Health Trends

November 1986 No.4 Vol 18

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The advice of Sir Raymond Hoffenberg during the preparation of this article is also gratefully acknowledged.

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Trends in blood transfusion practice in England and Wales

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Introduction

The Blood Transfusion Service in England and Wales is organized on a regional basis. There are 14 Regional Transfusion Centres (RTCs); one is located in each of the English regions except for South West Thames and South East Thames which are serviced by one RTC, and there is one Centre in Wales. In the North Western Region there is a second Centre which operates independently on a day-to-day basis, but to a common regional policy. Regional Health Authorities are responsible for the management of the RTCs.

The RTCs provide various services for District Hospitals. All are responsible for the recruitment of blood donors, the organization of blood collection sessions and the testing and issuing of blood and certain products prepared within the RTC. Also, there is an increasing commitment in each RTC to provide plasma suitable for fractionation into various products at the Blood Products Laboratory, Elstree (BPL) funded by the Department of Health and managed by a Special Health Authority. Each RTC provides consultant medical and scientific advice to District Hospitals for the whole range of transfusion medicine, assistance in difficult transfusion problems, and organizes training programmes for doctors and scientists.

To a greater or lesser degree, RTCs provide other services such as tissue-typing for transplantation units and disease association, ante-natal serological screening, antibody quantitation, and research.

Whilst there have been several notable trends during the past decade such as the greater involvement of transfusion service staff in clinical management, two events have dominated this period, viz.: the development of component therapy and the drive towards self-sufficiency in fractionated plasma products. It is these two aspects which will be discussed in this article.

Blood collection

The predominant source material for the preparation of the majority of blood products remains the donation of blood obtained from voluntary non-remunerated donors. This is commonly, but in strict terms, inaccurately called whole blood since it is diluted with a preservative and anticoagulant solution. It can be seen from Figure 1 that the number of blood donations gradually increased between 1975 and 1980; since that time blood collection has remained at approximately 40 per 1,000 of the population.

Between 1975 and 1985 the usage of blood has increased by 23% whilst blood collection has only increased by 16% (Figure 1). There are two principal reasons why there is an improved usage rate during this period. Firstly, the gap between blood collected and blood issued has narrowed and secondly, there has been a reduction in the number of units of blood returned unused. The latter has been more noticeable since 1980 and coincides with changes in the preservative solution from acid citrate dextrose (ACD) to firstly citrate phosphate dextrose (CPD) and subsequently CPD with adenine which has allowed the storage period of red blood cells to be increased from 21 to 35 days.

Blood component therapy

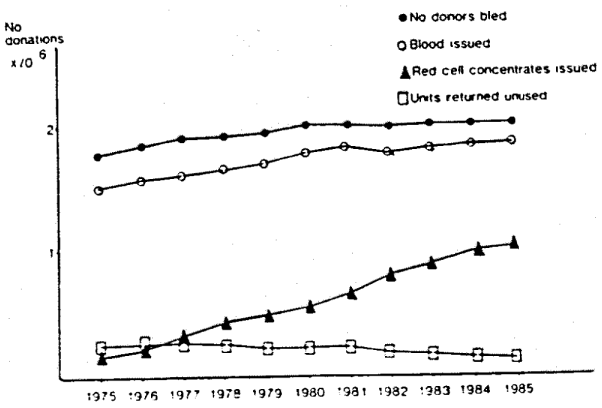
Red cell concentrates

During the early 1970s a significant change occurred in the containers for blood donations. The glass bottle, used for more than four decades, was replaced by the plastic bag. This facilitated the preparation of blood components since it was possible to attach secondary packs to the primary blood collection pack by means of plastic tubing to form multiple pack systems. This enabled the transfer of platelet-rich or platelet-poor plasma from the centrifuged blood donation into the secondary packs; component therapy was possible since the transfer could be effected in a closed system, thus obviating the need to enter the container, which was unavoidable with glass bottles, with its attendant danger of bacterial contamination.

From Figure 1 it will be noted that in 1975 90% of issues consisted of whole blood; in successive years the number of units of red cell concentrates (i.e. a red cell preparation prepared by the removal of plasma from the blood donation), has steadily increased to 50% of blood issues in 1985.

Initially, 180 ml plasma were removed from the donation of blood to leave a red cell concentrate, known as plasma reduced blood. The plasma, separated within 18 hours of collection, was used for the preparation of

Figure 1: *The number of donors bled, total number of units of blood issued, red cell concentrates issued and the units of blood returned unused in England and Wales for the years 1975-1985*



fractionated plasma products (*vide infra*, and as a source of coagulation factors for the correction of deficiencies in individual patients.

Whilst red cell concentrates are the product of choice for the correction of anaemia, experience has shown that in most patients with blood loss not exceeding 20-30% of total blood volume, supportive therapy can comprise red cell concentrates and crystalloid solutions. Thus, the first two or three units of blood transfused can be in the form of red cell concentrates.

Plasma reduced blood, which has an average packed cell volume of 65% has attracted criticism. The most important disadvantage has been the reduced flow properties of the red cells if these had to be administered quickly, due to the increased viscosity of the concentrate compared with whole blood. During the past five years additive solutions have been developed and the one used most commonly in England and Wales is saline, adenine, glucose and mannitol (SAG(M)). Blood is collected from the donor in the usual manner and within 18 hours is centrifuged to separate the red cells and plasma; as much plasma as possible is removed (approximately 275 ml) and 100 ml of SAG(M) solution is added to the red cell mass. Such red cells have flow properties similar to or even superior to those of whole blood.

SAG(M) red cell concentrates were first made during 1984 and are now being increasingly used; during 1985 approximately 50% of red cell concentrates issued were in this form. Clinically, they can be used in a manner identical to plasma reduced blood since there is such a large reserve of protein in the extravascular space, obviating the need to transfuse protein in instances of moderate blood loss.

In some countries the plasma is removed from over 80% of donations collected. This has led to a significant increase in the use of fresh-frozen plasma or 5% albumin solution for those patients with greater than 30% blood loss. Whilst it is argued that the use of fresh-frozen plasma is advantageous since it will contain higher levels of labile coagulation factors than plasma stored on red cells as whole blood, it is doubtful whether its use for this purpose is warranted. Should blood loss not be corrected by the transfusion of a red cell concentrate then it is logical to use whole blood for the additional units required. Providing that no more than 60% of blood donations are converted to red cell concentrates, this policy can be implemented.

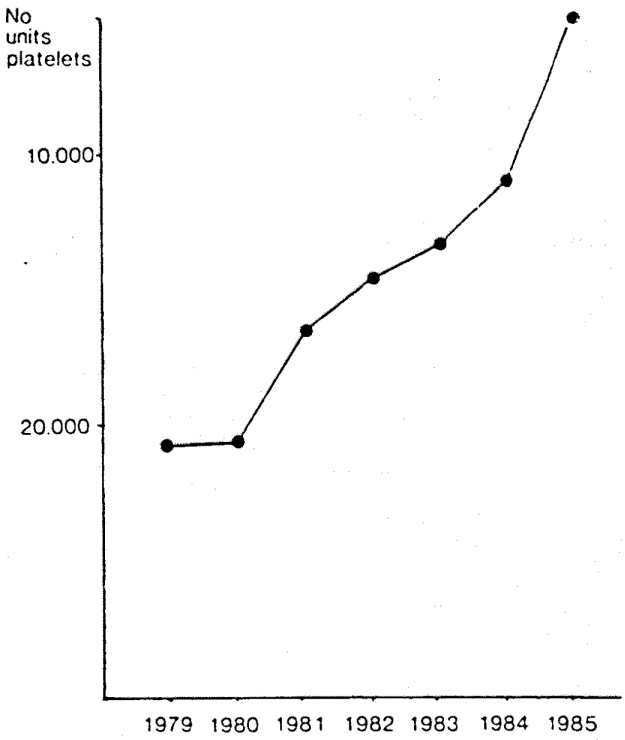
Platelet concentrates

An increasing pharmacopoea of drugs used in high dosage and in varying combinations, such as melphalan, cytosine arabinoside, cyclophosphamide and busulphan, together with irradiation can ablate bone-marrow function and prepare certain patients suffering from leukaemia for bone-marrow transplantation. This trend in leukaemia therapy has led to an increasing need for platelet concentrates for supportive therapy until marrow function recovers. National figures for the preparation and use of platelet concentrates are only available from 1982. In Figure 2, the platelet concentrates prepared in the North Western RTC are shown for the years 1979-1985. It can be seen that there has been an increase of 200%. This will be typical for other RTCs; indeed, some may have experienced an even greater percentage increase.

Platelet concentrates can be prepared from freshly collected donations of blood by an initial gentle centrifugation to separate the red cell mass from platelet rich plasma. The latter is expressed from the red cells in a closed system and further centrifuged to concentrate the platelets. The residual platelet poor plasma can either be returned to the red cells to give platelet-poor blood or placed in a separate pack and used for fractionation or the treatment of patients.

It is becoming increasingly difficult to obtain a sufficient number of units of platelet concentrates from blood donations. In England and Wales 330,000 platelet concentrates were prepared for use in 1982 and this increased to 435,000 in 1985 and the demand shows no sign of diminishing. More recently, machines have been devised by which either platelet-rich plasma or platelet concentrates can be obtained, returning the red cells to the donor, i.e. plateletpheresis. With a single procedure, occupying approximately one hour, it is possible to obtain the number of platelets which can be harvested from four or five donations of blood.

Figure 2: *The number of units of platelet concentrates issued from the Regional Transfusion Centre, Manchester, between 1979-1985*



With the increasing need for HLA compatible platelets one can forecast that automated plateletpheresis will be used more frequently in the future.

Leucocyte concentrates

Sporadic use is made of leucocyte concentrates to supplement treatment of patients suffering from agranulocytosis. For young children leucocytes can be prepared by differential centrifugation from donations of blood, but leucopheresis is generally preferred.

Cryoprecipitate

The treatment of haemophilia A has changed radically since 1970. Prior to that time freshly collected plasma was the only blood product available to correct the Factor VIII deficiency suffered by these patients. The discovery that Factor VIII was cryoprecipitable was an important landmark; a Factor VIII concentrate was available which could be simply made by freezing plasma, allowing it to thaw and harvesting the cryoprecipitate at 0°C.

In 1975, as can be seen in Figure 3, this was the principal product used for the treatment of haemophilia A. By 1977 approximately equal quantities of cryoprecipitate, and freeze-dried Factor VIII concentrates from commercial sources and the BPL were being used. This change coincides with the increasing practice of treating patients with haemophilia A at home, where cryoprecipitate, with its requirement to be stored in the frozen state, held considerable disadvantages. Thereafter the use of cryoprecipitate has declined and between 1982 and 1984 only 3·0-3·2 million international units (iu) have been used, largely for the treatment of young children. In addition another 1-2 million iu of cryoprecipitate are used in the treatment of Von Willebrand's disease.

Self-sufficiency in fractionated plasma products

Figure 3 also illustrates the increasing use of the Factor VIII concentrates. It can be seen that more commercial Factor VIII was used between 1975 and 1983 than Factor VIII produced by the BPL; this was reversed in 1984. Data for 1985 are not yet available but it is likely that, once again, more commercial than BPL Factor VIII was used due to the availability of a heat-treated commercial product from December, 1984, whilst such a product from the BPL was not produced in any quantity until April, 1985. Since heat-treated Factor VIII is thought to be free from the causative virus for acquired immune deficiency syndrome (AIDS), it was preferentially used from January, 1985.

It can also be seen from Figure 3 that between 1975 and 1978 there was increased production of Factor VIII concentrate at BPL. This reached a plateau between 1978 and 1980 due to limitations of fractionation capacity. Following upgrading of the BPL, additional fractionation was possible and supplies for the treatment of haemophilia A have steadily increased but now again have reached their maximum.

Attempts were made between 1975-1980 to achieve self-sufficiency in Factor VIII supplies but despite an increase in both plasma supplies [illegible] and BPL Factor VIII concentrate output demand for the product outstripped its manufacture. During 1980 plans were put forward to implement the proposals of the World Health Organization and the International Society of Blood Transfusion that countries should proceed towards self-sufficiency in fractionated plasma products obtained from plasma freely donated by voluntary non-renumerated persons.

England and Wales lack self-sufficiency in three products, namely Factor VIII concentrate, intravenous immunoglobulin and albumin preparations. Based on the premise that if sufficient plasma was obtained to provide

Figure 3: *The use of BPL Factor VIII concentrate and cryoprecipitate in the United Kingdom between 1975 and 1984*

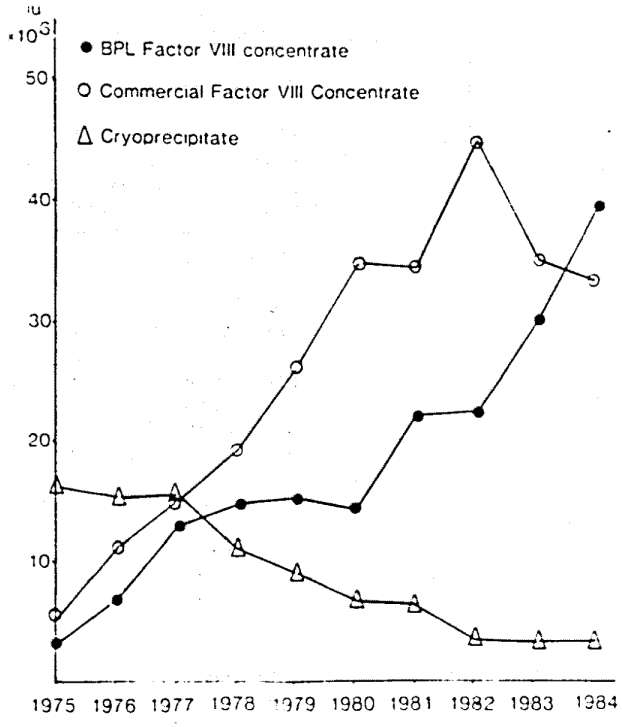
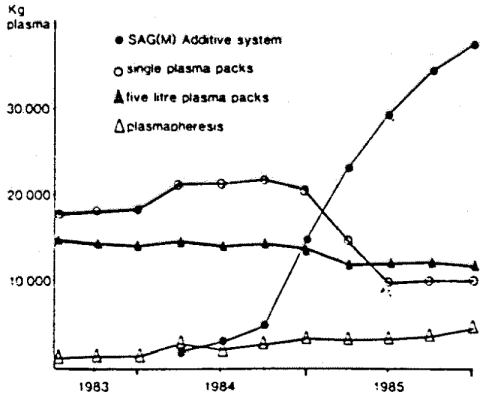


Figure 4: *The changing pattern of the methods for fresh plasma collection, in England and Wales, three-monthly statistics, 1983-1985*



an adequate supply of Factor VIII concentrate, sequential fractionation would provide self-sufficiency in other products, the UK Haemophilia Directors estimated in 1981 that 100 million iu of Factor VIII would be required each year between 1985 and 1990. This required a plant capable of the fractionation of 450,000 kg plasma annually with a yield of 225 iu. Factor VIII per kg plasma. Although higher estimates for the use of Factor VIII have been given since then, at present there is no firm evidence that the estimates above will not provide sufficient products in the foreseeable future.

It was necessary that two courses of action were taken without delay. Firstly, the construction of a fractionation plant capable of handling the required quantity of plasma, since further upgrading of the existing fractionation capacity was not possible. To this end, building the new fractionation laboratory at BPL commenced in 1982. At the time of writing, the building is nearing completion and commissioning should commence within the next few months with production at the rate to provide self-sufficiency of fractionated plasma products achieved during 1987.

Secondly, it was necessary to increase the plasma supply from RTCs from its level of approximately 130,000 kg per year in 1982 to 450,000 kg per year by 1988. It was anticipated that the build-up of plasma supplies could not be increased rapidly, but if plasma in excess of the current fractionation capacity of the BPL of 150,000 kg per year was collected prior to the full functioning of the new plant, it could be stored frozen until required.

RTCs have begun to respond to this increased demand for plasma and by 1985, plasma for fractionation had reached an annual level of 238,000 kg. It is essential that the plasma supplied for fractionation is separated from the red cells as soon as possible after collection and at least within 18 hours, otherwise Factor VIII will suffer unacceptable decay. Plasma obtained from time-expired blood whilst useful for the preparation of albumin, cannot be used for Factor VIII production whilst freshly collected plasma can be subjected to sequential fractionation to prepare all the required products. Part of the rise in fresh-frozen plasma collection has been at the expense of time-expired plasma; this is a welcome trend and if the return rate for unused whole blood can be further reduced it will assist this process further.

Plasma for fractionation can be obtained from two sources; donations of blood and by plasmapheresis. It can be seen from Figure 5 that at the end of 1985, only 8% of the plasma for fractionation was being obtained by plasmapheresis.

There are three methods of presentation of plasma from donations of blood, i.e. pooled into five litre packs, separated into single plasma packs and plasma obtained from units where the SAG(M) additive system is used to prepare the red cell concentrate. The advantage of this system is that 275 ml plasma can be obtained from each donation of blood whilst separation into a single plasma pack demands the maximum of 200 ml plasma extracted from each donation to provide a satisfactory red cell product. It can be seen from Figure 4 that the use of SAG(M) has increased dramatically since its introduction in 1984 largely at the expense of separation of plasma into single plasma packs.

There is an indication that the amount of plasma obtained from donations of blood is reaching its maximum. From the arguments presented earlier in this article, it is unlikely that the proportion of plasma separated from donations will greatly exceed 60%. If each RTC used the SAG(M) additive system, the maximum amount of plasma which could be obtained would be approximately 350,000 kg; it is more likely that there will be a mixture of processing used and the amount of plasma derived from whole blood will likely lie between 250,000 and 300,000 kg per year.

To achieve sufficient plasma for self-sufficiency in fractionated plasma products, it will be necessary to harvest plasma by plasmapheresis. Plasmapheresis is a process whereby blood is collected from the donor, the plasma is separated and the red cells are returned to the donor during the procedure.

There are several plasmapheresis centres operating within RTCs. The preferred method is the use of automated procedures and several machines operating on centrifugal or filtration principles are now available. There is evidence that blood donors respond well to requests for plasmapheresis. It is important that the procedure involves a single venepuncture and the collection of 500-600 ml plasma in 25 to 30 minutes with safety. Advantages of plasmapheresis are that donors can attend up to 25 times per year rather than two or three to donate blood, although most RTCs restrict attendances of donors to less than 10 per year. Since the plasma can be frozen within one hour of collection, it may lead to an increased yield of Factor VIII following fractionation.

The production of plasma for self-sufficiency in fractionated plasma products is feasible but requires investment by RHAs in their Regional Transfusion Services. In many regions this has already occurred, in others it is still required. The benefits not only accrue from products derived from a voluntary blood donor system, but also from the savings from the purchase of Factor VIII concentrates and albumin preparations, both of which have doubled in price during the past year.

Quality of products

It would be wrong to assume that in striving to keep pace with the clinical demands for component therapy and self-sufficiency in fractionated plasma products the Transfusion Service has ignored the requirement for safety of products which every patient has a right to demand.

Blood donations have been tested for syphilis since the inception of the Service. Routine screening tests for the presence of the hepatitis B surface antigen began in 1969, and at present the most sensitive tests available are used. In October, 1985, screening tests were introduced for anti-HTLV III, the antibody produced after exposure to the causative AIDS virus. Many RTCs screen donations for antibodies to cytomegalovirus (CMV) so that donations of blood which are safe from transmission of CMV can be made available for patients at greatest risk, e.g. newborn infants, mothers during pregnancy and patients undergoing treatment with cytotoxic drugs such as children with acute leukaemia or patients having transplants.

Another approach towards increasing safety has been the introduction of automation and data processing. With appropriate programming the checking procedures can be made secure; with existing manual procedures the increasing scale of operations are costly in staff time for these tedious procedures which take scientific staff away from the skilled work they are required to undertake.

Finally, application of the Medicines Act to the Transfusion Service has led to a critical appraisal of methodology from the time of collection of the blood, through the processing of products to the issue of the blood and product to the hospital.

The Transfusion Service responds to demands from the clinical services. New developments often have an impact on the Service which are not always recognized until after they are introduced; changes in treatment regimens for leukaemia during the past year have resulted in a large increase in demand for platelet concentrates. Rapid changes in blood collection cannot be made since both blood donors and resources have limitations. Increased demand for one blood product may be at the expense of others and the only long-term policy which will be effective is close co-operation between the "producers" and the "users". It is hoped that this will be given high priority in the future trends for blood transfusion.

Acknowledgements

The author wishes to thank the Department of Health and Social Security and the Central Blood Products Laboratory for permission to publish the statistics, and the help received from the Regional Transfusion Directors, Dr C Rizza, the Oxford Haemophilia Centre, and Mr N Pettit, Blood Products Laboratory for supplying information which was essential for the compilation of the article.

Unemployment and health: some pitfalls for the unwary

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Introduction

Concern has been expressed frequently by politicians, the medical profession, academics and the mass-media, that unemployment—and fear of unemployment—may have serious adverse effects on physical and mental health.[1] Contrary to what is often asserted, however, the evidence regarding the impact of unemployment on health is far from clear-cut.[2,3] This inconclusiveness stems from the fact that much of the research to date has been based on research strategies which are ill-equipped to overcome the complex methodological problems facing investigators wishing to research efficiently in the area. Because, however, these methodological problems are so complex, it is frequently difficult for the non-specialist to evaluate