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II.—New Approaches to the Supply of Blood and Plasma.

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Synopsis

One unit of donor blood may be used to treat several patients. Each recipient is given the appropriate blood component. Proper component therapy is more effective and less hazardous than whole blood transfusion. In addition, valuable human blood is conserved.

Transfusion services require facilities to process fresh blood and separate otherwise labile components such as cryoglobulin precipitate and platelet concentrates. The production of large amounts of these components and of fractions such as plasma protein solution is facilitated by the clinical use of concentrated red cells rather than whole blood. Recurrent shortages of fresh donor blood are inevitable. Components which can be preserved for long periods should be stockpiled.

Plasmapheresis, plateletpheresis and leukapheresis allow the frequent collection of selected components from individual donors. Some of these donors may be hyperimmunised by the injection of an appropriate immunogen, and a specific immunoglobulin IgG can be prepared from the donated plasma. Hazards such as wrong identification and protein depletion must be avoided by individual attention to plasmapheresis donors.

Automation and modern transportation may increase the availability of blood. The importance of the blood donor to the health service and to the community should be fully recognised.

1. Introduction

Blood transfusion is primarily a medical matter. However, from the simple act of transfusing human blood a new science has developed. At the same time the utter dependence of transfusion services on blood donors introduces sociological considerations. It is thus particularly appropriate that this Symposium should be sponsored jointly by the Royal College of Physicians of Edinburgh and by the Royal Society of Edinburgh. The exchange of views in this historic, yet enlightened and progressive environment must surely act as a catalyst in the future development of blood transfusion in Scotland.

The availability of blood components and fractions depends upon processing and fractionation facilities and upon the supply of raw material, namely human blood. The separation of each unit of blood into several therapeutically useful components shortly after donation is advocated (Greenwalt 1969). Each donor thus serves multiple recipients. Whole blood transfusion should be relegated to the limbo of the shotgun prescription.

There is a variation in the clinical demand for different blood products and in the shelf-life of these products. For example platelet preparations can be stored at present for only a few hours, whereas stable fractions particularly in the lyophilised state may be preserved for years. In advocating a policy of total fractionation (Greenwalt 1969) recognises this inherent difficulty, and considers that computers will have to be used to control effectively the collection, storage and distribution of all the components of blood. Thus computer assistance should make it possible to operate so efficiently that there will be no wastage of donor blood or of its components.

This is surely an ideal at which transfusion services should aim. In the next few years it is essential to gain experience of an off-line computer system in the organisation and management of a transfusion service. Such experience is needed to assess the likely size and work load of a subsequent on-line system. Meantime the current position will be reviewed with particular reference to the Western Region of Scotland which covers a population of almost three million. While blood transfusion problems are similar from region to region, it must be emphasised that dissimilarities occur because of factors such as geography, industry and the size and distribution of population.

2. Optimal Use of Donor Blood and Component Therapy

Table 1 shows the number of donors during each of the past five years. Many of those not accepted have recently had some transient minor illness and probably feel well. It is wise, however, not to accept volunteers if any doubt exists about fitness to donate. A lowering of standards of acceptance to increase the intake of blood would be medically and socially wrong and unacceptable.

TABLE I

Acceptance of Volunteers as Donors—Western Region

Year	Number of volunteers	Accepted	
		Numbers	% age
1967	107 751	95 545	88·67
1968	109 354	100 242	91·67
1969	115 824	102 982	88·91
1970	113 208	99 717	88·08
1971	117 622	105 251	89·48

There has been a slight upward trend in the clinical demand for whole blood during the past five years, but a much more striking development has been the rapidly growing request for more sophisticated blood components and fractions. In particular there has been a need to supply cryoglobulin precipitate for the control of haemostasis in haemophilia and platelet concentrates as supportive therapy in patients treated with massive doses of cytotoxic drugs. Because of loss on storage in whole blood, these two components must be prepared from freshly donated blood. Facilities for immediate processing have been provided in the Western Region of Scotland by two recently developed laboratories. One is located at the static donor centre in Glasgow. The other is a mobile laboratory which accompanies the conventional mobile blood collecting unit.

Table 2 reflects the potential of this dual laboratory development. Not only have greatly increased quantities of cryoglobulin precipitate and of platelet concentrate been supplied to hospitals, but substantial volumes of the supernatant plasma from cryoglobulin precipitate and of fresh frozen plasma have been sent to the national Protein Fractionation Centre in Edinburgh. The full potential of these processing laboratories has not yet been reached. It is estimated that operating to full capacity, these two laboratories could together process 30 000 fresh donations per annum. A

word of warning is, however, necessary. Past experience in blood processing has shown that mass production may result in a lower quality of product. Transfusion services are well aware of the need for quality control in laboratory testing, and will pay increasing attention to the quality control of blood products.

TABLE 2

Issues from Western Regional Transfusion Centre

	To hospitals			To PFC	
Year	Concentrated red cells	Cryoglobulin ppt.	Platelet conc.	Cryosupernate	Fresh-frozen plasma
1967	3 374	1 673	48	Nil	Nil
1968	5 440	2 755	78	921	375
1969	10 099	6 258	136	6 061	1 891
1970	13 314	11 439	750	7 340	2 021
1971	16 642	16 307	1 954	11 691	2 010

3. RED CELL CONCENTRATES

The provision of fresh plasma for the production of fractions yields red cell concentrates. Table 2 shows that there has been an encouraging increase in the use of these concentrates in the Western Region, but the usage is far short of that recommended by Greenwalt and Perry (1969), namely that at least 70 per cent. of all transfusions should be in the form of red cell concentrates. This recommendation should be clinically acceptable. Almost 30 years ago, Cooksey (1943) reported that red cells suspended in saline were as effective as whole blood in the treatment of blood loss and shock in surgical patients. Failure to adopt this earlier recommendation stems from two practical objections to the use of concentrates rather than from doubts about the clinical value of red cell concentrates *per se*.

Because of the danger of bacterial contamination when entering glass containers to remove supernatant plasma, most transfusion centres limited the shelf-life of red cell concentrates to a few hours. This restriction is no longer necessary since the units of donor blood which are predictably used for preparing labile components are collected into multiple plastic containers. The red cell concentrates prepared in this way may be stored for the same 21-day period as whole blood, and are available on demand.

A second practical objection to the use of concentrates is the mechanical difficulty in administering the viscous fluid. Ease of administration will be ensured if the final haematocrit value of the red cell concentrate is less than 70 per cent.

In the past great emphasis has been placed on the compatibility of red cells, and the performance of sensitive matching tests prior to transfusion must remain a *sine qua non*. It is being realised more and more, however, that many of the undesirable features of stored whole blood—immunogens, antibodies and unphysiological levels of electrolytes—reside in plasma. Removal of plasma not only facilitates production of components, but renders transfusion safer for recipients of red cells. Indications for whole blood transfusion might well be limited to extreme exsanguination. In preparing patients for surgery and replacing blood lost at operation, red cell concentrates are satisfactory and preferable to whole blood.

4. Plasma Volume Expanders

There is a clinical need for what was termed a blood substitute and is now more accurately described as a plasma volume expander. The possible complications of modern, well-tailored, synthetic plasma volume expanders such as the dextrans, the gelatins and hydroxyethyl starch must be recognised. In countries which have a modern transfusion service, the plasma volume expander of choice is surely Plasma Protein Fraction (PPF), which has several advantages over dried whole plasma. PPF can be presented in stable liquid form for immediate use. The protein and electrolyte contents of each unit are known. Above all Plasma Protein Solution (PPS) can withstand heating at 60°C for 10 hr. The pasteurised product is free from the risk of transmitting viral diseases, thus eliminating the hazard of hepatitis. Although it is an isolated episode, it is worthy of mention that the surgical teams engaged in the resuscitation of casualties at the recent Clarkston disaster, commented favourably on the suitability and clinical effectiveness of PPS.

Indeed the justifiable clinical demand for PPS may be greater in terms of donations required than for any other component or fraction. Table 3 shows the issues of dried plasma during the past five years. The decline in the use of dried plasma has almost certainly been associated with publicity about hepatitis. Although plasma is now prepared from donations found on testing to be negative for Australia (hepatitis associated) antigen, there will be a justifiable preference in future for the pasteurised product PPS. There is evidence that the reduced use of human plasma has been compensated by an increased use of synthetic plasma volume expanders such as the dextrans. The recent introduction of PPS will almost certainly result in a return to the human product. In this connection it should be noted that four donations of plasma are required to prepare one unit of PPS, compared with two and a half donations for one unit of dried plasma. A return to a human plasma volume expander at the peak 1967 usage would require almost 40 000 donations of plasma, that is approximately 40 per cent. of the annual intake of donor blood. In practice the appeal of a non-icterogenic product might result in an even greater demand.

Table 3

Issue of plasma—Western Region

1967	9 864
1968	8 952
1969	8 769
1970	7 518
1971	6 557

In addition 1 339 PPS issued in 1971.

5. Long-term Preservation

It is clearly desirable to be able to preserve components and fractions for long periods. Short of some form of conscription, fluctuations in the intake of donor blood are inevitable. Donors are rightly free to enjoy holidays and social pastimes, and are from time to time the victims of epidemic illness. With techniques for long-term

preservation of red cells now established (Blagdon 1972), there is a case for some stockpiling of red cells donated in times of plenty.

6. Plasmapheresis and Hyperimmunised Donors

Just as transfusion services are using chemical and mechanical means to split whole donations into components and fractions, there is a growing tendency to encourage donors to provide one special blood component. Plasmapheresis, plateletpheresis and leukapheresis are examples of this type of procedure. Conventional plasmapheresis may be combined with voluntary hyperimmunisation of donors for the production of specific immunoglobulin IgG. Examples are human immunoglobulin IgG anti-Rh(D), anti-vaccinia and anti-tetanus. Deliberate and artificial hyperimmunisation is attempted by injection of the appropriate immunogen to the volunteer, and if successful, is followed by intensive plasmapheresis. A new type of blood donor is being created, and the implications must be considered carefully.

Sturgeon (1971) describes one donor who, in the course of 17 years, has undergone plasmapheresis 709 times and has had a total of 352 litres of plasma removed. The general health has remained good. There has been no evidence of haematological abnormality or of biochemical disturbance in serum proteins. In particular, immunoglobulin levels have remained normal and there has been no impairment in immediate or delayed hypersentitivity. Protein and iron nutrition have been adequately maintained.

It must not be assumed that all other plasmapheresis donors would react in the same way as this one long-term donor. The programme should be supervised by a medical practitioner who fully understands the risks involved, can explain these risks to the volunteer and above all is interested in the donor's welfare. The essence of a plasmapheresis programme is individual responsibility for which there is no substitute (Shanbrom 1971).

There are two main classes of risk—those that are real and avoidable, and those that are theoretical or unknown. In the former category there are the obvious ones of wrong donor identification and of depletion of proteins. Less obvious but real are air embolism, pyrogenic reactions and cross-infection. The theoretical risks of hyperimmunisation include vasculitis and amyloidosis, and since there may be a long latent period it would be wise to proceed cautiously with intensive hyperimmunisation.

Small panels of plasmapheresis donors have been established in the Western Region. The total volume of plasma collected by plasmapheresis during the past three years has been respectively 69·8, 58·5 and 237·3 litres. In the main the yield has been anti-Rh(D) plasma, which is sent to the Protein Fractionation Centre for the production of anti-Rh(D) immunoglobulin. This system of collection is also being applied more for valuable laboratory reagents such as grouping sera and antibody to Australia (hepatitis associated) antigen. The work is performed by a small specially selected team of individuals with a genuine interest in the welfare of these donors.

The consequences of applying the values of the market-place to plasmapheresis have been elaborated (Titmuss, 1970). There is a natural reluctance in the UK to make payment or offer inducement to blood donors. The medical profession should, however, be realistic about what is required of the plasmapheresis donor. The normal donor spends half an hour of his time at a donor centre twice a year. A plasmapheresis

donor may well spend one and a half hours each week at the centre. It would seem not unreasonable to meet the travelling expenses of regular plasmapheresis donors or indeed provide transport for these donors.

Plateletpheresis would not appear to be widely practised in the UK. Platelet concentrates are prepared from freshly collected whole blood. This allows the use of other components from a normal donation. A development which would necessitate a greater use of plateletpheresis would be the introduction of platelet compatibility tests. Isoimmunisation to platelet antigens has not been a major problem in the treatment of acute leukaemia, probably because the patients are receiving immunosuppressive drugs. Platelet antibodies are, however, found in patients with aplastic anaemia treated with platelet concentrates. The therapeutic effectiveness of platelets may depend upon obtaining platelets frequently from the same compatible donors. In such circumstances, at least until a satisfactory method of long-term preservation is developed, plateletpheresis would appear to be the practical solution.

White blood cell replacement is a much more complex matter than replacement with erythrocytes or platelets. Utilising patients with chronic myelocytic leukaemia and a high granulocyte count, a large number of white cells can be obtained by leukapheresis. Whether such leucocytes are comparable to normal leucocytes in combating infection is equivocal. There is an increasing interest in leucocyte preservation. Lymphocytes can be well preserved, but adequate granulocyte preservation would not appear to have been achieved.

7. Transportation

This is an important aspect of the work of a transfusion service. Mention has already been made of the value of a mobile processing laboratory. The delivery of blood and of products to remote areas in the USA will cease to be a problem when rapid transportation systems now being developed are introduced (Greenwalt 1969). To ensure optimal use of skilled staff, centralisation of blood transfusion laboratory facilities with exclusive use of radio-controlled transport to peripheral hospitals is recommended (Royal College of Pathologists 1972). Since it is less than 40 miles by road from the Western Regional Transfusion Centre to the Protein Fractionation Centre, Edinburgh, it is relatively easy to transport plasma from the largest Scottish region to be fractionated.

Self-contained mobile blood-collecting vehicles are in use in several Western European countries. A vehicle of this type is shortly to be introduced in the Western Region of Scotland. It is proposed to use this vehicle in three situations (i) large villages and small towns, (ii) small factories which have no facilities for blood collection by conventional methods and (iii) to supplement existing facilities in larger factories where competing demands for space and shorter working hours are making blood collection by conventional methods more difficult.

8. Automation

Most regional transfusion centres have abandoned manual methods, and now use machines when grouping several hundred donors each day. These instruments not only facilitate the routine typing of donors in respect of ABO and Rh systems, but

permit the detection in large numbers, of donors of red cell antigens other than A, B and Rh(D). Special donor panels can thus be created and the provision of donor blood of less common or even rare groups accelerated.

It is predicted that computers will be used to control effectively all aspects of the work of transfusion services (Greenwalt 1969). In the Western Region (Hopkins and Milne 1969) have shown that a computer-assisted system for calling donors from a specialised antibody panel saves time and cost, and vastly improves efficiency in comparison with the previous manual system. Some centres including the Western Region are attempting to computerise entire donor panels in the hope that this will produce more effective use of available donors. Is it wishful thinking to suggest a single central data processing department for the entire UK blood transfusion service with its own large computer and on-line links to each transfusion centre, each hospital and each donor session—perhaps even with links to other European countries?

9. Implications and Conclusions

Clinical demand for blood products should be based on careful assessment of the value and safety of each product, and not on empiricism or worse still, emotionalism. Subsequent speakers will state a convincing case for a variety of blood components and fractions. The existing substantial facilities for fractionation are to be expanded within the next three years to an enormous potential (Watt 1972). Regional transfusion services, given the staff and equipment, can utilise fresh blood at the present level of intake to provide more components, and at the same time send greater quantities of plasma to the national Protein Fractionation Centre. Clinicians who rightly desire these sophisticated blood products can make an important, and indeed essential contribution to expedite availability. When transfusion of red cells is indicated, these should be given as often as possible in the form of red cell concentrates rather than whole blood.

The phenomenon of a long latent period between significant experimental observations and their application in clinical practice is not confined to blood transfusion. Part of the delay is caused by the need to develop new technical capabilities, and by having to await adequate financial support. Even more important is a human reluctance to depart from the familiarity of old habits and a natural suspicion of things new. In some respects progress in blood transfusion is being retarded, because new ideas are not easy to sell to old heads (Greenwalt 1969). Progress depends upon a proper understanding between clinicians and blood transfusion services. It is equally important that the general public should be fully informed of the need for blood donors. The altruistic individuals who are donors should be shown that their donations are being used in the optimal fashion for the benefit of their fellowmen.

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