An interesting shift from quantity to quality. D.P. (2875)

PATRON: H. R. H. THE DUCHESS OF KENT

THE HAEMOPHILIA SOCIETY

P.O. BOX 9 : 16 TRINITY STREET : LONDON, SE1 1DE

Telephone : 01 407 1010

Blood Products Sub-committee

Introduction

1. The last major review of the situation relating to supply of blood products in the U.K. was produced in January 1981. In view of developments affecting this subject it now seems appropriate once more to review the situation, and to consider whether our policies should be revised in the light of events since 1980.

Use and production of Factor VIII since 1975

2. The table below and the graph show the amounts of Factor VIII concentrate used each year since 1975 (cryo is shown only on the Graph) (1,2,3)

TABLE

Factor VIII used (million units)

Year	N.H.S.	Commercial	Total	NHS as % of total
1975	3.2	5.0	8.2	39.0
1976	6.8	8.2	15.0	45.3
1977	12.8	14.6	27.4	46.7
1978	14.8	18.8	33.6	44.0
1979	14.4	24.4	38.8	37.1
1980	14.5	35.1	49.6	29.2
1981	22.5	35.5	58.0	38.8
1982	22.9	45.6	68.5	33.4

3. It can be seen that the trend of increased usage has continued with no signs of levelling off. Extrapolation of the figures in the Graph implies a total Factor VIII requirement for 1985 of 95 million units, and a requirement of 100 million units per year in about 1986.

4. Since 1981 the facilities at the Blood Products Laboratory, Elstree, have been upgraded, and this has allowed an increase in production to somewhere near the current target of 30 million units. Further redevelopment of BPL, under the supervision of the newly established Central Blood Laboratories Authority, is still intended to make the U.K. self-sufficient in blood products by using present technology (i.e. without allowing for any progress in genetic manipulation techniques). However, the achievement of this target is dependent not only on provision of processing facilities. It also depends, as the last review pointed out, and as concedes, on both increased supplies of plasma to B.P.L. and increased yields in processing. In neither of these respects is there evidence that these requirements will be met. In view of this we must be somewhat doubtful that the NBTS could achieve the requirement, stated by the UK Haemophilia Centre Directors, of 100 million units by the middle of the present decade. To achieve this target would require NHS production to be trebled.

Demand for Factor VIII

5. The 1981 paper reviewed the factors contributing to the increasing demand for Factor VIII. These were:-

(a) Dosage levels increasing to those commonly used in other countries.
(b) Increased prophylaxis.
(c) Increased usage for home treatment.
(d) Increased treatment of inhibitor patients.
(e) Increased surgery.
(f) Lengthening life span; Increased reproductivity.

All these factors still apply, possibly excepting (c).

6. As indicated above, usage/demand for Factor VIII continues steadily to increase, with, as yet, no sign of a flattening off in demand. There certainly seems no reason to suppose that demand will level off at the arbitrary figures of 100 million units suggested by the Centre Directors or 110 million units suggested by the Council of Europe (4). Indeed calculations have been made attempting to qualify increases needed over the next 25 years (5).

7. Assuming 70 patients needing Factor VIII per million population:-

(i) Requirement for routine treatment/home therapy/prophylaxis [see Sub-Paras 5(a) - 5(c)] = 50,000 units/patient/year
>> 1.75×10^6 units/million popn./year

(ii) Routine treatment of mild/moderate haemophiliacs and von Willebrand's patients
= 7,000 units/patient/year
>> 250,000 units/million popn./year

(iii) Treating bleeding episodes in inhibitor patients [see (d) above]
500,000 units/million popn./year

(iv) Surgery [see 5(e) above]:-
150,000 units/million popn./year

(v) Increased longevity [see 5(f) above]:-
40,000 units/million popn./year for 25 years.

8. The requirement implied by 7(i) to (iv) totals
2.65 million units/million popn./year, equivalent to about 145 millions units/year for the U.K.

In addition 7(v) indicates a further need each year for Factor VIII of an extra 2.2 million units per year

Thus assuming 1985 as the starting point, the requirements are:-

1985	**145 million units**
1990	156 " "
1995	167 " "
2000	178 " "

9. The above calcuation may or may not be near the exact truth. The point is that there is absolutely no reason to believe that the present targets represent the actual need for Factor VIII over the next decade, any more than the calculations did for the past decade. In these circumstances we will inevitably have to rely on imported Factor VIII for a long time.

10. In view of this it seems worthwhile to consider whether the arguments in favour of NHS material compared with Commercial material which applied when our present policy was formulated still apply:-

(a) Ethical considerations

It remains W.H.O. (and W.F.H.) policy that countries should, as far as possible, be self-sufficient in blood and blood products. However, this policy seems to derive from the (wholly justified) desire to avoid exploitation of third-world countries by trading in plasma (e.g. export of plasma from Central America to W. Germany or the U.S.A.) (6). This policy does not seem relevant to trade between the U.S.A. and the U.K., where the differences in plasma supply arise from social and organisational differences and not from economic differences. Although commercial donors are paid in the U.S.A., the quality of the donors and of the finished product is subject to stringent standards imposed by the Food and Drugs Administration, and there is no reason to suppose that the use of paid donors by commercial companies results in a product of poorer quality than that from the U.K. (see also para 10(c) below).

(b) Price

It was feared that over-dependence on commercial material would make us vulnerable to price rises. This fear has not been realised, as competition (in a commercial sense) between the companies and (in a sense of supply only) with the NBTS has kept prices low (lower now in both real and money terms than 5 years ago). Indeed the view of WFH Task Force II is that "the only country with honest prices is the United Kingdom", and that we are effectively insulated from the risk of major price changes (7).

Because the British system of blood collection and Fractionation is very inefficient, and consequently expensive, use of commercial material is almost certainly cheaper. The only economic argument in favour of NBTS material is that its use saves the recurrent negative effect on the balance of payments involved in importing material. The balance of payments is not now an important factor in the British economy, however, so the argument carries little weight.

It also releases cash for HM

(c) Hepatitis

The main ground for believing British-made products to be medically preferable to imported material was the greater risk of hepatitis infection from the latter, and particularly Hepatitis B. However, development of "third-generation" tests for screening plasma for the Hepatitis B antigen, coupled with more stringent donor selection, has resulted in commercial material being of comparable standard to NHS material in this respect, although Hepatitis B remains a transfusion hazard. The incidence of hepatitis in British Haemophiliacs fell from a peak of 5.2% of those treated in 1974 to 2.5% in 1980, including only 2 deaths in the period 1975-80 inclusive (1).

In the case of non-A, non-B Hepatitis (also apparently included in the above figures), however, no screening test is available. Recent work, however, suggesting that British material is no better (and may be worse) than imported material in this respect (8,9). Similarly, a considerable incidence of hepatitis has been noted in Australian haemophiliacs, whose blood products all originate from volunteer donors (10).

Much effort has been put into development of Factor VIII having reduced hepatitis risk. Three types have been developed (11):-

Type 1: Factor VIII concentrates heated for a length of time known only to reduce the activitiy of Factor VIII by an acceptable amount in the hope that the viruses of hepatitis will be inactivated. These products are the one currently available but present evidence suggests that in fact the viruses are not inactivated, at least not completely. Even so these concentrates (Hemofil T and Factorate HT) are significantly more expensive than unheated concentrates.
Type 2: Chemically treated concentrates, mainly produced in Germany and Austria, in which there is about a 25% loss of Factor VIII activity.
Type 3: Products pasteurised to an extent that should kill the viruses, but this leads to about a 50% loss of Factor VIII activity and the cost would be very high.

Types 2 and 3 have not yet been made available for therapy, but may be tried soon in view of the disappointing results obtained with the Type 1 concentrates. Because of the loss in yield in making these products, the NHS would be placed in great difficulty if their use became medically accepted. On the one hand, the NBTS could not produce enough, because of its shortage of plasma, while the commercial material would inevitably cost more to produce, so that the NHS would have to pay more for the materials.

This would help us convince Ethel!

11. In view of the above I would submit that there are no grounds for favouring NHS Factor VIII over commercial materials in the respects we have in the past considered relevant. In addition, of course, the marginal factors of stability and more convenient presentation favour commercial material.

Future prospects in Factor VIII technology

12. As mentioned above, the production of hepatitis-free Factor VIII is becoming a distinct possibility. In addition we have the prospect, perhaps in 5-10 years, of Factor VIII being produced from micro-organisms which have undergone modification. There are also the possibilities of more sophisticated techniques for purifying proteins (e.g. using monoclonal antibodies) and of using porcine Factor VIII. Realistically, it is more likely to be commercial companies who invest enough to see such possibilities become reality.

AIDS

13. No discussion of blood products can be complete at present without referring to AIDS. Unfortunately facts are in very short supply. No infective agent has been identified for AIDS, and there is no reliable evidence that the disease is transmitted through blood products (although this still seems the most popular theory).
If this is the case, however, the "Mail on Sunday" reasoning - that importation of American blood products should cease - may prove to be an over-simplification, as AIDS could still be transmitted from the British donor population.
Certainly the immunological abnormalities which may be associated with AIDS are observable in haemophiliacs not exposed to commercial concentrates [e.g. in Scotland (12,13) and Australia (14)]. We might then pass from the frying pan to the fire, as the NBTS has made no real attempt to screen high risk groups from donating blood as recommended by the W.H.O. The NBTS approach so far compares very unfavourably with the measures taken by the commercial companies.

There is also a theory that the AIDS agent is closely associated with Hepatitis (15, 16), the AIDS agent being in some way harboured by the hepatitis virus. If this is the case then the quest for hepatitis-free concentrates and for hepatitis vaccines increases in importance. Similarly, the other possibilities mentioned in paragraph 12 above would also increase in importance, necessitating N.H.S. investment in other fields than conventional plasma Fractionation.

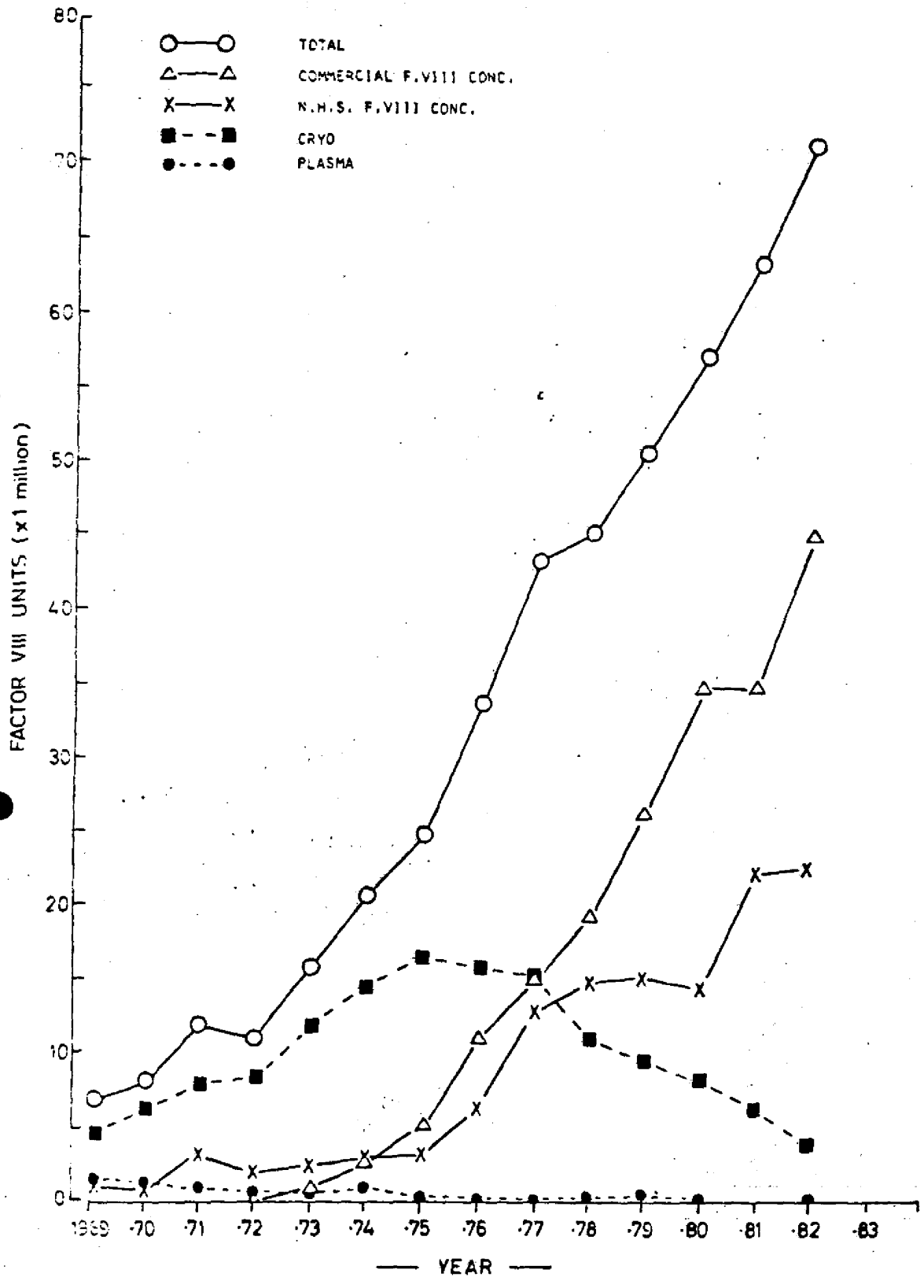
Conclusions

14. The AIDS scare has given us the opportunity, which we have not yet utilised; to campaign strongly for self-sufficiency in blood products. Given, however, that the original factors in our policy no longer apply or have reduced force, and that AIDS is still a great unknown, I submit that we should not undertake such a campaign. Now is not the time to ask that all our blood-product "eggs" should be placed in one basket. Instead, without necessarily abandoning our long-term objectives, we should take Mr. Asquith's advice "Wait and see". When more facts emerge about AIDS we would then be in a better position to press for whatever action these facts seems to demand.

Blood Products Sub-committee
9 January 1984

List of Sources referred to in text

1. Rizzo C.R., Spooner R.J.D. Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976-80. British Medical Journal 1983; 286: 929-33.
2. Rizzo C.R., Spooner R.J.D. Haemophilia Centre Directors' Annual Returns, 1981.
3. Rizzo C.R., Spooner R.J.D. Haemophilia Centre Directors' Annual Returns, 1982.
4. Council of Europe; Report of Committee of Experts on Blood Transfusion and Immunohaematology on "Preparation and use of coagulation factors VIII and IX for transfusion", 1979.
5. Josephson A., W.F.H. Council meeting, Budapest 1982.
6. Hagen P., "Blood: Gift or Merchandise", 1982.
7. Britten A.F.H. : Personal communication, 1982.
8. Fletcher M.L. et al. Non-A non-B hepatitis after transfusion of factor VIII in in frequently treated patients. British Medical Journal 1983; 287: 1754-7
9. Jones P. Acquired immunodeficiency syndrome, hepatitis, and haemophilia. British Medical Journal 1983; 287: 1737-8.
10. Rickard K.A. et al. Hepatitis and Haemophilia therapy in Australia. Lancet 1982; ii: 146-8.
11. Bloom A.L. : Personal communication, 1983.
12. Ludlam C.A. et al. disordered Immune Regulation in Haemophiliacs not exposed to Commercial Factor VIII. Lancet 1983; i : 1226.
13. Froebel K.S. et al. Immunological abnormalities in hameophilia: are they caused by American factor VIII concentrate? British Medical Journal 1983; 287: 1091-3.
14. Rickard K.A. et al. Absence of AIDS in Haemophiliacs in Australia treated from an entirely Voluntary Blood Donor System. Lancet 1983; ii : 50-1.
15. McDonald M.I. et al. Hepatitis B Surface Antigen could harbour the Infective Agent of AIDS. Lancet 1983; ii : 882-4.
16 Ravenholt R.T. role of Hepatitis B Virus in Acquired Immunodeficiency Syndrome. Lancet 1983; ii : 885-6.



AMOUNT OF BLOOD PRODUCTS (F.VIII UNITS) USED TO TREAT HAEMOPHILIA A PATIENTS IN THE U.K.