

# On transfusion medicine

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*History of transfusion medicine is one of continued progress from a primitive harmful procedure to an organized speciality. We have made an attempt to highlight the various aspects of transfusion medicine including a cost appraisal on blood and components. With no alternative to blood transfusion, the priority should be optimization of collected unit and adherence to quality standards. A centralized blood transfusion system based on a complete voluntary set-up and meeting the target of requirements, will be the answer in our context. Rational use of blood and better transfusion practices would decrease spread of transfusion-transmitted diseases and incidence of life-threatening transfusion reactions. Blood transfusion would then become safer than ever before.*

BLOOD has always held a mysterious fascination for all and is considered to be the living force of our body. Ancient Egyptians recognized the life-giving properties of blood and they used it for baths to resuscitate the sick, rejuvenate the old and infirm and as a tonic for the treatment of various disorders. Blood was also used for transfusion as a therapeutic measure as early as 1667 when animal blood was administered to humans. Though initially this met with success, it had to be stopped abruptly due to certain adverse reactions to transfused blood. Then, the practice of transfusion lay dormant for nearly 150 years. As medical knowledge advanced with better understanding of blood and its constituents, procedure of blood transfusion on humans was revived in 1818 by an English obstetrician, James Blundell but with limited success as reactions to blood still occurred<sup>1</sup>.

## Discovery of blood groups

By 1900 it was recognized that the reactions observed during initial therapy were the result of destruction of transfused red cells by immunological mechanisms due to individual differences in blood group antigens on the red cell. The epoch-making discovery of ABO blood group system by Karl Landsteiner paved the birth of a discipline called Immuno Haematology. Landsteiner in his discovery of ABO blood group system found that human serum contains agglutinating antibodies directed against antigens on other human red cells. Agglutination is the most widely observed phenomenon resulting from the combination of a red cell antigen and its antibody (Figure 1). He found that human beings could be divided into three groups depending on the presence of A or B antigens on the red cells (groups A and B) or by the absence of these two antigens (Group O). Group AB was soon recognized as comprising of individuals

with both A and B antigens. Antigens of ABO system are present on the red cells of the foetus and persist throughout life. They are inherited according to Mendelian laws. Table 1 shows distribution of blood groups among general population. Corresponding to the antigens A and B there are antibodies anti-A and anti-B, which occur as agglutinins in the sera of individuals whose red cells lack the corresponding antigen. Blood group substances A and B are not confined to red cells alone but can be detected in other tissue cells and body fluids as well. Other antigens such as Rh, MNS, Kell, Lutheran, Duffy, Kidd, Lewis have been discovered and at present there are over 600 antigens recognized, forming the basis for different blood group systems.

## Adverse effects of blood transfusion

Blood group antigens vary greatly in their immunogenicity. Among them, ABO and Rh are considered to













ABO GROUP	TYPING SERA (for cell or 'forward' grouping)		
	anti-A	anti-B	anti-A,B
Group A			
Group B			
Group AB			
Group O			

Figure 1. Red cell agglutination pattern – ABO blood groups.



be most important for transfusion purposes as these are the ones mainly responsible for haemolytic transfusion reactions and haemolytic disease of new borns. Hence, it is important that antibody screening and compatibility tests are designed to exclude the presence in the recipient's serum of clinically significant antibodies against these blood group antigens. ABO system has naturally occurring antibodies in serum. Antibodies of most other systems develop only through transfusion of antigen-positive cells and during pregnancy when antigen-negative women conceive children with corresponding antigen-positive cells.

Though blood transfusion is regarded as the very essence of life, it is not without problems. Some of them can be prevented while others cannot. These include both immune and nonimmune mediated-complications and transmission of infectious diseases to the recipient (Tables 2 and 3). Allergic reactions are the most commonly encountered transfusion reactions. They are thought to be due to plasma proteins in transfused blood reacting with recipient antibody. It can be severe in the

Table 1. Antigen and antibody content of red cells and serum ABO groups

ABO group	Antigen on red cells	Antibody in serum	Approximate % of frequency of ABO and Rh groups in general population			
A	A	Anti-B	A	25	Rh <sup>+</sup>	93
B	B	Anti-A	B	27	Rh <sup>+</sup>	7
AB	A and B	Neither	AB	6		
O	Neither	Both Anti-A and Anti-B	O	42		

Table 2. Adverse effects of blood transfusion

Immune-mediated reactions	Nonimmune-mediated reactions
Haemolytic	Volume overload
Febrile nonhaemolytic	Bacterial contamination
Allergic <div>└ urticarial</div>	Transfusion-transmitted diseases
<div>└ anaphylactic</div>	
Transfusion-related acute lung injury	Physical destruction of blood
Graft versus host diseases	Iron overload
Post-transfusion purpura	Citrate toxicity

Table 3. Current risk estimates of transfusion-transmitted diseases

HIV	1/225,000
Hepatitis B	1/200,000
Hepatitis C	1/6600
HTLV 1/11	1/50,000
Others	1/500,000
Overall risk	1/5000

Source: Dodd, R. Y., *New Engl. J. Med.*, 1992, **321**, 419; Connecticut Red Cross, 1993.

form of an anaphylatic reaction. Febrile reactions occur in patients who have multiple transfusions and in multiparous women due to leukocyte antibody. Before the days of disposable plastics, pyrogens and bacterial contamination also resulted in such febrile non-haemolytic reactions. Graft versus host disease occurs when immunologically competent lymphocytes are introduced into host recipients who are severely immunosuppressed. These immunocompetent donor lymphocytes will engraft in the recipient and react against 'foreign tissue' of the host and progress to a fatal outcome. It is a rare complication following transfusion in patients who are intensively treated with chemotherapy and irradiation. Pulmonary reactions characterized by rapid onset of acute respiratory distress occur during or immediately following transfusion. Leuco agglutinins or activated complement components are thought to cause aggregation of transfused leucocytes. These aggregates get trapped in microvasculature of lung and cause symptoms of acute respiratory distress. Circulatory overload occurs following rapid transfusion of large amounts of blood in anaemic and elderly patients. Bacterial contamination of blood though uncommon now can still occur if improper storage techniques are used.

Acute haemolytic transfusion reactions are the most severe form of transfusion reactions, amounting to a medical emergency. Delayed transfusion reactions can also occur as the transfused cells circulate and get destroyed by the increased antibody synthesis. This secondary response may occur within 7 to 10 days. Site of haemolysis can be either intra- or extravascular. Intravascular haemolysis is immediate and occurs when transfused cell combines with recipient's allo-antibody, fix complement, and results in rupture of cell membrane and development of osmotic haemolysis. In an extravascular transfusion reaction, there is only partial fixing of complement due to the nature of the antibody involved; this antibody combines with transfused donor cells and are cleared by the reticulo-endothelial system. They rarely produce clinical symptoms. Increased awareness of potential complications of blood transfusion has led to identification of proper indications for transfusion so that unnecessary donor exposures are avoided.

## Ensuring safe blood

Safety of blood transfusion begins with proper selection of donors. A person who volunteers to give blood is different from a patient in the sense that he is unaware of any abnormality that he may have. Hence, it is essential that proper history of any illnesses is sought and thorough medical examination is undertaken to decide whether the donor is acceptable. These measures safeguard the interests of both the donor and the recipient.



Each collected unit undergoes various testing of parameters like ABO and Rh grouping, detection of antibodies, screening for transfusion-transmitted diseases (TTDs) like hepatitis type B and C, human immunodeficiency virus, syphilis and malaria. Compatibility testing is done with patients' serum and donor red cells by different methods to detect any clinically significant antibody active at 37°C capable of destroying transfused cells in the patient's circulation.

Any type of blood whether whole blood or components, can produce adverse reactions due to transfer of infectious agents. Viral, bacterial and parasitic infections are transmitted by the parenteral administration of blood. Various steps that help to minimize this route of infection are (i) insisting on voluntary blood donations, (ii) eliminating persons with high risk behaviour by a detailed questionnaire, (iii) screening of all donor units for TTDs; (iv) viral inactivation of plasma products, (v) creating an awareness among the public of the routes of infection and emphasizing on 'window period' when the screening tests will be negative, but the donor may be in the infectious stage. For avoidance of bacterial contamination, quality check has to be ensured at each step of blood collection, testing and storage to prevent the introduction of bacteria and its growth in the unit. Storage temperatures vary for different components. Red cells are best stored at 2–6°C and plasma products at temperatures below –40°C. Platelets survive better at ambient temperature.

To prevent TTDs, it is imperative that all donor units are screened serologically for markers of infectivity. Third generation assay kits like radioimmunoassay (RIA), enzyme immunoassay (EIA) and reversed passive haemagglutination assay (RPHA) which are of acceptable sensitivity are available for 'hepatitis B, C and HIV. Both RIA and EIA are solid phase sandwich type assays. RPHA uses red cells coated with purified antibody to test for antigen in the serum samples. Its presence will cause red cells to agglutinate. It is not sensitive as the other two and is less specific. EIA has the advantage of minimal requirement for expensive equipments compared to RIA, larger shelf life of reagents and little biohazard. Relative sensitivity of third generation assay is 100–10,000 times more over the previous assays<sup>2</sup>.

Tests employed for syphilis (VDRL and RPR) detect nonspecific anticardiolipin antibodies. Hence biological false positives can be a problem. Though the usefulness of testing for syphilis has been doubted, it is still a mandatory requirement as it is suggested that syphilis testing might screen out donors at risk for other sexually transmitted disease such as HIV. Treponemal spirochetes do not survive if blood is stored for 72 h at 4°C.

There are no practical lab screening tests for malaria. Unless there is a high parasitaemia, it will not be detected on routine peripheral smears. Exclusion of

donors at high risk by careful detailed questioning is the only way by which malaria can be prevented. Potential donors should be educated on the importance of 'window period' for TTDs and advised to exclude themselves from donation if they belong to high risk groups.

### Organization of transfusion services

The goal of transfusion services is to provide effective blood products which are safe and adequate to meet patients' needs. The task of meeting country's needs for blood and products requires cooperation among blood transfusion services, health authorities, media and general public. A transfusion service could be centralized, regionalized or hospital-based. If it is just hospital-based, the needs of the peripheral areas will not be met, leading to inadequacy of services. A large service with wider network is needed to fulfil the requirements. The recruitment and selection of blood donors are critical for the organization of any blood transfusion service. Problems inherent in donor selection are reduced to a large extent if transfusion services are laid on a strong voluntary base and detailed guidelines are set for donor eligibility. Estimates of the need for blood should be based on the number of acute hospital beds or by estimating five per cent of country's population. It has been calculated that 7 donations/year are needed to cover the needs of one acute hospital bed or a yearly average of 40,000–60,000 blood donations/million inhabitants to meet the demand for red blood cells<sup>3</sup>. Essential functions of the service should be donor recruitment, blood collection, testing of donor blood, component preparation, distribution and training and reference services. A model is shown in Figure 2. The basic requirement of any service is maintenance of strict standards and application of quality assurance programme in all its operations.

### Recent advances in transfusion medicine

Clinical practice of blood transfusion has changed considerably over the years as a result of our increased knowledge and development of new technologies. Discovery of citrate and dextrose as important for blood preservation has greatly revolutionized the storage and preservation of blood. Newer formulation of anticoagulants, additives and rejuvenating fluids and cryobiology have enhanced the storage period, thereby improving the viability and survival of stored cells. Blood transfusion therapy has become a highly specialized science with blood components available in concentrated form, allowing the patient to receive only the specific components required. This has been made possible by the advent of refrigerated centrifuge and multiple blood bag system (Figure 3) by which various blood



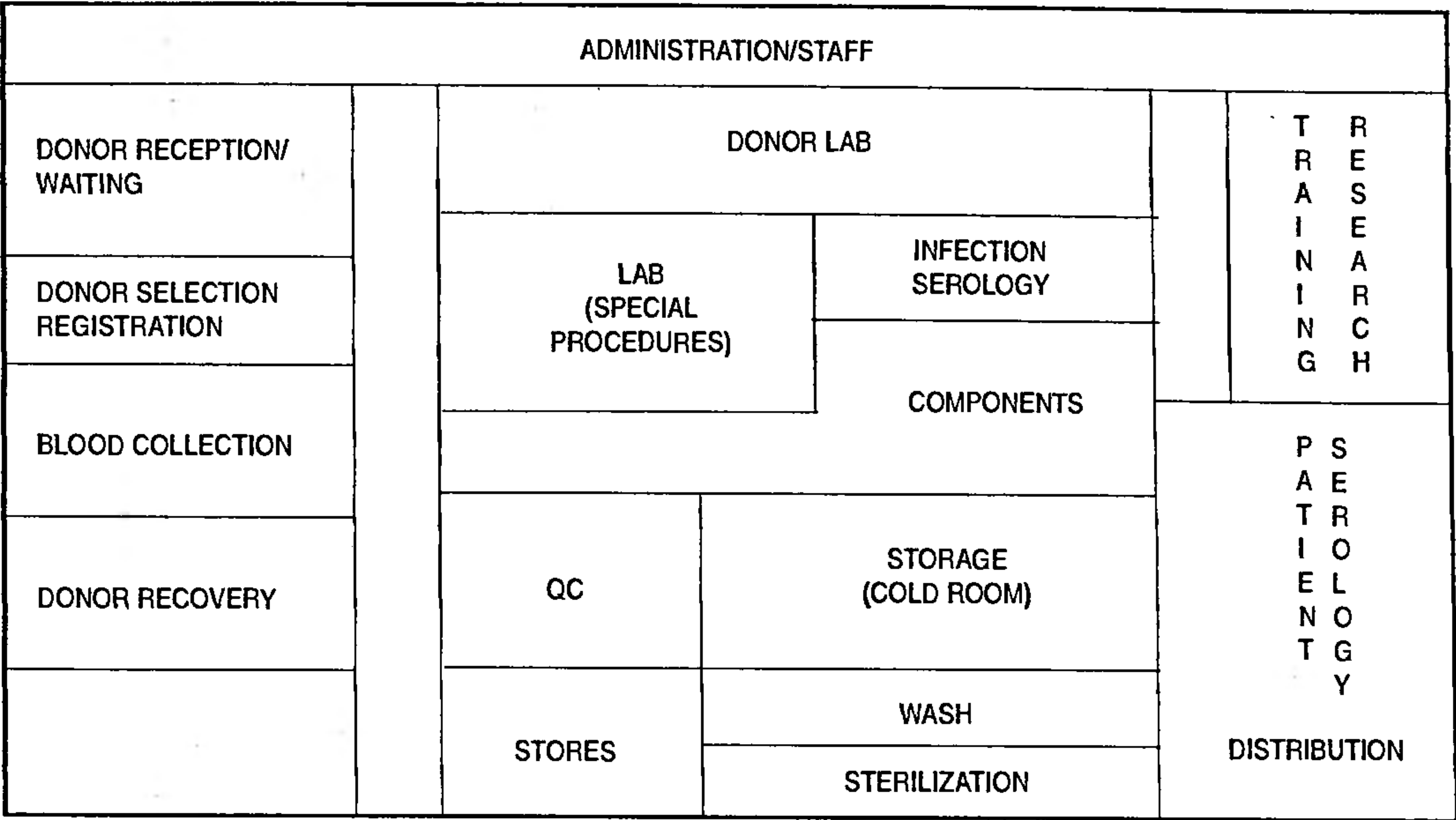


Figure 2. Model outlay – Transfusion services.

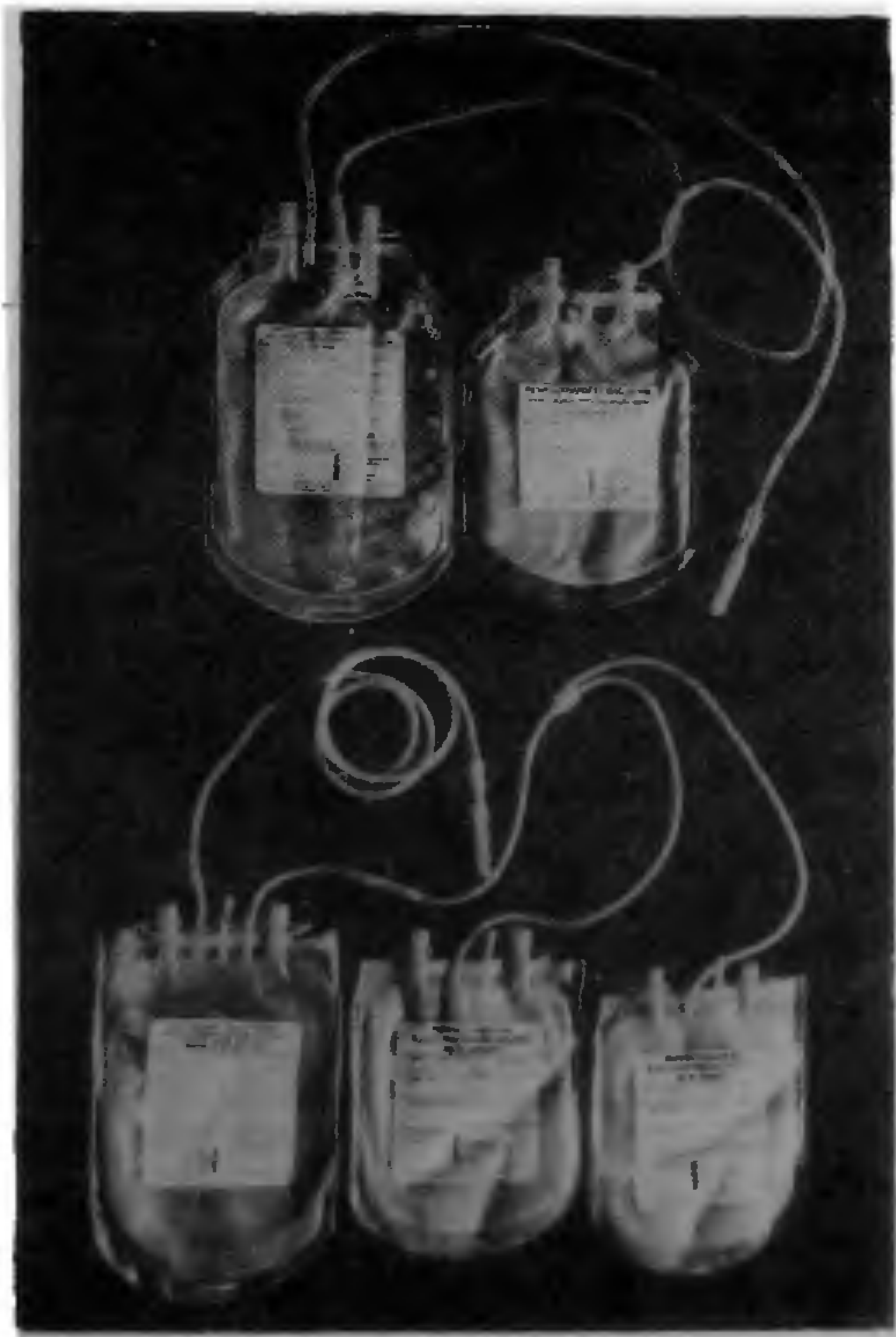


Figure 3. Double and triple blood collection bags.

components can be prepared in a closed system. Multiple donor pools of plasma harvested by apheresis can be processed to yield derivatives such as albumin, factor concentrates and immune serum globulin fractions. Preparation of components permits efficient utilization of whole blood for better patient care. Blood components frequently used in transfusion practice and their indications are given in Figure 4. Cell separators that separate components by centrifugal force have also found application in therapeutic haemapheresis. The advantage of these machines is that only needed component is removed, allowing reinfusion of the rest of the blood back to the patient or donor as the case may be. Another advantage is that pheresis of the desired component can be done at more frequent intervals. It is also possible now to recycle blood which is lost during surgical procedures using 'cell saver'. Use of such salvaged autologous blood will reduce unnecessary donor exposures and prevent alloimmunization.

Antigens of human leucocyte antigen (HLA) system are important in influencing the survival of transplanted organs. Better understanding of transplantation immunology has proved to be of immense value in the treatment of end-stage failure of certain organs. Emergence of techniques for cell survival studies, flow cytometry and polymerase chain reaction have revolutionized the diagnostic field of transfusion medicine.

Marked progress has also been made in the preparation of blood substitutes as an alternative to blood. Current research has focused mainly on the development of

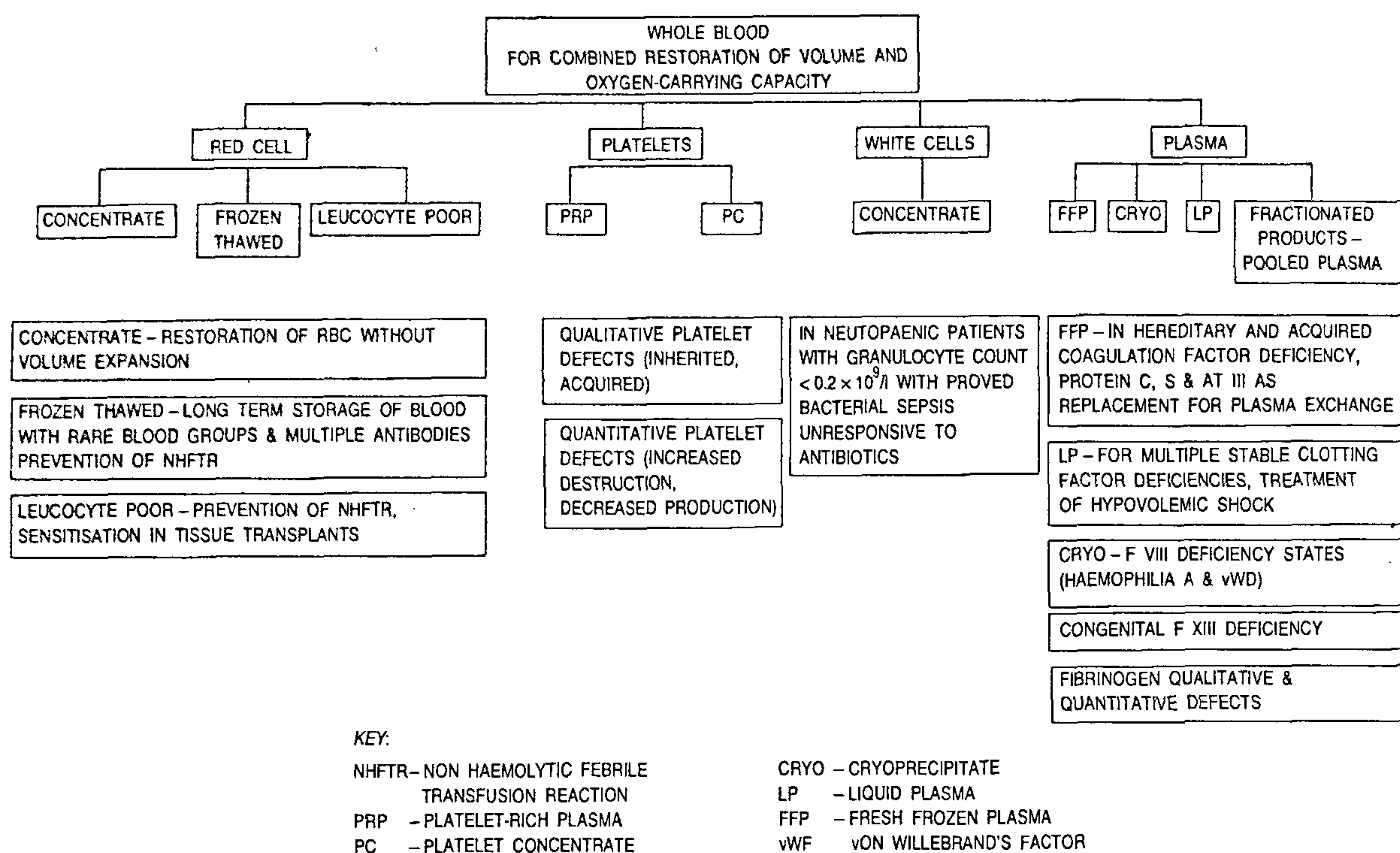


Figure 4. Blood and components - Indications.

oxygen-carrying red cell substitutes. Synthetic oxygen transport fluids based on perfluorochemicals (PFCs) and modified haemoglobins have emerged. PFCs are cyclic or straight chain hydrocarbons in which all the hydrogen atoms are replaced by fluorine atoms. PFCs are stable and chemically inert and have a high solubility for gases. The first commercial PFC emulsion developed and tested in man is Fluosol-DA 20%. Owing to certain limitations of F-DA, second generation PFCs are under development.

Interest in using haemoglobin as a red cell substitute is based on its capacity to bind oxygen chemically and to become fully oxygen saturated. Stroma-free haemoglobin is prepared from outdated human red blood cells by washing and lysing them with distilled water to obtain a solution free of red cell stroma. Problems like short intravascular retention time and high oxygen affinity have led to modifications of hemoglobin molecule by pyridoxylation and polymerization. Liposome-encapsulated hemoglobin with reasonable period of survival in the circulation is also under way<sup>4</sup>. Gene therapy is emerging as a new treatment modality for many inherited diseases. As a result of these developments, blood transfusion, at one time a rare and hazardous procedure to both donor and recipient, has now become a common life-saving practice.

### Cost estimates

In India under ideal conditions we have estimated the cost of one unit of blood to be Rs 490 (Table 4). This can be brought down to Rs 370 provided we fully utilize the existing capacity of the capital equipment. A further cost of Rs 95-125 is incurred for the production of blood components from one unit of whole blood. The variation in estimate reflects the differences in assumptions.

### Indian scene

Blood transfusion service (BTS) in our country is still in its infancy. The need for blood is growing day by day as a result of advancement in clinical medicine. Depending on the facilities and infrastructure of different hospitals, requirement of blood may vary from 9.6 units of blood/bed/annum in general hospitals to 8-15 units of blood in larger hospitals having specialized departments and more than 20 units per annum in super speciality hospitals<sup>5</sup>. In India for a population of 900 million and a bed strength of little over half a million, blood needs met in relation to population per thousand are less than 10 donations per year<sup>6</sup>. As is seen, blood is always in short supply and recruitment of donors is



Table 4. Cost estimates for blood transfusion (in rupees)

	Estimate I	Estimate II
<b>Fixed costs</b>		
Building and space (imputed rent at standard rates)	3000.00	3000.00
Equipment (actual prices brought up to current value by correction with Wholesale Price Index and monthly rates calculated to include depreciation and opportunity cost)	5486.89	4231.24
Overheads and utilities	848.69	723.12
Total salaries per month	72,770.00	72,770.00
<b>Variable costs</b>		
Consumables	51,695.00	51,695.00
Additional cost of equipment for blood components	22,599.69	17,427.84
<b>Average costs</b>		
Average cost of 1 unit of whole blood (at 273.2 units per month)	489.75	484.70
Average cost of 1 unit of whole blood if the facility is working at full capacity (at 360 units/month)	371.67	367.83
Average additional cost of producing blood components from one unit of whole blood*	123.29	95.08

\*From one unit of whole blood, several components can be separated, capable of being transfused into different patients.

never met fully. This state of affairs can be overcome to a large extent by optimization of blood usage by way of blood component therapy. Adoption of novel techniques for recruitment of voluntary blood donors

will motivate people at large to donate blood. Apart from the overall shortage of blood, there is still dependency on professional donors and other problems like inadequate infrastructure and shortage of trained personnel. Most of the blood banks are hospital-based. As there is no organized blood transfusion service, mushrooming of small blood banks is on the rise. It is essential that we have a centralized system of collection, processing, storage and distribution of blood.

There is an increasing concern about quality and safety of available transfusion services in the wake of AIDS. What we require today is to set up a centralized blood transfusion service, with emphasis on safe blood and safe transfusion practices relying on quality and adequacy of services. Creation of such a service would provide scope for cost containment as well.

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## MEETINGS/SYMPOSIA/SEMINARS

### XIIth International Biophysics Congress

Date: 11-16 August 1996  
Place: Amsterdam

Topics include: Macromolecular structure; Nucleic acids; Membranes; Molecular recognition and assembly; Bioenergetics; Cell shape and motility; Sensory and neural biophysics; Advanced experimental approaches; Education and development and Hot topics.

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### XIth Annual International Conference of National Environmental Science Academy

Date: 15-17 March 1996  
Place: Calcutta

Sustainable development and environment is the main theme of the conference. Topics of symposia will be: Conservation and management of lakes; Iodine deficiency in developing countries; Environment and reproduction. Plenary session will cover the topics of Medical science, Natural science, Social science and Geological science.

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