National Blood Transfusion Service

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Our Ref. CCB/MS
Your Ref.

17th December, 1973.

Dear Colleague,

Treatment of Haemophilia

The meeting in Sheffield of the Directors of all the (42) recognised Haemophilia Treatment Centres, which is to be attended by representatives of the Regional Transfusion Directors, has now been confirmed for Thursday, January 31st.

You will recollect that a paper by Dr. Rosemary Biggs, which many of us haven't yet been able to see, requested that fractionated human anti-haemophiliac concentrate should be made available from approximately 33% of all the donations currently collected by the Service. This was only a beginning and there was in fact a suggestion that eventually she estimated the need could be as great as all the plasma from twice the number of donations which the Service now collects. In the light of this I prepared a sort of counter-blast, a draft copy of which I enclose. I have since been down to Oxford and discussed this with Drs. Biggs and Rizza. I am afraid I didn't learn too much except that they feel sure that nobody can treat haemophilia adequately using less material than they do. Dr. Biggs has produced some figures however which show that Oxford use a very great deal more material (per case) than anybody else. They also are catering for extra cases who they say at present refuse to have treatment but "lie in bed at home with an ice bag on their knee". I don't believe that this happens very much and they didn't explain in fact how they were going to get these people to accept treatment, if they exist. It sounded rather like trying to give blood transfusions to Jehovah's Witnesses!

Furthermore, since getting interested in this two or three months ago, I have spoken with a number of senior haematologists, e.g. at the MRC Path examinations and so on, and they all thought, given an adequate supply of good quality cryo and just a small supply of super concentrate for the major surgery or the patient with inhibitors, they would be very happy. Many insist that they would still want cryo, even if concentrate was more freely available, and I don't think we ought to involve ourselves in a completely open-ended commitment in this way. Bearing in mind that Factor VIII is inevitably wasted at all stages of preparing and using concentrate, it may well be that money and effort should be channelled towards more and better cryo. I think we must accept that the supply of cryo has sometimes been inadequate and it may have been of poor quality in some parts of the country in the past. We certainly had difficulties in the Sheffield region until we got organised right at the beginning of 1973.

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DIRECTOR Dr CC Bowley MB BS FRCOG FRCPath

I thought you might like the background to this, and if you do have any facts, figures, or supporting evidence one way or the other I would indeed be most grateful to have it well before the meeting on January 31st.

Yours sincerely,

GRO-C: Bowley

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The Department of Health is currently contemplating a major expansion of human blood plasma fractionation at the Blood Products Laboratory (BPL), primarily to produce a greatly increased supply of human Anti-Haemophilic Globulin (AHG) concentrate. The stimulus for this development is not unrelated to the fact that early in 1973 product licences were granted to two firms to import AHG concentrate, making it available in this country on a commercial basis. The scale of operation proposed by the Department is such that it represents a change in policy and a major new undertaking for the regional centres of the NBTS. As a first step the current proposal requires plasma separation from fresh blood in excess of one third of all donations collected in England and Wales, rapid freezing, and storage and subsequent transport to the BPL in the frozen state. The repercussions of this will be considered in detail later. Sufficient at this stage to acknowledge that at the transfusion centres the capital cost of equipment alone will reach a six-figure total and the initial cost, depending upon the amount of new accommodation or modification to buildings necessary, may reach several hundred thousand pounds, without any allowance for subsequent running costs. The ambivalent attitude of the Department towards the commercial provision of AHG concentrate compared with its enthusiasm to involve commercial enterprise in the provision of biochemical standard sera rather than make arrangements within the NHS, is not easily understood.

In the circumstances it is important to collect all available information and informed opinion concerning the need for this programme in order that any final policy decisions will be as soundly based as possible. To date the Department has apparently relied almost exclusively upon the advice of an Expert Group on the Treatment of Haemophilia which met in March of this year in order to assist the Department ".. to make proposals on which realistic planning for the future can be based.". Three senior clinical haematologists provided the expert opinion, which was essentially agreement by two of them, with a paper produced by a third, "Factor VIII Concentrates and the Treatment of Haemophilia" by Dr. Rosemary Biggs. This paper is apparently still classified as confidential and has only a limited distribution. As it forms the raison d'etre of the Department's proposals it deserves more detailed scrutiny than it has yet received. Dr. Biggs has attempted to "estimate the total amount (of therapeutic materials containing Factor VIII activity) needed in this country each year".

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Many widely differing figures are quoted for the incidence of haemophilia in various populations but unfortunately Dr. Biggs is unable to give a convincing figure for the incidence in this country and it is not even clear whether the figures suggested refer to all cases diagnosed as haemophilia after clinical and laboratory examination, to all cases requiring an anti-haemophilic infusion in a two-year period, or only to "severely affected" patients. Reliable figures are urgently needed.

In the Sheffield region, routine ABO and Kell grouping and Rhesus genotyping by the Blood Transfusion Centre of all "bleeders" likely to suffer repeated transfusions, and referred from either the Sheffield or Derby Medical Research Council haemophilia registration units, was instituted in the early 1950s. By the late 1950s arrangements had developed to the point where, with the official approval of the Regional Hospital Board's various medical advisory committees, all haemophilics in the region were treated only at the major medical centres in Leicester, Nottingham, Derby or Sheffield, where originally Consultant Pathologists and latterly Consultant Haematologists, with special experience, were involved in their management. The transfusion centre did not provide anti-haemophilic material other than to these centres, and any new cases were added to the central register at the BTS. Any therapeutic material issued was recorded on the patient's individual record card, except for human AHG concentrate, stocks of which were held only by Professor Blackburn in Sheffield, whose original MRC Registration Unit has now become one of the three officially recognised centres for the management of haemophilics requiring major surgery. Until recently all the haematologists appointed at Nottingham, Derby and Leicester had been Senior Registrars in the Department of Haematology at Sheffield, so that these arrangements were relatively easy to maintain. The fact that many of the haemophilics have been diagnosed within the first year of life, and that only recently a case was registered of "classical haemophilia" in a man aged 73, who has apparently never had any transfusion therapy in his life, suggests that these arrangements are effective.

Coincidentally, in connection with another investigation, the germane transfusion centre records were reviewed and analysed early in 1973, up-dating addresses, eliminating duplication, and recording deaths etc. The current situation is shown in Table 1.

TABLE 1

Population: 4,500,000

Registered Cases (confirmed by clinical and laboratory diagnoses)

Haemophilia	306	= 6.8/100,000
von Willebrand's disease	144	= 3.2/100,000
Christmas disease	36	= 0.8/100,000
"Others" (primary and secondary capillary defects etc.)	423	

The figures in Table 1 include 7 haemophilics, one case of von Willebrand's disease, 2 cases of Christmas disease and 2 other cases of capillary defect who are resident in the adjoining Leeds, Manchester or Birmingham regions. They also include 9 haemophilics now deceased. All have been retained to counterbalance any cases in the region already born but not yet diagnosed or any Sheffield region cases registered elsewhere. The latter is unlikely to be a significant factor as the special haemophilia centre in Sheffield tends to attract cases rather than vice versa. The intention is to avoid any underestimate of the problem.

TABLE 2

Treatment with fresh blood, fresh frozen plasma or cryoprecipitate issued from B.T. Centre over last 15 years

Disease	No Treatment	Treated	Incidence of Treated Cases
Haemophilia	227 (74%)	79 (26%)	1.75 / 100,000 population
von Willebrand's	91 (63%)	53 (37%)	1.18 / 100,000 population
		Total	2.93 / 100,000 population
Christmas	11 (31%)	25 (69%)	0.5 / 100,000 population

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TABLE 3

Analysis of Treatment Patterns

1	2	3	4	5
	Total No. of Cases Treated in last 15 yrs.	Treated		
		>once per annum	Several times per annum*	Frequently, virtually every month.*
Haemophilia	79 (100%)	76 (96%)	9 (11.5%)	16 (20%)
von Willebrand's	53 (100%)	3 (5.5%)	-	-

*Included in column 3

Table 1 includes all cases, Tables 2 and 3 do not include details of any cases treated solely with human (or animal) AHG concentrate who have not at the same time received any product direct from the Transfusion Centre. If fresh blood, fresh frozen plasma or cryo-precipitate has been given the case is included.

So far as Table 2 is concerned only cases always treated with concentrate and never given any other specific infusion over approximately the past fifteen years are not shown. If they exist such cases must be very few in number and would be limited to Professor Blackburn's unit in Sheffield. The frequency of treatment shown in Table 3 could be influenced by each occasion on which a case has been treated with concentrate only and it is known that there have been a growing number, particularly in recent years. It is hoped to obtain details of these. However Table II of Dr. Biggs' paper states that in 1971 freeze-dried human concentrate was prepared from only 8% of the total donor units used for making therapeutic materials for the treatment of haemophilia. As she also states that Oxford patients "... have half of the material given to them as freeze-dried concentrate" it seems doubtful that there has been a sufficient amount available in the Sheffield region as a whole to alter the Table 3 figures significantly.

Tables 1, 2 and 3 may be summarised to show that in a population of 4½ million 74% (227) of the 306 diagnosed haemophiliacs require no specific infusion treatment and the number of cases generating a significant demand for therapeutic material is just 25.

Comparison of these figures with those given in "Factor VIII Concentrates and the Treatment of Haemophilia" reveals disturbing contradictions which are not easily explained. Dr. Biggs states "...estimates for severely affected patients vary from 2 to 6 per 100,000 ... For Great Britain the total could be between 1,754 to 3,000 patients." The present population of England and Wales (excluding Scotland) is 49,000,000 and virtually static in recent years. Two to six "severely affected" patients per 100,000 gives a total load in round figure of 1,000 to 3,000 such patients. Dr. Biggs nowhere defines a "severely affected" patient. The population of the Sheffield region is 4,700,000 and in other surveys (e.g. birth rate)

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has not proved to be other than representative of the country. In fact for ease of calculation and to slightly overstate rather than understate the problem the incidence has been calculated on 4,500,000. Thus for a population of 49,000,000 we can forecast a total of 3,330 (say 3,500) diagnosable cases of haemophilia and a further 1500 cases of von Willebrand's disease. The incidence of haemophilia is more than 50% over the maximum "probable incidence" quoted by Biggs and Macfarlane in 1966 (Treatment of Haemophilia and other Coagulation Disorders). The total incidence of both haemophilia and von Willebrand's disease is 10 cases per 100,000 - a total of 4,900 cases in a population of 49,000,000.

As shown by Table 3, the treatment of von Willebrand's disease does not represent a significant drain on resources and need not be pursued. However, if a "severely affected" haemophilic is defined as one needing treatment about a dozen times a year (or more) the national total would be of the order of 275 such cases. If the definition is widened to include all cases requiring infusion more than once a year that figure becomes 830 cases, compared with the 1,745 to 3,000 figure on which the proposed planning has been based.

There are other disturbing aspects of Dr. Biggs paper. She states that over a 3-year period 1,754 different patients "attended" Haemophilia Centres. This is presumably not the same as being treated as numbers would attend for clinical and laboratory examination. The distinction is important as although the incidence of registration of cases in the Sheffield region is apparently high, only 25% of the total has received treatment over a 15-year period, although the majority have, during that time, attended one or other of the Haemophilia Centres. Dr. Biggs figures are based on the number "attending" some of the Centres. It would seem desirable to obtain returns of the number of confirmed haemophilics (a) attending at and (b) treated by all the Haemophilia Centres, including those which "did not make returns".

Dr. Biggs states ".. only about a quarter of the material at present prepared for the treatment of haemophilic patients in the U.K. is in the form of plasma (Table II). Table II in fact shows the figure to be 15%. On page 5 of her paper, a formula is given for calculating the overall yield of Factor VIII activity which uses as the divisor (denominator) the volume of starting plasma x 0.9. This presumably holds good for the coagulation workers' standard mixture of one volume of citrate to nine volumes of blood but does not represent the NBTS blood donation in a standard is not applicable to

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bottle or a plastics bag, for which the appropriate figure would be 0.77 and 0.86 respectively. The effect of correcting this error is to improve the yield.

On page 11 of "Factor VIII concentrates and the Treatment of Haemophilia" another formula is applied to calculate the average amount required per patient/dose to raise the plasma Factor VIII to 20%. The formula rightly allows for a 66% recovery from the starting plasma (Biggs and Macfarlane 1966) but in the next paragraph a further calculation is invoked to allow for the loss of another 60% of Factor VIII activity during preparation. Again the result is an inflation of the amount of basic material required.

There is also a calculation based on the assumption that during major surgery the level of Factor VIII will be raised to 100% for ten days. Local experience suggests that this is unnecessary, even without allowing for improved treatment by the use of cryoprecipitate 12 hourly.

A great deal of argument is based on the Oxford experience of patients at the Lord Mayor Treloar College. Other figures in the paper clearly indicate that these are a selected and on the whole badly affected group with the number of bleeds per boy varying from 0 to 70 per annum with a mean of 25. Using the questionable formula on page 11 already referred to, it is calculated that the average total number of donor units required per patient per annum for the treatment of 25 bleeding episodes was 210 to 240. However, this experience is then used to assess requirements "over the country as a whole".

From then on the calculations take on a certain air of fantasy. The statement that "each (dental) operation should require ... the material from 35 donors" is not in accord with the Sheffield experience (except for impacted wisdom teeth) where the average for extractions would be not more than 16 to 20 donors (frequently much less) when material is provided on demand from the Haematologist/Dental Surgeon team.

Furthermore Dr. Biggs then adds the material which "should" be required for dental operations to that already "estimated" to be necessary for treatment at "the optimum desirab level". Unless haemophiliacs all over the country are being denied dental treatment, the material for their management should already be covered in the estimate for general requirements, as is the case with the Sheffield figures, where dental treatment in association with the Charles Clifford Dental Hospital is particularly active (and sometimes performed without recourse to any Factor VIII at all).

It is difficult to escape the impression that either the very special experience in Oxford, with its international reputation and handling of difficult cases, has caused a lack of perspective of the situation elsewhere or else the paper is not a scientific analysis but a document compiled to support a preconceived aim. For example, the unqualified statement (page 7) that freeze-dried material is "probably less expensive in the long run (than cryoprecipitate)" should not be allowed to pass unchallenged. The wastage in

labile factor involved in bulk fractionation is admitted and made good by processing more material and the costs in "going plastic" and providing and maintaining centrifuging, freezing, storage, and transport, apart from the costs of fractionation and redistribution, should be considered. Costs for cryoprecipitate production are available. Similarly the statement that the administration of plasma "can" lead to the production of antibodies to plasma constituents (a condition sought but not detected in Sheffield cases) deserves statistical support in order that the non-expert administrator can reach policy decisions on the basis of balanced information.

Figures have been compiled for 1972 showing the number of donations per 10,000 population processed for anti-haemophiliac treatment at each Regional Transfusion Centre. The range is from 9 at Sheffield to 127 at Oxford (20 at Cambridge and 98 at Edgware). The Sheffield cases, mostly under the care of Professor Blackburn, have been rapidly returned to school or work, and although deliveries of infusion material sometimes had to be on a day to day basis at times of heavy demand, treatment in one form or another has always been available.

Since the institution of "cryoprecipitate banks" at the four haemophilia centres in the Sheffield Region, fresh supplies are obtained by means of a return showing the usage of the material to be replaced. This return includes pre and post treatment assays. This has led to general agreement that the average adult haemophiliac with 0 - 1% assay requires five individual donor units of cryoprecipitate per day to bring him up to a clinically satisfactory 20%+ post infusion level. Yet the rate of processing at Oxford is fourteen times that at Sheffield and there are wide variations from region to region. The lower figures may be too low but equally the higher figures must be greater than can really be required. The treatment of haemophilia cannot be inadequate everywhere except in Oxford. It is noted that more than half of the Directors of Haemophilia Centres "feel that present supply of anti-haemophiliac factor is inadequate" and that many feel "they could use at least twice as much". It would be interesting, and may perhaps be considered necessary, to correlate the views of these Directors (including those who "did not make returns") and the manner in which their anti-haemophiliac material is used, with the rate of production at their Regional Transfusion Centre.

Only when the size of the problem is known can a realistic policy be decided. Then will be the time to consider whether an open-ended policy of producing all the material demanded to prevent commercial purchase, whilst at the same time clinicians who prefer cryoprecipitate will continue to demand same, can be justified and subsequently controlled. Indeed when the true incidence of haemophilia is known, it may be possible to decide what

effort is justified for such a small group of patients with an incurable disease and the priority and financial expenditure which should be afforded to them. Perhaps more attention to living a full and satisfying life within the limits of their disability, rather than obeying the exhortation of the Haemophilia Society to live normally (and arrange for NHS therapeutic material to be sent abroad with them on holiday), backed up by improved cryoprecipitate production where necessary, and administration of the material only under very carefully controlled conditions by clinicians working in recognised units, might be considered a more suitable arrangement.

More facts are required. It is only too easy to abuse the NBTS and the blood donors of this country. Although the situation is slowly improving now, it has happened in the past with blood and could certainly happen with anti-haemophiliac material. Note Dr. Biggs suggestion that eventually the annual processing of more plasma than is at present collected each year from blood donors in the whole of England and Wales could be requested. It can be argued with equal justification that as a first step the use of the present supply of anti-haemophiliac material only at selected haemophilia centres and under laboratory control, would be a more logical and rewarding exercise.

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