MEETING ON THE UTILIZATION AND SUPPLY OF HUMAN BLOOD AND BLOOD PRODUCTS
(Organized by the World Health Organization and
the League of Red Cross Societies)

Berne, Switzerland, 9-13 December 1975

INTRODUCTION

1. The meeting was held at the Central Laboratory of the Transfusion Service of the Swiss Red Cross, Berne. It was attended by 15 participants, three observers and members of the World Health Organization (WHO) and League of Red Cross Societies (LRCS) Secretariat. Both the International Society of Blood Transfusion and the Council of Europe were represented (see Annex I).

Professor A. Hässig was elected Chairman, Dr A. Kellner and Professor S. Hollan Vice-Chairmen and Dr d'A. Maycock, Dr J. Morris and Dr R. Perrault were appointed Rapporteurs. The draft agenda was adopted (see Annex II).

On behalf of the World Health Organization, Dr F. Lothe explained that the main purpose of the meeting was to discuss how WHO and the League of Red Cross Societies might implement the resolution of the World Health Assembly on the Utilization and Supply of Human Blood and Blood Products (WHA28.72), the operative paragraphs of which reads as follows:

1. THANKS the Director-General for the actions taken to study the problems related to commercial plasmapheresis in developing countries;

2. JURGES Member States

   (a) to promote the development of national blood services based on voluntary non-
       remunerated donation of blood;

   (b) to enact effective legislation governing the operation of blood services and
       to take other actions necessary to protect and promote the health of blood donors
       and of recipients of blood and blood products;

3. REQUESTS the Director-General

   (a) to increase assistance to Member States in the development of national blood
       services based on voluntary donation, when appropriate in collaboration with the
       League of Red Cross Societies;

   (b) to assist in establishing cooperation between countries to secure adequate
       supply of blood and blood products based on voluntary donations;

   (c) to further study the practice of commercial plasmapheresis including the
       health hazards and ethical implications, particularly in developing countries;

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(d) to take steps to develop good manufacturing practices specifically for blood and blood components in order to protect the health of both donors and recipients; and

(e) to report to the World Health Assembly on developments in these matters.

On behalf of the League of Red Cross Societies, Dr Z. S. Hantchef briefly explained the activities of the League of Red Cross Societies in the area of blood transfusion and stressed the similarity of its aims and those of WHO.

2. PRESENT AND FUTURE NEEDS FOR BLOOD AND BLOOD COMPONENTS

It was considered whether a transfusion service, dependent upon voluntary unpaid donors, can provide the means for adequate component therapy and sufficient plasma for the preparation of albumin and coagulation factors, so that plasmapheresis has to be used only to collect plasma with special components (e.g. specific antibodies).

The experience of Switzerland might be used as an example of what could be achieved. In this country, as in other industrial countries, about 50 000 donations per year per one million population are necessary to meet the needs for red cells.

The need for albumin, which is high in Switzerland, is about 28 000 units per one million population, each unit containing 10 g of albumin. If 80% of the donations required to meet the demand for erythrocytes are included in a component programme, 85% of these albumin needs could be covered by the plasma thus obtained.

The need for antihaemophilic globulin, mainly provided as a freeze-dried small pool cryoprecipitate, could comfortably be met from a 80% component programme. If a concentrate of this globulin were to be used more extensively for treatment of haemophiliacs (including home treatment), more plasma would be needed and Factor VIII might then displace albumin as the governing factor for the amount of plasma needed.

It has been shown by pilot trials carried out in Berne and in Baden Württemberg, that the use of this high proportion of red cell concentrates is feasible; even so, such a programme would provide only about 85% of the estimated need for albumin. The deficit could be overcome by the judicious use of plasma substitutes such as gelatin or dextran, preferably the former. At the same time, it would be essential to ensure that albumin is used only when there is a definite medical indication, e.g. to repair a blood volume deficit in specific circumstances, provide transport protein in the presence of severe jaundice in haemolytic disease of newborn, and to treat interstitial pulmonary oedema and certain cases of ileus. Whereas albumin is indicated for the treatment of certain cases of hypoproteinaemia, it should not be used as a nutrient by the intravenous route.

If such a programme is to be developed in another country the national background cannot be ignored, as the availability of trained staff and finance are critical factors.

In Finland, a pilot study is now in progress to determine whether plasmapheresis of voluntary unpaid donors could serve as a supplementary source for meeting the national need for plasma. If the reasons for this procedure are fully explained to them, it seems that they can be recruited without undue difficulty. In the United Kingdom such donors have been obtained without much difficulty but they have been recruited only in small numbers for special purposes, e.g. as donors of specific antibody plasma.

The practice of screening donors to obtain plasma containing certain antibodies has shown that 3% of donors in France have eight international units per millilitre of tetanus antitoxin and that in certain parts of the United Kingdom 5% of donors have five or more units. This might meet the needs for antitetanus immunoglobulins. Screening for other antibodies, e.g. antivaccinia and antivaricella is also being undertaken.
Although placentae were a source of immunoglobulin and albumin, their collection and testing for the presence of hepatitis B antigen presents major problems. As a consequence the use of this source appears to be declining.

After a long discussion, the following principles were agreed upon:

A non-profit blood transfusion service relying upon unpaid blood donors and collecting enough blood to satisfy the need for erythrocytes can provide sufficient plasma for the preparation of albumin, coagulation factors and immunoglobulin. The consistent use of component therapy, a sound logistic organization and the judicious supplementary use of plasma substitutes and electrolyte solutions are essential for this purpose.

The small deficit of plasma needed for preparing albumin and perhaps Factor VIII concentrate that may be encountered in a components programme, and the collection of certain specific antibody plasma (haemaglutinins or antibacterial or antiviral antibodies) are indications for plasmapheresis. Voluntary unpaid donors should be recruited for this.

Specific antibody plasma can be obtained to a significant extent by screening normal blood donations.

The use of human plasma or serum for reference purposes or quality control should whenever possible be replaced by the use of animal sera.

Although generally agreeing with the views expressed above, the observers felt that these ideas, if strictly followed, were not realistic, as voluntary agencies could not provide for the full needs of the world at the present time; whilst irresponsible commercialism is recognized and condemned by the responsible sector of the industry, the world needs the participation of private enterprise because their products are still very much required today. Finally, it was recognized that although it is not feasible to alter the present system from one day to another, it should be nevertheless the aim to change it as soon as possible.

3. PHYSIOLOGY OF REPLACEMENT OF PLASMA CONSTITUENTS AFTER PLASMAPHERESIS

Considerable differences exist in the recommended maximum volumes of plasma that may be collected annually from a donor by plasmapheresis:

<table>
<thead>
<tr>
<th>Location</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>10 l</td>
</tr>
<tr>
<td>Council of Europe, Sub-Committee of Specialists on Blood Problems</td>
<td>15 l</td>
</tr>
<tr>
<td>Food and Drug Administration, USA</td>
<td></td>
</tr>
<tr>
<td>Average adult</td>
<td>50 l</td>
</tr>
<tr>
<td>Above 175 lb</td>
<td>60 l</td>
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</tbody>
</table>

Albumin is the protein removed in the greatest amount during plasmapheresis. Just as whole blood donations are spaced so as to allow recovery of iron reserves, the intervals between plasmapheresis should be long enough to allow albumin synthesis to return to the normal rate well before the next session. More frequent plasmapheresis will impose an unwarranted burden on the body due to prolonged periods of raised albumin synthesis.

There is evidence to suggest that in a healthy subject, from whom 300 ml of plasma are removed, an interval of one to two weeks between two consecutive plasmaphereses is necessary to allow the liver to synthesize enough albumin to replace that removed as well as that catabolized in the normal way. This timetable would permit the safe collection of about 13-15 l of plasma per year. Re-examination of published data on concentrations of plasma protein after various plasmapheresis programmes reveals significantly depressed plasma protein concentrations. Thus, at the present stage of knowledge, not more than 13-15 l of plasma should be removed annually from healthy donors and the removal of plasma from undernourished or otherwise unhealthy donors should be discontinued. More details on this subject are presented in Annex III in a report on "Volume Limitations of Plasmapheresis".
Although albumin is the substance removed in greatest quantity, there may be others which are of greater importance.

There is a need for a more sensitive test for overall plasma protein depletion as the total plasma protein concentration may be within normal limits in the presence of a protein deficit in the extravascular space.

The observers pointed out that as the Food and Drug Administration, United States of America, permits the taking of 50-60 l per year, this would still have to be considered a safe limit in that country. They noted also that the lowering of the limit to 15 l per year would make it much more difficult to practice commercial plasmapheresis. However, this limit could well be followed by non-commercial plasmapheresis.

4. HEALTH HAZARDS OF PLASMAPHERESIS

Plasmapheresis appears to be relatively safe if carried out in accordance with adequate regulations but there is a scarcity of data, particularly regarding long-term follow-up.

No consistent clinical abnormalities have been detected during periods of up to six years in donors who have undergone adequately controlled plasmapheresis, but possible effects on lipid transport and deposition, decreased resistance to infections through frequent removal of immunoglobulins and even changes in immune response towards oncogenic viruses cannot be ruled out on the existing evidence. Disorders might arise out of too frequent plasmapheresis, active immunization and frequent restimulation of the donors, genetic or environmental conditions or other as yet unknown factors. Both retrospective and prospective studies are required, but almost no clinical, statistical or epidemiologic methodology currently exists for performing satisfactory long-term studies of this type. Retrospective studies might indicate the areas to which prospective studies should be directed, but a very large and lengthy investigation would be required.

Animal experiments would be of only limited value and do not offer useful models of disease conditions. No attempt should be made to draw final conclusions from a simple retrospective study and therefore a long-term prospective investigation should be undertaken.

Regarding dangers to recipients of plasma derivatives, the discussion was confined to the transmission of infectious disease, particularly hepatitis. Albumin and immunoglobulin appear to be safe in this respect, although on rare occasions a faulty manufacturing technique has resulted in transmission of hepatitis and the detection of hepatitis B antigen in the respective preparations.

The main risk of transmitting hepatitis appears to be associated with the coagulation factor concentrates and its degree depends on the source of plasma, particularly whether the donors were paid or unpaid. The recently reported outbreak of hepatitis in the United Kingdom associated with intravenous injection of Factor VIII concentrate was cited as an example.1

5. BLOOD TRANSFUSION AND PLASMAPHERESIS IN DEVELOPING COUNTRIES

The general situation of blood transfusion and plasmapheresis in developing areas of the world was reviewed.

Blood transfusion services in Latin America have mainly been developed and are run by individual hospitals, private persons, communities and local Red Cross organizations rather than by the national health authorities. Frequently blood is obtained from relatives of the patients and often from paid donors, but the number of voluntary unpaid donors is increasing due to the efforts of National Red Cross Societies and Latin American Associations of Voluntary Donors. Large national blood programmes are only now being developed as an increasing number

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1 Craske, J., Dilling, N. & Stern, D. Lancet (1975) 2, 221.
of nations recognize the need for controlled technical standards, for centralized administration and organization and for laws regulating the utilization and supply of blood and blood products. Component therapy is used in some of the larger centres but fractionation of the plasma is only done in three countries. Commercial plasmapheresis is still performed but the tendency has been for governments to stop such activities except where fractionation plants exist.

In the Maghreb countries, the blood transfusion services are restricted to providing whole blood and no plasmapheresis or fractionation is practised. The services are under the control of the health authorities and exist either as national blood transfusion services or as independent blood transfusion services for individual hospitals. The blood donors are unpaid and their recruitment is difficult for social, religious and cultural reasons. The National Red Crescent Societies assist in the recruitment of donors. Most frequently, blood donors are relatives of the patients.

Anti-A, Anti-B and Anti-A-B blood group sera are produced, but in insufficient amounts for the needs, and anti-D is only produced in one centre from women immunized through pregnancy.

The transfusion services in the Asian Pacific area are well developed in Japan, Australia, New Zealand and Singapore. Japan has converted to voluntary donations since 1966. Provision of whole blood is now entirely voluntary, whereas the production of plasma fractions is still in commercial hands. Australia has one government-operated fractionation plant.

The requirements of the Pacific Islands are small and simple, and are based on individual hospitals in larger towns. They will not grow quickly.

In other Asian countries there is a wide variation in the standard of services but most need help, particularly in the recruitment of donors, training of staff and provision of equipment. Some services have limited funds and therefore function only intermittently and without good supervision.

The Australian Red Cross runs regular group training courses under the Colombo Plan for blood bank physicians and technologists and gives individual training on request. An important problem is the fact that the courses are restricted to people speaking English. People with only a knowledge of a local language have an additional difficulty regarding access to scientific literature. A further problem is that professional workers in many countries have private practices in addition to their work in blood banks and so are reluctant to leave home for training as this results in loss of income.

Blood transfusion in the Pacific is now entering a stage of rapid development and will need a considerable and growing amount of help and support over the next decade.

After this review there was a general agreement that:

1. National health authorities should have the responsibility of blood transfusion services in all countries; such services should be completely independent of any control by commercial interest. The participation of national societies which are members of the League of Red Cross Societies should be encouraged; their role and activities should be determined in consultation with national health authorities. Blood donation would be a suitable priority field for their contribution, starting with donor recruitment.

2. Although in certain parts of the world it may still be necessary to enlist the cooperation of commercial firms to produce plasma fractions, priority should be given to establishing fractionation plants as part of national transfusion services or on an intercountry basis. In either case they could carry out fractionation for several countries. The establishment of such a plant in a national service acts as an incentive to improve the service because it has control of its plasma and is able to prepare those fractions that are needed.
3. The particular attention of governments should be drawn to the importance of transfusion services. This might be done through the inclusion of this subject on the agenda of WHO regional meetings.

4. It is a moral obligation of the most advanced countries to help others in the field of blood transfusion and thus enable them to resist incentives offered by commercial firms in return for permission to set up plasmapheresis centres and use paid donors.

The optimum form of aid has to be adjusted to individual countries. The general technical training is still the greatest need, but assistance might also be required in the organization of donor panels, management of blood transfusion services and provision of certain equipment and reagents. Prolonged support, even up to 10 years or more, might be necessary to ensure a firmly established blood transfusion service.

Finally, there was general agreement that bilateral or multilateral aid be given to assist countries when needed in the establishment or further development of national transfusion services; the decision concerning the form in which the aid is delivered (bilateral or multilateral) is left to the donor nation and the technical coordination might be provided by WHO in close cooperation with the League of Red Cross Societies. An outline of a suitable programme is presented in Annex IV.

6. LEGAL AND ETHICAL PROBLEMS

The therapeutic use of human blood and its derivatives has become of enormous importance in medicine during the last few years and has given rise to considerable commercial involvement in the collection of human blood and plasma as well as in the production of their derivatives.

This situation, created by the commercialization of human blood, raises ethical and legal problems, besides the health aspects, and has already been discussed by the World Health Assembly and the League of Red Cross Societies.

Rules and legislation are urgently needed in most countries to govern the whole field of utilization and supply of human blood and blood derivatives, and should include good manufacturing practices as strongly recommended by the Twenty-eighth World Health Assembly. Importation and exportation of human blood and its derivatives should be carefully considered in any legislation. WHO has prepared a draft report on Good Manufacturing Practices and this document is now being circulated to experts for their views and comments. It is expected at a later stage that it will be distributed to health authorities to assist them in the preparation of their national legislation.

The collection of blood and the preparation of its components and derivatives should be under the control of medically-directed establishments, on a non-profit basis. The voluntary non-remunerated donation of plasma as well as blood was considered to be the only acceptable basis for a sound development in this field.

7. INTERNATIONAL COOPERATION BETWEEN NATIONAL NON-PROFIT BLOOD TRANSFUSION SERVICES FOR THE EXCHANGE OF BLOOD AND BLOOD PRODUCTS

The basis of international exchange of blood and blood products is the avoidance of wastage and therefore any surplus components or derivatives should be sent to where they are needed. An example of this was given where surplus red blood cell concentrates were sent from one country to another; however, such a transfer requires good organization and the risk of transmitting disease should be considered. Countries should aim at self-sufficiency and should avoid bleeding more than the required amount for their own needs. Their own plasma could be processed abroad when necessary and their derivatives returned.

The movement of blood and blood products across national boundaries would naturally be subject to the approval of health authorities.
9. ROLE OF THE WORLD HEALTH ORGANIZATION AND THE LEAGUE OF RED CROSS SOCIETIES IN THE FIELD OF BLOOD TRANSFUSION

The level of assistance to Member States in the field of blood transfusion depends on the availability of funds and therefore it was suggested that WHO should look for extra-budgetary funds to support the development of such activities. This also applies to the League of Red Cross Societies.

Although standard techniques and practices should be established on a global basis, plans must be drawn separately for each national programme as there are considerable differences in the socioeconomic development of Member States. Therefore, some activities might be established on a regional or intercountry basis, such as the facilities for fractionation and training of personnel. For this purpose regional meetings are strongly recommended.

New transfusion services need to go through various stages of development. A basic whole blood programme must operate before component therapy is introduced.

Plasmapheresis should be restricted to those countries where substantial amounts of component therapy are used.

In brief, the main role of WHO and the League of Red Cross Societies in the field of blood transfusion is to promote the development of national services and coordinate activities carried out on an international basis. Within the limits of their budget they should also provide advice and technical assistance to Member countries.

9. FINAL RECOMMENDATIONS

The participants unanimously adopted the following recommendations:

**Recommendation 1**

A non-profit national blood transfusion service should rely upon voluntary unpaid donors and relate its activities to the country's need, particularly for erythrocytes. In so doing it could provide most if not all of the plasma needed to prepare albumin, coagulation factors and immunoglobulins. The use of component therapy consistent with the stage of development of the health services in the country, a sound logistic organization and the judicious supplementary use of plasma substitutes and electrolyte solutions are essential.

Plasmapheresis should only be a part of a national blood transfusion programme and used to cover any deficit of plasma needed for the preparation of clinically useful derivatives. As in the case of whole blood donation, only voluntary unpaid donors should be recruited for plasmapheresis.

Routine screening of blood for the procurement of specific antibodies should be employed to the greatest feasible extent to minimize the need for active immunization of donors.

The use of animal plasma and artificial substrates should be encouraged whenever possible for the preparation of reference materials and quality control and other diagnostic reagents.

**Recommendation 2**

Because the plasma protein which is most slowly regenerated after plasma withdrawal appears to be albumin, the interval between plasmapheresis should be long enough to allow the total body content of albumin to return to normal well before the next donation. The donation of plasma by a healthy individual should therefore not exceed 600 ml on each occasion with a maximum of 15 l per annum. The interval between two consecutive plasmaphereses should in general not be less than two weeks.
Recommendation 3

As the long-term effects of repeated plasmapheresis and hyperimmunization on the health of the donor are not well known, both retrospective and prospective controlled studies should be undertaken to identify and evaluate the health hazards that may be inherent in these procedures, and to serve as a basis for future regulations and operating practices.

Plasmapheresis should not be performed if there is any reason to suspect that latent disease or malnutrition might be present.

Recommendation 4

International aid programmes should be established to assist countries to set up or improve national blood transfusion services; this aid might be given through WHO in collaboration with the League of Red Cross Societies or at least coordinated by these organizations. Suitable guidelines concerning such assistance are contained in Annex IV.

Recommendation 5

National blood services which have a surplus of blood, blood components or derivatives should be encouraged to offer them on a non-profit basis to other national non-profit voluntary blood services in need of them with due recognition of the possible hazards which may be involved.

Recommendation 6

National health authorities should have the responsibility of blood transfusion services in all countries. The participation of national societies which are members of the League of Red Cross Societies should be encouraged; their role and activities should be determined in consultation with national health authorities.

Recommendation 7

Effective legislation should be enacted in all countries regulating blood donation (including the collection of plasma by plasmapheresis), processing, distribution, export and import of blood and blood products. Such legislation should take into account the medical and ethical problems involved, and protect donors and recipients against commercial exploitation.
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Annex I

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ANNEX II

AGENDA

1. Introduction
2. Present and future needs for blood and blood components
3. Physiology of replacement of plasma constituents after plasmapheresis
4. Health hazards of plasmapheresis
5. Blood transfusion and plasmapheresis in developing countries
6. Legal and ethical problems
7. International cooperation between national, non-profit blood transfusion services for the exchange of blood and blood products
8. Future role of the World Health Organization and the League of Red Cross Societies in the field of blood transfusion
9. Final recommendations
VOLUME LIMITATIONS OF PLASMAPHERESIS

by

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In recent years, the increasingly widespread practice of plasmapheresis has posed a number of problems, conspicuous among which is that of the maximum permissible yearly "harvest" of plasma from one individual. Regulations have been issued in France and in the United States of America, whereas the Council of Europe has formulated recommendations.

The French "Arrêté du 27 janvier 1967 relatif aux conditions des prélèvements de sang" declared a yearly plasma volume of 10 l per individual to be the acceptable limit. The volume of plasmapheresis was furthermore restricted to 300 ml per week and 2000 ml per month.

Also in 1967, the Sub-Committee of Specialists on Blood Problems of the Council of Europe laid down the following recommendations:25

(1) not more than 2 x 250-300 ml of plasma should be withdrawn in one session;
(2) not more than 1000 ml of plasma should be taken from the donor within one seven-day period;
(3) not more than eight single units of plasma (each of approximately 300 ml) should be removed in one month, and not more than 50 single units should be removed in one year.

According to those figures, the maximum permissible yearly volume of plasma harvested per individual would be 50 x 250 to 300 ml = 12.5-15 l.

From the rather detailed United States regulations published in the Federal Register, Vol. 38, No. 139, 20 July 1973, para. 273.3105, it can be calculated that the maximum yearly volume considered to be acceptable in that country is 50 x 2000 ml of whole blood = 100 l, or 50 l of plasma. In a donor weighing more than 175 lb, the analogous figure is 60 l of plasma.

Altogether, then, we have European stipulations in the range of 10-15 l versus the American specification of 50-60 l per year. To answer the question which of these two widely diverging precepts is appropriate, we shall consider the effects of plasmapheresis on serum protein levels and their relationship to albumin metabolism, the accepted safeguards for the donation of whole blood, and the disease known as the nephrotic syndrome.

An average-sized human being with a blood volume of 5000 ml and a hematocrit of 40% has a plasma volume of 3000 ml and - with a normal serum albumin concentration of 4.0-4.5 g % - 30 x 4.0-4.5 = 120-135 g of circulating or intravascular albumin. This quantity is equivalent to 40% of the total albumin stores, the rest being extravascular.12,18,19 The normal, steady state is maintained by the balance between the fractional synthetic rate FSR and the fractional catabolic rate FCR, each of which amount to 10% of the circulating albumin mass per day, or, in our example, 12.0-13.5 g.

Five hundred millilitres of plasma contain 5 x 4.0-4.5 g = 20.0-22.5 g of albumin. A single loss of circulating albumin of this magnitude in a young and vigorous volunteer is, in the first instance, easily replaced within 24 h by the net influx of albumin from the extravascular space, to which the deficit is shifted and thus becomes invisible. The normal state must subsequently be restored by an increase of the hepatic synthesis of albumin. A young and vigorous volunteer having suffered such a single albumin loss can accelerate
synthesis so as to produce a 5% lead of the fractional synthetic over the fractional catabolic rate.\textsuperscript{23} In our example, a surplus amount of 6.0-6.75 g of albumin would then be produced per day and the deficit of 20.0-22.5 g would be replaced after 20:6 or 22.5:6.75, i.e. after 3.33 days.

This response of albumin synthesis may appear to be modest. However, in adequately nourished man as well as in experimental animals subjected to the intense (oncotic) stimulus of induced nephrosis, an increase beyond twice the normal average is exceptional and albumin synthesis has never been found to exceed three times the normal level.\textsuperscript{2,7,9,10,13,14,20,27} Therefore, the 5% lead of the FSR over the FCR is actually equivalent to half of the attainable increment. If it were maintained in the face of repeated albumin losses, 500 ml of plasma could in fact - though at the price of a continuing and definitely non-physiological acceleration of albumin synthesis - be harvested twice weekly (i.e. about 50 l per year), without any permanent encroachment upon the total body stores of albumin.

However, there is ample evidence that this is not so even in healthy plasmapheresis donors. During the first stage of albumin depletion, the primary loss of intravascular albumin is balanced by a net transfer of protein from the extravascular space, which is thus depleted in the face of an apparently normal status.\textsuperscript{6} This first stage of albumin depletion might have been present in the donors examined by Shanbrom et al.,\textsuperscript{22} who found no change of the serum protein levels. Be that as it may, the second stage or a manifest intravascular albumin depletion, which occurs when the extravesacular reserves have been exhausted,\textsuperscript{6} has been recorded by the majority of authors as a sequel of intensive plasmapheresis.

Salvaggio and co-workers\textsuperscript{21} harvested 2 x 800 ml of plasma per week for periods of more than two years from healthy, volunteer prison inmates and found a significant (p < 0.01) and chronic depression of the serum albumin level by 0.5-0.6 g %. Cohen & Oberman\textsuperscript{3} removed 2 x 500 ml of plasma per week in a small group programme predominantly involving medical or paramedical house staff members. The total serum protein (TSP) level decreased by 0.5-1.5 g % within one to three months of beginning plasmapheresis in 85% of these donors, and the phenomenon recurred in 70% upon resumption of the programme after a rest period of one to three months. The albumin fraction in percentage was reported to be unchanged, but as the TSP went down, the absolute albumin levels must also have been lowered. In a more recent study published by the same group,\textsuperscript{4} the immunoglobulins were found to decline significantly, but data on the absolute albumin levels were omitted.

Kliman et al.\textsuperscript{11} investigated the sequels of weekly plasma losses in the whole range between 0.5 and 5.0 l per week in healthy blood donors. Their comment that - except for the highest rate of loss - "no obvious effects on the serum protein levels were seen" is refuted by a statistical analysis (by student's t-test) of the paired original data presented in their Table 3, which is summarized below:

<table>
<thead>
<tr>
<th>Plasma loss, l/week</th>
<th>N</th>
<th>Δ TSP, g %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-0.7</td>
<td>7</td>
<td>-0.66 ± 0.39</td>
<td>&lt;0.001</td>
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<tr>
<td>1.0</td>
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<td>-0.71 ± 0.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>4</td>
<td>-0.83 ± 0.57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3.0</td>
<td>3</td>
<td>-2.80 ± 0.10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The inescapable conclusion is that even with weekly plasmapheresis harvests in the order of 0.5-0.7 l, these presumably healthy donors failed to maintain their pre-existing serum protein levels, i.e. they showed the signs of a "second stage" depletion. What can we deduce from these data on the long-term response of albumin synthesis to plasmapheresis?

Table 1 summarizes the relationship between the lead of the fractional synthetic rate FSR over the fractional catabolic rate FCR as a percentage of the circulating albumin mass, the surplus quantity of albumin produced per day, and the number of days required to compensate.
for the loss of albumin contained in 500 ml of normal plasma. The calculation is performed for a pre-existing serum albumin level of 4.0-4.5 g%, with a resulting loss of 20.0-22.5 g and the production figures given in the Table, the time intervals being independent of these variations.

**TABLE 1**

<table>
<thead>
<tr>
<th>Δ FSR - FCR % of circ. albumin</th>
<th>Daily surplus production of albumin, g</th>
<th>Days required to produce 20.0-22.5 g (±500 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5^2</td>
<td>6.00-6.75</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>4.80-5.40</td>
<td>4.2</td>
</tr>
<tr>
<td>3</td>
<td>3.60-4.05</td>
<td>5.6</td>
</tr>
<tr>
<td>2.5</td>
<td>3.00-3.38</td>
<td>5.7</td>
</tr>
<tr>
<td>2</td>
<td>2.40-2.70</td>
<td>8.3</td>
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<tr>
<td>1.25</td>
<td>1.50-1.69</td>
<td>13.3</td>
</tr>
<tr>
<td>1</td>
<td>1.20-1.35</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Δ Response found by Skillman et al.\(^{23}\) after a single loss of 500 ml of plasma in healthy, young volunteers.

First, it is clear from the published reports as well as from the figures in Table 1 that the 5% difference FSR-FCR observed after a single 500 ml plasma loss in healthy volunteers\(^{23}\) is not maintained during prolonged plasmapheresis. Second, the fact that the serum protein level declined even with weekly "harvests" in the order of 0.5-0.7 l of plasma\(^{11}\) shows that the long-term response of albumin synthesis in these donors did at any rate not exceed a 2-2.5% difference FSR-FCR, since such a difference would have replenished the albumin stores within one week - and they were not. This means that even in healthy donors, the long-term synthetic response cannot be relied upon to exceed half of that observed after a single albumin loss.

It is, moreover, an established fact that a large proportion of plasmapheresis donors belongs to underprivileged populations or population groups. There are three essential prerequisites for an adequate synthetic response to an albumin loss:\(^8\) first, a sufficient increase of the protein intake over and above the normal daily needs. Second, an intact digestive apparatus ensuring a normal breakdown and absorption of the surplus protein intake. Third, an intact liver function capable of utilizing the absorbed surplus of amino acids for a sufficient increase of albumin synthesis over the normal level. Beyond any doubt, considerable numbers of underprivileged donors are incapable of fulfilling all of these prerequisites simultaneously. They will, therefore, be even less able than their healthy counterparts to maintain an adequate response during repeated, long-term plasmapheresis.

The assumption that the underprivileged donor may only be capable of reacting with a minimum FSR-FCR difference in the order of 1% is therefore not unreasonable, since it equals a synthetic achievement of roughly half of that actually attained by the healthy donor participating in a long-term plasmapheresis programme. With such a difference, two weeks are required to compensate for the quantity of albumin lost with 500 ml of plasma, and we arrive at the conclusion that a maximum yearly volume within the 10-15 l range of the published European specifications\(^1,25\) is the appropriate one.

To answer the conceivable objection that this deduction is unreasonably cautious, we may examine the accepted temporal safeguards for the donation of whole blood. Although the pre-donation haemoglobin level is normally restored after about one month,\(^{15,26}\) it is known that a longer interval is required for the iron stores of the donor to be replenished prior to the
next donation. For this reason, the minimum interval between two conventional blood donations has been variously defined to be between two and six months. If we regard a four-month interval as reflecting a sound, middle-of-the-road policy, we end up with the same safety factor as that deduced for the plasmapheresis donor: the 5% difference between the FSR and the FCR observed after a single plasma loss in a perfectly healthy volunteer is four times greater than the response assumed for a long-term plasmapheresis donor whose ability to accelerate the synthesis of albumin may be open to doubt.

Finally, it may not be irrelevant to compare the plasma protein losses inflicted upon plasmapheresis donors with those occurring in the disease known as the nephrotic syndrome. An accepted classification based upon the renal loss of protein per 24 hours labels proteinuria as "slight" with <0.5 g, "moderate" with 0.5-4.0 g, and "severe" with >4.0 g/24 hours. The lower limit for the development of ascites is 10 g/24 hours. The weekly harvest of 2 x 500 ml of plasma, as now tolerated by American regulations, equals an albumin loss of 40-45 g per week, or a daily drain of 5.7-6.4 g. It thus puts the plasmapheresis donor squarely into the category of a nephrotic patient with severe proteinuria.

The time-honoured medical principle of "primum nil nocere" is nowhere more compelling than in the case of living persons who consent to their bodily integrity being violated for the benefit of others. In their situation, adequate safeguards must be provided not only against the generation of manifest illness by such violation, but also against any prolonged deviation from the normal state of their body. Faced as they are with greater health hazards than the more fortunate members of society, the underprivileged have a special claim to protection.

A transient haemoglobin deficit following a donation of whole blood is now considered acceptable, but no one would seriously advocate bleeding at a pace maintaining that state. There is no reason why plasmapheresis donors should be treated by different standards, nor why they should be made to suffer plasma protein losses equaling those of severe nephrotic disease. The conclusion must therefore be that they should not deliver more than 10-15 l of plasma per year, as now recommended by European authorities. Not more than 500 ml should be withdrawn per session, and the interval between two such sessions should not be less than two weeks.
REFERENCES

1. Arrete du 27 janvier 1967 relatif aux conditions des prélèvements de sang. Journal officiel de la République française, 11.2.67


Annex III


DEVELOPMENT OF A NATIONAL BLOOD TRANSFUSION SERVICE IN A DEVELOPING COUNTRY AND THE ORGANIZATION OF A TRAINING COURSE IN THAT FIELD

GENERAL PROPOSALS FOR A PROJECT

by

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Objectives of the project

It is the intention in the first year of this project to assist the development or improvement of a national blood transfusion service based on voluntary unpaid donations of blood. Following upon such an improvement of the service, it is intended in the second year to run a training course to improve the knowledge of senior staff of countries in the area in the organization, administration and operation of a blood transfusion service. It is visualized that this project will form part of a future WHO programme in the development of blood transfusion services.

Action proposed

In order to achieve these objectives, assistance will be needed to improve the work already being done and to introduce new methodologies where needed. Provision of a moderate amount of equipment and reagents will be necessary and it is possible that certain internal modifications in the blood transfusion centre may be required.

The target country of this project would have to be decided through consultations between the donor country, WHO, the League of Red Cross Societies and prospective recipient countries.

Personnel

One consultant, who will make a preliminary visit of two weeks, will later be required for approximately two months to help staff of the selected blood transfusion service to improve the performance in basic aspects of their work. Such assistance would include the handling and storage of blood, grouping and cross-matching, preparation of giving and taking sets, anticoagulant solutions, grouping sera and other reagents, cleaning and sterilization of bottles, recruitment of donors and organization of bleeding sessions, as well as all administrative matters involved.

In order to help with the implementation of the recommendations of the consultant, a medical or technical officer experienced in the field of blood transfusion would be needed for a longer period, for example, six to 12 months. It is envisaged that the consultant and medical or technical officer will be supplied by the donor nation whenever possible.

Equipment and reagents

It is expected that some equipment will already be available. However, there may be inadequate facilities for refrigeration, centrifugation and deionization and distillation of water that would have to be supplemented, as well as minor equipment such as bottles, tubes,

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1 This consultant who will be accompanied by a WHO staff member will make the final selection of the country for this assistance as well as assess the local needs during these two weeks.
Annex IV

needles and syringes. The reagents that might be needed would include blood grouping sera, bovine albumin and antihuman globulin. It is likely that certain internal structural alterations will have to be made in the premises of the blood transfusion service such as the provision of extra benches, electric points, taps and wash basins in view of the extra work load and to improve the facilities for training.

Training course

In the second year of the project, it is proposed to run in the improved blood transfusion centre, a six-week training course in basic essentials for the organization and operation of a blood transfusion service for 15 participants from countries with a similar social and environmental background. One consultant for two months and one for one month would be needed as well as extra equipment and reagents, allowances and travel costs for the participants and allowances for national teaching staff.