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INCREASED PROVISION OF FRESH FROZEN PLASMA FOR FACTOR VIII:
Improvement in Design of the Fenwall Blood Pack System

SUMMARY

NBTS production of factor VIII has remained stationary at 12.5 M i.u. per annum for 24 months. Reasons are lack of a general programme co-ordinating RTCs and the BPL Elstree and the lack of financial support.

Improvement in factor VIII yield from fresh frozen plasma (FFP) forms an important part of the programme to increase output and this has implications for the quality of the FFP and therefore the method of collection.

FFP utilization from existing total donations is too low (19%) and should approach 50-55% of available plasma. A more flexible approach to blood collection at RTCs would generate a significant amount of the factor VIII at present used from the current blood supply (1.9 million donations p.a.)

Problems of plasma collection, separation and hepatitis testing at RTCs should be solved by economic streamlining of the process. More general use of multiple 'closed-system' blood collection packs, abolition of 5-litre plasma pooling and introduction of an inexpensive NBTS radio-immunoassay for HB_sAg testing should enable RTCs to produce more fresh plasma in single frozen donations to BPL.

The new proposals for plasma supply would give the best available safeguards for the safety and quality of the plasma and substantially facilitate processing and yield of factor VIII.

Removing the problems from 14 RTCs and solving them centrally at BPL provides an economic basis for future planning.

Changes in the configuration of the blood pack collection system currently in general use will facilitate handling during the stage of pack opening at BPL. Discussions have therefore started with the manufacturers to consider a 'closed' plasma container better suited to receive fresh plasma and capable of rapid freezing and opening in its frozen form. Details of these proposals are awaited.

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INCREASED PROVISION OF FRESH FROZEN PLASMA FOR FACTOR VIII:
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The following commentary on the problems of blood and plasma collection in the NBTS is a review of discussions held recently during a tour of N. America. Places visited included:

(1) Travenol Laboratories Plastics Division, Deerfield, Illinois
(2) Hyland Fractionation Plant, Glendale CA
(3) AABB meeting.

Problems of plasma collection:

(1) The past 20 years practice in the NBTS has been concerned mainly with the handling of whole blood, platelets and cryoprecipitate. However, the next decade at least will be spent dealing with the problems of self-sufficiency in protein components fractionated from fresh plasma: factor VIII, factor IX and albumin. In this respect, the philosophy of the Service must change in that, when collecting plasma and fractionating factor VIII and albumin, the NBTS becomes directly comparable with the cost-effectiveness of the commercial sector. The NBTS therefore needs a central policy, forward planning and an investment programme in order to achieve its long-term aims.

(2) DHSS supports the notion of self-sufficiency in blood products for the NHS, but the means to obtain self-sufficiency are not properly financially supported or coordinated between the regional blood collection centres and the fractionation centre at Elstree.

The facts speak for themselves:

(i) In spite of the Ministerial initiatives (some four years ago), the gap between NBTS supply of factor VIII and clinical demand is greater now than at the start. Recently-produced figures from the Haemophilia Centres show total usage of factor VIII as 34 million i.u. (1976); 48.4 million i.u. (1977); and an increasing rate of use in 1978. Input of commercial and NHS factor VIII concentrates kept parallel rates until the beginning of 1977 when NHS production levelled off because of a plateau in fresh frozen plasma collection in the regions. Thus in 1977 and 1978 commercial factor VIII purchase increased significantly - approximately £1.2 million (1977); £1.9 million (1978) projected. The present rate of expanded use of factor VIII is caused by progressive placement of haemophiliacs on home-treatment with commercial factor VIII

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concentrates; in the absence of a further increase in NHS factor VIII production, purchase of this material over the next five years can be estimated to cost £14.5 million (1978-1982 inclusive) viz. £1.9 M, 1978; £2.5 M, 1979; £3.0 M, 1980; £3.4 M, 1981; £3.7 M, 1982. This estimate is conservative as it allows only for a doubling in the requirement for commercial factor VIII in five years.

(ii) The Trends Working Party estimated use of factor VIII to rise to 50 M i.u. per annum over the decade 1977 - 1987 and this was subsequently revised to 60 M i.u. by the Standing Medical Advisory Committee. It is clear from the previous paragraph, that the approved S.M.A.C. estimate has probably been exceeded already in 1978.

(iii) Albumin requirement in NHS has not been properly estimated, although at present demand acutely exceeds supply. The Trends Working Party figures of 100 - 200 g albumin per 1000 population were influenced by the Council of Europe report on 'The Indication for the Use of Albumin, Plasma Protein Solutions and Plasma Substitutes'. Advent of albumin replacement in therapeutic plasmapheresis significantly alters the requirement from NBTS and this particular aspect of use was not dealt with in the Council of Europe document. There is a considerable potential to increase albumin production through the NBTS fractionation laboratory at Elstree which hopefully will be exploited. In the NBTS, source material for albumin fractionation is not a limiting factor.

This document deals with the need for efficient blood and plasma collection; the move to change the blood pack collection system is only one part of a set of proposals aimed at more flexible working of the existing 1.9 M blood donations obtained annually in the NBTS.

To illustrate these proposals, examples are given of calculations which are based on provision of 60 M i.u. of factor VIII as NHS concentrate.

Present performance is as follows:

i. Of 1.9 M donations, approximately 360,000 (19%) are converted to FFP for factor VIII concentrate production. This provides 65,000 L plasma, processed at approximately 1,200 L per week, resulting in 12 M i.u. factor VIII concentrate per annum.

ii. Of 1.9 M donations, approximately 1.0 M (53%) are converted to source material for albumin. This includes plasma already used for factor VIII preparation. Approximately 180,000 L plasma yields 26 g/L albumin i.e. 4680 kg equivalent to 95 g/1000 population. (At present only half this potential is utilized, approximately 50,000 bottles PPF are not realised

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per annum because they cannot be filled in the cramped accommodation).

iii. Donation of whole blood increases at approximately 5% per annum, i.e. 100,000 donations, which could increase factor VIII production by 4.5 M i.u./year, i.e. supplementing existing output by 40 - 50 M i.u. per annum after ten years which is the 'Trends' period.

iv. The present percentage of whole blood being used to prepare FFP is unacceptably low. The utilization factor of plasma as FFP should be between 50 - 60%.of all donations. This would produce

(a) 1.0 - 1.25 M units of FFP per annum

(b) essentially phase out time expired plasma.

From this volume of FFP at current yield of 230 i.u./L, approximately 41 M i.u. factor VIII could be prepared and this yield can be improved to 50 - 55 M i.u. given better quality of starting plasma.

v. 50 - 55 M i.u. factor VIII (see (iv) is close to current usage rates. Adding (iv) + (iii) a figure approaching 100 M i.u. factor VIII is obtained during the next decade: this approximates with some views of a more rational therapeutic demand and significantly can be achieved by a co-ordinated policy of plasma collection from blood donated at the existing rate and from the likely natural growth rate of whole blood donations over the next ten years.

Major areas for attention and financial support will be:

1. 'Closed system' blood collection systems to permit increased separation of FFP.
2. Redevelopment of the fractionation areas at BPL.
3. Extension of some regional facilities to cope with the natural increase in blood collection, i.e. 2.0 M → 3.5 M donations during the next decade.

N.B. Even at 3.5 M whole blood donations per annum, the rate is only 70 donations per 1000 population - a figure already achieved in some European countries.

To achieve self-sufficiency within the above framework of donations, the programme should include:

1) More flexible management of existing blood donations.
2) Tighter control on quality and rate of supply of plasma to BPL.
3) Extension of the fractionation process
   (a) buildings
   (b) process methodology.

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An important part of the policy is that the 'open-process' 5-L pooling system for plasma in RTCs is replaced by the flexible 'closed system' multiple blood collection pack, permitting fresh plasma to be separated under ideal conditions and be rapidly frozen at the earliest moment after donation as a single unit. For optimal use, existing multiple pack systems need modification to the plasma transfer pack to facilitate rapid opening of the frozen unit after its arrival at BPL and this problem has recently been discussed with the manufacturers (Travenol). See below.

General motivation is towards easing the problems of plasma collection at the Regional Transfusion Centres. This has implications for

a) staffing
b) revenue expenditure
c) forward planning and capital expenditure

(a) Staffing Plasma separation is an important task which has, unfortunately, a low interest content. The system for plasma collection should have a low demand on staff performance but have intrinsic to its design means of securing safety and quality of product and ease of operation.

Loss of 5-L pooling eliminates duplication in a process and saves staff time.

(b) 'Closed-process' multiple pack systems cost more money which may be substantially offset by the higher return on blood products achieved by an increased rate of collection of FFP.

(c) The proposed programme for self-sufficiency in plasma collection does not include or depend on a major capital investment programme in 14 RTCs. Streamlining of the regional process should permit fuller exploitation of existing facilities: in addition, future extension in plasma separation facilities for 'closed-process' operation will not require such high environmental specification by Medicines Division.

Short-term cold-storage problems at RTCs caused by the more bulky single packs (opposed to 5L packs) could be offset by more frequent dispatch to BPL where cold storage facilities could be rationalized to accommodate the new requirement. This would represent another way in which regional difficulties could be resolved by handling the problem centrally at BPL.

In a general equation defining a centralised programme for increased fresh plasma utilisation, the improved supply of final product (factors VIII, IX and albumin) plus savings on regional capital development (Medicines

Division Specification for sterile areas) would be expected to largely offset the increased costs of 'closed-system' multiple blood packs and the capital development costs of the fractionation plant at BPL. It is unfortunate that the present system of accounting and financing the various units comprising the NBTS, denies such an equation an opportunity of being solved. However, self-sufficiency in blood products is a viable proposition and money not invested in the NBTS will be spent on much more expensive equivalent commercial products.

The Single Packs Commiteee was convened this autumn to consider the difficulties and benefits which should arise from abolishing 5-L pooling of plasma and preserving FFP in single donations. From the first meeting it was learned that several RTDs regretted that the cost-effectiveness of abolishing 5-L pooling at RTCs was not more readily apparent and had accordingly set out to provide figures on this point. These reports will be made available in due course.

The objectives of this committee deal with two substantial deficiencies in the recent Council of Europe document:

(a) A major accent on improved production through improvement in yield

(b) To promote the contribution made by efficient blood component management rather than depend primarily on an initial increase in blood supply and/or plasma production by pheresis.

Present state of plasma supply:

The initial programme to increase FFP was not wholly satisfactory. Accountability was not built into the DHSS investment, thus not all the money has materialised in FFP production. Additionally, no realistic expenditure occurred in BPL to build a satisfactory process area. However, lack of money is not the sole reason for this inadequate response.

The move to collect more FFP, used blood collection systems that were available at the time, thus little thought was given to the possibility that 5L-pooling could be detrimental to the quality of the starting plasma and could complicate the process.

It is evident that:

(a) 5L-pooling by a dilution effect on a single plasma donation among thirty others can dilute HB_sAg missed by haemagglutination at RTCs to a point not recognised by radioimmunoassay of the pool.

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All single donations should be tested at RTCs by RIA and the single units sent to BPL for processing. This is the best safeguard for factor VIII, IX and I preparation and is in accordance with FDA requirements in the USA.

(b) 5L-pooling enables activation of fibrinogen to occur which in turn hinders extraction of factor VIII from cryoprecipitate. Yield from pooled plasma obtained in the 14 regions varies by 150%.

(c) Activated fibrinogen must also influence solubility of the end product. It should be noted that purification of factor VIII is in reality purification of its constituent fibrinogen since this is about 55% of the end product.

(d) 5-L pooling does not take into consideration the advantage of rapid thawing of FFP on yield of factor VIII from cryoprecipitate. Rapid thaw can be more readily achieved starting with smaller single donations of FFP.

(e) Also applicable here is the expected 15% improvement in yield of factor VIII from FFP when blood is taken into CPD anticoagulant rather than ACD. The latter is still used in many regions.

Redesign of the Blood Collection Pack:

Abolition of the 5L-pooling process at RTCs will mean that single transfer packs of FFP come to BPL for processing. In any one batch, the number of items increases by 30 times (i.e. the number of single donations in a 5-L pool).

There are different spatial requirements for cold storage and for opening the frozen units.

The 'Fenwall' pack design is over 25 years old and has not materially changed during this time. The transfer pack for FFP does not require 'ports' for giving-sets nor hangers for suspension of the pack to rails etc.

The problem taken to the manufacturer is a need to design a 'closed-system' receptacle as a blind loop appendage to an existing conventional 'Fenwall' bag system. Because of its simplicity, the bag should be economical and should be suitable for freezing between plates or within formers to produce a flat-sided slab of FFP. The need for regular geometry of the FFP unit in its container relates to the extra facility for cold storage in minimum volume by obtaining tight packing and so that the pack can be orientated in a simple mechanical system to provide rapid automated opening.

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The matter was discussed at a preliminary meeting in BPL (9th October 1978) which was attended by plastics engineers and design experts in blood bag fabrication from Travenol, Deerfield, Illinois. Directors from BPL and RTCs Oxford and Brentwood put the general problem to the manufacturers and demonstrated existing crude methods used here and in the USA to effect rapid single-pack opening. Environmental problems involved with automated single-pack FFP opening were outlined.

At the main plant (Travenol, Deerfield, Illinois, November 1st/2nd 1978) the discussions were resumed and support for the proposals gained from the Heads of the Domestic and International Fenwall Divisions.

Alternative proposals for a new bag design were submitted:

a) Based on existing vinyl Fenwall pack material. A simple 'closed-system' accessory receptacle for FFP could be linked up to conventional Fenwall systems to provide a primary pack plus a plasma bag, or a double pack plus a plasma bag etc. depending on RTC requirement for blood, platelets etc.

Advantages would be economy due to existence of the vinyl material and the absence of need for further research and development. Procedures for vinyl bag welding are in routine use and the only requirement would be a template for the new plasma pack design. In addition, a vinyl plasma pack would be homogeneous with the vinyl blood pack at the point of welding; heterogeneity at weld-points may cause structural strains during deep-freezing.

Disadvantages were discussed: vinyl is fragile at low temperature ($-60^{\circ}C$), but this would be overcome in practice by protection of packs during transit in storage containers. Vinyl is non-rigid, but regular geometry of the frozen plasma pack can be obtained between formers.

Ease of opening would best be achieved by cutting into the pack through an air-vinyl-air interface i.e. having a sterile air bubble in the plasma receptacle orientated to occupy the pack segment used for opening before freezing the FFP. This would be easier with some pack designs other than vinyl systems, where the pack material incorporates semi-rigidity into the shape independent of contents or formers. However, the difficulty with vinyl bags was not more than an inconvenience.

b) Blow-moulded bags in non-vinyl. Release from a vinyl system would allow a wide range of approved non-toxic cryo-resistant plastics to be used which could introduce any desired degree of rigidity and any shape into a plasma container without welding.

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The blow-moulded system would permit much greater freedom of design and facilitation of easy opening but would have general immediate disadvantages in terms of cost. There would be research and development overheads and the higher intrinsic cost of the plastic. Additionally, the union between plastic and the primary vinyl pack line would need testing for stability under a variety of conditions. A cost factor of 2 - 3 times more for a plastic bag than a vinyl bag was thought to be realistic.

For the above reasons it was decided that a vinyl system would be the most suitable compromise and it was appreciated that the development time for this system would be shorter i.e. less than 6 months: the latter point being very important to the BPL programme. Travenol agreed to produce detailed statements of these developments which included costs of alternative 'Fenwall' pack configurations.

Future of this project

Expectation of a favourable response from Travenol is influenced by the fact that resolution of this problem of opening single-pack FFP in the UK would significantly assist the Hyland production division of Travenol (Glendale, California) deal with American Red Cross FFP in their fractionation plant. This became apparent during the visit to Hyland Laboratories. Difficulty with opening single packs of Red Cross FFP has been experienced for some years and has been overcome by a labour-intensive process. The BPL initiative was welcomed at Hyland Laboratories and this information carried back to the Heads of the Travenol Plastics Division.

The new collaborative programme between Travenol and the American Red Cross which has received U.S. Congressional approval (November 1978) makes it more likely that Travenol will be more active in the management of Red Cross plasma fractionation and more accountable for yield of protein fractions from Red Cross FFP. It seems logical that an improved single pack design for FFP which facilitates the fractionation process would be seen as worthy of development.

These discussions have been without obligation and the initiative to provide detailed proposals and costs now rests with Travenol. The importance of this aspect of the overall plasma collection programme has made it imperative, however, that independent endeavours to cope with existing blood pack systems continue independently at BPL and PFL (Oxford).

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