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MODERN TRANSFUSION PRACTICE

by **Major General H C Jeffrey**

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Introduction

The principal objectives of a blood transfusion service may be summarised under two headings:

1. *Supply.* The provision of an adequate supply of safe blood and blood products to meet patient needs in the prevention, treatment and diagnosis of disease and injury. This includes the effective collection, processing, storage and utilisation of resources.
2. *Quality.* The high standards which have been achieved in blood transfusion practice by applying existing scientific knowledge to the full must be further advanced by continuous research and development.

It is still a popular misconception that a transfusion service exists to remove blood from donors and transfuse it into recipients, with due precautions to prevent untoward reaction to either donor or recipient, but this is only a small facet of the practice of modern transfusion organisation. Transfusion of whole blood achieves its effects by replacing missing or deficient components, but at the same time introduces other components which may be unnecessary or even harmful. The modern approach to transfusion must be to give the patient only those components of blood which he lacks, thus eliminating to a very considerable extent sources of reaction, infection and sensitisation and enabling optimal use of the blood collected. Table I lists the components which can be obtained from whole blood and the main indications for their use.

General Principles

Some general principles concerning the voluntary donor and commercial intrusion, blood transfusion immunology, advances in transfusion practice and trends in clinical applications have a considerable bearing on the organisation of the transfusion service and the supply of and demand for blood and blood products.

The voluntary donor

The keystone of any transfusion service is the blood donor as only human blood is suitable for transfusion. The same is largely true of blood products; such preparations as equine antitetanus serum or animal Factor VIII have been available, but they rapidly lose their effectiveness if repeated doses are required and they may so sensitise the recipient that severe, sometimes fatal, reactions may follow further injections. Some patients may already be hypersensitive to horse serum and an adverse reaction may follow the first injection; acute thrombocytopenia may be precipitated by animal Factor VIII.

Table I: Blood Components and the Main Indications for Their Use

Component	Indications
1 Red Cells	
a. Fresh, (i.e. stored at 4°C) concentrated	(1) Anaemia with normal blood volume requiring urgent rectification—acute surgery and obstetrics. (2) Chronic or long standing anaemia (a) Not responding to haematinics (b) In bone marrow hypoplasia or aplasia (3) Exchange transfusions in infants.
b. Washed, from fresh or frozen red cells	(1) Indications as for fresh concentrated cells (2) Patients who have had multiple transfusions and have become sensitive to leucocytes, platelets or plasma constituents. (3) Patients likely to have frequent transfusions; to prevent such sensitisation. (4) Renal dialysis and transplantation units.
2 Leucocytes (Obtained by leucopheresis)	(1) Complicated leucopenic states. (2) Other indications under assessment.
3 Platelets	(1) Thrombocytopenia not associated with rapid platelet destruction, including iatrogenic causes.
4 Whole Plasma	
a. Fresh, fluid or dried	(1) Blood volume expansion in (a) Traumatic shock (b) Burns (c) Peritoneal shock. (2) Defibrination syndromes. (3) Source of platelets (see 3); platelet concentrates are more effective. (4) Deficiency in clotting factors I, V, VII, VIII, IX and X. In specific factor defects concentrates are more effective.
b. Outdated (dried)	(1) Blood volume expansion. Purified protein factor is preferable.
5 Plasma Components	
a. Albumin, salt-poor	(1) Severe protein deficiency (a) Nephrotic syndromes (b) Protein losing enteropathies (c) Liver diseases.
b. Purified Protein Fraction	(1) Shock due to (a) Haemorrhage (b) Trauma (c) Infection. (2) Burns. (3) Peritonitis.

Table 1—(*contd.*)

Component	Indications
c. Fibrinogen (Factor I)	(1) Hereditary afibrinogenaemia. (2) Defibrination syndromes.
d. Cryoprecipitate (Rich in Factor VIII)	(1) Haemophilia A (Classical). (2) Von Willebrand's disease.
e. Factor VIII concentrates	(1) Haemophilia A. (2) Von Willebrand's disease.
f. Factor II, IX, X concentrates	(1) Haemophilia B (Christmas disease). (2) Coagulation problems in the newborn.
g. Factor II, VII, IX, X concentrates	(1) Haemophilia B. (2) Haemorrhage complicating liver disease. (3) Reversal of effects of anticoagulant therapy.
h. Immunoglobulins	
(i) Normal	(1) Congenital or acquired hypogammaglobulinaemia. (2) Passive immunisation against certain infectious diseases (especially measles, poliomyelitis and hepatitis A).
(ii) Specific	(1) Prevention of certain infectious diseases including tetanus, rubella, hepatitis B, smallpox, possibly others. (2) Treatment of complications of smallpox vaccination. (3) Treatment of tetanus. (4) Prevention of sensitisation of Rh(D) negative mothers by Rh(D) antigen from the foetus.
i. Blood cell antibodies	(1) Diagnostic reagents.

Since the inception of the blood transfusion service in this country, blood has been obtained from voluntary donors and in this material age it is refreshing to acknowledge the spirit of public service and altruism shown by the many donors who freely give their leisure time and their blood to benefit others. As the maintenance of an effective transfusion service for whole blood and its derivatives is entirely dependent upon adequate panels of volunteer donors, their goodwill is essential and the greatest care is necessary to ensure that no individual nor collective causes for dissatisfaction arise. This entails attention to the donor, who must be given every considaraion, and careful assessment of any change in transfusion policies which could have repercussions among the donor population.

Commercial Blood Products

Of recent years improvements in protein fractionation have led to the preparation of such blood products as purified protein fraction, concentrated Factor VIII, human anti-tetanus immunoglobulin, etc. As it takes time for regional transfusion and fractionation centres to increase their facilities to meet demands, a temporary national shortage of some of these plasma fractions has arisen. The pharmaceutical industry has taken advantage of these shortages and commercially produced blood

products, probably from paid donors, have become available by import into this country. This has caused disquiet on a number of counts, mainly of an ethical nature.

'For the first time in Britain we have begun to rely on professional donors; not from Leeds, Liverpool or London, but from people in such countries as Puerto Rico, Chile and Colombo' (BMJ, 1974). Requirements for patient care must take precedence, but we, who pride ourselves on the voluntary blood donor system in this country, would be quite hypocritical if we did not make determined efforts to avoid having to use products from paid donors elsewhere. International organisations, including the World Health Organisation and the International Red Cross, have affirmed their rejection of paid blood donations. It is unlikely that plasma products obtained by fractionation in any country exceeds its own requirements and export deprives its own population of transfusion material.

The presence of hepatitis B surface antigenaemia varies in different countries. In the light of present knowledge it is reasonable to assume that there is greater difficulty in excluding the risk of transmission of transfusion hepatitis from blood products prepared from plasma obtained from a population with a high incidence of this antigenaemia than from those with a lower incidence.

The aim of the National Health Service, therefore, should be self-sufficiency in the production of acceptable preparations. This implies facilities for regional transfusion centres to provide adequate supplies of plasma to fractionation centres, education of clinicians in component therapy including the use of red cell concentrates so that optimal use is made of donations and ensuring that protein fractionation centres have the facilities required, including strict quality control procedures, to make products which are as good as, if not better than, commercially prepared equivalents.

Blood Transfusion Immunology

Since Landsteiner described the ABO blood groups at the beginning of this century, a tremendous amount of work has been devoted to red cell serology and it is probable that little remains to be discovered about red cell blood groups and associated antibodies in man. A few more rare groups may still be found, but these will have no tangible effect on the great majority of donors and recipients. Much remains to be discovered on the chemical, as opposed to the serological, aspects of the blood group systems.

It is only in the last decade or so, however, that much headway has been achieved in immunological aspects of other components of blood. Leucocytes and platelets carry some of the antigens found on red cells, including A, B and H. A number of antigens have been described which appear to be peculiar to leucocytes and/or platelets, but the alloantigens most strongly expressed on them are the histo-compatibility antigens of the Human Leucocyte A (HL-A) system and in tissue-typing tests on lymphocytes are commonly used.

The original discovery of HL-A antigens and antibodies was made in connection with investigations into the cause of leucopenia and non-haemolytic transfusion reactions. The technology and subsequent interest in this system underwent an explosive growth in the hope that this would lead to improved results following organ transplantation. It is now becoming apparent that tissue-typing has an important part to play in the field of routine clinical blood transfusion, including leucocyte and platelet transfusion. While the value of HL-A matching in unrelated cadaveric kidney transplantation is still very controversial, its role in bone marrow transplantation looks promising as an extended period is available for more thorough histocompatibility testing with the newer techniques which are being evolved.

Future advances in blood transfusion immunology may identify other important histocompatibility systems.

Advances in transfusion practice

Over the past 40 years there have been continued advances in many aspects of blood transfusion work which have simplified techniques or made for safer practice; examples are the introduction of plastic equipment, the drying of plasma and automation in the laboratory. There have been major developments in the long term preservation of blood, protein fractionation techniques, plasmapheresis, cell-separator machines and the discovery of a demonstrable agent associated with viral hepatitis, the hepatitis B antigen, which have had, or will have, important repercussions in both the laboratory and clinical aspects of blood transfusion.

The long term preservation of blood. Conventional blood banking techniques using an anticoagulant and storage at 4–6°C preserve blood for only a matter of weeks as the cellular elements deteriorate under these conditions. Much work has been done over the past 15 years or so in the long term preservation of blood —in terms of years—by freezing and this is now a practical proposition. Blood will freeze at a temperature of −2 to −3°C, but in ordinary

circumstances the red cells are almost totally destroyed by the formation of ice crystals causing damage mechanically or by the increase in salt concentration. A number of approaches to this problem have been described, in this country the technique generally adopted is glycerolisation of the red cells, freezing in liquid nitrogen at −196°C and storage in the gas phase of liquid nitrogen at −150°C. When glycerol is added to blood, it diffuses into the red cells and acts as an anti-freeze by limiting ice formation and hence avoiding excess hypertonicity. With this technique red cell deterioration appears to be arrested and the cells will maintain their integrity for years. As red cells containing glycerol haemolyse *in vivo*, a post-thaw process to remove it is mandatory. The final product, a suspension of red cells in a saline or sugar medium, contains no plasma, is virtually free from leucocytes and platelets, and compares favourably with conventional stored blood as regards post-transfusion life span and oxygen carrying capacity of the red cells.

Protein Fractionation. Plasma proteins, which include albumin, globulins and coagulation factors, vary in their solubility in organic solvents under differing physical conditions and may be separated in varying degrees of purity by appropriate adjustment of these conditions. Basically, the technique of plasma protein fractionation involves precipitation by ethyl alcohol and, by manipulating hydrogen ion concentration, alcohol and protein concentration, temperature, time and conductivity, a series of products is obtained each containing a predominant protein fraction. Recent advances include the invention of a continuous process, computer-controlled, which will achieve laboratory standards of precision on an industrial scale (Watt *et al.*, 1972).

The yield of the various fractions is influenced by numerous factors concerned with conditions of separation of the plasma from blood, freezing, storing, thawing and the type of plasma. The labile factors, and our interest here is particularly in Factor VIII, are especially susceptible to loss of activity if rigid precautions over these conditions are not taken, but, even with optimal conditions from the time of blood donation to final freeze-drying of the concentrated factor, a loss of some 60% of the activity occurs with present techniques.

The purity of any one fraction can be manipulated to a certain extent, for instance Factor VIII is now being prepared as an intermediate fraction containing 10 units of activity per ml of the reconstituted product, a superconcentrated fraction, containing 100 units per ml, is in the planning stage. The more pure the fraction, however, the greater the processing loss and a balance must be struck between purity and yield to give the conbination of an acceptable, potent clinical product and the efficient use of plasma.

The sequence of recovery of protein fractions depends on the type of plasma. Whole fresh frozen plasma can be fractionated to yield Factor VIII, mixtures containing Factor IX, fibrinogen, immunoglobulin and an albuminoid preparation, either purified protein fraction or albumin, in that order. The residue after preparation of cryoprecipitate has lost the antihaemophilic components and can yield fibrinogen, a Factor IX preparation, immunoglobulin and albuminoid fraction. Plasma from time-expired blood contains some fibrinogen and about 10% of the Factor VIII activity of fresh plasma, but these are not recoverable at present so that this material will yield immunoglobulin or an albuminoid preparation. Factor IX preparations may contain II, IX and X or II, VII, IX and X depending on the technique used. A 'supernine', a more concentrated Factor IX fraction, could be a further processing stage. The type of immunoglobulin, normal or specific, will depend on the donor's previous experience of natural or artificial contact with the antigens producing antibodies at present valuable for the production of specific immunoglobulins, for example Anti-D, anti-tetanus and anti-hepatitis B. The yield of the final albuminoid fraction depends to a certain extent on the intensity of effort put into harvesting previous fractions.

The final product must undergo an intensive quality control programme including estimation of total protein, the purity in terms of dose-measurement, electrolytic content, sterility (bacteriological and freedom from HBsAg) and pyrogenicity.

Plasmapheresis. When a donor's plasma contains some special quality, rare blood group antibodies, HL-A antibodies or specific immunoglobulins in high titre, it is desirable to obtain more plasma from him than can be made available by routine donation which is normally restricted to once every six months to avoid the development of anaemia from excessive bleeding. The technique of plasmapheresis has been developed for this purpose. 500 ml of blood is drawn by normal donation procedures into one of a special set of two bags, the blood centrifuged, the supernatant plasma squeezed into the second bag and the remaining red cells returned to the donor into whose vein saline has been run during the period of centrifugation to maintain

patency. The process can be repeated at least once more at the same session so that the donor contributes 400–600 ml of plasma, but has not lost any appreciable number of red cells. Such double plasmapheresis can be repeated fairly frequently, some programmes entail carrying out the procedure weekly for ten weeks, thus obtaining 4–6 litres of valuable plasma from one donor. After a rest period of 6–12 months the ten-week session can again be carried out, with preliminary re-assay to ensure that the specific immunoglobulin is still present in worthwhile quantities. The possible long-term hazards of such intensive plasmapheresis, due to plasma protein depletion if synthesis does not keep pace with loss, are not yet known so that at present new donors should be obtained every few years.

The technique is complex, costly and time-consuming and is not at present used to any extent to obtain normal plasma in this country. However, double plasmapheresis carried out on one occasion every six months should not carry any greater long term hazard than normal blood donation and the time may come, as demands for blood products, in particular the albuminoid fractions, increase considerably in comparison with the requirements for red cells, that serious consideration will have to be given to the routine adoption of this technique in a proportion of normal blood donors.

Continuous flow blood cell separators. These machines have been developed as an extension of the technique of plasmapheresis, enabling large quantities of red cells, white cells, platelets or plasma to be collected, blood being returned to the donor deficient only in the constituent it is desired to collect. The principle is that, on centrifugation at predetermined gravitational forces, anticoagulated blood separates into layers—red cells, white cells and plasma (containing platelets); these components can be selectively removed.

The proven and potential clinical applications are many. The removal of red cells in exchange for normal plasma (to maintain blood volume) may have a place in the treatment of idiopathic and some types of secondary polycythaemia.

If the patient's plasma contains abnormal constituents such as in hyperviscosity syndromes, protein-bound toxins, deleterious antibodies or immune complexes, intensive plasmapheresis may play a significant part in management, the removed plasma being replaced by normal plasma, fresh or freeze-dried, or purified protein fraction, so that the blood volume is maintained.

Cell separator machines enable the collection of large quantities of leucocytes. of the order of thousands of millions, from a normal donor (leucopheresis). By adjustment of centrifugation speeds, the yield may be mainly granulocytes or lymphocytes.

The platelet-rich plasma obtained by low gravitational force centrifugation may be again centrifuged by conventional methods to concentrate the platelets. The platelet-poor supernatant plasma may then be returned to the donor in exchange for a further supply of platelet rich plasma which is treated in the same way. A succession of manoeuvres of this nature enables very large yields of platelets—tens of thousands of millions—to be obtained from one donor without rendering him thrombocytopenic and will simplify the provision of a sufficient quantity of HL-A compatible platelets.

Hepatitis B surface antigen (HBsAg). The discovery of an agent associated, *inter alia*, with a number of cases of long-incubation, transfusion-induced hepatitis has enabled important advances in the safety of the transfusion of blood and blood products, but has also introduced complicating factors. The necessity for screening all blood donations for HBsAg and rejection of those positive has imposed a considerable additional work-load on the transfusion service. The isolation of patients with HBs antigenaemia decreases the risk of hospital cross-infection, but raises clinical and nursing problems. Demands for plasma, fresh or dried, have increased following screening programmes and the development of purified protein fraction, which undergoes a period of pasteurisation during processing and is hence HBsAg-free, will mean that this preparation, when freely available, may largely supersede the fluids at present used for blood volume restoration; this will mean a considerable increase in the amount of plasma required by fractionation centres.

HBs antigenaemia may be followed by the development of HBs antibody which can be recovered as a specific immunoglobulin and used for passive protection of those at special risk. When the agent is more specifically identified and reproducible by viral culture techniques it may be possible to produce a vaccine and protect those frequently exposed to infection by an active immunisation programme.

Trends in clinical applications

The introduction and probable extension of surgical procedures such as open cardiac surgery

increase the demand for blood and blood products. Organ transplantation, in particular the contemplated bone-marrow transplant programme, entails an extension of tissue-typing facilities and requires large quantities of leucocytes and platelets for follow-up therapy. Advances in transfusion techniques, particularly in protein fractionation, plasmapheresis and development of cell separator machines, enable advances in treatment to be made, such as home and prophylactic therapy for haemophilia, the more widespread use of present and new specific immunoglobulins, the use of fractions containing Factor IX in coagulation problems in the new born and liver biopsy, intensive plasmapheresis with fresh plasma replacement in pregnant women sensitised to the Rh D antigen, and an extension of platelet and leucocyte transfusions in many haemotological disorders.

All these trends in clinical practice will influence the demand for the various blood components.

Component Therapy

The essence of component therapy is to give the patient only that part of blood which he lacks, promoting more effective and safer treatment and the optimal use of blood.

The place of whole blood transfusion in modern practice

While some clinicians, particularly of the older generation, still consider that there is some special quality in whole blood given as such, the rationale for its present widespread use should be critically examined.

The essential value of whole blood lies in the fact that it increases both intravascular fluid volume and oxygen carrying capacity; only if these require simultaneous augmentation should its use be considered. It must be remembered that there are a number of hazards associated with blood transfusion, in the present context the two most important are overloading af the circulation and allo-immunisation of the recipient.

Overloading of the circulation may lead to circulatory collapse, particularly likely when there is associated degenerative disease of the myocardium. It should hence be axiomatic that *whole blood should never be given to a person with a normal blood volume.* This category includes patients in many clinical situations; the traumatic case whose blood volume has been restored by a fluid other than whole blood, the anaemic patient requiring urgent operative treatment, the chronically anaemic patient not responding to haematinics, the pregnant woman approaching term whose physiological anaemia is dangerously accentuated, to mention a few.

Allo-immunisation, the development of antibody to foreign antigen, has not, except for red cell serology, received the attention it deserves in transfusion practice. It may follow the transfusion of any of the protein constituents of the blood, those in red cells, leucocytes, platelets and plasma. There is a considerable variation in individual response; the first experience of such a foreign antigen triggers off the immunological mechanism (the primary response), a second or subsequent experience may elicit the secondary response, with production of antibody which may combine with the antigen and lead to a number of serious consequences. Allo-immunisation to red cell antigens may cause haemolytic transfusion reactions and haemolytic disease of the newborn. Although in whole blood the number of leucocytes and platelets may be insufficient to have any worthwhile clinical effect, allo-immunisation can be stimulated by them and lead to allergic or febrile reactions or rapid destruction of these components should they again be transfused in whole blood *or in concentrated form.*

ABO and Rh blood grouping of donor and recipient is a routine in any transfusion service, but it is impracticable to investigate and find blood which is identical as regards the many other blood group antigens known as red cells in every case. Any transfusion may, therefore, result in the immunisation of the recipient to one or more of these. Allo-immunisation to red cell antigens should be minimised to ease the task of finding compatible blood for future transfusions, to prevent haemolytic reactions when circumstances do not permit of cross-matching and to prevent cases of haemolytic disease of the newborn. It is equally impracticable to investigate donors and recipients for the HL-A and other antigens found in leucocytes and platelets prior to blood transfusion.

The rational way to minimise reactions in future transfusions of blood or its components is *to transfuse the cellular elements of blood only when there is an absolute indication,* this in effect here means an indication for red cells.

Apart from the relatively small requirements for surgical machines, virtually the only indication for the transfusion of whole blood nowadays is the treatment of haemorrhage, but the relative importance of the restoration of intravascular fluid volume and of oxygen carrying capacity must be clearly understood. A sudden loss of 30% of the blood volume is serious, but the loss of 30% of red

cells is not of major consequence in a previously fit person. A sudden haemorrhage of 2 litres, about 40% of the average blood volume, will probably result in a fatal outcome if left untreated, but the loss of 40% of red cells can be well tolerated if further strain is avoided. Certainly in severe haemorrhage whole blood transfusion is the rational treatment, but in lesser episodes restoration of the blood volume, which can be done without red cells, is all that is required. One or two-unit whole blood transfusions should have no place in the treatment of haemorrhage in adults —if such quantities restore blood volume, then plasma, a plasma derivative or a plasma substitute would have been quite adequate therapy.

Red cell concentrates

If there is an absolute indication for red cells and the patient is normovolaemic or only mildly hypovolaemic, the preparation of choice for transfusion is a concentrate of red cells. This can be offered in a number of ways.

Centrifugation of blood and removal of the supernatant plasma has the merit of simplicity and, as it can be done in a closed system, contamination is avoided and the concentrated cells may be stored in the same way as whole blood. The packed cells, however, still contain appreciable quantities of plasma, leucocytes and platelets and have the same disadvantage as whole blood in being capable of causing allo-immunisation to these components. The yield of plasma is not optimal as sufficient must be left to prevent undue viscosity which would make transfusion difficult. However, because of its simplicity, this is at present the method of choice for red cell therapy in patients unlikely to require repeated transfusions.

The addition of a washing cycle to the concentrated red cells removes plasma and markedly reduces the number of leucocytes and platelets; such a preparation is indicated for patients who have had, or are likely to have, multiple transfusions, to minimise the risk of allergic or febrile reactions. As the final product is a suspension in the wash fluid (saline), the cells may be tightly packed initially thus improving the plasma yield. The method is time-consuming and as closed methods are not available in all transfusion centres there is a risk of contamination and the concentrate must be used within a few hours of preparation.

Frozen red cells when thawed can be washed in a closed centrifuge system and, being virtually free from plasma, leucocytes, platelets and possible contaminants such as HBsAg, represent the purest form or red cells available. Ideally such preparations would be the choice for all red cell transfusions, but the cost and complexity of the process militate against this at present. It may well be, however, that advances in technique will make the routine use of processed frozen cells a feasible proposition in the future. The purity of such cells makes them of special value in the transfusion of patients on renal dialysis regimes or those who are candidates for organ transplantation. (In this connection, however, it should be noted that Opelz and Terasaki (1974) suggest that exposure to foreign leucocytes prior to renal transplantation may actually be beneficial by the active induction of immune unresponsiveness.)

The value of red cell concentrates in their own right is now more fully recognised, but the original aim of their preparation was to make plasma available for fractionation; this is becoming an increasingly important corollary to red cell therapy. The aim of the Health Departments in this country is for the National Health Service to become self-sufficient in the supply of blood products; this will require, not only an increase in donations, but better use of existing supplies of blood. One very important aspect of this will be an increase in the use of concentrated red cells instead of whole blood. In 1973–74 the average use of these concentrates in Scotland was 35·2%, one region achieved 44·1%. As the only major indication for the use of whole blood is in the treatment of oligaemia when more than 1 litre of resuscitative fluid is required (in adults), these figures should be capable of considerable improvement; an 80% use of concentrated red cells has been achieved in New Zealand. To meet such a target requires considerable effort on the part of Regional Transfusion Directors and their medical staff, in collaboration with Consultants in Haematology in promoting the concept of component therapy to all their colleagues involved in any aspect of transfusion work.

Platelets

When blood is centrifuged at low speed the platelets remain suspended in the supernatant plasma. On removal of this platelet-rich plasma, further concentration of the platelets may be achieved by centrifugation at higher speeds and removing the upper 80% of the plasma; the residual 30–50 ml of plasma contains up to 70% of the original platelets. Platelet preparations must be made from fresh blood; their storage life is short. Cell separator machines enable the collection of a very large number of platelets from a single donor.

Platelet therapy has proved effective in two main situations, acute thrombocytopenia associated with severe *depletion* of platelets, as may occur after the treatment of haemorrhage by massive blood transfusion or as a post-operative complication of cardiac surgery, and chronic thrombocytopenia associated with *decreased platelet production* as in aplastic anaemia, including that following irradiation or the use of cytotoxic drugs, or infiltration of the bone marrow by neoplasma, particularly leukaemias. It is of limited value in thrombocytopenia associated with *rapid platelet destruction* as in idiopathic thrombocytopenic purpura.

Histocompatibility antigens, particularly those of the HL-A system, but to a certain extent those of the ABO group, are important when multiple transfusions are indicated as repeated transfusion of mis-matched platelets result in decreased survival due to the development of allo-antibodies. In acute thrombocytopenic states it suffices if platelets are obtained from ABO identical donors as the requirement is a short-term one. In chronic thrombocytopenic conditions, however, the platelets must also be HL-A compatible; in such situations a cell separator machine is of especial value as only one, not many, suitable donors need to be found. It is also important that HL-A identical platelet therapy be used for patients who are potential candidates for bone marrow transplantation in order to prevent allo-immunisation and hyperacute rejection.

Leucocytes

Cell separator machines enable worthwhile quantities of leucocytes to be prepared. Reports from many centres indicate that leucocyte transfusion is now a practical proposition and is a potentially powerful therapeutic tool. Normal granulocytes would appear to be valuable in the management of some leucopenic states, particularly those complicated by severe bacterial infection unresponsive to antibiotic therapy. Lymphocytes, or transfer factor which can be extracted from them, influence cell-mediated immune responses and may have an important place in the future treatment of neoplastic disease and infections such as mucocutaneous candidiasis. There are fascinating possibilities in the future treatment of haematological neoplasms, such as the collection of leukaemic cells, irradiating them and using them to immunise the patient when in remission.

As with platelets, the strongest leucocyte antigens appear to be those of the HL-A system and in any long term course of treatment with leucocyte transfusions HL-A identity is of crucial importance, without this safeguard none of the transfused cells will survive more than one circulation in a sensitised patient.

Whole plasma

Whole plasma contains plasma proteins, including albumin, globulins and clotting factors, some platelets, electrolytes and other substances; the quantities of some of these may vary according to the origin and treatment of the plasma. The number of platelets is barely significant therapeutically and they are not viable in dried preparations. Gamma globulins (immunoglobulins) and albumin in the treatment of protein depletion are invariably better given as fractions of plasma. In effect, then, the value of whole plasma clinically depends on the albumin fraction, an efficient blood volume expander, and on the clotting factors, useful in some coagulation defects.

Fresh plasma (which can be frozen or dried to extend its keeping qualities) contains both these elements. If the purpose of transfusion is solely volume expansion, more acceptable preparations are available (see below). Although, in general, coagulation factors are of most importance in the treatment of specific factor deficiences, for example, haemophilia, and are more effective given as concentrated fractions, there are situations where there is actual or potential depletion or excessive consumption of all these factors and the transfusion of fresh plasma is the prophylaxis or treatment of choice. Massive blood loss and replacement are often complicated by coagulation defects as the amounts of coagulation factors supplied in whole blood may be insufficient; the addition of several units of fresh plasma to the transfusion regime may prevent such complications arising. In disseminated intravascular coagulation the excessive consumption of coagulation factors results in the blood becoming incoagulable and hence widespread haemorrhage may occur; mild cases may respond to fresh plasma transfusion, more serious cases with persistent bleeding may require fibrinogen and platelet transfusions in addition. There are numerous causes of disseminated intravascular coagulation, including bacteriogenic shock, obstetrical accidents, haemolytic transfusion reactions, certain types of surgical operations and traumatic fat embolism; fresh plasma could also be considered as a prophylactic measure in such conditions. Extensive plasmapheresis undertaken in the alleviation of hyperviscosity syndromes such as macroglobulinaemia or to remove dangerous circulating factors such as Rh D antibody require replacement of the blood volume and preferably coagulation factors; fresh plasma is indicated for this purpose.

Older plasma, such as that removed from outdated blood, has lost a large proportion of the labile coagulation factors and is only of value for blood volume expansion; purified protein fraction is preferable for this purpose.

There is a definite place for whole fresh plasma in transfusion practice; its use, however, should be restricted to prophylaxis or treatment of conditions in which a range of coagulation factors is indicated (such situations are generally associated with a requirement for volume expansion as well).

Plasma Proteins

Plasma proteins may be divided into albuminoid fractions, coagulation factors and immunoglobulins.

Albuminoid fractions. Protein fractionation centres can manipulate the final stage of processing to produce albumin solutions of varying purity. If the principles of component therapy were completely followed, albumin itself would be the physiological fluid of choice for blood volume expansion, but the greater the albumin percentage, the less the yield and a compromise has to be reached between highly purified products such as albumin (1 unit containing 45 g of this protein requires 2·25 litres of plasma), intermediate products such as purified protein fraction (1·5 units per litre) and dried plasma (2·5 units per litre) when considering fluids for volume expansion.

Many factors influence the type of blood volume expander favoured by clinicians.

Whole blood has been the choice for many years, but the red cell component is not always desirable. Apart from the necessity to avoid allo-immunisation already referred to, there are occasions, such as the early stages in the treatment of burns or in peritonitis, when only plasma is being lost from the circulation and a red cell-free expander is indicated.

Reconstituted dried plasma is an efficient, physiological volume expander, indeed the greatly improved results in the treatment of battle casualties in the Second World War, compared with those in 1914–18, can be largely attributed to the ready availability of plasma in forward areas. It fell into a certain amount of disrepute, however, owing to the danger of transmission of viral hepatitis. This risk is now decreased by screening all blood donations for HBsAg, but the tests used are not infallible and some risk remains. A logistic disadvantage is the necessity to reconstitute the dried preparation. Drying fresh plasma for use solely as a volume expander is wasteful of valuable coagulation factors; an occasional disadvantage of plasma obtained from outdated blood is alteration in the electrolyte content, particularly a rise in potassium ions which could be dangerous if given to anuric patients with large muscle wounds and therefore already hyperkalaemic, or to infants who are especially susceptible to increased plasma potassium levels.

Electrolyte solutions, particularly Ringer lactate, have had a vogue as volume expanders in some centres, but their effects are fleeting and circulatory overloading with resultant pulmonary oedemia is a hazard.

Dextrans are efficient, cheap and available in virtually unlimited quantities. They consist of a solution of polysaccarides of varying molecular weights. The smaller molecules are rapidly excreted in the urine, larger ones are retained in the circulation for some days, being slowly excreted or temporarily stored in the reticulo-endothelial system and eventually metabolised. Little is known about the long-term effects, if any, of such storage. Large quantities of the higher weight molecules may cause aggregation of red cells leading to blockage of small vessels. venous stasis and the possibility of focal necrosis, prolongation of the bleeding time which may lead to post-operative haemorrhage, rouleaux formation which can interfere with blood grouping and cross-matching and they can act as haptens (non-protein molecules not by themselves antigenic, but which may become so if attached to larger molecules and so produce sensitisation) causing reactions in future dextran infusions. Although Dextran 70, being of comparatively low molecular weight, is seldom associated with these disadvantages clinically, it is undesirable to give large quantities. As Dextran requires no special storage conditions and has a shelf life of at least five years, it has a place in emergency resuscitation while a more physiological volume expander is being obtained.

Of recent years purified protein fraction has been prepared by plasma fractionation and appears to have the advantages, but none of the disadvantages, of other volume expanders. It is a physiological fluid, consisting of a preparation of plasma proteins containing not less than 90% albumin, the remaining protein being α and β globulins. It is dispensed as a fluid preparation in 400 ml amounts, hence does not require reconstitution, and has a shelf life of at least five years at room temperature if protected from light. Processing includes heat treatment, destroying the

infective agent of type B hepatitis. It has proved clinically acceptable and effective in many centres and no serious adverse reactions to it have been reported in this country. It is now generally accepted that purified protein fraction is the volume expander of choice for routine use in any hypovolaemic condition where coagulation factors are not required and red cells not an immediate necessity.

As highly purified albumin is most expensive as regards plasma, its use should be restricted to cases in which the provision of albumin, not volume expansion, is the object of therapy, such as the prevention of severe protein depletion in the nephrotic syndrome and in protein-losing enteropathies.

Coagulation Factors. Natural arrest of haemorrhage is carried out by the haemostatic mechanism and involves a series of complicated interrelated reactions aimed at plugging defects in vascular channels, but incorporating safeguards to avoid accidental intravascular thrombosis. When a vessel wall is damaged, immediate haemostasis is attempted by the formation of a platelet plug, aggregation and adherence of platelets being stimulated by the damaged tissue. This is followed by deposition of fibrin to give a more permanent and effective seal. Many of the circulating coagulation factors exist normally in an inactive form, to prevent spontaneous clotting. The coagulation process is triggered off by intrinsic or extrinsic stimulants derived from vascular or tissue damage. This leads to sequential activation of inert factors, often involving adjuvants such as calcium, and culminates in the deposition of stable fibrin at the site of the injury. Coagulation inhibitors and the system which breaks down fibrin (fibrinolysis) enable a delicate balance to be maintained between requirements for haemostasis and the maintenance of patency of vascular channels.

From the point of view of transfusion practice, our interest lies in the fact that all the circulating coagulation factors are present in fresh plasma, the use of which has already been discussed, and some can be recovered in concentrated form.

Factor I. Fibrinogen, the precursor of fibrin, can be prepared by fractionation of fresh plasma, yielding a concentrate containing over 80% clottable factor. Apart from rare cases of hereditary afibrinogenaemia, its use may be indicated as an adjunct to fresh plasma in defibrination syndromes due to excessive consumption of coagulation factors, as in disseminated intravascular coagulation, or due to excessive fibrinolytic activity as seen in acute primary pathological fibrinolysis which may follow extensive tissue trauma and in clinical practice is particularly associated with complicated childbirth.

Factor VIII. In simple terms, classical haemophilia (A) is due to a genetically determined funtional deficiency of Factor VIII, causing blockage of the sequential activation of the coagulation system and leading to haemorrhage. The essential in treatment is to replace the missing factor, but this gives raise to a number of practical problems.

When whole blood or fresh plasma was used as the vehicle of replacement, it was generally possible to control early spontaneous bleeding into joints or muscles as this entailed transfusion of the order of one litre. Control of dangerous haematomata, such as into the muscles of the tongue, and of bleeding in the course of multiple dental extractions, requires at least twice this amount repeated on several occasions and replacement therapy for serious accidents or major surgery, which would involve the transfusion of up to 10 litres for a number of days pre- and post-operatively, would obviously be impractical. Concentrates of animal plasma, bovine or porcine, very rich in Factor VIII, can be used, but they rapidly stimulate the production of animal protein antibodies and become, not only ineffective, but liable to cause reactions if given again.

It is no overstatment to say that the introduction of cryoprecipitate has revolutionised the treatment of haemophilia. When plasma is rapidly frozen and slowly thawed at 4°C a precipitate, rich in Factor VIII, settles out and can be recovered by removing most of the supernatant plasma. This cryoprecipitate retains its activity if stored frozen below −25°C, when required it is thawed at 37°C to redissolve in the small quantity of remaining plasma and material from a number of donations is pooled. The final concentration of Factor VIII may be fifteen to twenty times that of the original plasma so that large quantities of the factor may be given in realistic volumes. Cryoprecipitate can be made in any transfusion centre and is an effective preparation. Its main disadvantages are that it is very variable in activity, from batch to batch and from centre to centre, and requires storage at −30°C.

A freeze-dried concentrate can now be made by fractionation. The present 'intermediate' factor has about twice the activity of cryoprecipitate in a given volume, and has the merit that it can be standardised, so that the activity given is known, and it remains stable at 4°C. As this preparation becomes more widely available it will gradually

replace cryoprecipitate for the routine treatment of haemophilia. It is particularly convenient for home treatment. An even higher potency material, containing up to ten times the activity per unit volume, can be prepared which would be of particular value in giving large quantities of Factor VIII to patients who have developed Factor VIII antibodies by allo-immunisation to foreign proteins or who are being prepared for major surgical operations. It is unlikely to supersede the intermediate factor to any extent in routine use, however, as its preparation involves a high loss of activity and hence requires considerably increased quantities of plasma.

Preparations containing Factor IX. There are technical difficulties in fractionating a pure Factor IX preparation; one product prepared from citrated plasma contains the factors II, IX and X. The main indication for its use is in Christmas disease (haemophilia B); its value in coagulation problems in the newborn is being investigated.

Christmas disease is very like classical haemophilia, but the deficiency is in Factor IX, not VIII, it is much less frequent and in general less severe. Replacement therapy is achieved by fresh plasma or the concentrated factor; cryoprecipitate does not contain Factor IX and is hence ineffective.

An alternative preparation, prepared from EDTA plasma, contains Factors II, VII, IX and X and, by virtue of the content of Factor VII, is of value in arresting haemorrhage complicating liver disease or rapid reversal of the effects of oral anticoagulant therapy.

Immunoglobulins. Iso-immunisation to microbiological agents or their toxins may result in the formation of protective antibodies in the form of gamma globulins.

Normal immunoglobulin is prepared by factionation of pooled plasma from normal adults. It is a heterogeneous mixture of many antibodies, reflecting the experience of the donors to infections, overt or sub-clinical, throughout their lives. Antibodies to the viruses causing measles, poliomyelitis and hepatitis A are present in most plasmas in quantities sufficient to confer some passive immunity and normal immunoglobulin can be used to protect the unvaccinated or debilitated young against measles, travellers against hepatitis A and poliomyelitis and to contain outbreaks of hepatitis A, particularly in institutions.

Specific immunoglobulins are prepared in the same way from plasmas containing a high titre of the appropriate antibody. They may be divided into groups according to the selection of donors used to supply potentially useful material.

1. A group of volunteers may be immunised with the appropriate antigen and good responders selected for plasmapheresis. Some Anti-D is obtained in this way from male volunteers.
2. Screening for suitable donors to obtain anti-tetanus and anti-vaccinial immunoglobulins can be restricted to those with a history of active immunisation with the appropriate vaccine; a booster dose may be offered before assay. The response to immunisation, as judged by the antibody response, is extremely variable.
3. Rh negative women who have been pregnant, particularly those with a history of having babies affected by erythroblastosis, may be screened for useful titres of anti-D.
4. For other specific immunoglobulins at present obtained or which may be developed in the future, such donor selection is more difficult. Occasionally it may be feasible to investigate a group of people connected with an epidemic (for example, of rubella), and liaison with community medicine specialists may be fruitful in this approach, but in general, as antibodies may have developed in individuals exposed to antigens in the past, but who may not have suffered clinical disease, only mass screening of large numbers of donors would reveal those of value in this context. This raises problems concerning staff and techniques.

The use of some specific immunoglobulins is now general, some have been prepared on a pilot or experimental basis, much work remains to be done on the supply, production and assessment of others which are of potential value.

Anti-D. Bleeding from an Rh positive foetus into the circulation of an Rh negative mother may immunise the mother and this may cause haemolytic disease of the newborn in subsequent pregnancies. Destruction of such Rh positive cells by Anti-D injected within 72 hours of abortion or labour prevents allo-immunisation and is now an established procedure; it is one of the rewarding advances in preventive pediatrics. Any excess of the passively administered Anti-D disappears within a few months and therefore itself is not a hazard.

Anti-tetanus. Although the value of equine anti-tetanus serum in preventing tetanus, particularly exemplified in battle casualties, should not be under-estimated, horse serum is a powerful foreign antigen and readily induces sensitisation leading to rapid elimination of antitoxin, and hence ineffectiveness, or the danger of serum sickness or anaphylactic reactions should the individual require the product again. For those reasons, and because of the introduction of active immunisation with tetanus toxoid, the use of equine anti-tetanus serum has largely become obsolete, surgeons relying more and more on wound debridement and antibiotics to prevent tetanus. Human anti-tetanus immunoglobulin is becoming more widely available and as indicated as a prophylactic measure in patients who have a tetanus-prone wound and have not been actively immunised. A tetanus-prone wound may be defined as one which has been sustained in an agricultural pursuit, one which is obviously contaminated with foreign material, or one where there has been a delay in treatment of over six hours after infliction. It should be noted that injured patients who have been actively immunised should receive a booster dose of tetanus toxoid, not tetanus immunoglobulin. When the latter *has* been given, a dose of absorbed tetanus toxoid should also be given and follow-up should include arrangements to complete the active immunisation programme. Human anti-tetanus immunoglobulin in large doses is also indicated in the treatment of an actual case of the disease.

Anti-vaccinial immunoglobulin is valuable for the prevention of smallpox in unvaccinated contacts of a case. The recent decision that progress in the world-wide eradication of smallpox has advanced to the point that routine vaccination of the population of this country need no longer be recommended means that the unprotected proportion will increase considerably. Air travel and population movements increase the risk of importation of smallpox and anti-vaccinial immunoglobulin should be readily available to passively immunise contacts and thus help to prevent or contain an outbreak. Selected groups of the population, for example the Armed Forces, are still vaccinated and another important use of anti-vaccinial immunoglobulin is the treatment of complications of smallpox vaccination such as generalised vaccinia.

Anti-hepatitis B immunoglobulin is now available in limited quantities and can be used to protect those involved in an accident exposing them to the virus; it may also have a place in protecting infants born to HBsAg positive mothers.

Anti-rubella. Much doubt has been expressed as to whether normal immunoglobulin has much effect in preventing rubella in those exposed and a high titre immunoglobulin is being developed which should be of value in pregnant women exposed to rubella, who are seronegative for rubella antibodies, and who wish the pregnancy to go to term.

Other immunoglobulins. Immuno-suppressed or debilitated patients may react very severely to infections and specific immunoglobulins against such viruses as mumps, chickenpox, whooping cough, herpes simplex and herpes zoster may be of value in restricted clinical situations; an experimental batch of herpes zoster immunoglobulin has recently been prepared. Little can be done at present against respiratory virus infections, a major cause of morbidity and mortality in infants; the future may see the development of specific immunoglobulins against these agents. One of the major factors preventing the healing of burns is infection by antibiotic resistant organisms such as *pseudomonas pyocyaneus* (*aeruginosa*); if a method of screening donors could be devised, passive immunisation is certainly a possibility.

Transfusion Centre Activities

Regional and even inter-regional differences exist in clinical and transfusion centre practice, creating a varying demand and supply situation; activities in one centre are not necessarily duplicated in another.

Blood donation

The Donor Organiser is a key figure in the organisation of donation sessions. She and her staff not only arrange dates, times and venues of sessions, maintain donor panels (which may be computerised in large centres) from which donors are invited to attend appropriate sessions, but they are responsible for the welfare of donors and maintenance of public relations. Donor teams consist of a supervising medical officer, nursing officers and donor attendants. In acknowledging the debt which patients owe to their fellows who donate blood, mention should also be made of the very considerable assistance given by local voluntary organisers and other helpers towards the recruitment of new donors, the maintenance of close personal relationships with donors, the organisation of transport to and from donation centres as well as the actual conduct of bleeding sessions. Employers, too, play their part in giving facilities and working time off, disregarding the cost to themselves in terms of lost working hours, to enable their employees to donate blood.

Donation sessions may be arranged in the transfusion centre or teams, equipped with beds, refrigeration facilities and medical equipment, may visit towns, villages or factories. A mobile donation centre, a specially adapted bus, is a great advantage when there are local accommodation difficulties and where the centre is responsible for a large geographical area a mobile laboratory may be used to process blood while the donation session is in progress, otherwise the laboratory staff have an arduous evening's work when the donation teams return. Plasmapheresis is a more complex type of donation and is normally carried out at transfusion centres.

Red cell serology

Red cell serology is one of the primary tasks of a transfusion centre and includes blood grouping of donors and often recipients, cross-matching for hospitals adjacent to the centre, grouping and antibody investigations on specimens from antenatal clinics and the investigation of transfusion reactions and auto-immune haemolytic anaemias. All these techniques are monitored by quality control procedures.

Tests are mainly for agglutination, enzyme techniques which enhance the reactivity of some reactions are frequently employed, and other sophisticated procedures may be required to elucidate unusual or unexpected results.

The responsibility which rests upon those carrying out these techniques and interpreting the results is seldom appreciated. Disastrous results can follow any error and clinicians must appreciate that laboratories must be given adequate time to carry out these tests in an orderly and unhurried sequence. Intelligent anticipation of the likelihood of transfusion being required in non-urgent cases should enable the laboratory to be given ample time to plan its work methodically and investigate anomalous findings, for example, an unexpected incompatibility in cross-matching. In emergency situations the imperative demand in the initial treatment of oligaemic shock is restoration of the blood volume which, as has already been pointed out, can be done without red cells. Transfusion with plasma, plasma protein fraction or a plasma substitute will, in practically every case, tide the patient over until modified compatibility tests are carried out. If for some exceptional reason it is decided that blood must be transfused without such laboratory control, the responsibility for any untoward reaction must rest with the clinicians.

Safeguards against infections

Apart from donor selection and meticulous attention to the aseptic handling of blood and its products at all stages, blood donated is also tested as a routine for syphilitic or Hepatitis B infection. Screening for the former is carried out by tests such as the VDRL. The discovery of Hepatitis B Antigen resulted in widespread demands for all blood to be tested for this agent and routine screening was adopted while techniques were still being developed. The test in current use, immunoelectroosmophoreses (IEOP) depends on the fact that when antigen and its specific antibody are placed in wells cut in an agar gel, they diffuse into the medium (immuno-diffusion) and a line of precipitation appears where they meet. The passage of a low-voltage electric current (electrophoresis) through the system accelerates the process so that the test may be read in 1–2 hours. The process can be reversed. using known antigen and unknown sera to test for the presence of antibody. Numerous factors influence diffusion and both the technique and interpretation require considerable expertise. The test is not sufficiently sensitive, however, to reveal all HBsAg infections. Techniques by reversed passive haemagglutination or haemagglutination inhibition have been developed and will probably be introduced into routine use shortly. They have the merit of being more simple, sensitive and rapid than IEOP and can be automated. Being more sensitive, however, a considerable number of false positive reactions occur which will require an extension of follow-up investigations. Radioimmunoassay, involving the demonstration of the uptake of radioactively labelled antibody by antigen, is equally sensitive, but the technique is much more elaborate and requires expensive equipment; it certainly has a place in reference laboratories, but more comparative experience is required between this method and haemagglutination techniques before it can be recommended for routine use.

Blood banking and processing

When blood donations have been grouped and have successfully undergone the tests for infection, they may be stored as whole blood at 4–6°C until issued as such. A considerable proportion is immediately processed to provide components. The first step is centrifugation and removal of the red cells which may be stored as concentrates, washed prior to issue or processed for freezing in liquid nitrogen.

The remaining plasma may be issued for transfusion as such, used to prepare cryoprecipitate or platelet concentrations, frozen at −20°C for issue later or transmission to a protein fractionation centre or be processed into dried plasma. The residue after cryoprecipitate or platelet preparation is frozen and sent for fractionation. Fresh plasma obtained by plasmapheresis, at present mainly

restricted to donors with high titre specific immunoglobulins and blood group antibodies is sent, frozen, for fractionation or used in the centre for blood grouping antisera. After the storage period of conventionally preserved blood has elapsed the plasma is removed and processed into dried plasma or fractionated.

In all these procedures constant attention has to be paid to the maintenance of sterility, the time factor is often of great importance as delay in separation and freezing of plasma greatly reduces the activity of the labile factors, particularly Factor VIII, and a variety of storage temperatures have to be supplied and maintained.

Diagnostic reagents

Individual or collective action on the part of the transfusion service in the provision of diagnostic reagents (red cell antibodies, cell suspensions, HL-A antisera and typed lymphocytes) lead to increased efficiency and economy. This involves considerable effort in screening potential donors or samples, obtaining material, frequently by plasmapheresis, processing the reagent and testing it for strength, avidity and specificity before issue.

Tissue typing

It is unfortunate that, as the identification of histocompatibility antigens was for a number of years predominantly required for organ transplantation, the term 'tissue typing' has been applied to these techniques. Fundamentally, the elements typed are lymphocytes and much confusion concerning responsibility for this service would have been avoided if the more accurate term 'lymphocyte typing' had been adopted instead. It would then have been more evident that tissue typing is a modern extension of the well established principles of blood group immunology and a logical responsibility of the blood transfusion service.

Tissue typing has a place in organ transplantation, clinical blood transfusion, particularly leucocyte and platelet transfusions including supportive treatment after bone-marrow transplantation, the investigation of non-haemolytic transfusion reactions and genetic marking of disease. This aspect of immunology is constantly expanding, at present the main practical implications lie in the identification of HL-A antigens and antibodies and the demonstration of compatibility of these and other systems between donors and recipients.

HL-A antibodies are cytotoxic, that is they cause the death of cells carrying the specific antigen when the two are incubated together in the presence of complement. Such cell death can be demonstrated in a number of ways, a common method is to add a dye which enters dead cells, but is excluded from living ones. An estimation of the proportion of stained (dead) to unstained (living) cells thus indicates the presence or absence of the antigen. The actual technique is complex and delicate involving the preparation of lymphocyte suspensions, control of incubation with a wide range of HL-A antisera in microquantities and expertise in reading and interpreting the results.

A corollary to a tissue typing service is the necessity to maintain supplies of HL-A antibodies and to detect new antigens. A similar microlymphocytotoxicity test is used, unknown sera being screened against a panel of known HL-A typed lymphocytes. HL-A antibodies develop by alloimmunisation and a suitable source of sera to screen are those from multiparous women who may have developed antibodies by immunisation with foreign antigens derived by the foetus from genetic material inherited from the father. Antenatal sera are already supplied to transfusion centres for red cell serological tests and can be used additionally for HL-A antibody screening. If any sera are identified as containing worthwhile quantities of antibody, the woman concerned can be asked to undergo blood donation or plasmapheresis.

As there are still unidentified histocompatibility and other antigen systems, it is desirable to cross-match donor and recipient before organ transplantation. In addition to attempts to demonstrate antibodies by cytotoxicity tests, a recent advance is the development of a mixed lymphocyte culture technique which may disclose incompatibility not revealed by HL-A testing. This technique is based on observations that when lymphocytes from two genetically non-identical individuals are mixed, they stimulate each other and are transformed into lymphoblasts, characterised by an increase in protein synthesis which can be quantified by radioactive isotope techniques. These tests are much more complex and delicate than this brief explanation would indicate. The closer the antigenic identity of the two sets of cells, and hence the greater compatibility, the less the activation.

Dried plasma plant

The drying of plasma is confined to selected centres. While dried fresh plasma is not quite as potent as the frozen material in some of the coagulation factors, it is adequate in this respect for most purposes and has good keeping qualities. Plasma removed from out-dated blood, however,

lacks adequate labile factors and, as fractionation facilities are improved, this material should be processed into purified protein fraction. While facilities for drying plasma will still be required the volume will be reduced and the process confined to fresh plasma.

Supply of specific immunoglobulins

Transfusion centres are responsible for screening suitable donor population for specific immunoglobulins; in some cases immunisation programmes are carried out on volunteers, in others boosting doses of vaccines may be given to donors already actively immunised.

Supporting Services

A transfusion centre provides its own back-up in most of the pathology disciplines. General microbiological facilities are required for environmental and quality control. Biochemical techniques must be available for monitoring products and preparation of reagents and intravenous fluids. Haematological methods are used in programmes for the prevention of haemolytic disease of the newborn, investigation of immunologically mediated haemolytic disorders and quality control of the clinical use of coagulation factors. Administrative control must be exercised to co-ordinate work, staffing and equipment in the various laboratories. Reference laboratory facilities are necessary for difficult serological or microbiological problems and liaison with other centres, national or international, with the exchange of products or reagents, is a valuable means of promoting quality.

Research and development

In practically every field of activity in a transfusion centre there is scope for improvement and basic or applied research. This important aspect must be catered for by ensuring that staffing levels are above the bare minimum for routine tasks and finance is available for extra equipment. Specific projects may be worthy of research grants.

Summary and Conclusions

This review of modern transfusion practice is intended to highlight many of the advances made since blood transfusion became more than the occasional event it was some 35 years ago. Technical advances have played their part, but much of the progress can be attributed to the close and active liaison maintained between members of the transfusion service and their colleagues in many other areas in medicine. Blood or its products play a most important rôle in practically every aspect of modern medical practice and an understanding of the underlying principles is essential if the optimal use is to be made of the blood so willingly donated by so many individuals. In conclusion it would be fitting to re-iterate three fundamental principles:

1. The keystone of the transfusion service is the voluntary donor.

2. There are strong ethical and financial arguments against the use of commercial human blood products; the National Health Service must be self-sufficient in this respect.

3. Component therapy is the logical way to approach modern transfusion requirements.

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References

Bellin L J (1974). *British Medical Journal*, **2**, 212.
Opelz G and Terasaki P I (1974). *Lancet*, **2**, 696.
Watt J G, Smith J K, Grant W and Turnbull C (1972). *Proceedings of the Royal Society of Edinburgh*, (B), 71, supp. 3.