1970s all work on glycerolized blood was stopped and the research effort was directed totally towards HES. Initially the method of Lionetti and Callahan (1979) was used and then modified, but subsequent human volunteer trials demonstrated an unacceptably high level of post-transfusion haemoglobinuria. Until this time it had always been accepted that HES had to be mixed with plasma to be an effective cryoprotectant, but the ABSD research group investigated the use of HES alone. The exclusion of plasma lowered the volume of HES required, thereby

reducing the total volume of the freezing mixture. This in turn allowed faster freezing rates with consequently less destruction of red cells (Thomas *et al.*, 1996).

In 1982 the Falklands Islands were invaded and a Task Force was despatched from Portsmouth on 5 April 1982. Until this time, all blood-supply plans had been based on the scenario of a war in NW Europe. There were no plans for the supply of blood to support a beach landing at a distance of 7000 miles. Memories of the problems of medical care in the Crimea, Gallipoli and the Norway campaign of 1940 only served to produce feelings of foreboding. However, two fortunate events helped ease the problems. The ABSD had just successfully completed the trials of a new lightweight blood transport box, the CIBITS, and CPD-A had recently been licensed thereby extending the maximum shelf-life of blood to 5 weeks (Högman *et al.*, 1983). Blood was delivered to hospital ships as they passed Ascension Island or was air-dropped into the sea alongside the ships. No supplies were actually made to the field hospital on the Falklands until after the cessation of hostilities. A number of valuable lessons were learned from this experience. Firstly, it was vital to have a flexible blood-supply plan that could be adapted to operations anywhere in the world. Secondly, central control of blood supply is vital and thirdly, the resources of the ABSD alone were not large enough to meet the total requirements of a military campaign. These lessons and the subsequent planning paid dividends as will be seen later.

The introduction of Product Liability in 1988 had major repercussions on the NBTS. As far as the MoD was concerned, it meant that locally organized donor sessions in military hospitals had to cease and all blood had to be supplied from ABSD, which, like other centres, had to seek MCA licensing. Trials were undertaken to validate mobile blood banks and to prove the safety of long-distance deliveries.

In 1985 the first of a series of Supreme Headquarters, Allied Powers Europe (SHAPE) Blood Conferences was held, which later became the North Atlantic Treaty Organization (NATO) Blood Conferences. At the conference held in Luxembourg in 1988, it became obvious that, for most of the NATO partners, the provision of blood for war could not be undertaken without the help of the civilian transfusion services. It was agreed, therefore, that the heads of civilian services should be invited to the next conference so that an integrated NATO civil/military blood plan could be developed. As 1989 was the 50th Anniversary of the ABTS it was agreed that the first NATO Civil/Military Blood Conference should be held in Aldershot in September 1990. This turned out to be a fortuitous decision because, in August 1990, Iraq invaded Kuwait. The conference provided an ideal planning meeting for all those NATO nations involved in the conflict and many useful ideas were exchanged.

The plans which had been developed and exercised over the previous 2 years were put into action. A forward element of ABSD was deployed, firstly to Bahrain and later to



1 10.12 The badge of the ABSD.

Riyadh. This unit was equipped with two 3000-unit mobile blood banks and freezers capable of storing FFP. As more troops and field hospitals were deployed so further sub-units of ABSD were deployed each with a 3000-unit mobile blood bank. In addition the hospital ship, *HMS Argos*, had a blood bank as well as cytopheresis machines capable of providing small numbers of platelet concentrates.

Initially the blood requirements were met from ABSD's own resources, but, as had already been learnt from the Falklands campaign, these would be inadequate to meet the requirements when the major conflict started. Arrangements were made between the MoD and the UK Blood Transfusion Services which were coordinated by the National Directorate

of the NBTS. Agreed quantities of red cells, tested and ready for use, were supplied to the ABSD whose task was limited to their control and onward delivery. Within minutes of the air campaign commencing, the plan was put into action and the first supplies were delivered to the ABSD within 8 h. The public response was immediate and overwhelming. Over 50,000 donors were bled in 4 days and more than twice that number of new donors were recruited (see Chapter 11). There was never any danger of shortage of blood to the military or restriction of blood to civilian hospitals.

The work on the HES Project had been continuing throughout this time and a UK patent on the method was granted in 1992. Subsequently worldwide patents were obtained and in 1993 the Dutch firm NPBI was granted a licence to commercially exploit the method on the MoD's behalf. Clinical trials are currently being undertaken at Guy's Hospital in conjunction with ABSD.

The need for blood support to British and other allied forces continues and ABSD is currently supporting the troops in Bosnia. It is said that history repeats itself. In May 1944 No. 4 FTU was located in Ancona, Italy. Fifty years later ABSD set up a forward blood bank in Ancona to act as a staging post in the supply of blood to support the humanitarian efforts of UNHCR in Sarajevo.

A quote from the February 1945 edition of the ABTS house journal, *The Bat*, seems a particularly appropriate tribute to all those who have served in the ABTS. 'We were offered 'blood, sweat and tears'. If 'blood is life', then we know that we have given life to many. If sweat was wanted it was forthcoming. And as for tears, well,...' The 'Bat' is also the badge of the ABSD (Fig. 10.12).

Chapter 11: The National Directorate, 1988-1993

It has been noted at the end of Chapter 3 that the NHS Management Consultancy Services team identified the need for a coordinated service to increase efficiency and improve performance. On 28 July 1988 Mrs Edwina Currie, Parliamentary Secretary for Health, announced that new management arrangements would be made to provide a formal national management structure for the National Blood Transfusion Service. In a written reply to a Parliamentary Question from Mr Ian Taylor, Mrs Currie stated:

"I have decided that new management arrangements are needed for the supra-regional and national dimension of the National Blood Transfusion Service (NBTS).

"I therefore intend that operational responsibility at the national level for the NBTS and the Central Blood Laboratories Authority (CBLA) will be exercised on behalf of the Health Ministers for England and Wales by the NHS Management Board and undertaken by its Director of Operations, in consultation in respect to Wales with the Director, NHS Wales. Day-to-day implementation of the national strategy will be delegated to a new National Director of the NBTS and a small supporting staff. The key objectives will be:

- a) to implement a cost-effective strategy for ensuring an adequate supply of blood throughout England and Wales;
- b) to implement a cost-effective strategy for the supply of plasma to the blood products laboratory of the CBLA;
- c) to co-ordinate the activities of the NBTS and the CBLA;
- d) to promote the efficiency of the NBTS.

"In implementing the objectives at a) and b) a priority task will be to remove financial disincentives by having a national system of processing and handling charges both between transfusion centres and between them and the CBLA. No charges will be made, of course, for freely donated blood.

"The National Director will be Dr Harold Gunson who is at present the Regional Transfusion Director for NW Region.

"I have arranged for copies of the Report to be placed in the Library."¹

Dr Gunson assumed the appointment of National Director on 1 October 1988. He reported to Mr Graham Hart, at that time the Director of Operations, the NHS Management Board. Mr Hart convened a coordinating committee whose membership is given in Table 11.1. It was the intention that it met no more frequently than once or twice a year to review the work of the National Directorate and to provide a bridge between the Directorate and top NHS management.

The National Directorate was funded by the DHSS through the NW RHA in whose premises it was based. Mrs Linda Johnstone, his secretary at the NW Regional RTC, was transferred as Dr Gunson's personal assistant. Dr Moore was seconded from the Department of Health and Social Security (DHSS) as Deputy Director (Administration) from 1 January 1989. His most recent appointment had been concerned with blood transfusion and he was involved with the formation of the National Directorate. An office manager, Mr Peter Cosgrove, and Mrs Debbie Wrigley as secretary to Dr Moore were appointed early in 1989. A few months later, Mr Stuart Orvis was appointed as Computer Services Manager. The six staff detailed above were the maximum number to be employed by the National Directorate.

Dr Gunson presented a report to the Regional Transfusion Director's (RTD) Committee on 4 October 1988. He announced that he intended to create a National Management Committee (NMC). Initially it was proposed to invite the Chairman of the RTD Committee and the Chairmen of Divisions as RTC members. At the next meeting in January 1989, RTDs agreed to disband their Committee, to be replaced by an annual meeting with a scientific agenda to which all consultants in the NBTS would be invited. The membership of the Management Committee was changed to the elected Chairmen of the Divisions and a second person from each Division, nominated by the National Director.

The terms of reference of the NMC were:

- to consider matters of importance in relation to the work of the NBTS and advise the National Director;
- to bring forward to the Committee matters of national importance to the work of the NBTS;
- to receive reports from:
 - i) meetings of the NBTS/CBLA Liaison Committee;
 - ii) meetings of the Head Laboratory Scientists, Nurse, Donor Service Managers and Administrators/Managers;
 - iii) *ad hoc* RTD working parties;

Table 11.1 Membership of the NBTS Co-ordinating Committee

DHSS	Mr Graham Hart, Chairman
RHA Chairman	Mr Colin Walker (Cambridge)
Chairman CBLA	Mr David Smart (later Mr Ron Wing)
Regional Medical Officer	Dr Michael O'Brien (Cambridge RHA)
Regional General Manager	Mr Bob Nichols (Oxford RHA)
Regional Treasurer	Mr Arthur Wilson (South Western RHA)

¹ Hansard, 28 July 1988.

- iv) National Publicity Sub-committee;
- to report to the Divisions the decisions reached by the National Directorate.

Of the committees mentioned above, those in sections ii) and iv) existed prior to the formation of the National Directorate. The National Publicity Sub-committee was chaired by a member of the publicity section of DHSS with RTD and Donor Organizer representation. Its function was to allocate central funds on a national basis for donor publicity. Later, it was incorporated in the Provision of Donors Committee, known throughout the NBTS as POD (see above).

The NBTS/CBLA Liaison Committee was created and chaired by Dr Gunson with the aim of coordinating the work of the RTCs and BPL. It provided the opportunity for the National Directorate, representatives of RTCs and senior managerial staff at BPL to discuss operational matters affecting both organizations and to provide a forum for problem solving. In addition to reporting to the NMC, this Committee also reported to the Board of the CBLA.

ACHIEVEMENTS OF THE NATIONAL DIRECTORATE

It is important to remember that the National Directorate had no executive authority with respect to the RTCs as they continued to be regionally managed. Its success in changing policies were achieved by persuading the senior management in RTCs that the change was beneficial for the good of the Service.

The inter-regional transfer of blood

Prior to the formation of the National Directorate there had been several attempts to organize the transfer of blood between RTCs to correct temporary shortages. None was successful. The first action taken by the Directorate was to arrange for each RTC to fax to the central office, daily, a statement of their blood stocks. These were collated and a national total of units of blood of each group was available, usually before 12 noon each day. RTCs who were short of blood telephoned the National Directorate and supplies from another RTC were arranged. The two centres made direct contact with each other and decided how best the transfer could be made.

This system continued successfully until the Directorate was disbanded. Whilst it might seem, in retrospect, to have been antiquated in these days of the Internet, the system worked satisfactorily and was welcomed by most RTCs. During the period from 1989 to 1993 there was only one instance when there was adverse publicity due to a shortage of blood which occurred when one RTC failed to inform the Directorate that they had asked hospitals in their region to

postpone some planned surgery. Some RTCs were reluctant to use the service, particularly after charges were introduced, and contractual arrangements between RTCs, although they existed were not as fully exploited as they could have been with national management rather than national coordination.

The difference in quantities between a satisfactory supply and a shortage was small. Whilst total daily red-cell stocks were in the order of 25,000, approximately 2½ days' supply, there was rarely a need to transfer blood between RTCs. Below this level there were shortages at one or more RTCs; above it there was a surplus. The advantage of having a national dimension for the blood stocks was that when the trend was downwards it was possible to initiate local, or if necessary national, publicity to increase the blood supply before a major shortage occurred. Indeed, it became possible to predict seasonal peaks and troughs with considerable accuracy and provide an understanding of the dynamics of national blood stocks, hitherto unknown.

The management information system

It will be recalled that a major criticism of the NBTS in the review by the DHSS Central Management Services was that it lacked management information on which to make decisions (Chapter 3). In order to achieve the objectives set by the DHSS, it was necessary to design and implement a management information system (MIS) for the NBTS.

A survey of RTCs revealed that there were variations and deficiencies in the management information available. At the first meeting of the NMC on 1 December 1988 it was decided to form a steering group to pilot the scheme. A timetable was drawn up which envisaged that the MIS would be operational by February/March 1990. The resources available within the National Directorate were insufficient to carry out the investigations necessary to develop the MIS; consequently specifications were prepared and the management consultants Ernst Young were appointed and funded by the DHSS.

During 1989, the system was developed and was programmed into the computer at the National Directorate. As there was a wide variation in the computer systems operating in RTCs it was necessary to provide each RTC with a computer and modem for the transfer of data. Most RTCs appointed a management information coordinator to assemble the required data on a monthly basis and send it on a disc to the National Directorate. The data was collated by the Computer Services Manager at the Directorate and each RTC received information on the activities of all 14 centres in England and Wales. The quality of the information was only as good as that received from the RTCs. Inevitably there were gaps as it proved difficult to obtain complete information from each RTC every month. Also, as time went by, RTCs required information which was not available on the national MIS and they developed their own programmes.

There was a tendency to refer to the MIS as the 'Directorate's information system'. This was not the intention because it was designed to provide timely information for the benefit of all tiers of local management as well as national use. It is fair to say, however, that the information proved more valuable and was used to a greater extent by the National Directorate than the RTCs. By the time the National Blood Authority (NBA) assumed responsibility for managing the RTCs the MIS needed replacing. If nothing else the development of the MIS served to illustrate to RTCs the need for accurate management information. Also, it was an indication that in the NBTS a nationally integrated computer system was essential together with a mechanism for continual review. The latter would have been undertaken by the National Directorate, but by 1991 it was clear that there would be fundamental changes in the management of the NBTS; the Computer Services Manager had left the Directorate to return to the hospital service and was not replaced as there was uncertainty concerning the security of this post in the future.

Quality assurance

Several pressures combined to bring quality assurance to the forefront of the NBTS agenda. It was recognized that a major degree of standardization was required and minimum standards set in order that the UK BTS could respond to possible litigation under product liability legislation. Also, it was the intention of the DoH to abolish Crown Immunity in the National Health Service and Community Care Act (1990). This meant that each RTC would require a Manufacturers' "Specials" Licence from the Medicine's Control Agency (MCA).

During 1988, prior to the formation of the National Directorate, a joint project was organized between the NBTS, the Scottish National Blood Transfusion Service (SNBTS) and the National Institute of Biological Standards and Control (NIBSC). Several working groups were formed to prepare operational guidelines for the UK BTS and by 1989 considerable thought had been given by the working groups to Standard Operating Procedures (SOPs) and specifications.

The National Directorate took the lead in focusing this activity. The key to the strategy was the adoption of the British Standard (BS) 5750, Part 1, as the guideline for NBTS quality systems. A programme to train quality managers and a system of peer audit was carried out against the requirements of BS 5750.

Quality assurance (QA) managers were being appointed at several RTCs but their appointments varied between centres according to the resources available.² Dr Moore reported to the NMC that the majority of QA managers in post and those likely to be recruited in the near future had been drawn from the Medical Laboratory Scientific Officers (MLSOs). Whilst this meant that they were adept at dealing with the technical

details of specifications and laboratory quality-control testing, they were less familiar with the requirements of total quality assurance systems.³

Dr Moore proposed a residential course for NBTS QA managers, to be specifically orientated towards the transfusion service by David Begg, a former Medicines Inspector. Two courses were held in November 1989 and subsequently Dr Gunson signed a NBTS Quality Policy Statement which was displayed in each RTC (Fig. 11.1). In association with this initiative the National Directorate launched the QUIN Strategy (Quality Initiative for the Nineties). Guidelines were given to each RTC on how best to approach this important task, regular meetings were held with QA managers and a series of audits were arranged which were designed to assist the QA managers in carrying out internal audits. Two QA managers, initially led by Drs Gunson and Moore audited selected activities, including laboratory work, blood collection and processing at RTCs outside their region. A major advantage of these audits was that QA staff visiting different

² Minutes of meeting of Regional Transfusion Directors, 13/4/88.

³ Minutes of meeting of the NMC, 13/4/89.

NBTS QUALITY POLICY STATEMENT

The National Blood Transfusion Service is dedicated to a system of quality management which will ensure that its blood products and services meet the requirements of clinicians and their patients. Because our products are administered to patients, our quality system will be comparable in excellence to those used in the pharmaceutical industry by licensed manufacturers.

The quality policy rests on four principles:

- *Our definition of quality is **conformance to requirements**. We will carefully specify the requirements for our suppliers (donors and manufacturers), our processes (collection, laboratory, distribution) and our product users.*
- *We will improve and maintain quality through a planned system of quality assurance management which will cover every part of our activity. Audit and review will be an essential part of this system.*
- *We will ensure that under the guidance of trained QA management each member of staff recognises their responsibility for quality improvement.*
- *We will ensure that education and training of staff are sufficient to maintain and improve quality.*



Dr H H Gunson
National Director
April 1990

Fig. 11.1 The NBTS Quality Policy Statement.



Fig. 11-2 Examples of successful national posters.

RTCs were able to identify best practices and often introduced them in their own centres; in this manner a standard format for some procedures was gradually achieved.

The first edition of the Guidelines for the UK Blood Transfusion Services, the *Red Book*, was published in 1990. This provided specifications for a comprehensive range of products, procedures in blood transfusion practice and included sections on quality assurance, blood collection, processing, testing, distribution and plasma fractionation. The NBTS accepted the contents and when writing policy statements for their hospital customers RTCs were able to state that they operated in accordance with the guidelines.

Arguably, the action taken by the National Directorate with respect to quality assurance was its most important success.

Dr Moore, with his previous experience in quality assurance, brought leadership and gained the respect of the Service. It is to his credit that when he left the National Directorate only three RTCs had failed to obtain the Manufacturer's "Specials" Licence.

Blood-donor retention and recruitment

Maintenance of the blood supply was a major priority and the National Directorate was instrumental in measuring the need and setting a strategy for the NBTS. The POD was

established in 1989. This was chaired by Dr Moore and membership consisted of three medical consultants and three donor-service managers, with observers from Scotland and Northern Ireland. The Committee replaced the former DHSS National Publicity Sub-committee and as such advised DHSS on the provision of national publicity material in the form of posters, leaflets and videos. An early move was to secure an 0800 telephone number for the NBTS. The cost of national publicity was met from a central budget held by the DHSS. Usually, three major campaigns were mounted each year. The first was in the Spring to cover Easter and the Spring Bank Holidays which often followed each other closely. The second was during the Summer when many donors took holidays and the third was immediately before Christmas. The national campaigns were supplemented by local publicity to correct deficiencies within a region. During the 4 years that this Committee was in existence several million pounds were allocated from the central budget. Examples of successful posters are shown in Fig. 11-2.

It was important, also, to take a long-term view of donor recruitment and retention. Research International Ltd (RIL) were engaged in September 1989 to carry out a survey of donors and the general population to answer the following two questions:

- to advise how all donors may be encouraged to continue giving blood regularly;
- to advise how people may be encouraged in the most

efficient and cost-effective way to become blood and plasma donors.

This was a major study of donor motivation and the results were reported by Moore (1991).

One significant finding in RIL's report, presented in March 1990, was that 27% of the general public interviewed had given blood at some time in the past. As current donor panels comprised only 4–5% of the population it was clear that the Service was not efficient at retaining donors. Proposals for a communication strategy were drawn up and circulated to RTCs in July 1990. The recommended strategy was considered under three headings:

- *what* we ought to be saying (the message, in words and actions);
- *who* we ought to be saying it to (the target);
- *how* we ought to be saying it (the tools).⁴

The message

Conveying the need for blood was the primary message which had to be given, i.e. blood was a national resource which must be maintained, that there was an increasing requirement as medical science progressed and that it was dependent upon a partnership between members of the public and the NBTS. Because blood can be stored for only a short time, the need, on every day of the year, must be communicated so strongly that it overcomes the reluctance of a person to donate. Other factors to be taken into account were, allaying anxiety of potential donors and projection of the identity and image of the NBTS as professional and caring.

The target

The main targets for the message were current donors, lapsing and lapsed donors, willing and non-willing persons who are not yet donors. Action taken might have a knock-on effect; thus an improved response of donors could increase the retention of lapsing donors and action taken to remotivate lapsed donors could help to recruit new donors.

The tools

There were several ways in which communications could be made with donors:

- *for current, lapsed and potential donors* — through the media, advertising and by word of mouth or contact through friends and families;
- *for current and lapsing donors* — through experience at sessions, e.g. the attitude of staff, by distribution of information leaflets and by direct communication by mail or telephone.

⁴ Extract from RIL report, March 1990.

RTCs were asked to take steps to improve the experience of donors at blood-collection sessions, to monitor the situation and to provide a comprehensive series of leaflets at sessions displayed in an attractive dispenser. Within 3 months all but two RTCs had responded with a timetable for introducing the communication strategy and some had begun to implement the proposals.

The National Directorate deliberately encouraged RTCs to run their own local campaigns in order to increase the feeling of local ownership, to reflect local donor attitudes and to meet local service needs. The role of the Directorate was strategic and facilitative. This approach was successful in maintaining the donor base and enabled the National Directorate to act as a focal point for national media interest. During this period, the national media were encouragingly positive and helpful with respect to donor recruitment.

Liaison with BPL—the plasma supply

In 1988 only 338 tonnes (338,000 litres) were supplied out of a target of 450 tonnes (Fig. 8.5). Moreover, the quantity supplied differed between RTCs; although the average rate for 1988 was 6.77 tonnes per million of the regional populations, the range was from 4.35 to 8.48 tonnes per million. Whilst this deficiency was not critical at that time due to the commissioning of the new factory and the consequent lack of increased fractionation it was important that targets were reached in the next few years.

A target of 8.82 tonnes per million of the population was set by the National Directorate and the aim was to achieve this level by 1990. It can be seen from Fig. 8.5 that this was accomplished. Two events assisted in increasing the plasma supply:

- Mr Graham Hart wrote to Regional General Managers stressing the need to give priority to plasma production at RTCs so that targets set by the National Directorate could be met;
- cross-accounting for plasma and plasma products was introduced in April 1989.

Transfer prices of £35/kg for recovered plasma, £60/kg for apheresed plasma and £80/kg for specific antibody plasmas were agreed with BPL. There was concern that once this funding had been transferred to RHAs it would not be spent on buying BPL products. If this occurred, and with devolvement of income to Districts it was a possibility, the transfer of approximately £14 million/year could result in a serious situation at BPL. Meetings at the DoH did not fully resolve this situation as the ethos of the strategy was that BPL should compete with industry. The price of plasma was a contentious matter between the RTCs and BPL, although it was unaltered for 2 years before rising in line with inflation. It was a major part of product cost initially but increased yields have lessened its impact.

The Gulf War

Working with the Army Blood Supply Depot (ABSD) the National Directorate appealed for additional blood supplies to support the British Armed Forces involved in the Gulf War. From the outbreak of hostilities on 17 January 1991 an additional 4000 donors each day i.e. 14,000 instead of 10,000 were requested. Regular donors were asked to make every effort to attend if called, but not to do so otherwise to conserve stocks for the future. New donors were asked to telephone the freephone number. In fact, during the first day of the appeal 19,000 donations were collected and 20,000 on the following day. In 4 days, 50,000 donations were collected and 60,000 persons had given their names for call up in the future. The National Directorate had harnessed the media to support the appeal and the publicity given in the press, on radio and on television was extensive. A few examples of the headlines in the newspapers are shown in Fig. 11-3. It was an exceptional example of how the public responded to an emergency and it demonstrated also how difficult it was to control such a situation. Indeed, the effect was not confined to this country. The number of donations collected in Adelaide, Australia, a country not involved in

the Gulf War, doubled during this period (R. W. Beal, pers. comm.).

The RTCs were overwhelmed with donations for several weeks. The number of donations collected far exceeded those required for the Middle East and by careful management blood stocks were at higher than normal levels until the Autumn of 1991.

The medical assessment of donors

In the UK BTS/NIBSC Guidelines there was a section on the medical assessment of donors. This was included in an attempt to change the disparate action taken by RTCs in the selection of donors. There were, however, a number of illnesses for which decisions were required after publication of the guidelines. The National Directorate, working in conjunction with the Standing Advisory Committee on Donor Selection of the *Red Book*, published a compendium of these illnesses and how they should be handled.

Early in 1993, Dr Gunson received a number of complaints from donors that they had been accepted for blood or plasma donation at one RTC but had been rejected at another.

The collage features several newspaper headlines from the early 1990s:

- THE DAILY TELEGRAPH TUESDAY JANUARY 22, 1991 13**
- The silent army raises its arms**
Blood banks are so full that donors are now on stand-by, says Jeremy Laurance
- NHS ready for the worst from Gulf**
- Rush to give blood**
by Lois Rogers
Some of the volunteers today at the West End blood donors' clinic, off Oxford Circus
- Red alert for blood**
MORE than 100,000 blood donors have answered a war appeal. It was an enormous response. Large queues formed outside donor centres across the country and phone lines have been swamped. Transfusion bosses called for an extra 4,000 plus A & B to maintain stocks.
- Doctors pay tribute as donor Brits flock to do their bit for our front-line troops**
- YOU'RE BLOODY MARVELLOUS!**
- 'Readiness' alert on blood supplies**
- 14,000 give an 'armful' for the lads**
- Plea for blood to save the wounded**
- vital blood supplies**

Fig. 11-3 Examples of newspaper headlines at the beginning of the Gulf War.

He set up a working party on the medical assessment of donors, whose work continued after the National Directorate was disbanded.

The demise of the National Directorate

In 1990, the DoH published a White Paper, *Working for Patients*. The result was that, from April 1991, RHAs planned to devolve RTC budgets to Districts. From that date RTCs would have to recover their operating costs through reimbursement for products and services. For this system to be effective, it was necessary for RTCs to work closely with users on the details of their supply requirements across the range of products and services.

To assist RTCs, the National Directorate established a financial sub-group which looked at methods of costing and related matters. Efforts were made to achieve a national costing system which was adopted by most but not all RTCs. The introduction of budget devolution was not standard throughout the country. In some regions cost per item was introduced, in others block contracts were negotiated either for both products and services or for services alone.

Drs Gunson and Moore were concerned at this fragmentation of the Service which had the effect of marginalizing the National Directorate. The lack of executive authority to implement national strategies was a major disadvantage. Successful initiatives, such as quality assurance and the MIS, could only be taken so far without a national strategy for capital and revenue investment. Agreement for such expenditure had to be given by 14 regions. With the devolution of budgets, users were involved with developments in the NBTS since any extra funds would have to be raised from the price they had to pay for products and services. Although the blood transfusion expenditure was a small percentage of the total hospital budget, increased costs of blood products were not popular with hard-pressed budget holders. Without national management, it was difficult to put forward novel policies that would be acceptable to all RTCs or to define savings which might help to pay for developments.

With the support of the NMC and the majority of the RTDs, although some reluctantly, the advantages of a nationally managed service were put forward to the DoH. Indeed, these had been adequately summarized by the authors of the 1987 management report, viz: "...a nationally managed BTS would provide the most certain method by which organizational change, and hence cost savings, can be achieved. It alone provides the potential to completely and effectively rationalize the blood collection and processing functions; the location of centres in which these tasks are undertaken; and to ensure that supply and demand can be balanced and the requirement for plasma achieved. Furthermore, it offers the best prospect of achieving uniformity, where this is desirable, and co-ordination throughout the BTS."

The request for a nationally managed service was turned down. It has to be recognized that, at that time, DoH policy was directed towards devolution and the creation of a Special Health Authority to manage the NBTS had little appeal.

However, during 1991, CBLA asked the management consultant company, Touche Ross, to recommend options for its future strategy and organization. Because any organizational change at the CBLA would have an effect on the NBTS, the National Directorate commissioned Ernst Young to investigate whether there was a continued role for a central body in the NBTS, and what were the organizational options for any such body. Several options were put forward and these were discussed by RTDs at a meeting held in June 1991. The favoured option was that a National Blood Authority was formed and that it should establish contractual arrangements with RTCs for cellular components and plasma for fractionation.

Events moved quickly. After a meeting of interested parties in July 1991, the DoH issued a consultative document on 19 September. The proposal was to establish a Special Health Authority, the National Blood Authority (NBA), which would replace the National Directorate and the CBLA. RTCs would contract with the NBA for the provision of blood, cellular components and plasma, but would continue to be managed locally.

A technical working party was set up by the DoH to consider how the NBA could operate on a contracting basis. As discussions proceeded it became apparent that it would be difficult for the NBA to intercede between RTCs and their hospitals as it would be too remote a body. For the NBA to contract directly with the hospitals was considered impractical. These considerations, together with the impending changes for RHAs, led to the conclusion that the NBA should directly manage BPL, IBGRL and the RTCs. An announcement was made to this effect by Tom Sackville, Parliamentary Undersecretary of State for Health, on 27 November 1992.

REPRISE

Despite the limited powers of the National Directorate, it was able to harness effectively the talents and resources of the RTCs across a wide range of activities, e.g. quality assurance, blood donor recruitment, the plasma supply, costing and pricing issues and the medical assessment of donors. That so much was achieved in the short time it existed is a testament to the quality of the advice and the cooperation of the RTCs.

The National Directorate guided the NBTS at a time of rapid change within the wider NHS, as the reforms of the NHS and Community Care Act led to Trusts and Health Authorities developing new management and financial structures of their own. Support was given by the Directorate to RTC management with more rigorous insights into matters essential to their business. More importantly, perhaps, it

helped to establish that the NBTS code of ethics towards its donors and patients need not be prejudiced by a more business-like approach to management.

The National Directorate encouraged the growth of co-operative working in many different disciplines and at many

different levels, provided valuable cross-fertilization of ideas and gave meaning to the term 'national' in the NBTS. It provided an essential foundation and developed a common ethos in preparation for changes which were to follow.

Chapter 12: The National Blood Authority

On 27 November 1992, the DoH announced its intention to establish a National Blood Authority on 1 April 1993. The aims of this Special Health Authority were stated as follows:

- “to replace and co-ordinate the work of the Central Blood Laboratories Authority (CBLA) and the National Directorate of the NBTS;
- to maintain and promote blood and blood-products supply based on the outstanding system of voluntary, unpaid donors; to implement a cost-effective strategy of ensuring an adequate supply of blood and blood products to meet national needs;
- to ensure that the high standards of safety and quality in the blood supply are maintained throughout the blood service; to ensure that blood products meet a consistent standard of safety and quality;
- to ensure the cost-efficient operation of the transfusion centres and the Bio Products Laboratory (BPL) both individually and together as parts of the national service.”¹

From 1 April 1993, the NBA was responsible for the management of BPL and the International Blood-Group Reference Laboratory (IBGRL), and from that date the CBLA and the National Directorate ceased to exist. It was anticipated that the management of the Regional Transfusion Centres (RTCs) would be transferred to the NBA on 1 April 1994, providing that the necessary documentation could be completed.

The run down of the National Directorate began in January 1993. Dr Roger Moore returned to the DoH and the Office Manager was transferred to a vacant post in the NW Regional Health Authority (RHA) to avoid redundancy. Dr Gunson remained in the Manchester office with one full-time personal assistant and one part-time secretary. The Management Information System was co-ordinated on a part-time basis by a member of the staff of the computer department at the Manchester RTC.

Despite having fewer staff, the National Directorate carried on, as far as possible, with its essential activities. The daily blood stocks were collated and transfers made as required, the quality audits at RTCs were continued by the quality assurance (QA) managers and their reports were assessed by Dr Gunson. Perhaps the most difficult task was

the monitoring of blood-donor publicity, which had been undertaken, so successfully, for several years by Dr Moore (Chapter 11).

As appointments were made, work was transferred from Manchester to the offices of the NBA in Watford which were opened on 1 June 1993. Mr Alan Slopecki, National Quality Assurance Manager, commenced duties in June 1993, Mr Gary Barr, National Information Technology (IT) Manager, in July 1993 and Mrs Sue Cunningham, National Public Relations and Donor Services Manager, in October 1993. The last tasks to be transferred to the NBA were the monthly HIV and HCV antibody statistics (following Miss Rawlinson's retirement in March 1994) and the collation of the daily blood stocks in April 1994. The Manchester office was closed in June 1994.

MEETINGS OF THE NBA EXECUTIVE

In anticipation of the formation of the NBA, Dr Gunson discontinued meetings of the National Management Committee in December 1992. In order that the Service could be kept informed of developments, meetings of Regional Transfusion Directors/Chief Executives (RTDs/CEs) of the RTCs were convened with Dr Gunson in the Chair. These meetings were continued by Mr John Adey, Chief Executive of NBA, who took over the chairmanship in May 1993. In October 1993, the name was changed to the NBA Executive to denote that this committee was empowered to make policy decisions.

Much had to be accomplished during the first year of the NBA's existence. Staff contracts had to be transferred to the NBA as the employing Authority. The professional accountability of medical and nursing staff had to be resolved. Manufacturer's "Specials" Licences and Wholesaler's Dealers Licences had to be transferred to the NBA and assets of RTCs had to be acquired from RHAs. As RHAs no longer managed transfusion centres the term RTC could not be used and was changed to blood centre (BC). The name National Blood Service (NBS) was used instead of NBTS to counter the criticism from some members of the public that 'transfusion' engendered the thought of needles. The existing logo (Fig 11.1) was described as portraying a Service which was caring but old-fashioned. Indeed a number of RTCs had been using their own logos, either completely different from the national one or variations of it. It was decided to design a new logo which would more accurately reflect the Service in the 1990s (Fig. 12.1). Transfer of the BCs to the NBA took place, as planned, on 1 April 1994.

¹ Parliamentary Under-secretary of State for Health, November, 1992.



Fig. 12.1 The new NBS logo.

MEMBERSHIP OF THE AUTHORITY

Sir Colin Walker was appointed Chairman of the Authority. The Non-Executive and Executive Directors who attended the first meeting of the NBA Board in April 1993 are given in Table 12.1. Later two additional Non-Executive Directors joined the Board; these were Professor Wilhelm G. van Aken, Director of the Central Laboratories of The Netherlands Red Cross and Professor Sir Keith Peters FRS, Regius Professor of Physic, University of Cambridge. Dr Angela Robinson succeeded Dr Gunson on his retirement in June 1994.

MANAGEMENT CONSULTING

There was a requirement for the NBA to produce strategic plans for BPL AND BCs. Bain and Company were the Management Consultants chosen to lead a comprehensive investigation into the activities of both BPL and BCs, essential if consideration was to be given to proposals for the future. It was decided that between July and October 1993, Phase I of the study would concentrate on BPL. Phase II, to be completed by January 1994, would involve the long-term strategy for the blood supply and an examination of the BC infrastructure. Finally, Phase III would encompass the analysis of the data and consideration of the options which had emerged. The end of the project was scheduled for May 1994.

Phase I

A detailed study of the activities of BPL was undertaken with the involvement of their senior staff. The provision of a more

effective service has resulted by modifying certain procedures after considering data from the study. Two examples will be given.

Using plasmapheresis as a method for obtaining plasma as a single product from a donation was not cost-effective. There were successful negotiations to replace some of the single-purpose apheresis machines in use with those having the latest technology. Such machines allow the harvesting of several products from a single donation in a cost-effective manner. When the number of donors were limited, e.g. those with high-titre antibodies, it was recognized that plasmapheresis was inevitable.

In 1993, the production of factor VIII at BPL had reached a level of between 60% and 70% of the total annual consumption. The introduction of increasing quantities of recombinant factor VIII in the near future will, almost certainly, change the pattern of operations in fractionation laboratories worldwide. When this happens human plasma based factor VIII will no longer be the product which determines both the quantity of plasma required and the scope of fractionation. Arguably, the product which will fulfil this role will be intravenous immunoglobulin; to this end, it was important that BPL had this product licensed and increased production. Both had been achieved by 1996 and it is hoped that in the coming years BPL intravenous IgG will have a significant share of the market.

With respect to the long-term future of BPL, several options have been considered. A decision has not yet been taken on the implementation of a preferred option.

Phase II

Investigation of the functions of BCs was more complex than that of BPL. Detailed statistics were obtained on each of their activities for a specified period. A large number of staff at the centres collected and verified the data, and 28 senior staff were involved with its analysis. There were representatives from the medical, nursing, administrative, finance, and donor service staff from 10 BCs. More than 100

Table 12.1 Persons attending the first NBA Board meeting

Non-Executive Directors

Sir Colin Walker, OBE, Chairman Cambridge RHA
Mr Lawrence Banks, Deputy Chairman, R. Fleming & Co.
Mr Dennis Allison, CB, Regional General Manager, NW RHA

Executive Directors

Mr John F. Adey, Chief Executive
Dr Harold Gunson, CBE, Medical Director
Mr Barry J. Savery, Director of Finance and Administration

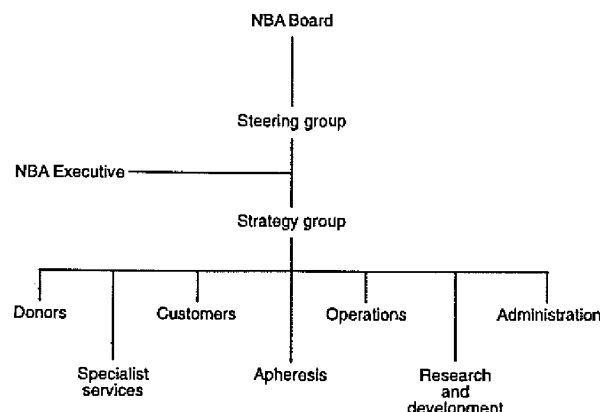


Fig. 12.2 Schematic representation of the organization for the investigation of the activities of the NBTS.

consultant haematologists were interviewed to obtain their views on the provision of services by the BCs.

A number of Working Groups were formed to discuss certain aspects of the operations (Fig. 12.2). Each was chaired by a senior member of the transfusion service with the exception of Research and Development, which was chaired by Dr David Anstee. Bain allocated a person from their staff to each Working Group.

A Strategy Group, chaired by Dr Marcela Contreras, met regularly to consider the information provided by the Working Parties and this, in turn, reported to a Steering Group comprising the executive Directors of the NBA. Detailed presentations were given to the NBA Executive and to the NBA Board on a monthly basis.

A striking feature of the data collected, although it was not surprising given the history of the regional management of the NBTS for almost 50 years, was the considerable variation in procedures carried out at the centres. It became clear, as the study progressed that there was a degree of duplication that could only lead to inefficiency.

Phase III

In this account it is possible to give only a brief summary of the findings. On the whole the centres received praise for the service they provided but some of the findings did not leave room for complacency. For instance, almost 20% of hospitals claimed that their local centre failed regularly (i.e. more than once a month) to meet all blood and product requirements. The great majority of donors were satisfied with the treatment they received but the remaining 3% were dissatisfied; if those questioned were representative of the donor population this meant that, approximately, 60,000 donors had grounds for complaint.

The more effective use of blood and blood products could only be brought about by improving credibility with the

hospital clinical staff. Hospital consultants had differing opinions on the effectiveness of their colleagues at the BCs. They were anxious, in most instances, to have the involvement of transfusion medicine specialists and, in particular, to receive educational material in the form of guidelines.

The strategy for improving the Service was summarized under three headings, viz:

- improving clinical practice;
- improving the donor interface;
- increasing operational effectiveness.

Encompassed within the above headings were 35 separate initiatives. It was recognized that without a coordinated national information technology policy any improvements to the Service would be limited. As potential changes were identified they were discussed in detail with the NBA Executive.

The provision of more effective clinical support was an improvement which the medical staff in each centre would have to consider and discuss with their hospital colleagues.

The estimated expenditure on blood collection was £65 million each year, approximately 50% of total costs. Several opportunities to improve donor care were identified including the identification of 'best practices' and transferring them across the NBS, the out-posting of teams to reduce travelling times, training of staff and the introduction of advanced information technology.

Improving operational effectiveness was the initiative which would cause major changes in the NBS. Inevitably, with regional management for so many years there was excess capacity. Each centre was equipped to perform every procedure and each had comprehensive administrative and donor-service functions. Analysis of the data from the study led to the conclusion that some functions could be consolidated into fewer centres. These were blood grouping, processing, apheresis, research and development, major administration and blood-donor management. The NBA Executive agreed that the above operational changes should be made. Indeed, there was considerable enthusiasm for change and the majority of directors considered that Bain had provided a stimulus for this to take place.

There was unanimous agreement that three administrative zones should be created. One BC in each zone would be nominated as the Administrative Centre and would be responsible for major administrative and donor management functions.

FORMAL PUBLIC CONSULTATION

Such major changes required public consultation before consideration by Ministers. The Consultation Document was published by the NBA in September 1994.

The key proposals and recommendations were:

- "the creation of three Administrative Zones, London and the South East, Midlands and the South West and Northern, with one Administrative Centre in each, based in North London (Colindale), Bristol and Leeds;
- the consolidation of testing and processing activities leading to the amalgamation of Lancaster with Manchester and Plymouth with Bristol in 1995; Liverpool with Manchester and Oxford with Birmingham and Bristol in 1996; and Brentwood with North London in 1997;
- an increase in the number of stockholding units to ensure that all hospitals are within 2 h travelling time for emergency deliveries."²

Over 1700 responses were received by the Chairman of the NBA. As one might expect the majority were critical of one or more of the proposals. In particular, this applied to the consolidation of certain functions into fewer centres, when concern was expressed that such changes would be detrimental to the provision of services. Regrettably, the Chief Executive of NBA suffered unjustified obloquy. A significant number of responses provided constructive comments and there was support for the proposals both from some professional correspondents and from members of the general public.

The NBA appointed a small independent panel, under the chairmanship of Professor Alistair Bellingham, to advise them whether replies to the Consultation Document had been properly documented and that due consideration had been given to the responses received. Comments were also invited on the consultation process itself.

In their report of June 1995, the Panel concluded that the NBA had carefully considered the responses from the consultation and as a result had modified some of the original proposals. The major change was the retention of the Brentwood Centre for testing and processing and the transfer of this activity from Cambridge to Brentwood. This change would make additional laboratory space available for research and developmental work at Cambridge. The term 'stockholding unit' was changed to 'reserve blood-supply bank'. Two further sites were proposed, one in South Lincolnshire and one in Central London. Additionally, the old regional boundaries would be removed so that each hospital could be serviced from the bank which was the closest in journey time to it.

The time-table for the implementation was amended and the modified proposals were presented to DoH. Approval was given in November 1995.³

² Proposals for the future of the National Blood Service, (Consultation Document), NBA, September 1994. ³ Plans for the future of the National Blood Service, Department of Health, November 1995.

OTHER SUCCESSFUL ACTIONS TAKEN BY THE NBA

Whilst the event which overshadowed all other activities during the first 18 months of its existence was the Bain study and the subsequent consultation process, the NBA has managed to undertake other measures which have had a beneficial effect on the work of the NBS.

Zonal management and coordination

There was a long delay between the proposal to create three Administrative Zones and its approval. In order that consideration could be given to the inevitable problems which would arise when the changes were implemented, directors and other key staff in the zones were appointed on a designate basis.

The NBA Executive now comprises the Executive Directors of the NBA, the Zonal Administrative Directors, the Chief Executive of BPL and the National Public Relations Manager. Within the zones there are multidisciplinary management teams, who meet regularly and also meet as specialist groups with their counterparts at the NBA. The managerial structure which has been developed allows a greater coordination between BCs and between BPL and BCs than has existed in the Service at any time in the past.

Medical assessment of donors

For many years RTCs had adopted different policies for the selection of donors whilst working within a general framework, so that a donor might be accepted in one region and rejected in another. Dr Gunson chaired a working party, formed during the latter months of the National Directorate, which consulted each centre to obtain information on how donors were medically assessed. Comprehensive guidelines were written and issued to all BCs as a controlled document. Also there was concern that the present method of selecting donors might not be optimum and, certainly, it varied throughout the country. As an alternative, it was decided to investigate the technique of direct interview. Two seminars were held in January 1994 for those staff responsible for donor assessment. The participants interviewed actors, who portrayed donors with a variety of ailments, to decide whether the 'donor' should give blood. The seminars were welcomed and the system was piloted at Brentwood and Sheffield to identify resource and staffing implications.

Those who attended the courses were asked to pass on the skills to others who would be involved with the selection of donors. A video recording was produced which proved a useful teaching aid for the national training courses being developed. In April 1995 personal interviews for medical

assessment were introduced nationally. Initially some donors were concerned that these changes would increase the time they had to spend at the session; however as the programme has proceeded these fears have been allayed. This initiative has been included in the Blood Donors' Charter (see below), with the commitment to provide facilities at sessions where donors can be interviewed in a confidential manner.

Development of a national computer system

A survey of the existing information technology infrastructure, carried out in 1993, confirmed that the systems had been purchased from a large number of suppliers, using differing hardware and software coding standards, resulting in incompatibility. The NBA Board agreed that the Service needed a single information system and that it should be an existing proven system.

A multidisciplinary group of staff worked with the consultants, CSC Computer Sciences Ltd, and prepared a statement of need, a process which took several months. These specifications were advertised throughout Europe and of 29 companies who replied, a British company, Savant Enterprises, were awarded the contract to install the new system. The work should be completed by December 1997.

Increasing efficiency of blood collection to accommodate demand.

Over the past 2 years the demand for blood has increased by 3–4% each year. To meet this increase in demand the NBS is reviewing its collection programme to achieve flexibility so that donors can more easily find a convenient blood-collection session. Collection venues are being assessed for accessibility, the provision of general facilities and for confidential donor interviews (see above). Working practices are being reviewed to improve session organization and reduce waiting times.

It has been noted previously that blood-collection teams have not always been based in the most convenient venues; several hours each day have been spent in travelling when

some of this time could be used for collecting donations. The process of siting collection teams closer to the donors has begun, with one based on the Isle of Wight and one in Thetford, Norfolk. Apart from logistical advantages, such teams can engender closer links with the local community, improve knowledge of blood-collection premises and provide opportunities for publicity and recruitment.

A blood donor's charter

It has been mentioned, above, that donor interviews for medical assessment were included in the Charter, written in 1995. Donors have been informed in the Charter of the standards they could expect and their rights including how to complain. Thus, they would be given about 2-weeks' notice of blood donation, they would spend no longer than 1 hour at a blood-collection session and that each session would be supervised by an experienced doctor or nurse. In return, donors were asked to answer, conscientiously, all personal and health questions and inform their local centre about any illness they developed within 2 weeks following a donation.

CLOSING COMMENTS

The first attempt by transfusion directors to establish a centrally managed Service was in 1970. Those who began this dialogue with the DHSS have retired and, unfortunately, some have not lived to see the eventual success of their initiative a generation later.

Devolution might be the correct management policy for the diverse activities of the hospital service. However, over the years many staff in the NBTS have considered that central management and a major degree of standardization was the only way to obtain maximum benefit from blood support therapy. Standardization must not be confused with uniformity which can stifle ingenuity and progress.

It is important that the NBA has time and support from blood donors and NBS and hospital staff to demonstrate that this philosophy is correct.

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