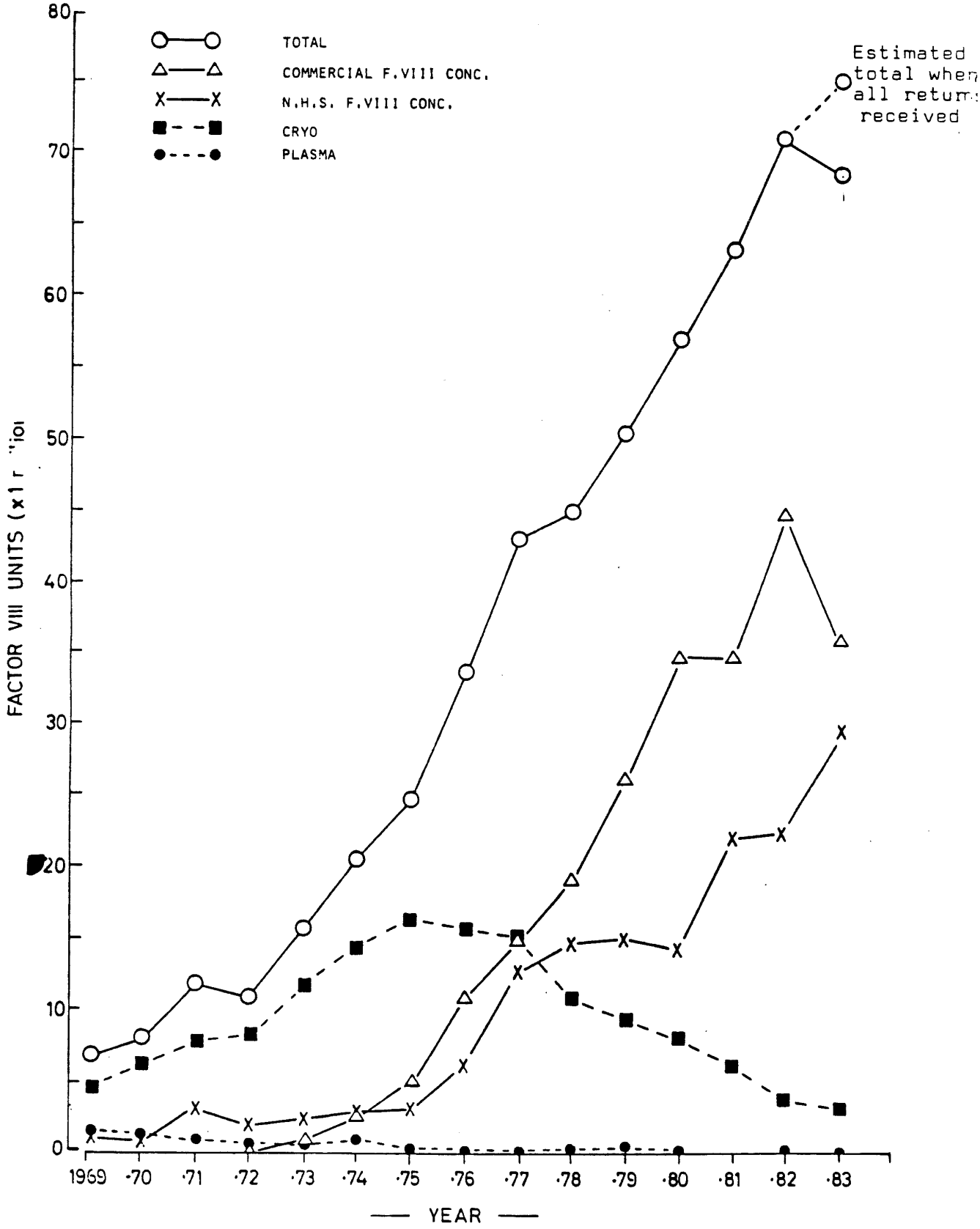
HAEMOPHILIA LITIGATION REPORT

A L BLOOM

APPENDICES

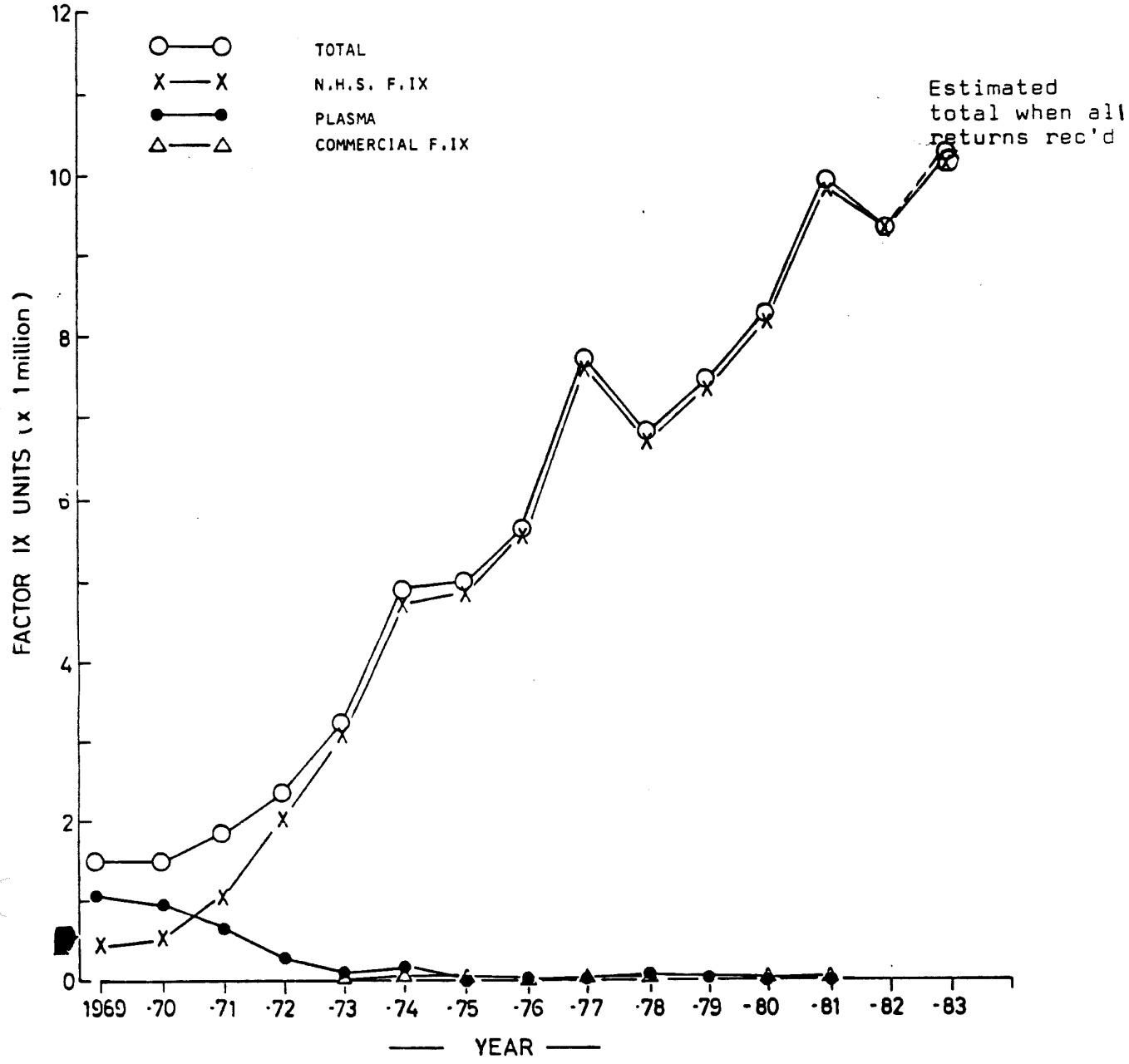
JUNE 1990

FIGURE 1A



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

Fig 16



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

FACTOR VIII CONCENTRATES

VIRAL SAFETY
RESUME OF ATLANTA MEETING

(Prepared from notes taken at Meeting. Accuracy not GUARANTEED)

The meeting was called in Atlanta as a result of reports of seroconversions to HIV in Canada, but also considered general viral safety of current factor concentrates.

Dr Fricke FDA outline fractionation and viral inactivation processes. These include:

1. Dry heat 60° 24 hours to 80° 72 hours
2. "Wet" Heat in heptane slurry
3. "Steam" heat Dried Material
4. Wet heat in aqueous solution with stabilisers
5. Chemical methods : solvent/detergent
   Beta propiolactone (for Factor IX)
   Chromatography
6. Monoclonal Antibody immuno affinity
7. Recombinant technology

The various factors which influence sterilisation temperature, moisture, stabilisers were discussed.

Dr Remis Described the Canadian experience. 370 Haemophiliac patients were followed prospectively.

By March 1987 over 190 were still seronegative 18 in British Columbia.

May - Oct 19987 5/18 seroconverted.

A good case - control study was established.

The patients had been exposed to :

a. Cutter 68° 72 hours dry heat

b. Armour 60° 30 hours dry heat

The study implicated 3 lots of Armour at p 0.00012 (Cutter ns)
2 of the 3 lots had been prepared from a single plasma pool.
Subsequently :

a. two more Canadian patients exposed to this pool seroconverted.

b. two USA patients exposed to the pool seroconverted but they had received other products.

The Conclusion was that Armour 60 30 (Factorate) was implicated.

The lots had been prepared from screened donors but 2 (so far) have seroconverted (and hence may have been infective at donation).

Dr S Dietrich (L.A.) described 6 possible seroconversions. Two implicated the suspect Armour lot. The other 4 were less definite with other risk factors etc.

Dr Dale Lawrence (CDC) reviewed all the reports and world anecdotes.

20 reported cases of seroconversion

1. Only the 7 Canadian cases hold up but nevertheless 16 of the reports referred to Dry Short period Heat-Treated.

Various contributors then presented the results of trials with various products.

Dr Levine Monoclate. Armour Monoclonal antibody purified heated 60 30.
19 cases. No hepatitis
No HIV seroconversion

Possible improvement in skin anergy induced by older impure concentrates (not convincing).

Dr Gompertz Hyland monoclonal product. 13 patients. No HIV seroconversions. 1 raised ALT but probably not hepatitis.

J Smith BPL Dry heat 80 - 72. 29 cases. No HIV seroconversion but not well assessed for hepatitis.

(My note: HIV in British donors 1 : 25,000. Therefore : antigen could be expected in say 1 in 10 = 1 : 250,000. Since pools are 8,000. Then only 1 in 30 batches infected before heat. Therefore need much more data)

Dr Hilgartner's Deputy New York Blood Center product. Solvent/detergent. 13 "naive patients" No hepatitis. No HIV seroconversion.

Dr Mannucci Reviewed the literature and his own experience on hepatitis. In summary his conclusions are:

1. Successful so far (a) Wet heat treated (60-10)Behring(Hoechst)
   (b) Factor IX - beta propiolactone

2. Reduced Infectivity. (2/9 lots)
   (a) Heptane Slurry 60 20 Profilate Alpha
   (b) Steam Heat (under pressure) Immuno (Kryobulin)

3. Still transmit hepatitis Dry heat up to 60-30 definitely Dry heat 68 - 72 highly probable.

4. Not known yet Dry heat 80-72 (British) not known yet. Monoclonal products. Solvent/detergent.

All type (4)are under test. Armour monoclate has terminal sterlisation at 60° 30 hours which is definitely not effective on less pure concentrate.

General Some disquiet about all dry treated products was expressed by some observers. It was noted that if dry heat products were withdrawn then there would be insufficient plasma to maintain wet heat products at current useage because of loss of yield. In this case there could be a lack of material for export and for a cost increase even beyond the times 2-3 expected, from a switch to wet heat material. Consideration of reduced treatment intensity was suggested by some observers.

CONCLUSION

1. Dry Heat-treated products at 60° 30 hours (or less) are definitely not safe. This includes Profilate Alpha (dry) not sold in UK and Factorate Armour, which licence was withdrawn in UK 12 months ago.

Both these products and Hemofil (60 - 72) are no longer produced by the manufacturers.

2. Dry Heat (68 - 72) Koate Cutter has not been implicated in seroconversion to HIV but probably transmits NANB hepatitis.

3. Dry Heat BPL (80 - 72) is probably safe from HIV (and has a cleaner donor pool) but hepatitis safety is still being assessed.

4. Some authorities are suspicious of all dry heat materials.

5. Profilate "wet" heptane slurry and Kryobulin steam heated are probably safe from HIV and reduced infectivity for hepatitis

6. Aqueous wet heat Factor VIII Behring Werke (Hemate) (published) Koate wet heat (unpublished) are the safest heat-treated products.

7. New generation solvent/detergent, and monoclonal immunoaffinity are still under assessment but are probably safe with the exception that Monoclate (Armour) has the 60° 30 hour dry heat terminal process.

Best Buy There isn't one. May be one needs a "safe" product for HIV negative's and new (unexposed to hepatitis) patients (eg wet heated) and a reasonably safe (eg heptane slurry) product for other patients to avoid risk of frequent superinfection. (BPL 8072 probably safe).

Some advocate only use of wet heat products but they cost 35-40p/unit and would triple current expenditure. There could then also be a world shortfall of plasma-derived factor VIII with cost escalation.

A L BLOOM
Jan 88

APPENDIX 2

OXFORDSHIRE HEALTH AUTHORITY

OXFORD HAEMOPHILIA CENTRE

575

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

11th January, 1982

To all Haemophilia Centre Directors

Dear Colleague,

You are no doubt aware that at least 4 commercial companies are about to introduce preparations of factor VIII and possibly factor IX that have been processed in an attempt to reduce the risk of transmitting hepatitis B and non-A non-B. As far as we know the products have been subjected to a heat treatment process such as pasteurisation after removal of the bulk of fibrinogen but other methods such as treatment with B-propiolactone and UV light or differential adsorption-elution may be used. Although initial production batches may have been tested for infectivity by injecting them into chimpanzees it is unlikely that the manufacturers will be able to guarantee this form of quality control for all future batches. It is therefore very important to find out by studies in human beings to what extent the infectivity of the various concentrates has been reduced. The most clear cut way of doing this is by administering those concentrates to patients requiring treatment who have not been previously exposed to large pool concentrates. Those patients are few in number but a study along those lines is being carried out at Oxford to determine the infectivity of factor VIII concentrates produced by the Plasma Fractionation Laboratory, Oxford and Blood Products Laboratory, Elstree. This study shows that it is possible to demonstrate infectivity using quite small numbers of previously untreated patients. It is very important also to find out as soon as possible whether the manufacturing methods used to reduce the hepatitis risk has resulted in a product with undesirable characteristics such as high content of denatured protein, reduced factor VIII recovery in vivo, reduced factor VIII ½-life in vivo, increased incidence of factor VIII antibodies or of immune complex disease.

Although there is no doubt that the introduction of 'hepatitis-safe' products would constitute a major advance we hope you will agree with us that their use on a 'named patient' basis would be undesirable and might seriously hinder controlled studies in the future. There are several reasons for thinking this:-

1. The best way of assessing efficiency and observing recovery of activity, side effects etc., is by properly conducted clinical studies. Since a number of products are likely to be introduced in the next few months a core of 'at risk' patients will be needed for this assessment. It is for the treatment of such patients that producers will make their products available. If patients at risk are treated on a 'named patient' basis they will be unavailable for clinical trials and the results will be of anecdotal value only.

2. For the purposes of a Product Licence the manufacturers are required to set out to the Regulatory Authority in the U.K. the evidence of product efficacy and safety and details of processing, batch to batch reproducibility toxicity tests etc., which help to ensure quality control. In addition there would be a requirement for samples of each batch or batch protocol to be submitted if requested to the Regulatory Authority for assessment at NIBSC. Manufacturers could be laible if subsequent batches failed to meet the original product protocols and import of such products could be prohibited. Although it will not be possible for the Regulatory Authority to check infectivity of batches as an ongoing control, measurement of total protein, clottable protein, factor VIII antigens and activity ratio etc., will help to ensure that the materials have been properly processed. Even if factor VIII concentrates are subjected to similar pasteurization processes as those used to sterilise albumin and other simple plasma protein fractions they may not withstand denaturation to the same extent. Formal trial of efficacy and on-going monitoring of quality control is thus important.

3. Use of a product on a 'named patient' basis is often justifiable but by-passes these regulatory controls which have been established in the interests of patients.

We are therefore writing to let you know that the Hepatitis Working Party are discussing plans for Clinical Trials of these products as they become available and will if necessary request exemption from a clinical trials certificate in respect of individual products in order to expedite trials. We hope that the companies concerned will collaborate in these trials and will offer appropriate supplies of their concentrate as well as financial support.

Unfortunately there is insufficient time available to air these problems at the next meeting of the Haemophilia Centre Directors but if you have any observations we would be most grateful to learn of them as soon as possible.

With all best wishes,

Yours sincerely,

GRO-C

GRO-C

A.L. Bloom

C.R. Rizza

U.K. HAEMOPHILIA CENTRE DIRECTORS HEPATITIS WORKING PARTY

Factors to be considered in the Selection of Hepatitis Reduced Products for Clinical Trial - Evaluation of residual infectivity for Hepatitis Viruses

Several manufacturers will shortly be in a position to offer trial batches for evaluation of their residual infectivity according to the trial protocols recently considered by the Reference Centre Directors and circulated to all Directors.

These products seem to be of 3 types:-

1) The freeze dried product is heated in the presence of compounds (e.g., sucrose) which stabilise the factor VIII activity, but reduce the quantity of infective virus in the product by pasteurisation. Heat inactivation is applied to the point where there is no sifnificant loss of factor VIII coagulent activity. The temperature is usually 60°C , the exact conditions are a commercial secret, but the heat is known to be applied after the freeze drying process.

Two such products are:-

(i) Hemofil T (Exception from Clinical Trial Certificate obtained) - trial now underway

(ii) Factorate HT - available in 3 months

2) The plasma is treated with chemicals (e.g., β-propiolactone + U.V. light in the presence of detergent) or (Tween 80) which render the viruses uninfective while preserving the coagulent activity. The products involved are:-

Factor VIII manufactured by BIOTEST in West Germany - no plans are likely to involve trials of this product in the U.K. There is about a 25% loss of factor VIII activity.

Kryobulin (Immuno) - still under development; available later this year?

3) The product is pasteurised by heating at 60°C in the presence of stabilisers for factor VIII, but this is done under conditions where hepatitis B virus may be inactivated. The strains of non-A, non-B hepatitis virus which are used experimentally in chimpanzees have been found to be more heat labile than hepatitis B and are assumed to be destroyed by this process. Unfortunately this reduces the factor VIII activity by 50% and this means that the product price would be high (? 40p per factor VIII unit).

Bellingwerke A.G., manufacturers of Germany have developed such a product which has undergone clinical trial in Germany. It is unlikely that they would consider applying for a British product licence unless an approach was made to them. Since their unheated product is not marketed here this may take some time.

Hemofil T is at present available for clinical trial. An exception for a Clinical Trial Certificate was granted by the British Licensing Authority on 1.6.83.

Factorate HT will be available within 3 months, and presumably exception for a Clinical Trial Certificate will be obtained in due course.

Opinion i) The degree of heat treatment received by both American products may lessen the infection risk for non-A, non-B hepatitis viruses, but by what degree can only be ascertained by clinical trial in human subjects.

It is unlikely that the hepatitis B virus infection will be significantly affected by the heat treatments used in the above products. Hepatitis B vaccine will have to be used to eliminate this risk.

ii) Both the German products from Bellingwerke and Biotest seem to be likely to have a significant reduction of their contamination rates with hepatitis B and non-A, non-B viruses, but the significant loss of factor VIII activity will increase the price of this product and might produce shortages of supply if the demand was high. Thirty-one batches have been used in a clinical trial with, so far, no cases of hepatitis. However, details of the precise classes of patient studied are not yet available.

iii) The Acquired Immune Deficiency Syndrome (AIDS) and transfusions of factor VIII. So far 16 cases of this syndrome which fit the criteria used by the Centre for Disease Control (CDC) Atlanta, Georgia, have been reported in the U.S.A. Five cases have been reported from Europe. This includes the suspect case notified to me recently in the U.K. Though the incidence in U.S. haemophiliacs is low (1 case per 1,500 persons at risk) and there is, as yet, no hard evidence relating specific products or batches to particular cases, the infective theory for the causation of this disease is still the one that fits all the known facts about AIDS.

Consideration must, therefore, be given to the possibility that factor VIII concentrate prepared from plasma donations obtained in the U.S.A. might be contaminated with a putative infectious agent associated with the cause of AIDS.

Since there is no information as to the physical characteristics of such an agent, the materials used to reduce the risk of transfusion hepatitis, such as heat treatment, cannot be relied upon to render factor VIII concentrate manufactured from the same plasma free from such an agent. The only product which may be free from the risk, and is made from U.S. commercial plasma, is the Merck, Sharp and Dohme hepatitis B vaccine and this is treated with formalin, pepsin at pH2 and 8 molar urea. All the commercial heat treated products and the Biotest brand of factor VIII are made in part from plasma obtained from commercial sources in the U.S.A. There is, as yet, no product which is not made from sources likely to carry a risk of a putative virus associated with AIDS being present in the plasma pool from which the factor VIII is fractionated and which is heat treated.

This will cause a problem when the criteria for clinical trials of these products in the U.K. have to be considered. Since the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received factor VIII or IX concentrate, a choice will have to be made between using heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non-A, non-B hepatitis.

There is, therefore, a considerable ethical problem when considering the evaluation of the new heat treated products for their residual infectivity in clinical trials in patients infrequently treated with factor VIII who have no prior exposure to freeze dried concentrate.

It is to be hoped that a hepatitis reduced product will be available from NHS sources before long.

J. Craske
Chairman, U.K. Haemophilia Centre
Directors Hepatitis Working Party

11.7.83.

APPENDIX 4

OXFORDSHIRE HEALTH AUTHORITY

OXFORD HAEMOPHILIA CENTRE

Tel: Oxford (0865) 64841
Ext.

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

29th March, 1984

MEMORANDUM

To: All U.K. Haemophilia Centre Directors

TRIALS OF 'HEPATITIS REDUCED' FACTOR VIII - AN UPDATE

Directors will recall the "aide memoire" circulated with paper for the September 1983 annual meeting which described the types of factor VIII concentrate which would be available for clinical trial in 1983-4. We have recently reappraised the situation and there are at present 8 different products in preparation or available for trial. Clinical trials have only been completed on one product, the "Hemofil HT" factor VIII, which is prepared using a 'dry heat' method. The results indicated that there was still a 63% attack rate of non-A, non-B hepatitis on first exposure to this product in patients who have not received factor VIII concentrate previously. These trials are difficult to evaluate as for ethical reasons no control group was used.

The products currently available are:-

(1) Heated products from Armour, Cutter, Travenol and Alpha Therapeutics. The 3 former are 'dry heat' preparations and the latter (Alpha Therapeutics) is a wet heat product.

(2) NHS factor VIII prepared from a specially selected donor panel which is monitored for abnormal LFT's, hepatitis, etc.

(3) Heated NHS factor VIII; one brand is manufactured at the PFC in Edinburgh and will be shortly available. The second, manufactured at Elstree, should be available later this year.

(4) A heated preparation manufactured by Behringwerke, the German Pharmaceutical Company. This is heated at 60°C for a period known to inactivate hepatitis B in the preparation. The problem is that the yield of factor VIII coagulant activity is considerably reduced, so that the cost is likely to be at least 4 fold higher - ?40p per unit. Trials have been carried out in Germany, but no published information is available. At least 30 patients have been studied.

All products except those derived from NHS factor VIII are made from plasma imported from the U.S.A., and, therefore, they carry a putative risk of transmission of AIDS. It is evident that 8 products will be shortly available on the market and, unless these

/are

are coordinated, there will not be enough patients available to evaluate each product carefully.

We would therefore ask that you take the following action:-

(1) Draw up a list of patients in your Centre who might be suitable for such a trial on the basis of previous blood product exposure, and who are likely to require treatment with factor VIII in the near future.

(2) Notify Miss R.J.D. Spooner at the Oxford Haemophilia Centre of the number of such patients available.

(3) If approached by a Pharmaceutical Company or you are proposing to try one of the NHS products, please let Miss Spooner know what product you intend studying and how many patients will be involved. She will circulate information about all the trials, so that any patients still available who are uncommitted can be used for one of the remaining products, subject to the wish of the local Haemophilia Centre Director.

(4) It is important to ensure that each Company obtains an exemption from a clinical trial certificate from the U.K. Licensing Authority. Studies conducted on a named patient basis carry no protection under the Medicines Act, as the patient's doctor and not the Pharmaceutical Company carries the liability for compensation arising out of unexpected hazards which come to light as part of the trial.

(5) We suggest that the protocol circulated by the Hepatitis Working Party last year should form the basis for the studies. Dr. Craske would be grateful for serial specimens from patients studied to form the basis of a collection for study if markers for non-A, non-B hepatitis become available.

We hope that Directors will collaborate as suggested in this document so that the maximum information about the relative merits of different products will become available with the most economical use of the limited number of patients available.

A.L. Bloom
Chairman, Haemophilia Centre Directors Organisation

John Craske
Chairman, Haemophilia Centre Directors' Hepatitis Working Party

C.R. Rizza
Secretary, Haemophilia Centre Directors Organisation

HEMOPHILIA INFORMATION EXCHANGE

AIDS UPDATE

October 13, 1984
MEDICAL BULLETIN #15
CHAPTER ADVISORY #20

THE NATIONAL HEMOPHILIA FOUNDATION MEDICAL AND SCIENTIFIC ADVISORY COUNCIL

RECOMMENDATIONS CONCERNING AIDS AND THE TREATMENT OF HEMOPHILIA

(Revised — October 13, 1984)

I. Recommendations for physicians treating patients with hemophilia:

A. For patients with factor VIII deficiency, it is recommended that cryoprecipitate be used to treat patients in the following groups, with the recognition that there are some circumstances where viral attenuated (heat-treated) factor VIII concentrate may be appropriate therapy:

- newborn infants and children under 4;
- newly identified patients never treated with factor VIII concentrates.

Similar guidelines should be applied to factor IX deficiency patients where fresh frozen plasma can be used.

B. Desmopressin (DDAVP) should be used whenever possible in patients with mild or moderate hemophilia A. When desmopressin does not provide adequate treatment, these patients should be treated as specified in A.

C. We do not yet have sufficient data of scientific nature to know with certainty that viral attenuated (heat-treated) coagulation factor concentrates should now be universally adopted. However, very preliminary data do suggest that HTLV-III is heat sensitive. Further, we do not know whether hemophiliacs who are positive for antibody to HTLV-III have been exposed to living virus capable of causing AIDS, or have developed effective immunity against AIDS.

Because heat-treated products appear to have no increase in untoward effects attributable to the heat treatment, we now recommend that treaters using coagulation factor concentrates should strongly consider changing to heat-treated products with the understanding that the protection against AIDS is yet to be proven. We again urge a prospective national study of the use of these and other materials in patients not previously exposed to pooled blood products. In addition, further basic studies on the efficacy of viral attenuation procedures are urged. The Medical and Scientific Advisory Council will continue to review its position on heat-treated products as more complete studies become available.

D. All elective surgical procedures should be evaluated with respect to the possible advantages or disadvantages of a delay.

E. We reaffirm our position that patients continue treating bleeding episodes with clotting factor as prescribed by their physicians, as the risks of withholding treatment far outweigh the risks of treatment. Therefore, it is important that patient education and psychosocial support be provided.

(over)

II. Recommendations to factor VIII concentrate manufacturers:

A. Serious efforts should be continued to exclude donors that might transmit AIDS.

1. Blood and plasma donation should not be obtained from prospective donors who are members of groups who are at higher risk of contracting AIDS. Such groups include: male homosexuals; intravenous drug users; those who have recently resided in Haiti; and sexual partners of members of those groups who are at higher risk. This effort should make use of educational materials and questionnaires in a discreet and sensitive manner.

2. Prospective blood donors should be excluded if they have symptoms associated with AIDS. This should be done by direct questioning and physical examinations as recommended by the Food and Drug Administration, Office of Biologics (March 24, 1983).

3. Research is encouraged in the evaluation and implementation (if verified) of surrogate laboratory tests that would identify individuals at high risk of AIDS transmission. With regard to HTLV-III testing, we urge the continued rapid development and study of this and other laboratory tests which can identify blood donors at risk of transmitting AIDS. When the sensitivity and specificity of HTLV-III antibody testing or other such tests are found to be sufficient, as verified by clinical trials, these tests should be then applied to all blood and plasma donors as soon as feasible.

4. Until effective blood donor screening methods are available, manufacturers should continue to avoid using plasma obtained from donor centers that draw from population groups in which there is a relatively high AIDS incidence.

B. Efforts should be continued to expedite the development of processing methods that will inactivate viruses potentially present in all clotting factor concentrates.

C. There should be an evaluation of the possibility that the yield of factor VIII in pheresis donors could be increased using DDAVP or exercise to maximize yield. This would permit a reduction in the size of the donor pool and would compensate for losses in plasma that might occur due to steps noted above.

D. Concentrate manufacturers should immediately cease purchase of recovered plasma for factor VIII concentrate from blood centers that do not meet criteria listed in II. A above. These criteria should also apply to the production of cryoprecipitate.

E. Manufacturers should withdraw any lot of concentrate if it includes material from an individual that has been identified as having AIDS, or from an individual that, in the best medical judgement of the manufacturers, has characteristics strongly suggestive of AIDS.

F. Manufacturers should accelerate efforts towards the production of coagulation factor concentrates by recombinant DNA technology. When such materials are ready for clinical trials and for introduction into clinical use, the necessary review processes should be carried out as expeditiously as possible.

III. Recommendations to regional and community blood centers:

The production of cryoprecipitate should also adhere to criteria detailed in II. A above.

The HEMOPHILIA INFORMATION EXCHANGE, under the aegis of The National Hemophilia Foundation, is made possible with funding support from the Division of Maternal and Child Health of the United States Department of Health and Human Services.

HAEMOPHILIA CENTRE DIRECTORS ORGANISATION

AIDS Advisory Document

At a recent meeting of Reference Centre Directors the following observations were discussed and recommendations made in consultation with Drs. Richard Lane, John Cash, Harold Gunson, Phillip Mortimer, Richard Tedder, John Craske and others.

Background

1. In U.S.A. There are over 6,000 cases of AIDS including 52 haemophiliacs.

   In U.K. There have been 102 cases with three reported haemophiliacs. No doubt other cases are developing in the haemophilic population.

2. Tests for HTLV III antibody are available for haemophiliacs via:
   Dr. Phillip Mortimer
   Central Public Health Laboratory Service
   175 Colindale Avenue
   Colindale, London NW9 5HT.

   Dr. Richard Tedder,
   Department of Virology
   School of Pathology,
   The Middlesex Hospital Medical School,
   Riding House Street,
   London W1P 7LD.

   Antibody positivity probably correlates with exposure to imported concentrates but there have been two notable recent episodes concerning U.K. concentrates.

3. Antibody tests indicate prior infection but do not imply immunity as antibodies may not be neutralising. Infective carriers can be antibody positive and there may also be a variable period of antigen positivity before seroconversion occurs.

   Antibody positive persons should therefore be considered at risk of transmitting or developing AIDS but antibody negativity does not exclude infectivity.

General Precautions

Donors

(a) the BTS is making increased efforts to ensure exclusion of donors at risk by questionnaires or leaflets or both.

(b) HTLV antibody tests either commercial or home grown should become available during 1985 but cannot be instantaneously implemented. Equipment, space and staff may be needed at Regional Transfusion Centres.

It seems probable that HTLV III has been incorporated into at least one BPL and one Scottish batch of factor VIII. Recipients are being followed up.

Concentrates

Factor VIII. Evidence is accruing that HTLV is heat labile but the data from "spiked" concentrate is entirely related to U.S. concentrates and is minimal. It seems that in concentrates HTLV III is inactivated by dry heat at 68°C for 24 hours. It is unlikely that this process completely inactivates Non A Non B hepatitis . Loss of yield is 15% for dry heat. Wet heat with stabilisers is probably more effective but evidence is lacking and loss of yield is up to 50%. Of current products heat treated Koate HT and Factorate HT are dry heated and sell at 12p a unit. Travenol Hemofil T is dry heat treated and sells at 15p a unit. Alpha Profilate (heated) is wet-treated (14p a unit). Immuno also have heated preparations.

Factor IX Profilnine (heated) (Alpha), heated Konyne (Cutter) and Immuno (heated Prothromplex) are available at prices up to 20p a unit but the effects on efficacy and thrombogenicity are unpublished. Since AIDS and laboratory changes seem (controversially) to be less common in Christmas disease than haemophilia A no firm recommendation can be given on heated factor IX.

Heated Feiba is also available from Immuno at 30p a unit but is probably not cost-effective.

BPL Factor VIII BPL can dry heat 30% of its output available from January 30th, 1985 and the rest in two months time when two more ovens are installed to supplement the existing one. The process produces an acceptablein vitro product but extensive clinical trials have not been undertaken.

Edinburgh From now on all Scottish factor VIII will be dry heated to supply Scotland and N. Ireland.

Options in probable decreasing order of safety from AIDS for Haemophilia A

1. Heated U.K. concentrate (note: still NANB hepatitis risk)
2. Single donor cryo. or FFP
3. Heated imported conc. (note: still NANB hepatitis risk)
4. Unheated U.K. conc.
5. Unheated imported conc - almost certain to be contaminated.

Note: Heated concentrates may still transmit hepatitis. Some of the distinctions e.g. between 3 and 4 are debatable and the long-term effects (e.g. immunogenicty) of using heated plasma proteins in this way are unknown. Even pasteurised albumin is not given as frequently to individuals as will be factor VIII.

RECOMMENDATIONS

1. Concentrate is still needed, bleeding is the commonest cause of disability and death.

2. Use DDAVP in mild Haemophilia A and vWd if possible.

3) For Haemophilia A needing blood products

(a) "Virgin" Patients those not previously exposed to concentrate, and childr use cryo or heated NHS factor VIII (if available).

(b) Severe and Moderate haemophiliacs previously treated with factor VIII use heat treated NHS factor VIII, if available or heat treated US commercial.

4) Haemophilia B

(a) Mild Christmas Fresh frozen plasma if possible (otherwise NHS Factor IX.

(b) "Virgin" Patients and those not previously exposed to concentrate use fresh frozen plasma (or NHS factor IX concentrate if essential)

(c) Severe and Moderate Christmas Disease previously exposed to factor IX concentrate continue to use NHS factor IX.

In individual patients there may need to be a choice. In general heated concentrate appears to be the recommendation of virologists consulted but individual Directors may wish to make up their own minds. This is particularlytrue of unheated NHS material. The evidence that heated U.S. factor VIII is safer than unheated NHS is debatable and some Directorsmay wish to continue using unheated NHS material until all supplies are heated. This is valid for carefully selected patients but must be on individual decision based on the assumption that some batches of NHS materials will be contaminated with HTLVIII. The argument that HTLV III positive patients have already beeninfected and could receive unheated American material is probablyscientifically true but this material would pose an additional risk to staff and families and its continued use would pose logistic problems.

Supplies

It seems that as from January 30th, 1985 a limited supply of BPL heat treated British factor VIII will be available. Preference will be given (a) to treat patients defined in recommendation 3a above and possibly (b) to those willing to participate in clinical trials.

NOTES

1. The Blood Products Laboratory cannot take back for reissue unused unheated concentrate. Do not ask your BTS to order more of this than you are willing to use because this would prejudice supplies of heated material later in the year.

2. If the bill for heated commercial concentrate is heavy at first it can be put to your Authority that increasedsupplies of heat treated BPL material could be available later in the Summer asstockpiled unheated material at BPL is heated.

3. Funding will need to be negotiated at local level although strong representations are being made to DHSS for central funding if needed. Please inform the Chairman (Prof A.L. Bloom) and Secretary (Dr. C.R Rizza) if you are experiencing difficulties. They cannot promise individual help but the information will be useful.

4. The need for elective surgery etc., should be assessed in the light of supplies of heated concentrate.

ANTIBODY TESTING

It is recommended that patients be HTLV III Ab tested.

Test should be repeated if positive.

Ab positive people should be informed, reassured and counselled regarding transmission to spouses etc., including the possible use of barrier contraception. This seems to be the most practical method available. Facilities are only available at present for HTLV III Ab studies on contacts as part of organised projects. Please note that sample bottles of serum must be leak-proof. The Laboratory Directors would prefer to liase with a small number of haemophilia doctors. Thus where possible samples should be chanelled through Reference Centres or the nearest large Haemophilia Centre from where suitable sample bottles may be obtained.

ORDINARY LABORATORY TESTING

Samples from patients with AIDS or PGL will be subject to the regulations promulgated by the AdvisoryCommittee on Dangerous Pathogens. Although very restrictive draft instructions have been circulated in an unauthorised fashion in various quarters we were assured that the definitive document is less so. Careful safety auditing of laboratory procedures is recommended. The recommendations apply to AIDS and high suspect patients. The rules for samples from healthy HTLV III Ab positive patients have not been specifically addressed but presumably these are also potentially dangerous.

CLINICAL

Plastic aprons could be used for preparing and administering all treatments (including home treatment). Home treatment procedures should be reviewed. Use of butterfly needles may be safer than ordinary syringe and needle as the risk of 'walk on' injury is reduced.

In the wards patients with AIDS or high risk thereof should be nursed in single rooms. Gloves and aprons should be worn by nurses when carrying out practical procedures. In general hepatitis B-like precautions should be taken. HTLV III Ab pos. patients should be dealt with for Dental care as for hep. BAg pos. In case of needle injuries virological advice from PHLS at Colindale should be obtained after applying the usual first aid measures. Aerosols and casual contacts do not constitute a risk and there is no need to isolate routinely HTLV III Ab positive patients.

STAFF

HTLV III Ab testing of staff is not recommended routinely but it could be useful to have organised studies in certain larger centres.

These recommendations will obviously need to be modified in the light of rapidly changing experience.

December 14th, 1984

APPENDIX 7

BLOOD PRODUCTS LABORATORY

National Blood Transfusion Service

Director:
R.S. LANE, MD MRCP MRCPath.

Telephone: 01-953-6191

Dagger Lane,
Elstree,
Borehamwood,
Herts WD6 3BX.

Our Ref.:PI8HT/02

7th February, 1985

Prof.A.L.Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park,
Cardiff,
CF4 1XW

Dear Prof. Bloom,

Supplies of Heated Factor VIII Concentrates - An Update

As you may have been informed by the Director of your Regional Transfusion Centre, stocks of the heated intermediate purity factor VIII concentrate will be distributed via Transfusion Centres, thereby guaranteeing satisfactory Regional allocation of resources. The first dispatches of concentrate should be possible in late February, and subsequently at monthly intervals.

Each consignment to an RTC will comprise individual packages identified for onward transmission to a designated haemophilia centre director. If you have not already written advising me of the names of patients you wish to treat with the heated NHS concentrate, I would be grateful if you could do so urgently. Without this information it will not be possible for BPL to make a sensible allocation of product within any region.

Several Haemophilia Centre Directors have enquired about the availability of heated factor IX concentrates. Acknowledging the thromboembolic potential of any prothrombin complex concentrate (heated or unheated), BPL are concerned that heated factor IX concentrate should be subjected to extended safety testing, including assessment in a dog model, prior to release for clinical use. This work is progressing and we confidently expect to be in a position to begin general issue of a heated factor IX concentrate during July.

Yours sincerely,

GRO-C

T.J.SNAPE
Head of Quality Control
jg

NATIONAL BLOOD TRANSFUSION SERVICE (WALES)
GWASANAETH CENEDLAETHOL TRALLWYSO GWAED (CYMRU)

Welsh Regional Transfusion Centre
Rhydlafar
Cardiff CF5 6XF

Tel: (0222) 890302

Director:
J.A.F. Napier, PhD, FRCPath

JAFN/pw.

Professor A.L. Bloom,
University Hospital of Wales,

Dr. H. Jones,
Consultant Haematologist,
Cardiff Royal Infirmary.

29th January, 1985

Dr. S. Ismail,
Consultant Haematologist,
Morriston.

Dear Colleagues,

re: Factor VIII Concentrates.

I circulated to each of you a copy of a letter from Mr. N. Pettet (BPL) dated 14th December, concerned with supplies of non-heat treated Factor VIII material.

As I have not heard from you can I take it that supplies of non-heat treated material are not required in the Welsh Region, and also that you are happy to use heat treated material as and when it becomes available as described in the letter from Mr. Pettet dated 23rd January, a copy of which I now enclose.

With best wishes.

Yours sincerely,

GRO-C

J.A.F. Napier.

BLOOD PRODUCTS LABORATORY

National Blood Transfusion Service

Director:
R.S. LANE, MD MRCP MRCPath.

Telephone : 01-953-6191

Dagger Lane,
Elstree,
Borehamwood,
Herts WD6 3BX.

Our ref : NP/KF

23rd January 1985

The Director
Welsh Regional Blood Transfusion Centre
Rhydlafar
St. Fagans
Cardiff
CF5 6XF

Dear Dr. Napier,

Progress Towards A National Supply of HT-Factor VIII

In my letter of 14th December 1984, I summarised the then current situation with regard to HT and non-HT Factor VIII and Factor IX concentrates. I am now able to provide further information on the progress towards a national supply of HT-Factor VIII, and the resultant effect on the pro-rata supply of the product.

Since the 14th December, we have restricted issue of non-HT Factor VIII to only those Regions who have indicated that this material will be used until supplies of HT-Factor VIII are available. Out of some 15000 vials of labelled non-HT product it is expected that approximately 9000 will be used between now and April, unless the circumstances surrounding its use are altered.

All batches of Factor VIII produced to December have been sampled and tested as to their availability for heat-treatment. Results so far have shown a loss of 20-25% on the original activity within the vial. Consequently, for those batches where heat-treatment can be applied, the activity per vial has been reduced to an average of 165-185 iu per vial. Batches not considered suitable for heating (either because the original activity per vial was low, or the solubility on reconstitution after heating would be too prolonged) have been passed to stock as non-HT Factor VIII.

All batches processed since December have been subjected to heat-treatment with the intention that they be released as HT-Factor VIII. The extra equipment ordered for a full heat-treatment programme is on schedule for delivery by March. It is expected that for the period January to April, we can make available 12-15,000 vials of HT-Factor VIII for use on a named patient basis. In addition, some vials are being made available now for pre-trial evaluation. Dr T J Snape, Head of Quality Control, BPL will shortly be writing to all Haemophilia Centres, advising them of the protocol to be followed in the use of HT-Factor VIII issued from BPL.

It is confirmed that supplies of HT-Factor VIII will remain issuable on a limited basis only until large scale manufacture of the product can be made in April. A new formulation product is now undergoing pilot production trials and it is hoped that this product will eventually replace the present heat-treated HL (and 8CRV) product.

As the HT-product will be unlicensed, all issues will be made on a named patient basis specifically labelled and packaged for use by a named clinician. It is assumed that unless directed otherwise, all issues will be made direct to the treatment centre, and will continue until a product license is obtained. It is expected that product requests will also be made directly to BPL.

Effect on pro-rata supply

Prior to January 1st 1985, supply of Factor VIII to Regions was via the RTC, and was pro-rata to the regional plasma input at BPL. Production capacity at BPL is limited to an output of 30 million iu (120,000 x 250 iu) per annum. The losses incurred through heat-treatment will reduce this total to at least 24 million iu p.a. for a 20% loss in yield. If higher losses are seen, then this figure will be further reduced. Much will depend on the yield obtained with the new formulation product where it is expected that the yield loss will be much smaller (if any) than with the present product.

For the interim period, Jan - April, pro-rata supply has been suspended, although plasma inputs will still be credited on a regional basis. Monthly returns of plasma inputs will still be produced. However, through the necessity of the heat-treatment programme, Regions should not expect a backdated return of non-issued product for this interim period unless non-HT product is requested. Until the new plant is in full manufacture, there can be no 'catching-up' in the present production facility, if this is ever possible. Thus Regions who have not taken up the option of non-heated product for this period should not expect an equivalent return of HT product in the short or medium term.

In order for Regions to maintain control over the use of Factor VIII, BPL will issue on a monthly basis to Regional Transfusion Directors an inventory of product supplied to each Region. It is emphasised that unlicensed product will be issued only if compliance with the protocol for use is agreed and maintained. Further information on this last aspect can be obtained from Dr T J Snape at BPL.

If there are any further points you wish to discuss, please do not hesitate to contact me at your convenience.

Yours sincerely

GRO-C

N Pettet
Product Services Manager

cc Col. R.C. Deacon,Army Blood Supply Depot,Aldershot,Hants,GU11 2AF

cc Haemophilia Reference Centre Directors

cc Regional Medical Officers, England & Wales

cc Mr A Williams,DHSS, Hannibal House,Elephant & Castle,London SE1 6TE

cc Mr W P N Armour,Central Blood Laboratories Authority

4th February, 1985.

Dr. J.A.F. Napier,
Director,
National Blood Transfusion Service (Wales),
Rhydlafar,
Cardiff. CF5 6XF.

Dear Tony,

. Thank you for your letter and I write to confirm that we will not require unheated factor VIII. We will reqqire some heat-treated material but according to the dictat from Elstree, we have to go directly to them for this.

All best wishes,

Yours sincerely,

A.L. Bloom.

BLOOD PRODUCTS LABORATORY

National Blood Transfusion Service

Director:
R.S. LANE, MD MRCP MRCPath.

Telephone : 01-953-6191

Dagger Lane,
Elstree,
Borehamwood,
Herts WD6 3BX.

24 July 1985

To: Haemophilia Directors, England & Wales.
Regional Transfusion Directors, England & Wales

INFORMATION SHEET: JULY 1985

DRIED FACTOR VIII CONCENTRATE:- HIGH PURITY, HEAT-TREATED

As reported in the Information Sheet (May 1985), a new Factor VIII concentrate (type 8Y) is now replacing the intermediate specific activity products HLH and 8CRVH. General issue will begin from September 1st 1985.

This high purity product, containing a nominal 250 iu per vial has been dry heated at 80°C for 72 hours to reduce the risk of infection by viral agents, although further assurance is sought over freedom from risk of viral transmission.

Solubility is much improved over HLH and 8CRVH; the vial containing less than 25 g/l total protein (expected range 6 - 14 g/l) in a reconstitution volume of 10 ml. A more detailed product information sheet is enclosed with this circular.

Safety and efficacy trials of the 8Y concentrate are already proceeding at several Haemophilia Centres. As of 1st July 1985, eight patients receiving fourteen infusions of three batches of concentrate have shown dose responses in the range 1.1 - 2.9, and a mean half-clearance time of 10 hours, entirely consistent with experience of unheated concentrates.

Clinical trials at six Haemophilia Centres are in progress to gain evidence of reduction or elimination of viral transmission, and several patients have safely passed the point at which first evidence of NANBH virus transmission would normally occur with unheated Factor VIII.

In accordance with the regulatory requirements, the product should be issued by clinicians on a named patient basis until a product licence has been granted: a product licence application will be lodged with The Medicines Division in the Autumn.

Factor 8Y will be issued through Regional Blood Transfusion Centres, unless special provisions exist by agreement for product to be sent direct to the Haemophilia Centre. Allocations to the BTS will observe the Pro Rata requirements for distributions agreed between BPL and the BTS except for 8Y required to fulfil the special needs of clinical trials to provide information for product licence application.

It is recognised that, until the new production unit at Elstree is completed, output of 8Y will meet about one third of current demand for concentrate and for this reason, attempts have been made to define those patients likely to benefit most from the security inherent in 8Y.

Therefore, Haemophilia Centre Directors are being asked to compile lists of their patients considered 'at risk' and most Centres have complied. It is the considered view at BPL that, where possible, liaison between the Haemophilia Services and the BTS should aim at directing Factor 8Y to these patients, using the existing framework of distribution and supply.

Haemophilia patients who are HTLV III Ab negative and have no history of hepatitis are being identified as suitable persons to comply with clinical trial requirements. This treatment group is under separate discussion between the Trial Centres and BPL. For your information, a trial protocol is attached.

For any further information, please contact:

Product Services Department
01-953-6191 Extn. 200

F8/7/85

To the Medical and Pharmaceutical Professions only
DRIED FACTOR VIII FRACTION, HIGH PURITY, HEAT-TREATED

1. Dried Factor VIII Fraction, high purity, heat-treated (type BY) is a purified dried concentrate prepared from large pool fresh frozen plasma obtained from donors of the National Blood Transfusion Service. Each unit of plasma has been found negative for HBsAg using a third generation test capable of detecting at least 2 BSU/ml.

2. The product has been prepared using a new highly selective procedure to remove most of the fibrinogen and fibronectin, leaving factor VIII in solution. After recovering the factor VIII from the supernatant by precipitation with glycine and sodium chloride, the factor VIII is redissolved at high potency.

   Precipitants are removed by gel filtration and are replaced by a solution of lower ionic strength containing stabilisers. The solution is sterilised by filtration, lyophilised and subjected to dry heating at 80°C for 72 hours, to reduce the risk of infection by viral agents (including hepatitis and AIDS viruses) but it cannot be assumed to be free from viral infection.

3. Sucrose, at a level not greater than 200 mg/vial is added to the product prior to lyophilisation. This may be of significance in the interpretation of the results of some biochemical tests.

4. Each vial of product contains the labelled amount of Factor VIII:C activity as determined by assay, expressed in international units (iu). The product should be reconstituted before use, <u>using the volume of Water for Injections indicated on the label.</u>

5. The heating conditions used have little or no effect on the factor VIII content or solubility of the concentrate.
   Additionally, after heating

   a) Prekallikrein activator activity and pH are unchanged and no other parameter measured in conventional pharmacopoeial tests (including animal tests for pyrogen and acute toxicity) is altered.
   b) The product has a specific activity in excess of 2 iu factor VIII/mg protein, some ten times greater than intermediate purity concentrates HL or SCRV.
   c) There is little or no effect on the electrophoretic properties of the concentrate.
   d) Preliminary studies indicate that the in vivo recovery and clearance of Factor VIII:C activity are unaffected.

6. <u>VIRUS INACTIVATION</u>

   Published experiments now suggest that heating lyophilised Factor VIII concentrates at 68°C for 72 hours will inactivate infectious ARV (1); but this remains to be confirmed by prospective studies.

   The heating conditions used for this product (80°C for 72 hours) are more severe than those used in published attempts to inactivate HANBH (2)(3) and would be expected to inactivate the "model" retrovirus used by Levy et al (4).

Non-transmission of virus can only be confirmed by follow-up studies after clinical infusion.

7. **STORAGE**

The label carries the instruction: "Store in the dark below +6°C". Short periods of storage at normal ambient temperature are not deleterious.

8. **POTENCY**

The label carries a statement of the activity in terms of blood coagulation factor VIII expressed in International Units (iu), as established by the World Health Organisation.

9. **DOSE**

The number of units needed and duration of treatment depend on the lesion being treated. If the rise in the concentration of factor VIII in the plasma following administration of concentrate is expressed in international units per 100 ml plasma and the total dose given in international units of factor VIII per kg body weight is calculated, "the response" is defined as follows:

$$\text{Response} = \frac{\text{Rise in plasma factor VIII (in iu per 100 ml)}}{\text{Dose in iu/kg body weight}}$$

The 'theoretical value' of 2.4 for this ratio is rarely reached. It is variable even in the same patient; a range of 1.6 - 2.2 is usual but values outside this range may be found. A low value may indicate that the patient's plasma contains an antibody to factor VIII and appropriate tests should be done.

The following table indicates the approximate levels of factor VIII required for haemostasis in various circumstances.

Lesion	Concentration of factor VIII desired in patient's blood immediately after transfusion (iu per 100 ml)	Initial dose of factor VIII (iu/kg body weight)
Minor spontaneous haemarthrosis, and muscle haematoma	15 to 20	7 to 13
Severe haemarthrosis and muscle haematoma, haematoma in potentially dangerous situations; haematuria	20 to 40	9 to 25
Major surgery	See below	

A dose of 1 iu/kg will give, on average, a rise of about 2 iu/100 ml plasma. If the desired concentration or clinical response is not

achieved, another dose should be given the same day. If an abnormally low response persists, carry out a test for specific antibody to factor VIII. The doses mentioned are only rough guides since there is considerable variation in response from patient to patient. It is usual to give the contents of the number of whole vials nearest to the calculated dose. Doses may be repeated at intervals of 8, 12 or 24 hours as needed to maintain the desired concentration of factor VIII.

10. **MAJOR SURGERY**

Major surgery should be undertaken only where there are facilities for assaying factor VIII so that the patient's response can be assessed. The patient's plasma should be tested for antibody to factor VIII before operation. If antibody is not present, a pre-operative dose of 35 to 50 iu per kg is given to raise the plasma factor VIII concentration to 80% or more of average normal. During the first few days after operation the plasma factor VIII concentration is monitored and the dose repeated 6-hourly or 8-hourly as needed, so that the concentration does not fall below 30 - 50% of average normal. After the first few days the frequency of the dose may be reduced. The course of treatment is usually continued for ten days or longer.

As indicated previously, if the plasma factor VIII concentration does not reach the expected level, or falls off with a reduced half-life (less than twelve hours), the presence of an antibody to factor VIII should be suspected and the appropriate laboratory tests done. The treatment of patients with antibodies to factor VIII is outside the scope of these notes.

11. **RECONSTITUTION**

The container of concentrate and the Water for Injections should be brought to 20° - 30°C, prior to removal of the "flip-off" closures. The volume of Water for Injections indicated on the product label is drawn up into a suitable syringe, and the syringe transferred to the vial containing the product. On piercing the seal, water will be drawn into the vial which is under vacuum. (In the unlikely event of there being no evidence of a vacuum, the vial must not be used and the defect should be reported to BPL Quality Control at the address given below). The container is agitated gently until solution is complete before releasing the vacuum. A clear or slightly opalescent solution is usually obtained in about fifteen minutes or less. If a gel or clot forms discard the solution and inform BPL Quality Control. Should more than one vial be required to make up the dose, the contents of the required number are pooled. The solution should be used immediately, and in any event within 3 hours.

12. **ADMINISTRATION**

The solution should be drawn from the vial into a plastic disposable syringe through the filter needle supplied with the product. For administration, a Number 21 "butterfly" needle is convenient. Although the material is unlikely to cause side effects, the dose, especially the first dose, should be given slowly (approximately 3 ml per minute). The solution must not be stored and infusion should be completed within three hours of reconstitution. It should not be given by "continuous infusion", over many hours, and it must not be added to or mixed with any other fluid given, including whole blood.

13. **WARNING**

(1) The material contains blood group antibodies derived from the starting plasma in amounts which are insignificant in the normal treatment of haemarthroses and muscle haemorrhage. If very high dosage is necessary in patients with blood groups A, B or AB, the patient should be monitored for signs of intravascular haemolysis.

(2) Patients congenitally deficient in factor VIII may develop antibodies to factor VIII following treatment. This risk does not appear to be increased by the use of concentrate (5) but patients should be monitored from time to time, especially if there is any doubt about the clinical effectiveness of a dose of factor VIII.

14. **CAUTION**

Circumstances outside the control of BPL can reduce the efficacy of the product. It is important that instructions for storage and handling and reconstitution are followed.

Where possible, pre and post-infusion factor VIII assays should be carried out, at least for the first course of treatment. It is recommended that where the patients treatment history permits, follow-up studies be made to confirm freedom from viral infection.

Observations on response to treatment and results of follow-up studies should be returned to Dr J.K. Smith, Plasma Fractionation Laboratory, Churchill Hospital, Oxford, using the forms provided.

15. **REFERENCES**

(1) Levy et al. Inactivation by wet and dry heat of AIDS-associated retrovirus during Factor VIII purification from plasma. Lancet p.1456/7, June 22, (1985)

(2) Dolana et al. Continued observations on the effect of a heating procedure on the inactivation of HANDK and NB viruses in clotting factor concentrates.
Thrombosis and Haemostasis 50 115 (1983)

(3) Mosen et al. Heat inactivation of viruses in AHF concentrates. WFH XVI Congress, Rio de Janeiro, (1984).

(4) Levy et al. Recovery and inactivation of infectious retroviruses added to factor VIII concentrates.
Lancet p.722/23. Sept 29 (1984)

(5) Bigge, R. Jaundice and antibodies directed against factor VIII and IX in patients treated for haemophilia or Christmas disease in the United Kingdom. British Journal of Haematology, 26, 313-329. (1974)

These notes are intended for guidance in the use of Dried Factor VIII, Type 8Y, manufactured and distributed by:
BLOOD PRODUCTS LABORATORY, ELSTREE, HERTS WD6 3EX

July 1985

Tel: 01-953 6191.

Clinical response to heated high-purity factor VIII concentrate

DESCRIPTION OF PRODUCT

Unlike heated concentrates of "intermediate specific activity" currently provided as an emergency measure by BPL/PFL to combat possible transmission of AIDS, this concentrate 8Y has been designed to withstand severe physical treatments which can be expected to inactivate hepatitis viruses as well as HTLV III. At this point in product development, inactivation is by unusually severe heating of the freeze-dried concentrate in its final container.

Cryoprecipitate extract undergoes a new, highly selective procedure to precipitate most of the fibrinogen and fibronectin, leaving factor VIII in solution. After recovering factor VIII from the supernatant by precipitation with glycine and sodium chloride, the factor VIII is redissolved at high potency. The precipitants are removed by gel filtration and replaced by a solution of lower ionic strength containing stabilisers. The solution is sterile filtered, freeze-dried and subjected to protracted heating. The heating conditions have little or no effect on the factor VIII content, solubility or electrophoretic properties of the concentrate. pKA and pH are unchanged and no other parameter measured in conventional pharmacopoeial tests (including animal tests for pyrogen and acute toxicity) is altered. The effects of protracted heat on 8Y are significantly less marked than those observed in 8CRV or HL concentrate heated under less severe conditions, i.e. 70° for 24h or 60° for 72h.

Unpublished experiments suggest that the heating conditions used should inactivate HTLV III added to similar concentrates[1], but this remains to be confirmed by clinical infusions. Heating conditions are more severe than in some published attempts to inactivate NANBH[2][3] and would be expected to inactivate completely the "model" retrovirus used by Levy et al[4]. However, as always in this work, the precise constituents of the medium, including its moisture content, may have an unpredictable effect on rates of virus inactivation. Only clinical trial can confirm non-transmission of NANBH, which has a near-100% incidence in previously untreated patients infused with unheated large-pool concentrates. Although this product has a specific activity (purity) some 10 times greater than intermediate purity concentrates such as HL or 8CRV, the electrophoretic patterns might not reveal changes in the F.VIII:C molecule after heating which might nevertheless result in changes in immediate recovery of infused factor VIII or its rate of disappearance from the circulation. We therefore seek evidence of normal efficacy.

Detailed constituents of this batch of product, after resolution in the suggested volume of Water for Injections, are listed in the attached facsimile of our quality control record.

References

(1) Centres for Disease Control. Update: Acquired immunodeficiency syndrome (AIDS) in persons with haemophilia. MMWR 33, 589-91 (1984).

(2) Dolana et al. Continued observations on the effect of a heating procedure on the inactivation of NANBH and HB viruses in clotting factor concentrates. Thrombosis and Haemostasis 50, 115 (1983).

(3) Mozen et al. Heat inactivation of viruses in AHF concentrates. WFH XVIth Congress, Rio de Janeiro, 1984.

(4) Levy et al. Recovery and inactivation of infectious retroviruses added to factor VIII concentrates. Lancet p. 722/23, Sept., 1984.

BLOOD PRODUCTS LABORATORY, DAGGER LANE, ELSTREE, HERTS., WD6 3BX.
Tel: 01-953 6191.

Protocol for follow-up study of patients receiving heated high-purity factor VIII concentrate 8Y.

Patients to be treated and followed up

The physician in charge shall nominate to BPL those patients who may receive heat-treated concentrate and acknowledge receipt of individual batches of concentrate assigned to each patient or group of patients.

Information is sought on the safety, efficacy and possible transmission of virus diseases only on patients:

(a) not suspected of having liver disease at presentation (see definition of hepatitis below).

(b) having received no more than two transfusions of any blood product in the last 12 months.

(c) having received no blood products in the previous six months.

(d) found to have their serum negative for HBsAg, anti-HBs and anti-HBc.

(e) giving informed consent.

Procedure

(1) At first presentation for treatment with this concentrate 8Y, each patient will undergo a clinical examination with specific reference to liver disease. A record should be made of his detailed transfusion history and past attacks of hepatitis. Pre-treatment LFTs and tests for HB markers will be recorded. Blood will be taken for HTLV III antibody testing, immediately if possible, or a serum sample kept frozen for retrospective testing. Pre-treatment serum will be stored frozen for retrospective tests should the patient show later laboratory or clinical signs of infection, or should e.g. tests for NANBH be developed. If a patient is seen in an emergency, the control "pre" blood sample may if necessary be taken within 24h of first infusion with heated factor VIII.

On at least the first occasion on which the patient is treated with this concentrate, pre- and 30 minute post-infusion factor VIII assays are required, with further assays during the next 24h if this can be arranged, to confirm whether the half-disappearance time is in the usual range. It is assumed that on the patient's first infusion with the new concentrate, the physician will wish in any case to observe the patient for an hour or more in case any idiosyncratic unwanted reaction should occur.

Part 1 of the follow-up form will be started, and completed at the end of the course of treatment. Fresh Part 1 (Extension) sheets may be attached if there is not enough space to cover all infusions and factor assays in the first treatment. Part 1 will be photocopied to Dr. J.K. Smith, PFL, immediately after completion.

Part 2 of the follow-up form should also be started, to include the results of pre-infusion tests.

(2) At specified intervals after infusion, or at recorded dates as near as possible to these intervals, further blood samples will be taken for LFTs, hepatitis B markers and HTLV III antibody as indicated in Part 2

of the follow-up form. As with the "pre" sample, the replicate samples should be kept for retrospective tests. Part 2 should also be used for monthly post-infusion tests for HTLV III antibody, which may be done retrospectively on stored samples; this frequency may be altered during the course of the trial as new evidence accumulates on the range of delays between infection and seroconversion.

It must be emphasised that even monthly follow-up testing for LFTs and hepatitis markers, or samples which may be tested retrospectively, may provide very important information where the patient is not seen at the stated intervals.

On completion of each sub-table of Part 2, i.e. after 8, 24 and 52 weeks follow-up, Part 2 will be photocopied to Dr. J.K. Smith, PFL.

(3) If the patient shows laboratory or clinical signs of viral hepatitis, the clinician will initiate investigations, probably including anti-HBc, anti-HAV IgG, anti-HAV IgM, CMV and EBV. The physician should report to Dr. T.J. Snape, BPL, or Dr. J.K. Smith, PFL, his interpretation of these investigations, specifically which type of hepatitis has been diagnosed and whether this batch of concentrate is considered to have caused it.

(4) If the patient has to be treated with another batch of this product BY during the follow-up period

(a) record the immediate results of the second infusion on a new Part 1 Extension sheet and photocopy this to Dr. J.K. Smith, PFL.

(b) record infusion details for the second batch on the Remarks section of the original Part 1 and Part 2 relating to the first batch.

(c) continue to record viral follow-up on Part 2 relating to the first batch.

(5) If the patient has to be treated with another type of concentrate, plasma or cryoprecipitate:

(a) record infusion details for the second batch on the Remarks section of the original Part 1 and Part 2 relating to the first batch.

(b) continue to record viral follow-up on Part 2 relating to the first batch.

Definition of hepatitis

A patient will be considered to be suffering from hepatitis if he develops clinical symptoms and signs described in form C1, or shows an increase of at least 2.5 times the upper limit of normal serum aminotransferase levels, having had normal values previously.

Having excluded other causes, the physician should classify the disease as hepatitis B or non-A non-B; and acute icteric, anicteric or

symptomless.

Dr. Craske at the Public Health Laboratory, Withington Hospital, Manchester, M20 8LR, will advise on interpretation of tests, and may wish to receive replicate specimens.

THE PHYSICIAN SHOULD INFORM BPL OR PFL IMMEDIATELY IF ANY OBSERVATIONS INDICATE UNEQUIVOCAL INFECTION OF THE PATIENT BY A PARTICULAR BATCH - THIS MAY ALLOW US TO RECALL THE IMPLICATED BATCH BEFORE OTHERS RECEIVE IT.

Resolution of acute hepatitis

BPL is actively interested in the resolution of acute hepatitis occurring after treatment with our products and would like to receive results of any clinical studies in which the course of resolution has been observed.

Clinical response to heated high-purity factor VIII concentrate, 8Y

DELIVERY, ADVICE AND ACKNOWLEDGEMENT

Batch | 8Y

Consignment of _____ vials, each _____ iu VIII, dispatched _____

This consignment of unlicensed product is made to the prescription of _____ for treatment under his/her direction of the patient(s) named below:

A brief description of the product and instructions for use are enclosed in each box of 10 vials. Should you see any untoward effect attributed to this batch, or any apparent failure to correct bleeding, please telephone Dr. T.J. Snape, Head of QC, BPL or Dr. J.K. Smith, PFL, Oxford (0865 62002).

The physician should assess and record the efficacy of at least the first infusion of this product received by each patient, take blood samples for tests of HTLV III antibody and undertake follow-up for possible infection with hepatitis viruses.

SUMMARY OF ACTION REQUIRED BY PHYSICIAN IN CHARGE (see protocol for details)

Now

Please acknowledge that you have received the consignment of factor VIII and that you agree to the proposals for recording infusion data and follow-up of virus transmission in appropriate patients. Sign the attached duplicate of this page, retaining your own copy and post to Dr. J.K. Smith, PFL.

When patient is first infused with this batch

Before the first infusion, take a sample for factor VIII assay and HTLV III antibody. Take the samples indicated in Part 2 of the follow-up form for LFTs, hepatitis markers, and replicates for possible retrospective testing for HAV, CMV and EBV.

Enter patient's infusion and factor VIII recovery data on Part 1.

Enter patient identification and first infusion date on Part 2, and record the results of tests listed in the "pre" column.

On completion of this course of treatment

Complete all entries on Part 1, using further copies of the follow-up form (marked EXTENSION) if necessary, photocopy the page and post to Dr. J.K. Smith, PFL.

At (or near) stated intervals following first infusion

Take plasma samples, initiate tests and distribute samples as indicated in the accompanying protocol, and record results on Part 2. At 8, 24 and 52 weeks (i.e. at the end of each sub-table), photocopy the page and post to Dr. J.K. Smith, PFL.

If the patient is treated with another batch of this or another product during the follow-up period

Enter on Part 1 or Part 2 "Remarks" and see accompanying protocol.

If the patient shows laboratory or clinical evidence of virus infection

See accompanying protocol.

I acknowledge receipt of this consignment. This constitutes a prescription for the patients named above.

_____ Physician in charge

Clinical response to heated high-purity factor VIII concentrate, 8Y

Part 1. Efficacy of factor VIII infusion

Batch 8Y

Patient's surname: First dose (index date) _____

Forename(s): Haemophilia Centre _____

d.o.b. Case No. First dose ____ vials = _____ iu f.VIII

Last treated _____ using (product) (batch)

Previous history of hepatitis _____

Reason for current treatment _____

Use the table below to record data on the efficacy of successive infusions of this batch, and Part 2 (overleaf) to record viral follow-up data with reference to the first infusion.

If subsequent treatment with another batch of this product is necessary, complete Part 1 of the follow-up form relating to the second batch, but continue viral follow-up on Part 2 (overleaf) of this first batch infused.

If subsequent treatment with any other type of concentrate, cryoprecipitate or plasma is necessary, give particulars in the Remarks table below, but continue viral follow-up on Part 2 (overleaf) of the first batch infused.

Patient's mean weight _____. Mean resting level of factor VIII _____.

Date of infusion	Hour of infusion	F.VIII iu in dose	Sampling times Pre	Post	F.VIII levels Pre	Post	Rise %	Remarks No.

Remarks

No.

Return the photocopy of this page to Dr. J.K. Smith, PFL, as soon as the present course of treatment is completed. Continue viral follow-up on Part 2 overleaf.

(index date) _____ BY _____

Patient's name	Case No.	Haemophilia Centre

Please summarise data on possible virus transmission on the tables and photocopy the partially completed page to Dr. J.K. Smith, PFL, at 8, 24 and 52 weeks after the first dose with this batch, even if you have recorded further treatment with a different therapeutic material in Part 1 and Part 2.

Test enquiry / Date	Pre	Week 1	Week 2	Week 4	Week 6	Week 8
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Test enquiry / Date		Week 10	Week 12	Week 16	Week 20	Week 24
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Test enquiry / Date		Week 28	Week 32	Week 40	Week 52	
Bilirubin						
AST/ALT (delete one)						
Alk. phos.						
HBsAg						
Anti-HBs						
Anti-HTLV III						
Remarks/Note no.						

Summarise any treatment with other products/clinical notes during this period:

_____

_____

_____

i. the technical aspects of production of all blood products

ii. the evaluation of techniques

iii. the surveillance of recipients.

He said that the group could also consider the question of storage of blood products. The group would also carry out a retrospective survey of stored material to check if it contained antibodies.

14. The Chairman welcomed this development but stressed that the Group needed to liaise with the PHLS and also that Dr Tyrrell should be involved in any discussions on research. He asked if the group would first turn its attention to the problem of immunoglobulins. Dr Schild agreed and would report back at the next meeting of EAGA.

9.2 Safety of Factors VIII and IX - EAGA(9)7

15. Dr Rotblat spoke to her paper. She said that Dr Jones had made a statement at the Newcastle Conference in February to the effect heat-treated Factor VIII was not safe with regard to transmission of HTLVIII. In support of this statement he had cited a case in Holland and several in USA. He had subsequently written to the CSM advocating that material manufactured by Armour in particular should be withheld. Dr Rotblat then discussed the cases of sero-conversion after treatment with heat treated Factor VIII:

i. The Dutch patient had sero-converted after 15-16 months after receiving treatment from a batch of Factorate HT. The batch was withdrawn because a donor to the pooled material used in its manufacture had developed AIDS. However, the doctors treating the patient were not convinced that there was no other risk factor involved. The patient was still being treated with Armour material, as were others, none of whom had sero-converted. The Dutch medical profession were concerned at the publicity given to this case.

ii. In England 12 patients had received treatment from a batch of Armour heat treated material which was later withdrawn - the donor referred to in i. above had also contributed to this batch. One patient who had been treated with two bottles from the batch had sero-converted - the result had not been confirmed by Western Blot. The patient was a mild haemophiliac who had received no treatment since 1980. There were no other risk factors involved.

iii. In America, the Bureau of Biologics had confirmed that a patient, a long standing drug abuser, had sero-converted after being treated with Hyland products for injuries sustained in a road traffic accident. He had also received red cell transfusions.

Dr Cash reported that three patients in Scotland had also sero-converted after being given heat treated material.

16. In the dicussion, members were of the opinion that all except one, the mild haemophiliac who had not received treatment since 1980, could be explained by late sero-conversion which was possibly triggered by an accident such as the road accident. Professor Bloom, whilst agreeing that the clinical evidence pointed to the fact that heat-treated Factor VIII was safe, was concerned that Professor Montagnier had reported at a conference at the

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.lege of Pathologists that he had detected reverse transciptase in material ;ated for 96 hours at 68°C. [Also, the Lancet had reported that the virus .as still detectable in spiked material up to 34 hours.]

Dr Smith was of the opinion that the safety margins for Factor VIII which related to the source material and manufacturing processes were adequate. However, Professor Weiss thought it essential that since manufacturing processes varied they needed to be tested empirically and liaison with Dr Schild on this matter would be necessary.

17. The discussion then centred on whether there was a need to issue a statement on the safety of heat-treated Factor VIII to counteract that made by Dr Jones. Although haemophiliacs and their families were reassured about its safety it was recognised that the media were still interested. It was therefore agreed that a statement which included a reference to Factor IX, used in the treatment of Christmas Disease, should be made as follows:

> "The EAGA has carefully considered the safety of currently available Factor VIII and IX concentrates in the light of the most up to date medical information. As a result, the EAGA has concluded that there is no evidence that HTLVIII infection has been transmitted in heat treated Factor VIII and IX concentrates."

The statement would be subject to clearance in the light of discussions by the CSM.

Agenda item 6: AIDS SERVICE PLANNING GUIDELINES - EAGA(9)1

6.1 HTLVIII Infection: District Plans - EAGA(9)(i)

18. Dr Sibellas spoke to her paper. She explained that Health Circular (86)2 issued by the Department on resource assumptions and planning guidelines had asked District Health Authorities to draw up a plan of action with regard to AIDS. This would include special action in respect of high-risk groups and including provision for testing and counselling service and for treating clinical cases of AIDS. These plans were to be submitted to the Department in June. The Group agreed to the suggestion that it would be helpful if the Department was to draw up a checklist to be made available to health authorities of the points which should be incorporated in each District plan. The resulting checklist was designed to meet two principle objectives - the prevention of the spread of HTLVIII and the provision of diagnostic and treatment facilities.

6.2 AIDS SERVICE Planning Guidelines: Comments on the Department's District Outline Plan - EAGA(9)1(ii) - tabled

19. Dr Packer explained that his paper was commenting on an earlier draft of that of the Department. He felt that since service provision varied between health authorities it was right that they should be asked to develop such plans although the question of their implementation was one for the health authorities themselves. He thought it was essential that there was an identified person responsible for taking action and that the District General Manager was probably the best person to undertake this task.

20. The Chairman said it was the Department's view that each District Health Authority had a responsibility to develop on AIDS plan, even if there

EAGA(9)7

IN CONFIDENCE

NOT FOR PUBLICATION
EXPERT ADVISORY GROUP ON AIDS

THE SAFETY OF HEAT TREATED FACTOR VIII

A paper by the Department

NOT FOR PUBLICATION

COMMERCIAL IN CONFIDENCE

The Safety of Heat Treated Factor VIII

Introduction

At a meeting on AIDS held in Newcastle on February 12, Dr Peter Jones Director of the Newcastle Haemophilia Centre made a public statement that he felt heat treated Factor VIII was not safe as regards transmission of HTLVIII. He cited a case in Holland and several cases in the USA. Since then Dr Jones has written to the CSM with anecdotal evidence, particularly citing the Armour product "Factorate HT". Dr Jones' letter is included as an appendix to this paper.

The comments he makes are discussed below together with the results of discussion with physicians at the University Hospital of Amsterdam, Dr D Arenson of the Bureau of Biologics and representatives of Armour Pharmaceuticals.

1.1 Dr Jones Statement

	Product	Source of Information
"Adult haemophiliac followed for almost a year on HT material, heterosexual, no other risk factors, repeatedly tested after being seronegative.	Armour	Dr Breederveld, University of Amsterdam. Permission to quote given February 1986"

Comment

This patient has been discussed with Armour and with his physician.

The patient is a severe haemophiliac with no other apparent risk factors treated with cryoprecipitate and non-heat treated Factor VIII until 1983 when he switched to Armour heat treated material. He is getting 40-50 bottles/month of "high purity" concentrate. He was negative for HTLVIII antibody in Autumn 1984. In January 1985 he developed malaise and lymphadenopathy and was found to have seroconverted to HTLVIII antibody positive.

Over 1985 the antibody "titre" has risen from 1:200 to 1:1500 but no virus has been cultured from his cells despite repeated attempts in Holland and at the Pasteur Institute.

At present he is well and his lymphadenopathy has resolved. He is continuing treatment with the Armour product. No other patient in Amsterdam has seroconverted despite wide use of Armour material.

This patient received treatment from a batch of Factorate HT which was withdrawn because a donor to it had developed AIDS (see below).

1.2 Dr Jones Statement	Product	Source of Information
"3 haemophiliacs all reported to CDC who appear to "probably" fulfil criteria for seroconversion in one case and "possibly" fulfil criteria in 2 cases.	Not known	Dr Levine. Permission to quote given February 1986"
"Haemophiliac without other risk factors treated at Chapel Hill and reported as seroconversion after HT material.	Hyland	Reported to Professor Manucc February 1986"

Comment

Bureau of Biologics (BOB) confirm that there is a patient at Chapel Hill who seroconverted after receiving huge doses of heat treated material (Hyland) for injuries sustained in a road traffic accident. He also received red cell transfusions. This patient is a long standing intravenous drug abuser.

Dr Levine who is cited as the source of the other cases is the co-ordinator for the National Haemophilia Foundation in the USA. He is in close contact with the BOB and between them they know of no other case in the USA who has seroconverted after heat treated material.

1.3 Dr Jones Statement	Product	Source of Information
"Virus detected in material subjected to heating for less than 34 hours. One product said to cause seroconversion.	Armour	Dr Koerper, University of California, San Francisco, also quoting work of Dr Levy, December 1985."

Comment

Armour do not know of this, neither do the BOB. In fact there is no report in the literature of live virus ever being grown from Factor VIII heat treated or not.

1.4 Dr Jones Statement

"Seroconversions in the FDR were also reported to a meeting of the Haemophilia Society in November 1985.

David Watters, co-ordinator
Haemophilia Society,
London, February 1986"

Comment

I have not been able to confirm this.

2. Heat Treated Factor VIII

The status of currently used products is given below. The Hoechst material is not marketed in the UK at present.

FACTOR VIII - HEAT TREATMENT - CURRENT POSITION (FEBRUARY 1986)

Company	Wet/dry	Temperature	Duration	Screened donors
Licensed				
Armour	Dry	60°	30 hours	Yes
Alpha	Heptane Suspension	60°	20 hours	95%
Immuno Factor VIII	Dry	60°	10 hours	Yes
FEIBA	Dry	80°	10 hours	Yes
Cutter/ Miles	Dry	68°	72 hours	Yes
Hyland	Dry	60°	72 hours	Yes
Hoechst	Wet	60°	10 hours	Yes

- All the commercial companies are carrying out spiking experiments to show the safety of their procedures.
- The PFC in Edinburgh are setting up a system to test their own procedures and those of the Elstree Centre.

4. Armour Batch Number Y69402 (Heat-Treated)

This batch was withdrawn in the UK in 1985 because a donor contributing to it had developed AIDS. The same donor also contributed to another batch given to the patient in Holland (this second batch was not distributed in the UK).

12 patients in the UK received Y69402 and are being followed up.

5 patients were HTLVIII ab +ve before treatment with Y69402.
1 patient has died from liver disease (not related to AIDS).
5 are still seronegative 1 year after treatment.

1 patient has seroconverted. Information on this patient has been obtained from his physician

The patient is a mild haemophiliac who has no other risk factors. He was tested for HTLVIII antibodies in January 1985 and found to be negative. He had received no treatment since 1980.

In February 1985 he received two bottles of batch Y69402 and HTLVIII antibodies were found in May 1985 and confirmed in November 1985. Testing was by ELISA - no Western blot has been done. T cell subsets are normal although Trosettes are said to be "slightly abnormal". The patient remains well.

5. Summary

There are three known cases of seroconversion for HTLVIII antibody after heat treated Factor VIII.

One - the American case - appears to have other risk factors. This case is associated with the Hyland product.

Two cases seroconverted after treatment with Armour material from a batch known to contain an AIDS donor.

GRO-C

4 March 1986

DR F ROTBLAT

NORTHERN REGIONAL HAEMOPHILIA SERVICE
NEWCASTLE HAEMOPHILIA CENTRE
THE ROYAL VICTORIA INFIRMARY
QUEEN VICTORIA ROAD, NEWCASTLE UPON TYNE, NE1 4LP
TELEPHONE
NEWCASTLE 325131, Ext. 773
STD 0832

Ref: PJ/MB

18 February 1986

The Medical Assessor
The Committee on Safety of Medicines
Market Towers
1 Nine Elms Lane
LONDON
SW8 5NQ

Dear Sir

AIDS, heat treatment of clotting factor concentrates and haemophilia

I enclose information I have that suggests HTLV III seroconversion in previously seronegative haemophiliacs being infused with some types of factor VIII concentrate, especially that heat treated in the dry state for less than three days. I do realise that the evidence is only suggestive, but I thought it sufficiently worrying to mention the possibility that we were not out of the woods yet in my paper to the AIDS Conference. A copy of this is enclosed, together with a covering letter written to Haemophilia Centre Directors.

In this Centre, in addition to available NHS concentrate which is at least heated for 72 hours, we have changed our patients to the Alpha material because of a report to me by Dr Koerper that it was free of virus, after testing by Dr Levy in San Francisco. It is my personal opinion that, unless there is irrefutable evidence to the contrary, the Armour material should be withheld until its safety can be endorsed by the C.S.M.

Yours faithfully

GRO-C

PETER JONES MD FRCP DCH
Director

cc Dr J Smith
Director, P.H.L.S.

Dr A Smithies
DHSS

Evidence about seropositivity following heat treated factor concentrates	Product	Source of information
Adult haemophiliac followed for almost a year on HT material, heterosexual, no other risk factors, repeatedly tested after being seronegative	Armour	Dr. Breederveld, University of Amsterdam. Permission to quote given February 1986
3 haemophiliacs all reported to CDC who appear to "probably" fulfil criteria for seroconversion in one case and "possibly" fulful criteria in 2 cases.	Not Known	Dr. Levine. Permission to quote given February 1986
Virus detected in material subjected to heating for less than 34 hours. One product said to cause seroconversion.	Armour	Dr. Koerper, University of California, San Francisco, also quoting work of Dr. Levy, Decembe 1985
Haemophiliac without other risk factors treated at Chapel Hill and reported as seroconversion after HT material.	Hyland	Reported to Professor Manucci, February, 1986

Seroconversions in the FDR were also reported to a meeting of the Haemophilia Society in November 1985.

David Watters, co-ordinat Haemophilia Society, Lond February 1986

APPENDIX 10

OXFORDSHIRE AREA HEALTH AUTHORITY (TEACHING)

OXFORD HAEMOPHILIA CENTRE

Tel: Oxford (0865) 64641
Ext. 575

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

24th June, 1983.

Dear Professor Bloom,

Acquired Immune Deficiency Syndrome

A Meeting of Reference Centre Directors was held on May 13th, 1983 to discuss this problem in haemophilia, its implications and our recommendations. So far one possible case has been reported to our organisation. This patient (A/1) conforms to the definition published by the CDC in Atlanta, Georgia but cannot be considered as a definite case. We are not aware of any other definable patients amongst the U.K. haemophilic population.

At the above mentioned meeting on May 13th the following general recommendations were agreed.

1. For mildly affected patients with haemophilia A or von Willebrand's disease and minor lesions, treatment with DDAVP should be considered. Because of the increased risk of transmitting hepatitis by means of large pool concentrates in such patients, this is in any case the usual practice of many Directors.

2. For treatment of children and mildly affected patients or patients unexposed to imported concentrates many Directors already reserve supplies of NHS concentrates (cryoprecipitate or freeze-dried) and it would be circumspect to continue this policy.

It was agreed that there is as yet insufficient evidence to warrant restriction of the use of imported concentrates in other patients in view of the immense benefits of therapy but the situation will be constantly reviewed. Following the meeting on 13th May, the Licensing Authority was asked to consider any implications for us of the revised recommendations of the American Food and Drug Administration which were made on March 24th, 1983 to American plasma collecting agencies.

Two additional points have been drawn to our attention since the meeting of May 13th.

1. The first concerns the treatment of patients with haemophilia B. The evidence to incriminate factor IX concentrates in AIDS is even less than with factor VIII and it seems logical to continue to use our normal supplies of NHS concentrate.

2. Another point concerns the proposed trials of "hepatitis reduced" factor VIII concentrates. There is no evidence that the processes involved in the manufacture of these inactivate any other hypothetical viruses. However it is

APPENDIX 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta GA 30333

March 7, 1983

Professor A. L. Bloom
Welsh National School of Medicine
Department of Haematology
University Hospital of Wales
Heath Park, Cardiff CF4 4XN
Wales

Dear ~~Dr. Bloom:~~ Arthur

Thank you for your recent inquiry concerning the AIDS Syndrome. I will be happy to present an update on the current status of AIDS in North America during the Stockholm meeting. As you can imagine, AIDS is having a major impact on the treatment of hemophiliacs here presently.

The evolution of the epidemic is occurring with a frightening pace. We now know of over 1150 total cases in the United States. To give you an example of rapidity of development, approximately 80 patients with AIDS reported to us during the month of December; in January - 120; and in February the number is approaching 20% above that level. In fact, about 40% of the cases have been reported to us in the last 3-4 months.

We presently have 13 confirmed hemophiliac patients with AIDS in the United States. One of the patients has Factor IX deficiency and one is bisexual. In addition 5 more highly suspect cases are under investigation. The incidence rate has been increasing in hemophiliacs and the epidemic curve paralays that of the total epidemic curve. The first case appeared in a hemophiliac in January 1982; a total of 9 were reported by December. Of those, 8 died in 1982. From preliminary data obtained from a nationwide surveillance, the AIDS syndrome was the second cause of death among hemophiliacs in 1982 in the U.S. (hemorrhage was the largest cause of death.) AIDS has developed in both mild and severe hemophiliacs. Ages have been 7 to 62 years. The clinical course has been rapid after the onset of an opportunistic infection. Most have had Pneumocystis pneumonia and none have had Kaposi sarcoma. All have received Factor VIII concentrates, and all but one have received other blood products such as plasma or blood transfusions. Common lots among the concentrates have been rare. We have accumulated a large amount of clinical data on these patients, and it is very similar to that seen in other cases of AIDS. We are performing a longitudinal study of the immune status on hemophiliacs in Georgia and have performed immune studies on approximately 50 randomly selected hemophiliacs and compared them with patients who have chronic active hepatitis, or with patients undergoing chronic renal dialysis (to represent another group which receives chronic transfusions). Preliminary data suggest that one half of the hemophiliac population has T cell abnormalities and, in fact, 13% are markedly abnormal (in the range that we see with the AIDS patients). Patients with chronic active hepatitis, or patients undergoing chronic renal dialysis are not significantly different than normal. These patients will be followed and by the summer we should be able to give a status report on this study. Other additional groups are being added.

Transfusions as a source of AIDS infection is another cause for concern here. Approximately 12 patients have developed AIDS following blood transfusions. These cases are under intensive investigation by us. Of these patients, half are male and half are female. They appear to be located in the high incidence area of AIDS, i.e., New York, San Francisco, and Los Angeles, locations where we would expect the majority of donors with AIDS to be.

I hope this information is useful to you. I suspect it is a matter of time before you begin to see cases in the United Kingdom.

We have been aggressively trying to isolate a virus in the laboratory. So far, results have been negative. CMV is frequently isolated, however, DNA probes suggest that they are all different strains.

Look forward to seeing you this summer. If you have any further questions, please do not hesitate to ask.

Sincerely yours,

GRO-C

Bruce L. Evatt, M.D.
Director, Division of Host Factors
Center for Infectious Diseases

cc:
Craig Jackson

APPENDIX 12

OXFORDSHIRE AREA HEALTH AUTHORITY (TEACHING)

OXFORD HAEMOPHILIA CENTRE

Tel. Oxford (0865) 64841
Ext. 575

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

22nd March 1983

Dear Director,

Re: Acquired Immune Deficiency Syndrome (AIDS)

Recent discussions in both the Hepatitis Working Party and a recent meeting of the Reference Centre Directors have prompted us to circulate the enclosed papers so that a system for the reporting of possible cases of the Acquired Immune Deficiency Syndrome can be quickly set up to examine the problem as quickly as possible. This was initially prompted by a request from the U.S. Public Health Service to the U.K. Haemophilia Centre Directors, as a similar survey in the U.S.A. has been underway at Haemophilia Centres for at least a year.

The criteria for reporting cases are given in the accompanying paper AIDS/2. These are exactly the same as those used in the recent survey carried out in the U.S.A. The initial results of the survey may very well include many patients who will turn out not to have the syndrome, but we feel that every possible case should be reported and the results analysed critically at a later date when more information is available. Please use the form AIDS/3 to report each suspect case. We are aware that many other categories of patient will turn out to have abnormal markers of cell mediated immunity, for instance a low absolute lymphocyte count and low T-helper to T-suppressor cell ratios. However, reports suggest that the clinical picture and the profound changes observed in the AIDS syndrome are much more severe and very obvious when a case of this disease presents itself.

We do strongly urge you to collaborate in reporting cases of this syndrome as it is most important that the extent of the problem is quickly identified so that preventative measures can be instituted as soon as possible to minimise numbers of cases occurring in the U.K.

A report of the progress of this survey will be presented at the annual meeting of the U.K. Haemophilia Centre Directors

/and

and any developments of significance will be circulated to you before then as soon as information is available.

Yours sincerely,

J. Craske
Chairman, Hepatitis Working Party

C.R. Rizza
Secretary, Haemophilia Centre Directors' Organisation

A.L. Bloom
Chairman, Haemophilia Centre Directors' Organisation

OXFORDSHIRE AREA HEALTH AUTHORITY (TEACHING)

OXFORD HAEMOPHILIA CENTRE

Tel: Oxford (0865) 64
Ext. 575

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

24th June, 1983.

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At the above mentioned meeting on May 13th the following general recommendations were agreed.

1. For mildly affected patients with haemophilia A or von Willebrand's disease and minor lesions, treatment with DDAVP should be considered. Because of the increased risk of transmitting hepatitis by means of large pool concentrates in such patients, this is in any case the usual practice of many Directors.

2. For treatment of children and mildly affected patients or patients unexposed to imported concentrates many Directors already reserve supplies of NHS concentrates (cryoprecipitate or freeze-dried) and it would be circumspect to continue this policy.

It was agreed that there is as yet insufficient evidence to warrant restriction of the use of imported concentrates in other patients in view of the immense benefits of therapy but the situation will be constantly reviewed. Following the meeting on 13th May, the Licensing Authority was asked to consider any implications for us of the revised recommendations of the American Food and Drug Administration which were made on March 24th, 1983 to American plasma collecting agencies.

Two additional points have been drawn to our attention since the meeting of May 13th.

1. The first concerns the treatment of patients with haemophilia B. The evidence to incriminate factor IX concentrates in AIDS is even less than with factor VIII and it seems logical to continue to use our normal supplies of NHS concentrate.

2. Another point concerns the proposed trials of "hepatitis reduced" factor VIII concentrates. There is no evidence that the processes involved in the manufacture of these inactivate any other hypothetical viruses. However it is

/still

still important that the effectiveness of imported "hepatitis reduced" concentrates vis-à-vis hepatitis is subjected to formal clinical trials in mild haemophiliacs notwithstanding our general recommendations above. Directors are urged not to use these concentrates randomly on a "named patient" basis.

If you have any other queries or suggestions please write to us or telephone.

Yours sincerely,

GRO-C

A.L. Bloom
Chairman, Haemophilia Centre Directors Organisation

GRO-C

C.R. Rizza
Secretary, Haemophilia Centre Directors Organisation

Prof. A.L. Bloom,
University Hospital of Wales,
Cardiff.

APPENDIX 13

MINUTES OF SPECIAL MEETING OF HAEMOPHILIA CENTRE DIRECTORS held at ST. THOMAS HOSPITAL on 13.5.83. at 11.00 a.m.

Present: Professor A.L. Bloom (Chairman)

Dr. John Craske

Dr. Peter Hamilton

Dr. Peter Kernoff

Dr. Christopher Ludlam

Dr. Geoffrey Savidge

Dr. Eric Preston

Dr. Irvine Delamore

Dr. C.R. Rizza

Dr. Diane Walford (D.H.S.S. observer)

Apologies for absence received from Dr. Elizabeth Mayne

Professor Bloom briefly outlined the background to the meeting and its purpose. The recent publicity in the press, radio and television about the problem of acquired immuno deficiency syndrome (AIDS) had caused considerable anxiety to haemophiliacs and their medical attendants as well as to the Department of Health. There was clearly a need for Haemophilia Centre Directors to discuss what should be done with regard to the surveillance and reporting of suspected cases and the management of patients. To date in the United Kingdom one haemophiliac is suspected of suffering from AIDS. In London there are reported to be 10 cases of confirmed AIDS in homosexual males. Concern was expressed about the definition of AIDS. It was felt that there might be many individuals with evidence of impaired cell-mediated immunity but only a very small number of these might progress to a full blown picture of the condition. It is important that such individuals are not classified as suffering from AIDS. It was accepted that because of our lack of knowledge of the nature of AIDS,

decisions about diagnosis and reporting of suspected cases would prove difficult. Nevertheless the criteria laid down by the Centres for Disease Control, Atlanta, Georgia, and in the form prepared by Dr. J. Craske for use at U.K. Haemophilia Centres, should be followed for diagnostic purposes. The importance of opportunistic infection as a diagnostic criterion was stressed. It was agreed that any patient who was suspected of suffering from AIDS should be reported immediately on the form provided and thereafter the clinical course of the patient would be followed and a definitive diagnosis attached if the patient developed intractable disease.

The steps to be taken should a patient develop the features of the full-blown condition were then discussed. It was agreed that there was insufficient information available from the U.S. experience to warrant changing the type of concentrate used in any particular patient. Moreover once the condition is fully developed it seems to be irreversible so that there would seem to be no clinical benefit to be gained by changing to another type of factor VIII.

With regard to general policy to be followed in the use of factor VIII concentrates, it was noted that many directors have up until now ~~restricted their use of~~ National Health Service concentrates ~~to~~ for children and mildly affected haemophiliacs and it was considered that it would be circumspect to continue with that policy. It was also agreed that there was, as yet, insufficient evidence to warrant restriction of the use of imported concentrates in other patients in view of the immense benefits of therapy. The situation shall be kept under constant review.

It was noted that the Blood Transfusion Centre Directors were due to meet to discuss the problem of donor screening in relation to AIDS. The news of this meeting was welcomed by the Haemophilia Reference Centre Directors.

There being no further business the meeting closed at 2.15 p.m.

GRO-C: A Bloom

OXFORDSHIRE HEALTH AUTHORITY

OXFORD HAEMOPHILIA CENTRE

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Ext.

Churchill Hospital,
Headington,
Oxford OX3 7LJ.

29th March, 1984

MEMORANDUM

To: All U.K. Haemophilia Centre Directors

TRIALS OF 'HEPATITIS REDUCED' FACTOR VIII - AN UPDATE

Directors will recall the "aide memoire" circulated with paper for the September 1983 annual meeting which described the types of factor VIII concentrate which would be available for clinical trial in 1983-4. We have recently reappraised the situation and there are at present 8 different products in preparation or available for trial. Clinical trials have only been completed on one product, the "Hemofil HT" factor VIII, which is prepared using a 'dry heat' method. The results indicated that there was still a 63% attack rate of non-A, non-B hepatitis on first exposure to this product in patients who have not received factor VIII concentrate previously. These trials are difficult to evaluate as for ethical reasons no control group was used.

The products currently available are:-

(1) Heated products from Armour, Cutter, Travenol and Alpha Therapeutics. The 3 former are 'dry heat' preparations and the latter (Alpha Therapeutics) is a wet heat product.

(2) NHS factor VIII prepared from a specially selected donor panel which is monitored for abnormal LFT's, hepatitis, etc.

(3) Heated NHS factor VIII; one brand is manufactured at the PFC in Edinburgh and will be shortly available. The second, manufactured at Elstree, should be available later this year.

(4) A heated preparation manufactured by Behringwerke, the German Pharmaceutical Company. This is heated at 60°C for a period known to inactivate hepatitis B in the preparation. The problem is that the yield of factor VIII coagulant activity is considerably reduced, so that the cost is likely to be at least 4 fold higher - ?40p per unit. Trials have been carried out in Germany, but no published information is available. At least 30 patients have been studied.

All products except those derived from NHS factor VIII are made from plasma imported from the U.S.A., and, therefore, they carry a putative risk of transmission of AIDS. It is evident that 8 products will be shortly available on the market and, unless these

/are

are coordinated, there will not be enough patients available to evaluate each product carefully.

We would therefore ask that you take the following action:-

(1) Draw up a list of patients in your Centre who might be suitable for such a trial on the basis of previous blood product exposure, and who are likely to require treatment with factor VIII in the near future.

(2) Notify Miss R.J.D. Spooner at the Oxford Haemophilia Centre of the number of such patients available.

(3) If approached by a Pharmaceutical Company or you are proposing to try one of the NHS products, please let Miss Spooner know what product you intend studying and how many patients will be involved. She will circulate information about all the trials, so that any patients still available who are uncommitted can be used for one of the remaining products, subject to the wish of the local Haemophilia Centre Director.

(4) It is important to ensure that each Company obtains an exemption from a clinical trial certificate from the U.K. Licensing Authority. Studies conducted on a named patient basis carry no protection under the Medicines Act, as the patient's doctor and not the Pharmaceutical Company carries the liability for compensation arising out of unexpected hazards which come to light as part of the trial.

(5) We suggest that the protocol circulated by the Hepatitis Working Party last year should form the basis for the studies. Dr. Craske would be grateful for serial specimens from patients studied to form the basis of a collection for study if markers for non-A, non-B hepatitis become available.

We hope that Directors will collaborate as suggested in this document so that the maximum information about the relative merits of different products will become available with the most economical use of the limited number of patients available.

A.L. Bloom
Chairman, Haemophilia Centre Directors Organisation

John Craske
Chairman, Haemophilia Centre Directors' Hepatitis Working Party

C.R. Rizza
Secretary, Haemophilia Centre Directors Organisation

Last May Members of the Society were circulated with a statement from me concerning the acquired immune deficiency syndrome (AIDS). This statement was made in the light of information available at the time but it is clear that many of us, physicians, members, patients and their families continue to be worried. In view of the spate of publicity, often conflicting, regarding AIDS it seems opportune briefly to review more recent developments.

By August 1983 a total of 2008 cases of AIDS had been reported in the U.S.A. and 14 cases in the United Kingdom [redacted]. Most of the American patients were homosexuals, drug addicts or immigrants from Haiti. Twenty were heterosexual partners of persons in one of these AIDS-risk categories. Of the British patients twelve of the fourteen were homosexual and seven of these had American sexual contacts.

What is the relationship of AIDS to haemophilia? Fifteen cases have been reported to date amongst the 20,000 American haemophiliacs. Of these at least eight have died of the condition. Two cases have occurred amongst the four thousand British haemophiliacs and one of these has died. A similar handful of cases have been reported in several European countries.

What is the relationship, if any, of AIDS to blood transfusion in non-haemophiliacs? Nineteen American cases other than haemophiliacs had received blood or blood products within five years before their illness. One infant who was transfused developed AIDS and the donor subsequently developed the condition. Bearing in mind the vast number of blood donations each year (2.5 million in the U.K.: probably 10 million in the U.S.A.) the concurrance of AIDS and previous transfusion could well have occurred by chance in some of the patients but the possible association is not being ignored.

At the present time reported cases of AIDS have met certain strict criteria and many have thus apparently been severe. It is likely however that milder cases will come to light and the apparent severity of the condition will probably ameliorate in time. The most likely cause is still thought to be transmission of an infective agent (in blood products in the case of haemophiliacs) but a non infective cause, for example, a reaction to seminal fluid absorbed from the rectum (in homosexuals) or to blood plasma injected into the circulation has by no means been excluded. Urgent research on all thes aspects is under way at many centres throughout the world including several in this country.

In that the cause of AIDS has not definitely been shown to be an infective agent or virus it is not certain that imported factor VIII concentrates are more dangerous than those prepared from British blood. In this respect it has been shown recently that British concentrates are just as likely as imported concentrates to transmit viruses of hepatitis. In addition American blood banks have been instructed to apply strict criteria to exclude plasma donations from high risk donors and in this country leaflets about the condition have been made available at blood donation sessions. Nevertheless Haemophilia Centre Directors are being circumspect in the use of factor VIII concentrate. It seems unreasonable to withold imported concentrates from severely affected patients who have already received large amounts of them. [redacted] The role of the special modification of concentrates designed to inactivate hepatitis viruses is being assessed. Current evidence is not as encouraging as at first hoped and there is no evidence for or against the possibility that these processes also reduce the risk of transmitting AIDS.

In this country we hope to be self sufficient in factor VIII concentrate by 1986; we are so already for factor IX. Whilst this may not be an answer to AIDS it could at least simplify the search for a cause and at the same time remove one of the current reasons for aggravation and anxiety. In any case for the moment we have little choice. In spite of optimistic statements in the media genetically engineered coagulation factors do not seem to be a practical proposition for the next few years. In the meanwhile our more adventurous members may think it prudent to modify their life-style accordingly for the main risks are still from bleeding. Although we are all worried by the emergence and mysterious nature of AIDS, in the light of present knowledge the benefits of conventional factor concentrates far outweigh any real or hypothetical risks. We will reassess the situation frequently and keep you fully informed.

Dr. C.R. Rizza,
Oxford Haemophilia Centre,
Churchill Hospital,
Headlingtob,
Oxford.

12th March, 1984

Dear Charlie,

I am writing to you with a copy to John Craske about the difficulties which I can see are going to arise with reference to the assessment of "hepatitis reduced" concentrates. I have already passed on to you for the Hepatitis Working Party a copy of the letter from John Cash. Like you I have also had a visitation from Alpha concerning their wet heat treated material and am expecting a visit from Armour about their material at any moment. There is of course also a German material which is on the way. There will therefore shortly be products from all the American manufacturers, heated products from Scotland and BPL and also the BPL 'small pool' material. We shall therefore be faced with attempting to assess about eight products. I think it almost certain that some of the manufacturers will approach small Haemophilia Centres concerning their products which I would guess they will try to promote unofficially and I am sure within the law for use on a named patient basis.

Presumably larger centres will wish to collaborate with various producers in a more formal assessment of materials both on 'virgin' patients and on other patients. The excuse for the latter will be thatythey could be followed up prospectively in comparison with those treated with non-heated materials and various parameters such as liver function tests and lymphocyte markers measured. In attempting to plan any rational trials I am sure that it would be useful to know where the various materials are being used and to advise the body of Directors about the current situation with regard to these concentrates before they are approached by the manufacturers. I think it may therefore be time for us to circulate all Haemophilia Centre Directors again with recommendations for the use of these products, the desirability of maintaining an available pool of virgin cases for valid assessment of them, and to establish a registry of which centres have used, are using , or plant to use heat treated concentrates and to identify those which will be used at these centres. This information could be obtained by a simple questionnaire. I think that there is now ample evidence that the Travenol first generation material is poorly effective in preventing hepatitis and this may well apply to other first generation dry heat treated materials. I think it is important therefore that we proceed as rapidly as possible to put Haemophilia Centre Directors in the picture with regard to the current state of the art and I do not think that we should wait until the meetings in September. By then it will be too late.

I would be gratefulfor your views on this and I wonder if the Hepatitis Working Party could consider this with some priority , if necessary, by post.

With all best wishes,

Yours sincerely,

A.L. Bloom

c.c. J. Craske

Notes of the Haemophilia Reference Centre Directors Meeting, Blood Products Laboratory, Elstree 10/12/84

Present:

Prof. A Bloom (Chairman)
Dr R S Lane (BPL)
Dr T Snape (BPL)
Dr M J Harvey (BPL)
Mr P Prince (BPL)
Mr N Pettet (BPL)
Dr J K Smith (BPL)
Dr P Kernoff
Dr P Jones
Dr C Ludlam
Dr F Preston
Dr E Mayne
Dr H Gunson
Dr A Smithies (DHSS)
Dr J Cash
Dr I Delamore
Dr P Mortimer (PHLS)
Dr J Craske
Dr C Forbes
Dr C Rizza
Dr G Savage
Dr R Tedder (Middx Hosp.)
Dr I Temperlay

Agenda

In addition to the previously circulated agenda, an aide-memoir was tabled by the Chairman. This covered several points for discussion at the meeting.

Item 1 Introduction to the meeting

The Chairman outlined that the resulting publicity surrounding the events in Newcastle and Australia, and the continuing work on HTLV lll, has precipitated todays meeting.

Item 2 (i) HTLV lll antibody screening

Dr Tedder reviewed the current situation by saying that the Gallo cell line was available for investigation although the USA had made the isolates difficult to obtain. The British isolate required an organisation to handle the bulk virus culture: Porton (PHLS) and Wellcome are the only ones

so far interested. There are problems in obtaining the antigen. Dr Tedder's test uses a cruder antigen.

Several problems remained in getting the test into the NBTS:

1) cost of the kit ?
2) the extra staff required to run the tests ?
3) advice to donors found to be HTLV lll positive ?
4) how soon can the test be introduced ?

It was noted that G.U.M. clinics are resistant to screening because of the social problems created.

Dr Mortimer stated that the PHLS was under pressure to be involved with introducing a 'kit' for availability throughout the PHLS.

In summary, testing was likely to be recommended for patients and contacts in addition to the 2500 Haemophiliacs who would require regular testing, (the testing of contacts for Haemophilia alone would be of the order of 10,000).

If one broadened the test to take in the NBTS, it was clear that many thousands of tests would be required each year.

(ii) Availability of tests

Dr Craske advised that currently, the reagents were only available on a research basis, and that substantial resources would be required to enable the proposed workload to be undertaken.

It was considered that to know the antibody status of every haemophiliac would be advantageous in determining the regime for treatment. However, the limited resources made it impossible to do routine tests at the moment.

Some discussion took place on which organisation would be best placed to organise the testing, and whether DHSS financial support would be forthcoming. Dr Lane (BPL) suggested that if resources were available BPL would play a part coordinating the endeavour. Dr Smithies advised that she would take all these points back, to the DHSS for consideration.

The Chairman, in summary, advised the meeting that he would write to Dr Smithies after the meeting delineating precisely the problems.

(iii) Blood donor testing

It was suggested that the testing of donors requires either 1) mass commercialisation of a British test or 2) application of a current commercial test. Confirmed that testing would be introduced at two centres early in 1985 prior to widening availability to the rest of the NBTS.

Dr Gunson advised that it would be preferable to test all donors. However if resources were limited it might be better to concentrate testing at the major 'risk' centres.

Dr Cash was concerned that no central organising body was being contemplated for the test programme. This view was confirmed by Dr Tedder who was concerned that the pace of test advancement was so fast that the scientists were left to introduce a test as soon as possible. There was also considerable concern expressed over the lack of financial support from the DHSS.

(iv) Significance of HTLV lll antibody tests

Dr Tedder outlined the significance of HTLV lll from a virologist viewpoint.

a) the presence of antibody may be a suggestion of developing AIDS, but not necessarily so.
b) there could well be advantages in being able to remove the antibody positive donors from the donor pool.
c) It is likely that to be HTLV lll antibody positive suggests previous exposure to the antigen. Virus can be isolated from many antibody positive persons so that one must assume that many of them are infective. In haemophiliacs the presence of antibody is probably the result of infection rather than passive transfer in concentrates. There may be a period of viraemia preceding seroconversion.

It was also noticed that some patients do not produce antibody. Thus an infected batch of concentrate would not always result in the detection of antibody in patients who had received the batch.

Dr Ludlam confirmed that in Scotland, some patients who were previously antibody +ve are now -ve. Does this suggest passive transfer of antibody ?

In summary, the Chairman outlined that HTLV lll +ve persons should be considered a risk but that one still could not assume that -ve contacts are not infective. Haemophiliacs who are positive should therefore be considered a high risk until the situation becomes clearer.

Some discussions took place on how relevant the HTLV lll antibody test was in the scientific context. It was concluded that from a social and practical view it must be considered relevant.

(v) Advice to patients and donors

Dr Jones tabled the current Newcastle policy and made observations on the contents.

With regard to the treatment of Haemophiliacs there is no change in therapy except for the holding back of prophylaxis of children by home-treatment.

All concentrate is now heat-treated commercial; advice was sought on the use of non-HT Factor Vlll and Factor lX.

Dr Jones added that in Newcastle there are three cases of organ donation by Haemophiliacs. The patients are now under surveillance. He also commented that all of his 21 staff had been tested and found -ve for HTLV lll antibody.

A long discussion took place on whether persons found to be +ve were to be informed. Several differing views were expressed. It was agreed that each clinician would decide for each case depending on the facts of the case but in general to provide information if asked for.

Item 3 (i) Factor Vlll Concentrates

It was agreed that HT product should be given to all patients, if freely available, to include those found to be antibody +ve. In the case of antibody -ve patients, it was agreed that from now on, treatment must be with HT material.

Dr Savage commented that this has and would continue to create severe financial problems for treatment centres.

Dr Tedder asked that advice to patients should go hand in hand with treatment, and outlined the recent case in the USA of a child contracting AIDS from the wife of a haemophiliac. Thus sexual counselling was also an important aspect.

It was agreed that haemophiliacs should all be given the same advice with selective advice being given based on the results of HTLV lll testing.

Dr Kernoff commented that as some 70% of haemophiliacs are now +ve it may be considered irrelevant if one tells or dosen't tell the results of testing.

The Chairman summarised by saying that testing should be instituted as soon as possible, and that information on the test results, should not be given automatically but if asked for. HT material should be given preferentially in those cases where concentrate is required. The financial consideration must be considered secondarily to the primary aim of treatment.

(It was noted that recent unpublished data from Manucci supported the effectiveness of heat-treatment. Of 21 patients given Hamophil HT, none had yet seroconverted).

Some discussion took place on the use of Factor lX. It was felt that the main problem was in balancing the risk of HTLV lll against the risk of increased thrombogenicity associated with HT - Factor lX.

(ii) Advice and testing of Staff

Dr Jones following his own experience felt it was important to show the low (or zero) risk to staff. This was supported by Dr Ludlam who considered it would be a good morale boost.

Dr Kernoff advised that any such course of action would need to pass through an ethical committee.

The meeting agreed that they would issue no advice on general testing of staff but that it should be considered in specific circumstances for large Haemophilia Centres.

Dr Tedder referred to the first known case of needle-stick in the UK, to be reported in the Lancet 15/12/84, and suggested that each Centre should carry out a safety audit with special reference to avoidance of needle-stick and simular incidents. He also remarked that Biotest Anti-HBs/Anti-CMV Immunoglobulin were reported to contain high levels of anti-HTLV 111. None of the patients given this material had seroconverted so far.

(iii) Availability and use of HT Factor V111

The Chairman outlined the choices available for haemophilia treatment. There were differing opinions on the 'risk' and/or use of NHS non HT concentrate. Some Directors felt that this material should not be used in the current circumstances, although much would depend on financial resources and the progress with NHS HT - concentrate.

Much discussion took place on the legislative aspects of the use of HT concentrate. It was unlikely, that legislation would be recommended to prevent the use of non-HT material.

In some circumstances, the alternative to not using non HT material would be no treatment.

Dr Lane stated that there could be a case for legislation on the type and length of heat-treatment required. He advised that one needed to be realistic ie one can't accept that an HT label implied a safe product. Commerical companies were being asked to reapply for licences for HT product.

Dr Mortimer reviewed the situation in that the majority of recipients are or will be sero +ve in the next few months. The use of HT material may not be required in these majority cases, although he accepted that there were other benefits (moral, social family, staff etc). If further exposure to potential virus caused more problems, then one could justify clearly the use of HT materials even if there were financial problems.

Dr Savage suggested that a task group be set up to look specifically at the AIDS problem in relation to Haemophilia. The Chairman agreed that the Reference Centre Directors would consider this.

Dr Cash urged that the financial consideration be looked at seriously. The implications for the cost of treatment to Haemophilia were enormous for the small number of patients involved.

Dr Lane added that the cost considerations spread to the NBTS, which was not just concerned with Haemophilia management. Here the cost of screening donors would be added to by BPL who would wish to test independently the plasma received at BPL.

Further discussion took place on the current price increase with HT concentrates and the likely future cost of this material. It was pointed out that because of the current media interest, patients were not treating themselves as they should.

In summary, the Chairman said that one has to accept, for the present, that it is difficult to avoid the argument that non-HT constitutes a risk. There were problems in adopting a two-tier system of treatment.

Meeting adjourned for lunch

Afternoon session

Item 3 (iv) Progress with heat-treatment of NHS Factor V111

The Chairman began this session by outlining the current commerical supply of HT Factor V111. Cutter, Armour, and Travenol were dry heat preparations, whereas Alpha (at 14p/iu) was wet. Hoechst also were supplying a preparation.

Dr Lane stated that BPL had begun 1984 with two objectives:-

1) a product with inactivation of non A/non B
2) a product acceptable for general use, with non transmittance of virus

R & D had been making good progress on these points which now coincided well with the current AIDS problem.

Dr Smith (BPL) then reviewed the current work programme. He added that there had been difficulties with the effectiveness of dry heat for the inactivation of non A/non B and therefore this had not been progressed as the first option. The current product had been dry-heated at 60^0C in conditions suitable for recovery of Factor V111 activity. This material had been available since March 1984 on a limited basis in solution.

The alternatives to dry heat, ie heat in solution or virus inactivation by detergent offered additional prospects for a safer product.

Dr Smith stated that the priority had been given to Factor Vlll, although Factor IX was capable of being heat treated. However the problem of potential thrombogenicity was causefor concern and no HT-Factor IX would be issued even for clinical trial before animal experiments had confirmed safety.

The present stock of Factor Vlll is being considered for heat treatment. Not all batches were suitable and these would remain available as non HT product.

Current work is directed to making available limited suppies of a heat treated product to April 1985, when it is expected that all batches will be heat-treated. A new product of higher Specific Activity is already being prepared which will withstand more severe heat-treatments and other treatments designed to inactivate hepatitis viruses as well as HTLV III.

Dr Lane remarked that in order to determine the effectiveness of the heat-treatment, spiking of Factor Vlll with antigen was required prior to heating. The present methods used by the NHS and commercial companies may still leave an active antigen. BPL would therefore be looking for follow-up studies during 1985 with Haemophilia Centre support.

Dr Lane advised that HT material in large quantities could not be available before April as equipment had to be ordered. These had now been placed for all the required plant.

The Chairman commented that "CDC type evidence" for BPL HT batches was important. BPL would need to obtain this evidence in support of their marketing of the product. It was accepted that with limited trial facilities available, the NHS producers were in competition with commercials for trial studies.

Dr Lane advised that it was too soon to be precise on the yield losses involved, with heat treatment. Users should not assume that the higher purity product meant a higher loss yield. Observed losses so far for the standard heat-treated product were similar to those found by commercials.

Dr Craske in response to Dr Lane, advised that it was too soon to know whether the Aids implicated batch of NHS Factor Vlll had caused seroconversion.

It was agreed that on general evidence, the BPL HT product would be accepted for use. Normal recovery and half-life were seen with the HT trials done so far. It was also noted that through the loss of activity, BPL would by necessity reduce the annual output of Factor V111 from the present 30 Miu level (expected loss of 15-20%).

The meeting also discussed the need to control the licensing arrangements for the use of unlicensed product. It was seen that current rules allowed companies to exploit the named patient system eg FEIBA. It was also suggested that the regulatory bodies would need to consider applications for variation orders and to determine whether the products are new formulations requiring new license applications.

Paradoxically, if variation orders for HT products were approved, this would revoke the previous licensed application and therefore non - HT product could not be used for HTLV 111 positive patients !

Dr Savage raised the problem of treatment for haemophiliacs who had only received NHS product. Until NHS HT material was available, the alternatives were commercial HT or non - HT NHS material.

Opinions varied as to whether non HT NHS product would be used. The Chairman suggested that it be left to individual treatment centres to determine their policy.

Dr Lane advised that under the circumstances, BPL would not issue non - HT product in December, unless these were required for use and a specific request was made. Non used vials should not be returned to BPL as the BPL policy was not to reissue vials previously sent to users, in line with regulatory requirements. Any vials returned would probably be destroyed or put to research use. Some HT material will be available for clinical trail purposes, but the bulk will not be available until April:- three ovens are required, one is already in use, and two are expected in March.

It was agreed that priority for NHS HT material would be given to children and past users of NHS material.

Dr Jones commented that to continue to use non HT material would be against guidelines issued by the U.S.A. groups.

Dr Cash agreed but accepted that in the UK a phasing in period was bound to occur. There were risks other than HTLV lll with commerical concentrates.

The Chairman advised that he would issue guidelines following the meeting. In summary, the first choice would be HT material followed by the judgement of the individual clinican. He also suggested that peripheral treatment centres return all non HT commercial material to the Reference Centres for transfer back to the Company involved. Most companies had undertaken in writing to accept back non HT material.

Item 4 Follow-up of patients receiving HT Factor Vlll

It was seen to be important to follow-up all patients for any evidence of seroconversion.

Dr Craske was nominated to coordinate this with the help of a small task group. Dr Lane requested that BPL HT product be included in this study. Dr's Tedder and Savage agreed to help with the preparation of a protocol, along with Dr Craske.

Dr Mortimer suggested an intensive follow-up study for at least 3 months at 2 week/1 month/ and 3 months. Until variation orders were obtained these studies would be on a named patient basis.

A rethink might be necessary if an HT product was implicated in a seroconversion. In that case, all patients receiving the batch would be carefully monitored.

On the question of finance, Dr Savage suggested that a case be put to the DHSS for financial support by representatives of the Haemophilia Directors Organisation. Any recommendations for treatment would need to be supported by recommendations for financial support. The Chairman advised that the case for more money had already been put to the DHSS.

Item 5 (i) Handling of HTLV lll positive samples

The Chairman began by outlining problems encountered in Cardiff in obtaining pathology work, as no Category lll containment laboratory was available in Wales. The recommendations in the draft document on the handling of viruses such as HTLV lll were discussed. Several members were concerned as to its content and the practical implications likely to result from its introduction.

Dr Tedder voiced his concern over the report but suggested that it was time to introduce a safety audit and a level of laboratory practice sufficient to cope with the handling of future HTLV 111 problems, and sufficient to allay staff fears. He commented that past experience had shown test laboratories not to be areas of greatest risk.

The meeting was concerned on the social attitudes being adopted towards AIDS patients and Haemophiliacs. The situation was becoming very emotive, and commonsense was giving way to panic amongst donors, patients and contact groups. The Chairman advised that commonsense should prevail, and would write to David Tyrrel of the DPC expressing the members views.

(ii) Risk to Staff etc

Members agreed that the evidence so far showed little or no risk to staff treating patients. It was accepted that dental care constituted a higher risk and that steps should be taken to minimise the risk. The evidence from Hepatitis suggests that there is no aerosol risk, but that there is a risk from innoculation.

Dr Gunson advised that sexual contacts of risk donors were being discouraged from donating blood. This included haemophiliac family members.

Item 6 Advisory Statements

The Chairman stated that recommendations would be issued on the days proceedings and these would be widely circulated.

At this point Dr Lane suggested that for the remainder of the meeting, the Haemophilia Directors be allowed to have a private meeting with only themselves present. This was accepted.

The Chairman thanked Dr Lane and his staff for their presence at the meeting, and the hospitality afforded to the Directors by BPL.

N Pettet/KF/3.1.85

EHIV Screening

31st May, 1985.

Dr. E. Harris,
Chairman,
Expert Advisory Group on Aids,
D.H.S.S., Hannibal House,
Elephant & Castle, London SE1 6BY.

Dear Ed,

I am just writing to you to re-inforce the views that I have expressed at the Meeting on 29th May, concerning the rapid introduction of HTLV III antibody screening of blood donors. My anxiety is compounded by the paper from the Middlesex Hospital Group, published this week in the Lancet about the rising prevalence of HTLV III antibody positivity in London. I think that not only haemophiliacs receiving cryoprecipitate but also other groups such as some patients undergoing open-heart surgery or with acute leukaemia etc., could be at a real risk of infection by HTLV III. I therefore think that one or more of the FDA approved tests should be introduced immediately to test donations. Those which test as positive should be discarded and the logistics of re-testing confirmatory testing and donor counselling could then be dealt with as separate issues. I think that donors would readily accept witholding of all positive results as an interim measure because after all, they are themselves potential recipients. I feel that such testing should be implemented immediately in order to preserve confidence in the Blood Transfusion Service and any temporary increase in expense would just have to be borne.

Finally, I think you should know that I plan to submit a letter to the BMJ along these lines.

Yours sincerely

A.L. Bloom.

EAGA Screening

DEPARTMENT OF HEALTH & SOCIAL SECURITY
Alexander Fleming House, Elephant & Castle, London SE1 6BY
Telephone 01-407 5522 ext 7327

8 July 1985

Professor A L Bloom
Department of Haematology
University Hospital of Wales
Heath Park
Cardiff CF4 4XN

Dear Anthem,

Thank you for your letter of 31 May in which you express your concern about the need for rapid introduction of HTLV III antibody screening test for blood donors. It is accepted policy that the screening of blood donations should be introduced as soon as possible. However, it is clear from the evidence available that the performance of diagnostic kits licensed by the FDA is variable. It seems prudent therefore that before any large scale introduction of them into the Blood Transfusion Service they should be properly evaluated in the UK. The need for such an evaluation has been discussed at meetings of the EAGA and apart from discussion of the range of tests against which the kits should be evaluated there has been general support from the members.

Whilst the introduction of an unevaluated test into the Blood Transfusion Service and simply discarding any blood which gives a positive reaction is superficially attractive we are not persuaded that this is the right course. Be believe that it could lead to grave difficulties because of the large number of false positives. We consider that the introduction of the test to the BTS and to STD clinics should be on a national basis with appropriate facilities for counselling. If the test was initially only available in the BTS a lot of at risk individuals could attend donor sessions with the object of getting their blood tested. We want to avoid this.

I enclose a copy of the press statement reporting Mr Clarke's reply to a Parliamentary Question on the introduction of screening tests for HTLV III antibody in the Blood Transfusion Service and the Chief Medical Officer's statement which amplifies the background to the Ministers decisions.

Yours sincerely,

GRO-C

E L Harris
Deputy Chief Medical Officer

Enclos.

Department of Health
and Social Security

PRESS RELEASE

Alexander Fleming House
Elephant and Castle
London SE1 6BY

Telephone 01-407 5522

85/166

27 June 1985

AIDS BLOOD TEST SOON TO BE AVAILABLE

Kenneth Clarke, Minister for Health, announced today that an AIDS (Acquired Immune Deficiency Syndrome) blood test would be introduced within the next few months.

In a written reply to a Parliamentary Question from John Butterfill, MP for Bournemouth West, Mr Clarke said: "I am pleased to say that a test will be introduced within the next few months to screen all blood given by blood donors for antibodies to the virus which causes AIDS. Arrangements will also be made for Sexually Transmitted Diseases clinics to provide an AIDS test for people who fear they may have been exposed to the disease.

"I understand and share the concern to get these tests in use as soon as possible. However we must have tests which are accurate and can be trusted. A number of test kits are already available and in use abroad but reports from those countries suggest that the tests are not entirely reliable. We believe that no test should be introduced in the UK until its reliability has been established. There is no point in introducing a test which often fails to detect antibodies in blood or detects antibodies where there are none. An evaluation programme is being undertaken by the Public Health Laboratory Service and National Blood Transfusion Service experts as a matter of urgency. It is essential to complete this programme if we are to have a sensible policy that really does protect the public. Contrary to reports in today's press no decisions on choice of test kits have yet been made. We hope that we will be able to introduce a test within four to five months. We are also making arrangements to offer counselling to anyone whose blood is found to be positive.

"We expect that the number of blood donors found to have antibodies is likely to be very small. The risk of contracting AIDS from receiving a blood

transfusion remains extremely small and screening will reduce this risk still further. There is no risk at all to those giving blood of contracting AIDS."

NOTE TO EDITORS

The Government has provided funds of over £57,000 to enable the PHLS to carry out a full evaluation of all the test kits which are currently available. A further £750,000 will be provided for PHLS to set up laboratory facilities to confirm the results of any blood donations found positive and to test the samples taken in STD clinics.

BACKGROUND NOTE FROM THE CHIEF MEDICAL OFFICER

SCREENING BLOOD DONATIONS FOR HTLV III ANTIBODY

This note gives the background to today's announcement by the Minister for Health that a screening test for antibodies to HTLV III will be introduced within the next few months. Ministers have accepted that all blood donations should be screened for HTLV III antibody in order to give further assurance of the safety of blood transfusion and blood products. Evaluation of the various available tests is going ahead urgently with the intention of introducing testing throughout the Blood Transfusion Service as soon as possible. It is intended simultaneously to make diagnostic testing available through STD clinics. The PHLS is being funded to provide laboratory facilities for these tests.

More than two million blood donations are collected each year and it is clearly essential to ensure that any tests introduced on this scale must be known to give consistent results and be specific and sensitive. Specificity in this context means that a test which does not give rise to an unacceptable number of false positives each of which would require extensive further investigation and would waste the blood donations involved. Sensitivity is also of paramount importance in order that no genuine positives should be missed.

While the commercial products already on sale have been evaluated elsewhere on an individual basis no comparative evaluation is available. This requires that their performance should be compared against a single carefully chosen panel of sera and that the tests should be conducted under controlled conditions. The PHLS are currently conducting such an evaluation. A field trial designed to explore both the specificity of the test and the operational aspects of its routine use throughout the country is also essential. Ease of use and consistency in large scale screening are prime requirements in selecting a suitable product for use in screening blood donations. Laboratory and field evaluations, both undertaken on a large scale, will enable an informed choice to be made and will promote confidence in those kits which are subsequently chosen.

When screening is introduced into the Blood Transfusion Service those donors who are found to be genuinely positive following confirmatory testing will be informed so that they can be referred for counselling. Arrangements are being put in hand to provide this service. It is expected that the numbers who are detected as positive will be very small indeed.

The present policy of Regional Transfusion Centres is to dissuade people in high risk groups for AIDS from volunteering to give blood and this will continue after the introduction of screening. Alternative facilities will be provided to enable those in high risk groups to obtain tests and counselling.

It has been suggested that testing should be introduced immediately, before the reliability of the tests available has been evaluated. Early experience of other countries and the considerations outlined in this note have led Ministers to decide that it would be wrong to introduce a screening test until the further evaluations mentioned above have been carried out.

Blood transfusion

DEPARTMENT OF HEALTH & SOCIAL SECURITY
Alexander Fleming House, Elephant & Castle, London SE1 6BY
Telephone 01-407 5522 ext

Professor A L Bloom
Department of Haematology
University Hospital of Wales
Heath Park
CARDIFF CF4 1XW

15 August 1985

Dear Professor Bloom

HEAT TREATED FACTOR VIII

In the letter from the Haemophilia Reference Centre Directors to the British Medical Journal on the 22 June it was apparent that at certain Haemophilia Centres Factor VIII concentrate which had not been heat treated was still in use.

I am now writing to give you the latest information of the availability of heat-treated Factor VIII concentrate. The Blood Products Laboratory at Elstree has been heat-treating all their output of Factor VIII concentrate since April this year; whilst there was a period during which only limited supplies were made available, I am pleased to say that output has now been increased to the maximum level possible in the current BPL plant. Until the new BPL plant comes into production later next year, there will continue to be a need to obtain additional supplies of Factor VIII from commercial sources. I am understand that all commercial Factor VIII concertrate now imported into this country is also heat treated. There would thus appear to be no longer any need to use un-heat-treated Factor VIII concentrate.

Yours sincerely

GRO-C

E L HARRIS
Deputy Chief Medical Officer

VT3/A1

UK HAEMOPHILIA REFERENCE CENTRE DIRECTORS

RECOMMENDATIONS ON CHOICE OF THERAPEUTIC PRODUCTS FOR THE TREATMENT OF NON-INHIBITOR PATIENTS WITH HAEMOPHILIA A, HAEMOPHILIA B OR VON WILLEBRAND'S DISEASE

1. BACKGROUND

Recognition of HIV infection/AIDS as a hazard of blood product therapy for haemophilia has caused a heightened awareness of the general problem of transfusion-transmitted disease, particularly as regards non-A, non-B hepatitis (NANBH). Whilst it is clear that risk can never be completely eliminated, major advances have been made in risk reduction, and physicians are faced with the problem of choosing between therapeutic products of possibly differing risks.

The purpose of this paper is to present a consensus view of the UK Haemophilia Reference Centre Directors on the relative merits of therapeutic products which are either currently available in the UK, or likely to become so in the near future. We intend to update our recommendations as the rapidly changing situation evolves.

The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) in the USA have recently published their own recommendations. The situation in the UK differs from that in the USA, both in the availability of different therapeutic products, and in the legal framework which governs their use. Also, our opinions on the interpretation of available data differ in some respects from MASAC.

2. DATA ON WHICH RECOMMENDATIONS ARE BASED

It must be emphasized that our opinions about the risks and therapeutic efficacies of different products are based on evidence which is often incomplete, and in many cases unpublished. Despite these problems, physicians necessarily have to make therapeutic decisions in the best interests of their patients, within the resources they have available. It has always been the case in the UK that such decisions have often had to be made without guidance from the regulatory authorities. Whilst this situation is to be deprecated, it is important for physicians to be aware of the legal framework in which they prescribe therapeutic products, particularly as regards the 'named patient' use of currently unlicensed preparations. Whilst it may be that such preparations have advantages over fully licensed products, data supporting such conclusions is often scanty. At the very least, therefore, a physician using a product on a 'named patient' basis should be confident of peer group support if his/her decision to use that product is questioned. It is also important to remember that all manufacturers, including those within the NHS, have an

interest in interpreting data concerning their own products in the most optimistic light, and vice versa.

The strongest evidence on the magnitude of risk of viral transmission from any particular product is derived from 'virgin patient' (VP) studies, of which there have been relatively few. It is generally considered that at least 60 patients with uneventful follow-up are needed to satisfactorily prove safety (i.e. <5% risk) at the 95% level of confidence. To our knowledge, no studies yet carried out have fulfilled this criterion. While anecdotal reports can provide reasonable evidence of viral transmission (and hence the probability of product contamination), the lack of such reports is very poor evidence of product safety - what isn't looked for will often not be found. Extrapolation from apparently similar manufacturing processes is of doubtful validity, since subtle and sometimes unperceived differences may markedly influence viral inactivation/removal. We remain unhappy about the prognostic value of in-vitro and animal data, since both these sources have been proved to be fallible in the past.

3. GENERAL COMMENTS ON METHODS OF VIRAL INACTIVATION/ REMOVAL AND PROCESSING

All factor VIII and IX concentrates currently available in the UK are derived from HBsAg and anti-HIV screened source plasma. Additionally, commercial products are generally obtained from donors screened for elevated alanine aminotransferase (ALT), a possible surrogate marker of NANBH risk. The 'cut-off' limits for ALT screening, and its effectiveness on NANBH risk-reduction, are poorly defined.

Heat-treatment as a method of viral inactivation was initially developed as a means of reducing hepatitis risk. Since the introduction of methods of viral inactivation/ removal, it has become generally accepted that HIV is more easily inactivated than HBV or NANBH. Other agents, such as human parvovirus (HPV), may be less susceptible to inactivation than hepatitis viruses. Although such agents are not necessarily pathogenic in the context of haemophilia care, serological evidence of transmission may be useful as a marker of process efficacy.

It is important to appreciate that the method of fractionation, and not just the nature of any viral inactivation step, may contribute substantially or predominantly to final product safety. In the case of NHS concentrates, final safety may also be dependent on the lesser likelihood of contamination of the source donor plasma.

We have arbitrarily assigned groupings to products available to haemophilia care:

3.1 1st generation products are conventionally fractionated and usually heated in the lyophilized state ('dry' heated), according to various protocols. Clear evidence of NANBH

transmission by some of these products, and anecdotal evidence of HIV transmission (always disputed by manufacturers), has led to all these products except one (Koate HT, Cutter) being withdrawn from the market.

3.2 2nd generation products were developed in response to the perceived inadequacies of 1st generation processes, and have generally been found to have lesser risks of hepatitis transmission. A disadvantage of several methods is low yield, which results in needs for larger quantities of source plasma and higher production costs.

3.3 3rd generation products are prepared by monoclonal immunoabsorption, which results in extremely pure final products of high specific activity. It is claimed that fractionation processes, rather than any viral inactivation steps which may precede or follow them, are predominantly responsible for freedom from viral contamination. Assuming such 'sterility', the main conceptual advantage of these products lies in their potential to avoid the protein and antigenic loading which is an inevitable consequence of treatment with 1st and 2nd generation concentrates. Possibly, such loading may contribute to immune dysfunction, especially in HIV-infected patients, and it is claimed that therapy with monoclonal-fractionated concentrates may have a favourable influence on immune function. In our view, this claim is at present unsubstantiated.

4. PRODUCTS AVAILABLE OR SOON TO BE AVAILABLE

In the following list, comment is made on evidence or lack of evidence from virgin patient (VP) studies on hepatitis transmission compared with the near certain risk of NANBH transmission associated with unheated concentrates.

All the products listed below are considered to have a negligible risk of HIV transmission.

4.1 1st generation products

Koate HT (Cutter)
- 'dry' heated (72 hr, 60°C)
- full product licence
- VP studies: insufficient data, anecdotal evidence of HBV transmission

4.2 2nd generation products

4.2.1. Profilate HT (Alpha)
- slurry heated in immiscible solvent (n-heptane; 20 hr, 60°C)
- full product licence
- VP studies: reduced risk of NANBH transmission

4.2.2. Hemate P (Behringwerke - may be marketed by Armour)
- pasteurised by heating in solution (10 hr, 60°C)

- full product licence
- VP studies: minimal risk of NANBH transmission

4.2.3. Koate HS (Cutter)
- pasteurised by heating in solution (10 hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

4.2.4. Kryobulin TIM3 (Immuno)
- heated under controlled water vapour pressure (10 hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: minimal risk of NANBH transmission, possible risk of transmission of HBV

4.2.5. NHS 8Y (factor VIII) (Elstree)
- 'dry' heated (72 hr, 80°C)
- Clinical trial exemption certificate (CTX) for VP study; otherwise used on a 'named patient' basis
- VP studies: 'soft' data suggest minimal risk of NANBH transmission

4.2.6. NHS 9A (factor IX) (Elstree)
- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: 'soft' data suggest minimal risk of NANBH transmission

4.2.7. NHS Z8 (factor VIII) (Edinburgh)
- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

4.2.8. NHS DEF IX (factor IX) (Edinburgh)
- 'dry' heated (72 hr, 80°C)
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

4.2.9. Octa VI (Octapharma)
- solvent/detergent treated (TNBP/Tween)
- unlicensed: used on 'named patient' basis only
- VP studies: 'soft' data suggest minimal risk of NANBH transmission

4.3 <u>3rd generation products</u>

4.3.1. Monoclate (Armour)
- monoclonal purified
- 'dry' heated (30 hr, 60°C)
- unlicensed: used on 'named patient' basis only
- VP studies: minimal risk of NANBH transmission

4.3.2. **Hemofil M (Baxter)**
- monoclonal purified
- solvent/detergent treated before fractionation
- unlicensed: used on 'named patient' basis only
- VP studies: insufficient data

5. RECOMMENDATIONS FOR TREATMENT

5.1 General recommendations

We regard it as self-evident that all patients should be treated with the safest possible therapeutic products. HIV and the hepatitis viruses cause serious and often fatal disease, and every effort should be made both to prevent initial infection and re-exposure. In attempting to meet this ideal, however, there remain several problems:

5.1.1. Although it seems clear that different therapeutic products are associated with differing risks of contamination, it is not possible to quantitate these risks accurately. The data on which judgements should be based is to a large extent unavailable.

5.1.2. Not all the products listed are currently easily obtainable.

5.1.3. If there are supply problems patients at highest risk (e.g., those previously unexposed or only lightly exposed to blood products) should take priority in the use of products perceived to carry the least risk of viral transmission. It should be appreciated that it is not known whether re-exposure to HIV or hepatitis viruses in an already infected patient causes any additional hazard.

5.1.4. As noted in 3.3 above, the use of monoclonal-purified factor VIII is advocated by its proponents not so much because of its presumed lack of viral contamination, but because of its possible immune modulating effect in anti-HIV seropositive patients. While there will undoubtedly be a movement towards the use of more highly purified products, we do not consider current evidence sufficiently strong to justify adoption of such products as routine therapy, outside the context of formalised clinical trials.

5.1.5. Other factors being equal, we favour fully licensed products, or products having CTC or CTX approval, rather than those which have to be used on a 'named patient' basis. We recognise the anomalous situation of NHS concentrates in this respect, which we hope will be rectified in the near future.

5.1.6. Financial considerations inevitably influence availability of therapeutic products, and it is the responsibility of Haemophilia Centre Directors to make appropriate efforts to obtain adequate funding for

therapeutic products. We hope our recommendations will be of help in this respect.

5.2 Specific recommendations

5.2.1. For patients with haemophilia A who have received little or no previous exposure to blood products, and who need treatment with concentrate:

1st choice: NHS 8Y, patient to be included in current VP study if appropriate
2nd choice: Hemate P
3rd choice: Profilate HT.

5.2.2. For multitransfused patients with haemophilia A:

Any of the products listed in 5.2.1. above, plus Koate HT.

5.2.3. All other commercial factor VIII concentrates listed in Section 4 above are currently unlicensed, and in our view should only be used outside formalised clinical trials if the need is considered compelling by the prescribing physician, who must accept and understand the constraints of using on a 'named patient' basis.

5.2.4. For patients with haemophilia B: NHS 9A (Elstree).

5.2.5. We are unable to comment on the use of the Scottish NHS factor VIII or IX concentrates, since we have no data on which to base any judgements but the factor IX concentrate closely resembles the Elstree 9A concentrate in composition and method of manufacture and procedure for virus inactivation.

5.2.6. For mildly or moderately affected patients with haemophilia A and von Willebrand's Disease, desmopressin (DDAVP) should always be considered before use of blood products.

5.2.7. We consider random donor cryoprecipitate to have an only very limited application in the treatment of congenital coagulation disorders, mainly because of its non-HIV-related risks in particular NANBH and transfusion reactions. For the few patients with vWD who cannot be managed with DDAVP, NHS 8Y (Elstree) concentrate or Hemate P is recommended. Cryoprecipitate should only be considered if the haemostatic efficacy of concentrate therapy is in doubt.

5.2.8. Hepatitis B vaccination should be given to all patients likely to receive blood product therapy who have no serological evidence of past exposure.

Prof. A.L. Bloom
Dr. I.W. Delamore
Dr. P. Hamilton
Dr. P. Jones
Dr. P.B.A. Kernoff

Dr. G.D.O. Lowe
Dr. C. Ludlam
Dr. E.E. Mayne
Dr. G.A. McDonald
Prof. F.E. Preston
Dr. C.R. Rizza
Dr. G. Savidge
Dr. R.T. Wensley

5th May, 1988

KS

APPENDIX 20

DEPARTMENT OF HEALTH & SOCIAL SECURITY
Alexander Fleming House, Elephant & Castle, London SE1 6BY
Telephone 01-407 5522
From the Joint Parliamentary Under Secretary of State

PO(PS-HPSS) 2823/25

Professor A L Bloom MD
Ysgol Feddygol Cymru
The Welsh National School of Medicine
Department of Haematology
University Hospital of Wales
Heath Park
Cardiff
CF4 4XN

18 December 1980

Dear Prof Bloom

Thank you for your letter of 12 November addressed to Patrick Jenkin about the short-fall in the production of Factor VIII concentrate for the treatment of haemophilia and the possible redevelopment of the Blood Products Laboratory.

As you may have seen, on 26 November Dr Gerard Vaughan, the Minister for Health, announced in Parliament that there was no question of a commercial company taking over the management of the Blood Products Laboratory and I enclose for your information the text of his answer to Gary Waller MP together with a statement issued on the same day following Dr Vaughan's visit to a blood donor session.

I can assure you that we fully appreciate your concern about the level of NHS production of Factor VIII. Earlier this year, we agreed to an upgrading programme for the Blood Products Laboratory at a cost of £1.3 million which should enable production of Factor VIII to be doubled by the end of 1982. This will not of course meet all of the demand for Factor VIII. The data you have provided on projected requirements for Factor VIII by 1985 (which agree with our own estimates) are very useful. The increasing demand for Factor VIII and its implications for the National Blood Transfusion Service is one of the topics to which the New Advisory Committee on the NBTS is giving urgent consideration and I understand that it is the intention that you and your fellow Haemophilia Centre Directors will be consulted on this matter in the near future. We shall very much welcome your assistance with this difficult problem.

I am writing similarly to Dr Rizza, Director of the Oxford Haemophilia Reference Centre.

Yours sincerely

George Young

ENC

SIR GEORGE YOUNG

KS

DEPARTMENT OF HEALTH & SOCIAL SECURITY
Alexander Fleming House, Elephant & Castle, London SE1 6BY
Telephone 01-407 5522
From the Joint Parliamentary Under Secretary of State

PO(PS-HPSS) 2623/25

Professor A L Bloom MD
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I am writing similarly to Dr Rizza, Director of the Oxford Haemophilia Reference Centre.

Yours sincerely
George Young

ENC

SIR GEORGE YOUNG

ALB/ENAI

12th November 1980

The Right Hon. Patrick Jenkin,
Secretary of State for Social Services,
Department of Health and Social Security,
Alexander Fleming House,
Elephant and Castle,
London WE1 6BY

At the recent meeting in Glasgow of the UK Haemophilia Centre Directors disquiet was again expressed at the short-fall of freeze-dried concentrates of antihaemophilic factor (factor VIII) provided by the NHS manufacturers for the treatment of haemophilia and at the consequent need to purchase large quantities of factor VIII from foreign commercial sources.

There is general agreement amongst experienced haematologists and physicians that freeze-dried intermediate or higher purity factor VIII concentrate is the material of choice for the treatment of haemophilia. Statistics collected by the Haemophilia Centre Directors show that 50 million units of factor VIII were used during 1979, a figure accurately forecast in 1975. Medical progress, increase in the number of patients and changing patterns of treatment are reflected in the arithmetic increase in the annual use of factor VIII seen since 1969 when those statistics were first collected. If this trend continues at the present rate the annual requirement will rise to about 85 million units by 1985. At present NHS fractionation laboratories produce approximately 15 million units of factor VIII per annum and local Blood Transfusion Centres produce a further 8 million units of second-line material, namely frozen or freeze-dried cryoprecipitate. It is generally agreed that cryoprecipitate is not suitable for home treatment and has limited medical indications for use. Nevertheless even taking into account this latter material there is still a short-fall of 25 million units of factor VIII per annum and this amount is currently purchased from commercial sources at a cost to the NHS of £2.5 million. It is estimated that this will rise to about 60 million units per annum during the next five years at a cost of £6 million at today's prices.

The suggestion has been made that the short-fall in factor VIII be met by licensing the commercial production of factor VIII by private enterprise within the UK using plasma collection by the National Blood Transfusion Service. Although such a step may in the short term be advantageous to our patients we are concerned that the constraints and requirements which would be imposed by industry in order to ensure profitability would in the long term be detrimental to the Blood Transfusion Service of this country, to the spirit of voluntary blood donation and eventually to treatment, not only of the relatively small number of haemophiliacs but also of the much larger number of recipients of whole blood and other blood products.

The problem of supply of factor VIII cannot be divorced from that of these other aspects of the Blood Transfusion Service and in our opinion should be solved by improving NHS transfusion resources within the UK, both centrally at the Fractionation Laboratories and peripherally at Blood Transfusion Centres. We feel that the future of blood transfusion practice and plasma fractionation in this country is too important to be exposed to the vagaries of national and international commerce. Moreover once expertise in plasma fractionation has been lost and the staff dispersed it may prove difficult to set up plasma fractionation again within the NHS should the commercial organizations withdraw.

A.L. Bloom, M.D.,
Director, Cardiff Haemophilia Reference Centre,
Chairman, UK Haemophilia Centre Directors
Organization.

C.R. Rizza, M.D.,
Director, Oxford Haemophilia Reference Centre,
Secretary, UK Haemophilia Centre Directors
Organization.

APPENDIX 21

ALB/ENAI 10th March 1981

Dr. J. Holgate,
DHSS,
Medicine Division,
Market Towers,
1 Nine Elms Lane,
London SW8 5NQ

Dear Dr. Holgate,

I am writing to you in my official capacity as Chairman of the Haemophilia Centre Directors of the UK. At our last meeting of Reference Centre Directors the problem of possible irregularities in the supplies of factor VIII concentrate was discussed.

Two problems have been highlighted recently. The first concerns the preparation called Humanate, about which there was some adverse publicity in the National Press recently. My colleagues and I would like to be reassured that this material has been cleared for use and has passed the normal control processes for the UK. We would like to be reassured that it is possible from the protocol to trace actual batches to source in the event of an outbreak of hepatitis etc. attributable to it. Most of us are aware of rumours that this material originates with an American Company and is sold through brokerage or other means to Speywood Laboratories Ltd. where it is relabelled. This seems to us to be somewhat irregular and we would greatly appreciate your advice on its current status.

With regard to a similar subject I enclose a copy of a letter which Dr. Savidge of St. Thomas's Hospital has given to me. From this you will see that a firm called Inter-Pharma intend to market cut-price factor VIII obtained from Cutter Laboratories and from Hyland, and I wonder also if this material has been through the normal control mechanisms. I understand from Dr. Savidge that the Hyland material may in fact be a high potency factor VIII and not the much cheaper intermediate variety, being marketed in the ethical way in the UK.

The Haemophilia Reference Centre Directors have expressed disquiet at these developments although we are aware that by virtue of plasma brokerage arrangements in the USA it may be difficult sometimes to be sure of the exact origin of plasma used in any of the currently available concentrates. These problems highlight the importance of developing a UK potential within the Health Service to supply all the needs of the British haemophiliacs. I would be very grateful for your advice.

Yours sincerely,

A. I. Bloom

Inter-Pharma

36 Greenways, Haywards Heath, West Sussex RH16 2DT
Telephone (0444) 55893

LJC/EC

27th January 1981

Dr. G. F. Savage, F.R.C.S.,
Haemophillia Centre,
St. Thomas's Hospital,
Lambeth Road,
LONDON SE17EH

Dear Dr. Savage,

Following our recent meeting you will recall that you raised a number of questions in connection with the supply of Factor VIII to St. Thomas's Hospital by Inter-Pharma.

A meeting with our suppliers has been held and we are now in a position to answer your questions.

1. If, in the unlikely event of any Factor VIII supplies proving faulty, these will be exchanged free of charge upon Inter-Pharma being informed in writing within seven days of receipt of supplies to you.

2. Inter-Pharma has agreed to maintain prices of Factor VIII at £0.07 per unit plus VAT for a period of fifteen months, commencing 1st April 1981.

3. Delivery of Cutter Laboratories' Factor VIII:

   7 days minimum from receipt of order.
   14 days maximum from receipt of order.

4. Delivery of Hyland Laboratories' Factor VIII:

   14 days minimum from receipt of order
   21 days maximum from receipt of order

5. Inter-Pharma is able to supply in quantities of 250, 500 and 1,000 units.

6. We have pleasure in informing you of our rebate scale which is as follows:

Continued...

Inter-Pharma

36 Greenways, Haywards Heath, West Sussex RH16 2DT
Telephone (0444) 55893

Units	Rebate
250,000	£400
500,000	£1000
750,000	£1400
1,000,000	£1900
2,000,000	£3500
3,000,000	£5000
4,000,000	£8500

These rebates are for multiples of 250,000 units.

As we explained to you during our discussion, Inter-Pharma would be in a position to commence the supply of Cutter and Hyland Factor VIII, as from 20th April 1981.

We look forward to receiving a reply to our correspondence which we sincerely hope will be favourable and will lead to the eventual supply by Inter-Pharma of your requirements for Factor VIII.

If you require any further details please do not hesitate to contact us when we will be only too pleased to assist you in your requests.

We look forward with extreme interest to receiving your reply.

Yours sincerely,

GRO-C

Lewis J. Curry
Director
INTER-PHARMA

Department of Health and Social Security
Medicines Division
Market Towers 1 Nine Elms Lane London SW8 5NQ
Telex 883669 Telephone 01-720 2188 Ext 3128

Your reference ALB/ENAI
Our reference

23rd March 1981.

Dear Professor Bloom,

Thank you for your letter of 10th March drawing our attention to the recent disturbing press reports concerning Factor VIII concentrate and enclosing a copy of a letter given to you by Dr. Savidge.

As I am sure you are aware one of the cornerstones of our philosophy for the licensing of 'biological' products is to have detailed knowledge of and control over early stages of manufacture and in-process control - this including source material. I am particularly delighted to have your clearly expressed support for this attitude.

With regard to Humanate and Speywood Laboratories Ltd I can say no more at this stage as the matter is being dealt with at the present time.

With regard to the Inter-Pharma matter all I need to say is, I think, that any licence which may be granted will have to satisfy the basic philosophy on all counts.

May I thank you again for reinforcing our concern in this matter at this time.

Yours sincerely,

GRO-C

J. A. HOLGATE

Professor A. L. Bloom,
The Welsh National School of Medicine,
Department of Haematology,
University Hospital of Wales,
Heath Park,
CARDIFF CF4 4XN.

NOTES FOR JOINT MEETING OF REPRESENTATIVES OF HAEMOPHILIA CENTRES/BLOOD TRANSFUSION SERVICE DIRECTORS: APRIL 1981

1. BACKGROUND

Ministerial agreement for planning has been obtained for the building of a new plasma fractionation plant within the National Blood Transfusion Service. Although this plant is unlikely to operate until the late 1980s, consideration must be given now to the probable requirements for Factor VIII and other coagulation factor concentrates to meet genuine clinical needs in the United Kingdom by that time and during the 1990s.

2. FACTS TO BE BORNE IN MIND WHEN CONSIDERING REQUIREMENTS FOR FACTOR VIII

2.1 By the late 1980s separation of fresh frozen plasma (FFP) from 40-45% of all donations of whole blood to NBTS is likely to provide ca 35-40 M iu Factor VIII in the form of currently produced Intermediate Concentrates (240 iu).

2.2 To avoid the undesirable wastage of human red cells all additional FFP required must be obtained from plasmapheresis donors (pph.d).

2.3 If each pph.d. gives 10 donations per year, every 5000 pph.ds on national panel will result in ca 11 M iu Factor VIII (as Intermediate Concentrates).

2.4 It is a reasonable assumption that if sufficient FFP becomes available to meet genuine clinical needs for Factor VIII there will be enough available for the preparation of Factor IX Complex (and other blood products such as albumin and normal immunoglobulin).

3. MATTERS FOR DISCUSSION

3.1 Requirements for Factor VIII: total iu per annum.

3.2 Some countries (Switzerland, Belgium, Finland, Netherlands and France) have opted to make freeze-dried cryoprecipitate the major product for haemophilics. Dr Gunson is visiting Transfusion Centres in Switzerland and

Belgium in April and will report to the meeting on 23 April.

3.3 What are current views on the proportional annual requirements for:

3.3.1 A high purity concentrate. 10%

3.3.2 Intermediate concentrate 80%

3.3.3 Freeze-dried cryoprecipitate. 10%

4. CURRENT PROBLEMS

4.1 Pro-rata distribution.

4.2 Collection of data on Regional requirements for Factor VIII concentrates.

Question of commitment
100 million – 50m from ordinary bleeds (but will be enough RBC's).
rest – plasmapheresis – costly – regional support.

But have sent Monthly sheet to Regional Transf Centre.

? relationship between Elstree supply
BTS funding
& our purchases.

BPLL0001351_0099

JOINT MEETING OF REPRESENTATIVES OF HAEMOPHILIA CENTRES/ BLOOD TRANSFUSION SERVICE DIRECTORS: 23 APRIL 1981.

Present:	Dr G Tovey (Chairman)	
	Prof A Bloom)	
	Dr C Rizza)	
	Dr P Kernoff)	Haemophilia Centre Directors
	Dr P Jones)	
	Dr I Delamore)	
	Dr G Bird)	Transfusion Service Directors
	Dr H Gunson)	
	Dr R Lane	(Blood Products Laboratory)
	Dr J Cash	(SNBTS)
	Dr G Macdonald	(Scottish Haemophilia Centres)
	Dr D Walford	DHSS

SUMMARY OF THE MAIN POINTS DISCUSSED

The meeting was opened by the Chairman who explained that as part of their aim towards national self-sufficiency in blood products, Ministers had instructed officials to begin planning for a new blood products laboratory. This meant that it was vital to obtain the best possible estimates for blood products usage over the next decade. The meeting had been convened in order to consider the foreseeable requirements for blood products containing coagulation factors used in the treatment of haemophilia.

I QUANTITIES OF MATERIALS REQUIRED

I(i) Factor VIII. Members considered the statistics available from Haemophilia Centres, up to the end of 1979, which gave figures for the usage of coagulation factor preparations. In 1979, the UK usage of Factor VIII was an average of 23,000 i.u. per patient treated per year which was roughly one half of the average usage in the USA and one tenth of the usage in Germany. It was obviously important, in making such international comparisons, to bear in mind that the amount of Factor VIII which was used in different countries could well be in excess of the amount which was actually required. Nevertheless, the amount of Factor VIII used in the UK since 1969 had been rising linearly (fig 1) and in 1979 totalled 52 million i.u. per annum. Extrapolating from these figures, members felt that by the mid-1980s, some 80-100 million i.u. of Factor VIII would be required. An upper limit of 150 million i.u. for the end of the decade could be guessed at but the likely introduction of various technical innovations made it impossible to look further ahead to the requirement for the 1990s.

IT WAS AGREED THAT THE PROJECTED FIGURE FOR FACTOR VIII USAGE FOR THE MID 1980s WAS 100 MILLION I.U.

I(ii) Factor IX. The rate of increase in the usage of Factor IX concentrates appeared to be levelling off (fig 2) which was probably because many patients with haemophilia B were now on prophylactic therapy in which Factor IX had the advantage over Factor VIII concentrates in having a longer in-vivo half-life. No significant increase in Factor IX usage over the present 7.5 million i.u. was envisaged for the mid 1980s.

I(iii) Activated/non-activated Factor IX concentrates for the treatment of haemophiliacs with Factor VIII inhibitors. Recent studies showed that there was still a place for this type of material in the treatment of haemophiliacs with Factor VIII inhibitors. It would be necessary for suitable material to be manufactured in a comprehensive self-sufficiency programme for blood products, but the quantities required would be relatively small.

II TYPES OF MATERIAL REQUIRED

II(i) Frozen cryoprecipitate. Even if this were largely phased out for the treatment of severe haemophiliacs, there would still be a small requirement for its use in patients with Von Willebrand's disease and in mild haemophiliacs and some carriers with low levels of Factor VIII. In the last two categories, the small pool size with its lesser risk of hepatitis transmission was the main reason why frozen cryoprecipitate was preferred to concentrates.

II(ii) Freeze-dried cryoprecipitate. The advantages of a freeze-dried cryoprecipitate over the frozen material would be the easier storage and the greater standardisation which could be expected with the freeze-dried material. However, unless the pool size for the freeze-dried cryoprecipitate were small, the advantages of such a product in terms of lessening the hepatitis exposure of mildly affected haemophiliacs would be lost but such small pool material would be difficult to standardise and expensive to produce. In relation to these two conflicting factors, the different philosophies (and the Factor VIII yields) underlying the Belgian and Swiss programmes for the production of freeze-dried cryoprecipitate were discussed. Neither seemed appropriate for adoption by the UK fractionators. A satisfactory solution might be achieved by the use of larger plasma pools made from donations from a restricted number of plasmapheresis donors who would effectively comprise an "accredited" panel of donors with a low hepatitis risk. It was agreed that provided steps were taken to minimise the hepatitis risk from freeze-dried cryoprecipitate, a supply of this material would be useful for mildly affected haemophiliacs and could also satisfy the small demand for fibrinogen in special therapeutic situations. The demand would not be expected to exceed 10 per cent of the total Factor VIII usage (although it was felt that this figure required further consideration). Because of volume and solubility problems, members felt that freeze-dried cryoprecipitate would be generally unsuitable for use in home therapy for severely affected haemophiliacs.

IT WAS AGREED THAT PROBABLY NO MORE THAN 10 PER CENT OF THE FACTOR VIII-CONTAINING PRODUCTS SHOULD BE IN THE FORM OF FREEZE-DRIED CRYOPRECIPITATE. A SMALL AMOUNT OF FROZEN CRYOPRECIPITATE SHOULD STILL BE MADE FOR USE IN SELECTED CASES.

II(iii) Intermediate purity concentrate.

IT WAS ESTIMATED THAT A MINIMUM OF 80 PER CENT OF THE FACTOR VIII REQUIREMENT WOULD NEED TO BE IN THE FORM OF INTERMEDIATE PURITY CONCENTRATE.

II(iv) High purity concentrate. This was principally needed for major surgery in order to reduce the fibrinogen load to the patient from less pure products and, more rarely, to prevent haemolytic reactions due to isoagglutinins.

IT WAS AGREED THAT A MAXIMUM OF 10 PER CENT OF THE TOTAL FACTOR VIII REQUIREMENT WOULD BE NEEDED AS HIGH PURITY CONCENTRATE.

III CURRENT PROBLEMS

III(i) Pro-rata distribution of Factor VIII. It was explained that pro-rata return of blood products was an interim measure to stimulate regional collection of plasma. The basis for calculating the special allocation to the Lord Mayor Treloar School was explained and was agreed.

III(ii) Collection of data on regional requirements for Factor VIII. In considering the working of the pro-rata system, the Advisory Committee on the NBTS had felt that it would be essential for RTDs to have ready access to information on the total usage of Factor VIII in their regions. For this reason, the Advisory Committee strongly advocated that all supplies of Factor VIII (both NHS and commercial) should be held in, and issued from, RTCs. The system had worked well in the West Midlands Region where, in consultation with Regional Haemophilia Centre Directors, the RTD negotiates the purchase of all the commercial Factor VIII used in the Region and holds the stocks. The money for the purchase comes from the users' budget and not from the RTC budget. A similar system in the North Western Region had encountered problems which, it was felt, were due to these purchases coming out of the RTC budget. It was felt that with a separate budget, as in the West Midlands, these problems would be resolved. Haemophilia Centre Directors were opposed to the introduction of such a system in that they valued the flexibility of product supply which was inherent in their existing arrangements and they felt that the machinery for collecting statistics on Factor VIII usage was adequate without introducing this extra measure of oversight of product usage. Whilst agreeing the excellence of the Haemophilia Centre statistics, Transfusion members felt that the need was for a monthly tally of Factor VIII purchase and usage rather than for yearly returns in arrears.

IT WAS AGREED THAT THE PROPOSAL FOR ALL SUPPLIES OF FACTOR VIII TO BE HELD IN, AND DISTRIBUTED FROM, RTCs NEEDED FURTHER CONSIDERATION BEFORE A DECISION COULD BE TAKEN ON ITS ADOPTION.

Future meetings. As this was an ad hoc meeting, convened at the request of the Advisory Committee on the NBTS, no further meeting had been planned. However, members considered that there was a need for a further meeting of those present and then, perhaps, for a continuing forum in which "producers" and "users" could continue this useful dialogue.

IT WAS AGREED THAT A FURTHER MEETING SHOULD TAKE PLACE ON 8 OCTOBER AT THE ROYAL FREE HOSPITAL IMMEDIATELY PRECEDING THE ANNUAL MEETING OF THE HAEMOPHILIA CENTRE DIRECTORS.

DW
April 1981

LP2

Department of Health and Social Security
Hannibal House Elephant and Castle London SE1 6TE

Telex 883669 Telephone 01-703 6380 ext 3574
Room 1208

Professor A L Bloom
Dept of Haematology
University Hospital of Wales
Heath Park
Cardiff CF4 4XW

Your reference

Our reference
BLH/1

Date
5.10.81

Dear Professor Bloom

I enclose a copy of our file note of the Consultant Adviser's meeting with representatives of Haemophilia Directors on 15 September.

Yours sincerely

GRO-C

S GODFREY
Health Services Division 1A

Copies to those present at the meeting.

JOINT MEETING OF REPRESENTATIVES OF HAEMOPHILIA DIRECTORS, BLOOD TRANSFUSION SERVICE DIRECTORS AND DHSS: 15 SEPTEMBER 1981

PRESENT: Chairman

Dr G H Tovey (Consultant Adviser)

Haemophilia Centre Directors

Professor A L Bloom
Dr I W Delamore
Dr P Hamilton (in place of Dr P Jones)
Dr P B A Kernoff
Dr C R Rizza

NBTS
Dr J Cash - National Medical Director, Scottish National Blood Transfusion Service
Dr H H Gunson - Director, North Western Regional Transfusion Centre
Dr R S Lane - Director, Blood Products Laboratory

DHSS

Mr S Godfrey
Dr D Walford
Miss P Wall
Mrs S C Yuille

Apologies for Absence

1. Apologies had been received from Drs McDonald, Bird and Jones.

Plans for the Redevelopment of the Blood Products Laboratory

2. Mr Godfrey explained that Ministers had agreed to the setting up of a Policy Steering Group under the chairmanship of Mr D Smart of Glaxo Holdings Limited, to plan the redevelopment of BPL. The group, which included specialist expertise from the NHS and from industry, had met for the first time in August. It decided that as short a time-scale as possible for redevelopment should be set, and the Department agreed to 'fast-track' the building project, and to ensure that no undue delays occurred. One of the group's most immediate tasks, in consultation with the Advisory Committee on the NBTS, was to recommend the target capacity for the new Laboratory, taking into account the NHS' ability to increase the supply of plasma.

Plasma Supplies for Blood Products Manufacture

3. Dr Gunson said that the Working Party on Plasma Supply had estimated that to meet the anticipated demand for Factor VIII of 100 million international units by the mid-1980s, approximately 500,000 kilograms of plasma would be required. 200,000 kilograms could be collected from whole blood donations, which would also meet hospitals' requirements for red cells, and the remainder could be collected by plasmapheresis.

4. It was explained that there would be major financial implications for RHAs, and once the Working Party had refined its costings, Authorities would be approached to discuss the need to increase supplies to BPL, the costs and also the resultant long-term benefits to the NHS. Nevertheless, it had to be accepted that some Authorities might not consider that increasing the collection of blood was one of their financial priorities.

5. Dr Tovey thought that it would be necessary for Transfusion Directors and Haemophilia Centre Directors to unite in the task of persuading their RHAs of the need to increase plasma supplies, and to point out the benefits in the long-term. It was also hoped that the Regional Medical Officer, Regional Treasurer and Regional Administrator members of the Advisory Committee would make these points at their respective uni-discipline meetings.

6. There was a discussion of the recent ministerial decision to allow the sale of surplus materials derived from blood. Haemophilia Centre Directors were concerned that material which could be used in the NHS might be sold to British industry and abroad. Mr Godfrey assured them that Ministers had given their consent only to the disposal of 'surplus' materials which would otherwise be destroyed and there could be no question of selling products for which the NHS had a need. The sale of surplus products would also benefit the NHS financially.

Current Systems for Purchase/Distribution of Supplies of Commercial Factor VIII and a Proposal to Purchase Commercial Factor VIII Preparations Through the Regional Transfusion Centres

7. Dr Walford explained that it would be most helpful for the Department to have details of how Haemophilia Centres purchased their supplies of Factor VIII. Haemophilia Centre Directors explained that each Centre operated its own system of purchase. Dr Hamilton said that in his Region (Northern), Factor VIII was purchased for all Centres through the Pharmaceutical Officer. Dr Kernoff explained that in North East Thames, a contract was made with two commercial companies to supply all Haemophilia Centres. Each Centre then paid for the Factor VIII it required. The contracted companies made regular returns to the Regional Supplies Officer of the Factor VIII they had supplied.

8. Discussing the purchase of Factor VIII through Regional Transfusion Centres, Haemophilia Centre Directors were in general opposed to such a system because they felt that they might lose flexibility to choose the product they wanted. It was explained that clinicians would still retain the right to choose their products, and the RTC would only be responsible for ordering and delivery. Because of the pro rata distribution of BPL's Factor VIII, it was vital for Transfusion Directors to have up-to-date and regular information on the extent of commercial purchasing. After discussion it was agreed that Haemophilia Centre Directors would endeavour to keep Regional Transfusion Directors informed of commercial purchases by means of a monthly report. The Directors present agreed to inform their colleagues in other Haemophilia Centres and Haemophilia Reference Centres of this agreement.

Requirement for Freeze-Dried Cryoprecipitate

10. Directors agreed that they needed to reconsider their original estimated requirement for 10 million international units of freeze-dried cryoprecipitate and 10 million international units of high-purity concentrate. Dr Walford explained that to produce that amount of high-purity Factor VIII concentrate would require a disproportionate amount of plasma, and the costs of production would be very high. Directors agreed that if freeze-dried cryoprecipitate were not

available, then frozen cryoprecipitate would be an acceptable substitute. At present about 1-2 million international units of frozen cryoprecipitate were used to treat von Willebrands disease. However, if more intermediate-purity concentrate were made available, the need for frozen cryoprecipitate would drop even further. Directors thought that the need for high purity concentrate might be substantially less than 10 million international units, but the requirement and supply would need to be kept under careful review. (In view of the above requirements it is likely that the plasma requirement could be reduced to 435,000kg.)

Future Meetings

11. It was decided that meetings would take place as and when they were thought to be necessary.

Dr. C.R. Rizza,
Haemophilic Centre,
Churchill Hospital,
Headington,
OXFORD

22nd October 1981

Dear Charlie,

I am just writing to you concerning two points, both of them related to the minutes of the meeting on blood transfusion which we had in London on 15th September.

In paragraph 8 I am reminded that we promised to ask Haemophilia Centre Directors to advise Regional Transfusion Directors of purchases of commercial factor VIII by means of a monthly report. I must admit that I did not think that I emphasised this sufficiently at the meeting at the Royal Free. Do you think we should send a circular around to all the Directors emphasising this point?

My second query refers to the third page of the minutes, line 3-4, this seems to imply that intermediate-purity concentrate may be acceptable to treat von Willebrands Disease. I do not think that the minute actually means this but it could be interpreted in this way. Do you obtain this impression?

With best wishes.

Yours sincerely,

A. L. Bloom

Mr F. Godfrey,
Health Services Division, 1A,
Department of Health and Social Security,
Hannibal House,
Elephant and Castle,
LONDON SE1 6TE

22nd October 1981

Dear Mr. Godfrey,

I do hope that you manage to come to a satisfactory solution to the problem which we discussed on the telephone the other day. However, I am writing now concerning the minutes on the meeting on 15th September. In the first place, Dr. Rizza and I will certainly endeavour to emphasise paragraph 8 on page 2 possibly by means of a circular to Haemophilia Centre Directors. My only other comment on the minutes is that on page 3, paragraph 12, line 3-4. This seems to imply that intermediate-purity concentrate would be generally acceptible to treat von Willebrands disease rather than cryoprecipitate. I do not think that you actually meant this but the sentence could be interpreted in this way. In point of fact of course, cryoprecipitate, either frozen or freeze-dried is still the treatment of this in most patients with von Willebrands disease. Perhaps the answer would be to bring that sentence containing 'however' forward so that it is inserted in the first line on page 3 directly after the sentence ending with the words 'acceptable substitute'. I hope that this is reasonably clear.

With best wishes.

Yours sincerely,

A. L. Bloom

HIGHLY CONFIDENTIAL

MEETING AT BPL

Wednesday, 15th December 1982

Present: Professor A. Bloom
Dr. C. Rizza
Dr. H. Gunson
Dr. J. Craske
Dr. J. Cash
Dr. R. Lane
Dr. M. Harvey
Dr. J. Smith

Agenda

The implications for the Haemophilia and Blood Transfusion Services of Commercial Introduction of "Hepatitis-Safe" Factor VIII and IX.

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1. Commercial Consideration

Factor VIII concentrates occupy 13% of the gross operating turnover of blood products. Factor VIII therefore lies fourth to albumins, specific immunoglobulins and normal immunoglobulin which collectively occupy 86% of the market. Factor IX, with all other products, occupies less than 1% of the market.

Price instability in the world market on blood products has introduced many bizarre effects, particularly in Europe. The price battle for Factor VIII intermediate concentrate in the UK is an example. Intense competition and unacceptably low prices is alleged to have resulted in the withdrawal of Hyland Hemophil II from the UK market and the threatened possibility of a second major company withdrawal in 1983.

The withdrawal of standard intermediate concentrate allows certain logical predictions:

(1) Residual monopoly of standard concentrates allows lack of competition to move the price upwards.

(2) A clear-field entry for commercial "Hepatitis-Safe" Factor VIII, which by nature of its "special-product" status (unproven) can command a price structure more in keeping with market expectations.

(3) Through loss of yield in production of "Hepatitis-Safe" products, "special status" is augmented by scarcity value since there must be a shrinkage in world availability of the new concentrates.

2. UK Options in Production

(1) Expansion in output to meet UK demand

(2) Evaluation of "hepatitis-safe" status - incurred penalties - economic considerations

(3) Evaluation of acceptable methodology into hepatitis inactivation and acceleration into production.

3. Current Commercial Approach to UK Users

The random approach now being adopted by commercial manufacturers to haemophilia directors in UK to study "H-S VIII" has many severe disadvantages for the NHS and gives little or no payback to the UK in return for opportunistic and non-contractual use of the special potential of the UK Haemophilia Service as a collective entity.

(1) Legal/Regulatory basis

(a) Only importation of HSVIII HSIX for use in named-patients is permissible

(b) For Clinical Trial - import licence is needed and no exemption would be offered

(2) Product Status

HSVIII and HSIX are the end-products of new processes for which formal licensing is ultimately required. Under 1(a) above, the manufacturer is not obliged to reveal any data on process or product at the early stages of development and trial in patients. Under 1(b) above, the manufacturer would be required to set out to the Regulatory Authority all required details on process, final product and tests of quality control, batch-to-batch reproducibility, toxicity test data and interim basis for claims of improved safety and efficacy.

N.B. In the final analysis, the licence application will be judged, amongst other factors, on process but particularly on evidence of safety and efficacy. It is essential to know that process and product used to demonstrate inactivation of virus in products at an early stage of product development (prior to trial) is the same, or as good as, the process to be used in normal manufacture. It is essential to bear in mind that the virus inactivation process may carry significant (and undeclared) yield penalties and that primate-based batch control is unlikely to support QC data in regular production. The true basis for claims of safety in regular production lies with on-going prospective studies in humans.

3. Efficacy and Safety of HSVIII and HSIX

The above statement defines the need for centralised, fully controlled prospective trials of "HS" materials, best operated through a properly executed National Clinical Trial lodged with the Regulatory Authority.

End results will carry a level of significance of value to user and producer. Information beneficial to the UK will be optimised.

Manufacturers entering the trial should undertake to make positive contributions of data and financial support in return for a properly conducted trial in a well-documented community of haemophiliacs.
[It is realised that overseas producers do not have access to trial facilities of equivalent quality and veracity elsewhere.]

4. Proposals

(a) That random exploitation of the haemophilia service by commercial organisations for the study of "hepatitis-safe" products should be discouraged.

(b) That the Haemophilia Services should create a formal basis for controlled clinical trial of alleged "hepatitis-safe" products in line with the requirements of Medicines Act.

(c) That the Haemophilia Services, PHLS and NBTS should combine resources in a manner likely to advance economic treatment of NHS haemophiliacs with safe products.

R. S. LANE,
Director, BPL.
15th December 1982.

DEPARTMENT OF HEALTH AND SOCIAL SECURITY
HANNIBAL HOUSE
ELEPHANT AND CASTLE LONDON SE1 6TE
TELEX 883669 TELEPHONE 01-703 6380 EXT 3487

Your reference:
Our reference:

Professor A L Bloom
Dept of Haematology
University Hospital of Wales
Heath Park
CARDIFF
CF4 4XW

19 January 1983

Dear Arthur

As you can imagine, recent publicity about cases of aquired immune deficiency syndrome in haemophilics in the USA has generated quite a bit of interest in the Department.

I believe that the topic was to be discussed at a recent meeting of Haemophilia Centre Directors and I should be most grateful if you could possibly let me know what conclusions were reached at the meeting. Perhaps it would be simplest if you could telephone me whenever convenient rather than bothering with a letter.

I look forward to hearing from you.

With best wishes.

Yours sincerely

GRO-C

DIANA WALFORD

Please Sign On
ID FDA219 ON SYS57
Dialcom International Computer Services 18.3B(57)
On At 12:55 03/25/83
Last On At 15:09 03/24/83

Mail Call (1 Unread)

>fdamail

Please wait...

>MAIL R FILE SESSION ALL

From: FDA901 Posted: Fri 25-Mar-83 10:44 Sys. 57 (66)
Subject: PRESS RELEASE ON AIDS

TO: All Field Offices, attn: RFDDs and Consumer Affairs Officers
EDRO Federal State Relations
EDRO Emergency Operations
Claudette Guilford
National Center for Devices and Rad. Health
Office of Biologics, NIH & Rkwl

FR: FDA Press Office

PRESS RELEASE

P83-6
FOR IMMEDIATE RELEASE
March 25, 1983

OASH - Shirley Barth GRO-C
FDA - Faye Peterson -
(Home) -- GRO-C

Dr. Edward N. Brandt Jr., assistant secretary for health, today recommended that plasma centers and blood banks around the country initiate procedures to reduce the risk of transmitting Acquired Immune Deficiency Syndrome (AIDS) through plasma, blood and blood products.

"These measures are necessary to help prevent the spread of this lethal disease while at the same time ensuring a constant supply of lifesaving blood products," Dr. Brandt said.

"The guidelines which we are recommending are intended to serve as interim measures to protect recipients of plasma, blood and blood products until specific laboratory tests are developed to screen blood for AIDS. They carry out the March 4 recommendations of the U.S. Public Health Service."

The new FDA guidelines say plasma centers and blood banks should:

-- set up educational programs to inform persons with increased risk of AIDS that they should refrain from donating plasma or blood;

-- instruct plasma center and blood bank personnel in how to use medical history questions to uncover the early symptoms of AIDS -- such as night sweats, unexplained fever and sudden, unexplained weight loss -- or exposure to AIDS;

-- and establish procedures for the handling and disposition of plasma and blood collected from known or suspected AIDS patients.

Plasma collected from donors suspected of being at increased risk of transmitting AIDS should not be fractionated into derivatives that have the

-MORE-

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

March 24, 1983

FROM: Director, Office of Biologics,
National Center for Drugs and Biologics

SUBJECT: Source Material Used to Manufacture Certain Plasma Derivatives

TO: All Licensed Manufacturers of Plasma Derivatives

Extensive discussions among licensed manufacturers, the Office of Biologics and concerned groups such as the National Hemophilia Foundation, have led to a consensus concerning an appropriate approach to decreasing the potential risk of transmitting Acquired Immune Deficiency Syndrome (AIDS) by certain plasma derivatives.

Plasma collected from donors suspected of being at increased risk of transmitting AIDS (as presently defined: persons with symptoms and signs suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners, Haitian entrants to the United States, present or past abusers of intravenous drugs* and sexual partners of persons at increased risk of AIDS) should not be fractionated into derivatives already known to have a risk of transmitting infectious diseases. Plasma from donors in any of the groups identified above may be collected for use in manufacturing only albumin, plasma protein fraction (PPF), globulin or in vitro diagnostic products. To prevent the possible misuse of such plasma, all licensed establishments collecting Source Plasma (Human) are being advised that in accordance with 21 CFR 606.120(b)(6) each unit must be conspicuously labeled either with the statement "CAUTION: For Use in Manufacturing Albumin, PPF, or Globulin Only," or "CAUTION: For Use in Manufacturing Noninjectable Products Only". HBsAg positive plasma for use in manufacturing vaccine or in vitro diagnostic products is already subject to additional special labeling and shipping precautions.

We request that you immediately institute procedures with your plasma suppliers to assure that they have adopted appropriate donor screening practices and procedures. Copies of notices that are being sent to all establishments collecting blood or source plasma concerning measures which should be taken, are enclosed for your information along with the recent Public Health Service Interagency Recommendations.

Please advise the Office of Biologics, in writing, of the procedures you have instituted to comply with this notice. The restrictions applied by your establishment on source plasma received for manufacturing high risk plasma derivatives should be effective immediately.

GRO-C

John C. Petricciani, M.D.

Enclosures
RETURN - RECEIPT REQUESTED

*Such intravenous drug abusers are already excluded by existing regulations.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda, MD 20205

March 24, 1983

FROM: Director, Office of Biologics
National Center for Drugs and Biologics

SUBJECT: Recommendations to Decrease the Risk of Transmitting Acquired Immune Deficiency Syndrome (AIDS) from Blood Donors

TO: All Establishments Collecting Human Blood for Transfusion

The Acquired Immune Deficiency (AIDS) Syndrome has caused serious concern among members of the blood banking community because of the implications for transfusion recipients if this disease is proven to be transmissible by blood or blood products. The major organizations engaged in blood collection have recently reached a consensus as to steps which should be taken to decrease the risk of transmitting AIDS by blood transfusion. Consistent with the recommendations of the American Red Cross, the American Association of Blood Banks, the Council of Community Blood Centers, and the Public Health Service Interagency Committee (copy attached), the Office of Biologics is advising all establishments collecting blood for transfusion to institute additional measures designed to decrease blood collection from individual donors and donor groups known to be at increased risk for transmitting AIDS. The following steps should be included:

1. Educational programs should be instituted to inform persons at increased risk of AIDS that until the AIDS problem is resolved or definitive tests become available, they should refrain from blood donation because of the potential risk to recipients of their blood. As presently defined this group includes: persons with symptoms and signs suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners, Haitian entrants to the United States, present or past abusers of intravenous drugs,* and sexual partners of individuals at increased risk of AIDS. Educational programs should include the individual donor as part of the donor screening procedure.

2. Re-education of personnel responsible for donor screening should be conducted with special attention to recognition of the early signs and symptoms of AIDS. The donor medical history should include specific questions designed to detect possible AIDS symptoms or exposure to patients with AIDS. Standard Operating Procedures (SOP) should be revised to include questions which elicit a history of night sweats, unexplained fevers, unexpected weight loss, or signs of lymphadenopathy or Kaposi's sarcoma.

* Such intravenous drug abusers are already excluded by existing regulations.

3. The SOP should specifically inform staff that all blood or blood products inadvertently collected, or collected for therapeutic purposes, from a donor known or suspected of having AIDS should be considered potentially highly infectious and must be immediately quarantined and disposed of expeditiously unless designated for investigative use related to AIDS. If not destroyed, such products must be labeled, stored and shipped in accordance with the standard procedures for handling infectious materials. Appropriate disposal procedures include autoclaving or controlled incineration; overwraps are required to protect staff in case of breakage.

Approved procedures developed by one of the major organizations such as the American Red Cross, the American Association of Blood Banks, the Council of Community Blood Centers and the American Blood Resources Association may be referenced in the licensed establishments' SOP without individual submission to the Office of Biologics. Alternatively, licensed establishments which develop their own procedures should submit them directly to the Office of Biologics for approval concurrent with implementation.

This memorandum is intended to be an interim measure to protect recipients of blood and blood products until specific laboratory tests are available.

GRO-C

John C. Petricciani, M.D.

Attachment

Dr. D. Walford,
Principal Medical Officer,
Department of Health and Social Security,
Hannibal House,
Elephant and Castle,
London SE1 6TE.

17th May, 1983

Dear Dr. Walford,

Following the meeting of the Haemophilia Reference Centre Directors on Friday last, 13th May, there is one outstanding point which I do not think was finally cleared. This refers to the possibility that some of the American factor VIII manufacturers may consider it advantageous to export products which were made from plasma collected before March 14th rather than retain them for domestic use. You are no doubt aware that on that date the American Food and Drug Administration circulated all American establishments collecting source plasma giving revised guidelines for collecting plasma with regard to AIDS. I have some misgivings concerning the possibility that stocks held by the manufacturers and source plasma collected before that date will be preferentially exported. Whilst I do not wish to overstate the risk from imported American factor VIII concentrates, nevertheless I think that Haemophilia Centre Directors would wish to be reassured that factor VIII concentrates imported are at least up to the standards recommended for use in the U.S.A. I was glad to learn therefore that you intend to take this up with the Medicines Division and I hope that it will be possible rapidly to vary the Product Licence for relevant imported products to take account of these recent developments.

Yours sincerely,

A.L. Bloom
Chairman,
U.K. Haemophilia Centre Directors.

c.c. Dr. J. Holgate
Dr. C.R. Rizza

DEPARTMENT OF HEALTH AND SOCIAL SECURITY
HANNIBAL HOUSE
ELEPHANT AND CASTLE LONDON SE1 6TE
TELEX 883669 TELEPHONE 01-703 6380 EXT 3487

Your reference:
Our reference:

IN CONFIDENCE

Professor A L Bloom
Dept of Haematology
University Hospital of Wales
Heath Park
CARDIFF
CF4 4XW

16 May 1983

Dear Arthur

Following our telephone conversation, I have today both spoken to and minuted Dr Keith Fowler of Medicines Division to draw his attention to the possible need to institute new labelling requirements for FVIII concentrates derived from plasma taken before the new FDA regulations came into force.

I have also asked him whether, for products currently available in the UK, it would be possible to find out the period in which the donors were bled and whereabouts in the USA the donor centres supplying each manufacturer are situated.

I have asked if he will treat this as a matter of the utmost priority.

With best wishes.

Yours sincerely

GRO-C

DIANA WALFORD

NBSB

NATIONAL BIOLOGICAL STANDARDS BOARD

A W.H.O. International Laboratory for Biological Standards

NATIONAL INSTITUTE FOR BIOLOGICAL STANDARDS AND CONTROL

Holly Hill, Hampstead, London, NW3 6RB

telegrams Nibsac London NW3
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From The Director

27 July 1983

Dear Professor Bloom,

The Committee on Safety of Medicine considered the AIDS question last Thursday and Friday and endorsed the recommendations that came from the Sub-Committee, as briefly set out in the attached paper. The Chairman of the committee, Sir Abraham Goldberg, asked me to convey his thanks and those of the committee to you for the help you gave.

I am afraid that it is necessary to ask that the recommendations remain confidential, largely because of the commercial implications.

Many thanks for your help.

Yours sincerely,

GRO-C

J W G Smith

Professor A L Bloom
Department of Haematology
University Hospital of Wales
Cardiff CF4 4XN

SUMMARY OF MAIN POINTS FROM A CONSIDERATION OF AIDS AND LICENSED BLOOD PRODUCTS BY CSM(B) 13 JULY 1983

The Sub-Committee was helped by the following expert advisers: Professor A L Bloom, Professor of Haematology, University Hospital of Wales, Chairman of the Haemophilia Centre Directors Committee; Dr J Craske, Consultant Virologist, PHLS; Dr N S Galbraith, Director, PHLS Communicable Disease Surveillance Centre; Dr H H Gunson, Director, Regional Blood Transfusion Centre, Manchester, DHSS Adviser on Blood Transfusion; Dr P P Mortimer, Consultant Virologist, PHLS.

Consideration was given to the current information available on incidence and epidemiology, aetiology and related factors. Strategies for limiting or eliminating risks from blood products were examined, together with possible practical measures.

The following conclusions were reached:

(1) The cause of AIDS is unknown, but an infectious aetiology seems likely. A previously unrecognised or new agent may be responsible, but repeated exposure to, or reactivation of, known agents, (eg CMV, EBV) may be involved. Heightened susceptibility may be an important factor, e.g. immunological deficiencies induced by unusual sexual practices or exposure to blood products. Based on the clinical evidence, transmissibility of the supposed agent(s) appears to be low, requiring intimate contact or introduction into the tissues.

(2) Patients who repeatedly receive blood clotting-factor concentrates appear to be at risk, but the evidence so far available suggests that this risk is small. The risk appears to be greatest in the case of products derived from the blood of homosexuals and IV drug abusers resident in areas of high incidence (eg, New York and California),and in those who repeatedly receive concentrates in high dosage. Balanced against the risks of AIDS (and of other infections transmitted by blood products) are the benefits of their use; in the case of haemophilia they are life-saving.

(3) The possibility was considered of withdrawing clotting factor concentrates from the market and replacing them with cryo-precipitate. It was concluded that this is not feasible in the UK on grounds of supply.

(4) The possibility was considered of withdrawing US preparations from the UK. It was concluded that this is not at present feasible on grounds of supply. Moreover, the perceived level of risk does not at present justify serious consideration of such a solution. Efforts are however being made to secure UK independence of foreign suppliers of clotting factor concentrates. This should reduce markedly, although not eliminate, the risks to recipients of these products, and the Sub-Committee strongly supports this aim. The Sub-Committee was also informed that the UK Haemophilia Centre Directors have adopted a policy for use of US Factor VIII in order to minimise risks as far as possible.

(5) It is advisable that all clotting-factor concentrates derived from US plasma sources and intended for use in the UK be prepared only from material manufactured from plasma collected after new regulations were introduced by the FDA on March 23rd 1983. These regulations were introduced specifically to minimise the likelihood of collecting blood from affected donors. This step is recommended notwithstanding the possibility that its practical value may be relatively small. It cannot, however, be taken until supplies of post-March 23rd material can be assured. It is recommended that close contact is maintained between the Licensing Authority and Supplies Division with the aim of introducing this step immediately it becomes feasible.

(6) The introduction of products treated in ways likely to inactivate viruses is a promising future development. At present no such products are available in the UK but it is known that manufacturers are working upon their development. When licence applications are received it is important to examine not only possible improvement in the safety margin but also the clinical effectiveness of material treated by heat or by other means. Thus, for example,treated material could possibly induce reactions in recipients which could render them more susceptible to infectious agents.

(7) The Sub-Committee learnt that manufacturers were producing advertising material for use in the UK which appeared to make unjustified claims concerning the safety of heat-treated Factor VIII. It is advised that this should be stopped. It is feared that unlicensed material could be used on a named-patient basis, despite the fact that its safety and effectiveness had not been established or considered by the Licensing Authority.

(8) Hepatitis B vaccine was considered. At present there is no evidence of any risk from the material licensed in the UK, and it was concluded that the licence should remain unchanged, i.e. for use in high-risk groups only. Such groups have a clear risk of hepatitis B, which is a serious and potentially fatal disease. The position should, however, be kept under close observation. It is recommended that the manufacturer be asked to provide ongoing data relating to the safety of the product in respect of AIDS. It is understood that ARVI have recommended that the PHLS undertake surveillance of recipients of Hepatitis B vaccine, and such a study has been planned by the PHLS; the Sub-Committee supports this recommendation. The currently licensed vaccine, manufactured by MSD, has been subjected to three separate inactivation processes, and it is recommended that any new vaccines derived from human blood should be licensed only if subjected to similar stringent treatment.

(9) Both immunoglobulins and albumins were considered. At present there is no evidence of risk from these products, and no action was thought to be justified However, the position should be kept under close observation.

(10) Many groups,inside DHSS and outside, are professionally involved in the AIDS question. The Sub-Committee recommends that the DHSS makes sure that adequate arrangements are maintained to ensure coordination of activities between these groups.The PHLS, through its Communicable Disease Surveillance Centre, is co-ordinating clinical observations on the condition and the Sub-Committee believes it essential that this co-ordination continue and that all relevant departments of the DHSS continue to keep in close touch with its findings.

(11) There is need for research work on AIDS in the UK, especially in relation to the possible new introduction of this disease into the virgin soil of the United Kingdom. The Sub-Committee was glad to learn that a number of groups, including the Medical Research Council, are planning and have started research work.

15 July 1983

IN CONFIDENCE

Suggested 'agenda' for discussion on AIDS in relation to licensed blood products. CSM(B) July 13, 1983.

Notes:

(1) The aim of the discussion is to help the sub-committee to formulate advice to the CSM on whether any action is needed, and if so what action, in respect of AIDS and blood products licensed under the Medicines Act. These products include Factors VIII and IX, Immunoglobulin G, Albumin and hepatitis B vaccine.

(2) The names of those invited to attend in order to help the sub-committee are: Professor Bloom, Dr Craske, Dr Galbraith, Dr Gunson and Dr Mortimer.

(3) It is assumed that participants will be familiar with the problem and with at least a proportion of the many publications.

(4) This 'agenda' suggests headings for the discussion and a suggested first speaker is given. As a target for discussion, brief possible conclusions are indicated - doubtless these will be changed radically.

A. FACTOR VIII AND OTHER CLOTTING FACTORS

1. Aetiology. Current possibilities.

Dr Mortimer.

Conclusion? An infectious cause seems likely and a single new agent could be responsible. Repeated exposure to, or reactivation of, known viruses cannot be excluded. Although possible agents have been proposed (eg CMV, EBV, HTLV) their relationship to the disease remains very uncertain. The infectivity of the supposed agent(s) appears to be low, requiring for transmission intimate contact or introduction into the body tissues.

2. Epidemiology. Current position.
Assessment of risk from Factor VIII.

Dr Galbraith.

Conclusion? Recipients of clotting factor concentrates are at risk. The degree of risk cannot yet be quantified. The risk is likely to be greatest from products derived from the blood of homosexuals and i.v. drug abusers resident in areas of high incidence, and in those who repeatedly receive concentrates in high dosage.

3. Possible scientific approaches to avoiding or reducing the presence of viruses in clotting factor preparations.

(i) Screening of donors to identify high risk individuals.

Dr Gunson.

Conclusion? The new US procedures are noted and approved. They could have some effect in reducing risk, but this effect may be relatively small, since the procedures are unlikely to exclude all high risk donors, and the causative agent(s) may also be present, although less frequently, in apparently healthy donors from non-high risk groups. The advantages of requiring more stringent procedures than those now adopted in the USA are questionable, and the practicalities of doing so are clearly difficult and beyond the sub-committee's expertise.

(ii) Screening of donor blood for evidence of virus infection in addition to Hepatitis B (eg EBV, CMV), or for evidence of infection (eg Th/Ts ratio).

Dr Craske.

Conclusion? Additional measures are not at present feasible on the scale needed. Tests, which need to be speedy and simple, for known agents may become available which could be introduced into the requirements for source plasma, but only a test to detect the presence of an identified aetiological agent(s) could be expected to control AIDS.

(iii) Screening the product for infectious agents.

Dr Schild.

Conclusion? Such tests are generally insensitive, but tests too cumbersome or slow for use on donor blood may be practicable for the end-product and could, eg, lead to standards for levels of contamination. Development work is justified.

(iv) Treatment of blood products with heat or chemicals.

Dr Fowler.

Conclusion? Although the value of such measures in respect of unidentified agents can be proven only by long-term epidemiological studies, they are likely on general grounds to reduce infectious hazards but may not eliminate them.

(v) Other.

4. Consideration of the different operational "possibilities" for reducing the risks from clotting factor preparations.

(i) Withdraw Factor VIII and IX concentrates (ie use only cryoprecipitate for treatment).

Professor Bloom.

Conclusion? This step cannot at present be recommended: (a) it is probably impossible to satisfy UK needs in this way; (b) even if needs could be satisfied it would involve a major rethink of UK policy for preparing blood products; (c) the perceived level of risk at present does not justify serious consideration of this solution.

(ii) Withdraw US preparations from the UK market.

Dr Fowler.

Conclusion? Impracticable on grounds of supply.

(iii) Use US blood products as sparingly as possible.
NOTE: This possibility is largely a matter for physicians treating haemophilia, but it could in theory be decided to modify product licences, eg "not for use in children with mild haemophilia".

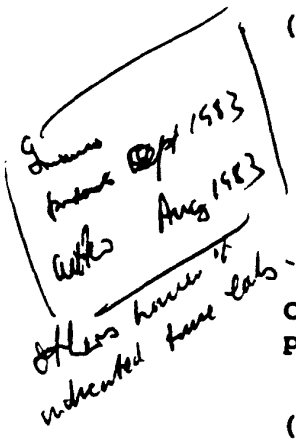
Professor Bloom.

Conclusion? The uncertain balance of risk/benefit considerations in various categories of patient are too finely balanced to justify action via licensing: the matter should be left to clinical judgement.

(iv) Promote UK self-sufficiency in supply of concentrate.

Dr Fowler.

Conclusion? This is highly desirable since it should reduce risk appreciably, although not completely.



(v) Use US blood products only if the source plasma was collected after the new regulations were introduced (March 23rd 1983).
NOTE: It is known that US manufacturers have stocks of 'pre March' plasma, and that the US Office of Biologics to consider this matter on July 19th.

Dr Fowler.

Conclusion? This should be adopted as soon as practicable, even though its value may be limited.

(vi) Use products treated by heat or other inactivation methods.
NOTE: Hyland are now licensed in the USA for heat-treated Factor VIII, and Armour is shortly to apply for a US licence. The cost of these products are apparently at least double that of untreated material.

Conclusion? This is desirable, but is impracticable at present, since no such products are yet available in the UK. This development should, however, be encouraged, notwithstanding the cost penalty.

When these products become available in the UK, should licences for non-treated Factor VIII from the USA and/or elsewhere be continued?

Conclusion? When these become available, the quantity that can be supplied should be established, and the advisability of this step then re-examined in the light of this information and of up-to-date knowledge on AIDS at the time.

(viii) Other.

B. HEPATITIS B VACCINE

1. Epidemiology - is there evidence of a risk?

Dr Galbraith.

2. Aetiology - are all classes of possible causative agents likely to succumb to the inactivation procedure?

Dr Schild.

Conclusion? There is no evidence of risk from hepatitis B vaccine at present. The licence should remain unchanged, ie for high-risk groups. The position should be closely observed.

C. IMMUNOGLOBULIN AND ALBUMIN

1. Epidemiology - is there evidence of risk?

Dr Galbriath.

2. Aetiology - are viruses or other possible pathogens likely to survive the Cohn process or the heating to which albumin is subjected? Is an AIDS agent in IgG likely to be neutralised by antibody?

Dr Schild.

Conclusion? As yet there is no evidence of risk and no action is at present justified. The position should be closely observed.

D. OTHER RELATED MATTERS

1. A number of organisations are involved in the question of AIDS, including the plasma fractionation laboratories and their Authorities, the National Blood Transfusion Service, the PHLS and NIBSC and their Boards, the Haemophilia Centre Directors, the JCVI, ARVI, the CSM and the DHSS departments with responsibilities related to the work of these various bodies. The MRC is also setting-up a working group. It is clearly necessary to avoid conflicting actions or conclusions by these bodies and to ensure that they can each quickly take into account new information.

   Could there be advantages, therefore, in setting-up a system for ensuring prompt interchange between these various groups, either in the form of meetings of representatives, or by means of circulated information sheets from a coordinating office.

2. Although opportunities for research are possibly limited in comparison with the USA (owing to the paucity of cases in the UK) are there identifiable areas in which work should be encouraged?
   eg. - epidemiological studies of the introduction and spread of AIDS in the UK,

- study of the causes of death in haemophilia patients, in part to establish the background,
- clinical and laboratory studies of at-risk groups, in part to identify early diagnostic methods,
- treatment of blood products,
- testing of blood products.

E. OTHER

J.W.G.S.
28.06.83

Department of Health and Social Security
Medicines Division
Market Towers 1 Nine Elms Lane London SW8 5NQ
Telex 883669 Telegrams Healthmin London SE1
Telephone 01-720 2188 ext 3139
GTN 2814

Professor A L Bloom
University of Wales College of Medicine
Department of Haematology
Heath Park
CARDIFF CF4 4XN

Your reference

Our reference

Date 29 November 1984

CONFIDENTIAL

Dear Professor Bloom

HEAT-TREATED FACTOR VIII CONCENTRATES

Alison Smithies has passed to me your letter of 21 November 1984.

The Committee on Safety of Medicines recently discussed the subject of heat-treating Factor VIII concentrates and advised that the Licensing Authority should actually approach the appropriate manufacturers in order to prompt them to make applications for abridged Product Licences or variations so that the heat-treated product would be available on formal licences. This is, as a high priority item, in hand and the Senior Medical Officer dealing with it is Dr Mary Duncan. The Supplies Division of the DHSS is also fully alert to the problem.

We were grateful for your enquiry - I hope that this is the information which you were seeking.

With best wishes.

Yours sincerely

GRO-C

R D MANN
MD, MRCGP, FCP
PRINCIPAL MEDICAL OFFICER

CONFIDENTIAL

Dr. Alison Smithies,
Principal Medical Officer,
D.H.S.S. Room 102bA
Hannibal House,
Elephant and Castle
London

21st November, 1984

Dear Alison,

I am sure that you have been involved in all the recent furore regarding AIDS. It looks very much that we are going to be driven into using heat treated concentrates. It could give unfavourable publicity if these concentrates are freely available in the U.S.A. and say Germany, but are not licenced in this country making prescription difficult. Could you advise me if steps are being taken to review the licencing of heat treated factor VIII consequent upon applications from the manufacturers?

All best wishes,

Yours sincerely,

A.L. Bloom

DEPARTMENT OF HEALTH AND SOCIAL SECURITY
HANNIBAL HOUSE Room No. 1025a
ELEPHANT AND CASTLE LONDON SE1 6TE
TELEX 883669 TELEPHONE 01-703 6380 EXT 3487
GTN (2916)

Your reference:
Our reference:

12 February 1985

Professor A L Bloom
Chairman
Haemophilia Centre Directors Organisation
University of Wales College of Medicine
Department of Haematology
Heath Park
CARDIFF CF4 4XN

Dear Professor Bloom

RE HTLV III TESTING FOR HAEMOPHILIACS

Thank you for your letter of the 16 January. I regret that you have not yet had a formal reply.

Following the meeting on the 10 December at CBLA, Elstree Dr Abrams discussed with the PHLS Director Dr Whitehead the priority which should be given to the testing of haemophiliac patients and the follow up of those given heat treated concentrates. I understand that Dr Mortimer has already been provided with some extra clerical support and is expecting further additional help. The Department meets representatives of the PHLS regularly and will certainly treat any requests for further assistance sympathetically.

Dr Tedder was invited to make an application to this Department for further support and this has quite recently been approved in principle.

I hope you will accept that the Department are well aware of the importance of AIDS in relation to public health and are taking all practical steps in this respect. As you will know the radioimmunoassay test developed in the UK is now being developed commercially. The Department are arranging that all tests for antibody to HTLV III should be evaluated in order that recommendation can be made of the most suitable to use in the blood transfusion services and also by the NHS.

Yours sincerely

GRO-C

Dr Alison Smithies

16th January, 1985.

Dr. Alison,Smithies,
Principal Medical Officer,
D.H.S.S.,
Hannibal House, Room 1025A,
Elephant & Castle,
London.

Dear Dr. Smithies,

Re: HTLV III Testing for Haemophiliacs

You may remember that at the meeting at CBLA on December 10th, 1984, the need for satisfying staff requirements for HTLV III testing was discussed. Dr. Phillip Mortimer of the PHLS Laboratories at Colindale and Dr. Richard Tedder of the Middlesex Hospital Medical School stated that theoretically they could offer a service to test haemophilic patients, and for organised studies se family contacts and of the staff of Haemophilia Centres. An additional important task will be to exclude seroconversion after the use of heat treated factor VIII or IX concentrate on seronegative patients. All this work is of the utmost importance in preventing the spread of AIDS not only in haemophiliacs but also in the rest of the population but will require repeated testing.

The two laboratories named above are presently undertaking a limited amount of this work and other AIDS-related work eg. in non-haemophilic subjects. They are, however, severely constrained by lack of staff. I am therefore writing to ask if sympathetic consideration could be given to the requests of Drs. Mortimer and Tedder for additional staff funded centrally, if needed, in the first instance in this emergency situation.

In addition, I would like to draw the attention of the Department to the importance attached by the U.K. Haemophilia Centre Directors to the provision of adequate funding for the development of the British HTLV III isolate and for the development of British HTLV III antibody test kits which could be used in the Blood Transfusion Services and at CBLA for the detection of dangerous donors.

Yours sincerely,

A.L. Bloom,
Chairman, Haemophilia Centre Directors Organisation.

c.c. Dr. C. Rizza,
Director, Oxford Haemophilia Centre,
Churchill Hospital, Headington, Oxford OX3 7LJ.

21st February, 1985.

Mr. D. Smart,
Chairman,
Central Blood Laboratories Authority,
Elstree, Borehamwood, Herts. WD6 3AU

I am writing to you in my capacity as Chairman of the U.K. Haemophilia Centre Directors. At our "Committee" meeting on February 18th, I was asked to write to you to seek clarification of our responsibilities as physicians when undertaking clinical trials of new products. Our immediate concern obviously relates to heat-treated intermediate concentrate and the new 8Y materials. My colleagues inform me that when undertaking initial trials of commercial products, individual companies will undertake to offer indeminity in the event of serious untoward reaction in recipients. We would be grateful to learn if such facilities are available also in the case of BPL products.

We all appreciate that the AIDS scare is causing Richard Lane and his colleagues some difficulties with regard to the time scale for introduction of new or heat modified products. I may have added to his embarrassment in a letter which was recently published in the Lancet. Sometimes my roles as a Physician and Chairman of the Haemophilia Centre Directors and Medical Advisor to the Haemophilia Society may appear to conflict with immediate pragmatic issues at CBLA. Nevertheless, I hope that I can act in a reasonably objective manner.

On this occasion we would value your advice on this particular issue of indemnity.

With all best wishes,

Yours sincerely,

A.L. Bloom.

CENTRAL BLOOD LABORATORIES AUTHORITY

Chairman:
R. D. SMART, C.B.E.

Secretary/Chief Financial Officer:
W. P. N. ARMOUR, L.H.A., M.I.P.M.

Telephone: 01-953-6191

The Crest,
Blood Products Laboratory,
Dagger Lane,
Elstree,
Borehamwood,
Herts WD6 3AU

Professor A. L. Bloom, M.D., F.R.C.Path.,
Department of Haematology,
Heath Park,
Cardiff CF4 4XN

from GRO-C

5th March 1985.

Dear Arthur

Thank you for your letter of 21st February and for raising, on behalf of the U.K. Haemophilia Centre Directors, the question of indemnification of those participating in clinical trials of new products against unforeseen deleterious sequelae. While the provision of such cover by commercial companies is neither invariable nor uniform, there can be no doubt that the majority of ethical companies within the pharmaceutical industry do provide indemnity which is entirely satisfactory to the Physicians conducting the trials. In the case of BPL products, as I am sure you appreciate, the Authority has not the ability at the present time either to provide insured cover or to underwrite appropriate indemnity from its own resources. However, this is clearly a matter which requires early resolution and I believe that the best course which we can follow is to consult D.H.S.S. on the best means of providing adequate cover whether that be by central guarantee or by seeking insurance in the London market.

I did, of course, see your letter in The Lancet and quite understand the difficult position in which your dual roles must sometimes place you. I hope that the new BPL 8Y development will fully justify Richard Lane's confidence in it and that it will then be possible for you to make an objective judgement of the qualities of the product in practice which are so encouraging as to impel you to write a further letter extolling its virtues!

With kindest regards.

Yours sincerely

GRO-C: David

DEPARTMENT OF HEALTH AND SOCIAL SECURITY
HANNIBAL HOUSE Room No. 1025A
ELEPHANT AND CASTLE LONDON SE1 6TE
TELEX 863669 TELEPHONE 01-703 6380 EXT 3487
GTN (2916)

Your reference
Our reference

Professor Bloom
University of Wales College of Medicine
Department of Haematology
University Hospital of Wales
Heath Park
CARDIFF
CF4 4XN

22 August 1986

Dear Arthur.

Your letter of the 12 August to Dr Pickles has been passed to me for reply in her absence on leave.

As you correctly surmised, the meeting to which Haemophilia Reference Centre Directors have been invited on the 15 September has been convened to discuss with them, and with staff at the Blood Products Laboratory, the manufacture and issue of blood products and other matters.

In the meantime I would like to reassure you that since the 2 June all plasma processed by BPL has been from screened donations. I enclose a fairly detailed reply to a well informed PQ in the House of Lords. As far as factor 8 Y is concerned, from September all that issued will have been manufactured from screened donations, apart from a small number of vials which have not yet satisfied quality assurance protocols. The distribution of these latter would be a subject for discussion, together with the programme for the release of factor IX A and other coagulation factors.

Thank you for brining Tissucol to our attention, I will ensure that it is included amongst the numerous products made from blood, which the CSM are considering. I look forward to see you on the 15 September.

With best wishes.

Yours sincerely

GRO-C

Alison Smithies
Principal Medical Officer

BLOOD PRODUCTS: SCREENING

Lord Irving of Dartford asked Her Majesty's Government:

Whether they will confirm that all plasma derived products, particularly Factor VIII and Factor IX concentrates, which are currently being distributed from blood products laboratories and commerical companies have been individually donor-screened for anti HIV; and

Whether they will state the dates from which distributed products have been manufactured from donor-screened anti HIV plasma, both in the commercial market and in British products manufactured at blood products laboratories.

Baroness Trumpington: It is necessary to distinguish Factor VIII and Factor IX from other plasma derived products, as these are the only ones for which Human Immunodeficiency Virus (HIV) transmission has been established.

Factor VIII and Factor IX are made by the Blood Products Laboratory (BPL) at Elstree for distribution in England and Wales, and by the Protein Fractionation Centre (PFC) in Edinburgh for distribution in Scotland and Northern Ireland. In addition, commercial Factor VIII is imported for distribution in England and Wales. No commercial Factor IX products are licensed for marketing in the United Kingdom. All Factor VIII and Factor IX manufactured or used in the United Kingdom is heat treated to inactivate HIV.

By the end of 1985 all licensed commercially manufactured Factor VIII released in the United Kingdom was made from individually donor-screened plasma. The heat treatment used by the BPL is more rigorous than that used in commercial processes. The product has a good record of safety in clinical trials and has been shown to be safe when made from screened and unscreened plasma. All plasma processed at BPL since 2nd June 1986 has been derived from individually screened donations.

Products derived from screened plasma will become available from BPL for distribution in England and Wales during August 1986. By December 1986 all issued products will be derived from donor-screened plasma. All plasma processed at PFC since January 1986 has been derived from individually screened donations. By the end of August 1986, all products distributed by PFC in Scotland and Northern Ireland will be derived from donor-screened plasma.

PROHIBITION OF FEMALE CIRCUMCISION ACT 1985: IMPLEMENTATION

Baroness Jeger asked Her Majesty's Government:

What action has been taken to implement the Prohibition of Female Circumcision Act 1985; and how many prosecutions have been brought under this legislation.

Baroness Trumpington: The Prohibition of Female Circumcision Act 1985 came into force on 16th September 1985. Information on court proceedings for 1985 is not yet available. The Government have agreed grants totalling £86,000 to voluntary organisations to fund schemes to promote an information and education campaign about the implications of the Act and the potentially adverse effects on health of the practice of female circumcision.

EXERCISE BRAVE DEFENDER

The Earl of Bessborough asked Her Majesty's Government:

Whether they will make a further statement about exercise Brave Defender?

The Minister of State for Defence Procurement (Lord Trefgarne): I informed your Lordships last October that I was placing in the Library an unclassified initial assessment of Exercise Brave Defender. This gave our initial judgment that the exercise had been an overall success and in particular demonstrated that the revised military home defence concept for guarding vital installations worked in practice.

The exercise was not designed to test our total military home defence capability nor could it realistically simulate wartime conditions in the nation as a whole. Nevertheless, further detailed analysis has confirmed our first impressions. We were particularly pleased with the co-operation between all three services, the integration of US forces and the participation of the reserves on such a large scale. The participation of civilian police forces nationwide was particularly useful since it underlined the fact that the primary responsibility for the internal security of the United Kingdom rests with the police. Following the exercise, studies are under way into improvements to mobilisation procedures; refinements in the deployment of static and mobile guard forces in the defence of vital installations; and the training and equipment available for Home Defence Forces.

We intend to build on the foundation of Brave Defender by conducting further military home defence exercises on both a local and national scale, although no date has yet been fixed for any future national exercise.

APPENDIX 33
EAGA 5/11/85

19th September, 1985.

Dr. E.D. Acheson,
Chief Medical Officer &
Chairman of EAGA,
Department of Health &Social Security,
Alexander Fleming House,
London SE1 6BY.

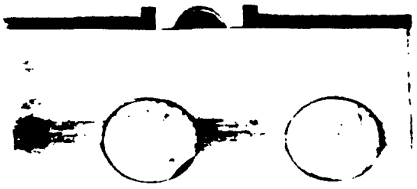
Dear Dr. Acheson,

I am writing to you in your capacity as Chairman of the EAGA. Following publicity in the Press recently concerning a haemophilic child and his attendance at school in the Bournemouth area, some Haemophilia Centre Directors are experiencing problems with parents. The latter are worried concerning the possibility that head-teachers may take steps to exclude haemophilic children from their schools or to attempt to elucidate their HTLV III sero-status. Although it is possible to counsel parents and teachers in a reassuring manner on an ad hoc basis, I wonder if you feel it appropriate that such advice be given in a more formal manner. It may help for instance if official guidelines to schools were made available by the Education Departments indicating that these pupils pose negligible risks. No doubt such guidelines could be formulated following discussion with the EAGA.

I think that the haemophilic community and Centre Directors would be helped by such a development.

Yours sincerely,

A.L. Bloom.



ALB/EMS

5th December 1979

Dr. C.R. Rizza,
Haemophilia Centre,
Churchill Hospital,
Oxford.

Dear Charlie,

I am enclosing a letter which I have received from Mr. Polton which I think is self-explanatory. I wonder if we should put this on the Agenda for the next Referenee Centre Directors' meeting, but if you have any other ideas in the meanwhile I would be most grateful if you could let me know.

I hope the rest of the meeting on November 21st went well. I returned from Japan straight into an industrial dispute of the MLSO's and have not really had time to ask Ian or Jenny Orchard how it went.

Kindest regards,

Yours sincerely,

A.L. Bloom

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

Professor A. L. Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park,
Cardiff, CF4 4XN.

15th November 1979

Dear Professor,

I am writing to seek your advice in respect of prescriptions covering Factor VIII concentrate.

Since the development of home treatment patients now appear to be in the following groups:

1. Those who obtain their supplies of concentrate direct from the Haematology Department at their Centre, free of charge.
2. Those who are given prescriptions by the Haematology Department to obtain concentrate from the hospital pharmacy department.
3. Those who get prescriptions from their General Practitioner and obtain concentrate from a local chemist. A problem with this group is that the material usually has to be ordered and there is sometimes a wait.

We have received a number of complaints from those in Groups 2 and 3 because unless they are under 16 or over 65 they have to pay prescription charges which will be quite a consideration when the proposed increase comes into force. Some therefore feel that by going on home treatment they will be at a financial disadvantage. Also, there is no consistency in the issue of prescriptions, some get them for 2 bottles, some for 10 bottles!

We are, therefore, wondering if this is a problem that might be resolved by the Reference Centre Directors asking the DHSS to include haemophilia in the list of people suffering from certain specified conditions for which they require specific substitution therapy as listed on NHS Form FP91. We feel that haemophilia now comes within this category.

Alternatively, do you feel that it would be better for us to pursue this with the DHSS ?

Another problem that has arisen is that some patients in Group 1 are having difficulty in arranging for

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ALB/EMS

5th December 1979

Mr. K. Polton,
Hon. Sec., The Haemophilia Society,
P.O. Box 9,
16nTrinity Street,
London SE1 1DE

Dear Mr. Polton,

Thank you very much for your letter about prescriptions covering factor VIII concentrate. I can well understand your concern and am rather surprised that some haemophiliacs have to obtain their factor VIII concentrate through a G.P. or from hospital pharmacies. I was not aware that this was the practice in some centres and can quite understand your members' concern and do not feel at all that this throws any reflection upon their attitude to the facilities available.

I think that it is a matter which should be brought before the Reference Centre Directors. I also see no reason why you should not at the same time pursue this with the DHSS. I will send a copy of your letter to Dr. Rizza and ask him if he would put it on the Agenda for the next meeting of the Haemophilia Centre Directors. This is scheduled for February 26th. At the same time we shall consider your other points regarding the collection of material at individual centres.

With kindest regards,

Yours sincerely,

A.L. Bloom

supplies of concentrate to be made available for collection from a local hospital so as to avoid, in some cases, a journey of 30 or 40 miles. Their complaint is that they are told they must attend the Centre to see a doctor but usually they do not see one. They therefore tend to feel that their journey is a waste of time and expense.

Please do not feel that the patients are ungrateful for all that is done for them but we felt that we should convey these complaints to you.

Yours sincerely,

GRO-C

Honorary Secretary.

Mr. K. Polton,
Honorary Secretary,
The Haemophilia Society,
P. O. Box 9,
16, Trinity Street,
London SE1 1DE

14th April, 1980

Dear Mr. Polton,

re: Prescriptions covering factor VIII concentrate

The above matter to which you drew my attention in your letter of the 15th November, 1979, was discussed recently at a meeting of Haemophilia Reference Centre Directors. The directors noted the difficulties some of your members were encountering when obtaining their factor VIII from their local chemist on prescriptions issued by their general practitioner. It was felt that the most appropriate and effective way to deal with this matter would be for the patients involved to go to their Haemophilia Centre Directors and to their G.P.'s and try to resolve the problem at a local level, preferably by obtaining factor VIII from the Haemophilia Centre or Associate Centre.

The directors were surprised to hear that some patients were receiving factor VIII from local chemists and felt strongly that wherever possible factor VIII should be supplied through the Haemophilia Centre and not in this way. For medical reasons we feel there is still need to supervise closely the use of the different preparations and batches of factor VIII and this becomes extremely difficult if the material is supplied by chemists on prescription. In addition, because of the various additional charges made when prescriptions are supplied through the local chemist, this must mean a significant increase in the price of factor VIII with a consequent reduction in the amount of factor VIII which can be purchased by the money available in any given region.

I trust this letter is of some help to you.

Yours sincerely,

A. L. Bloom

THE HAEMOPHILIA SOCIETY

P.O. Box 9
16 Trinity Street
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Telephone: 01-407 1010

Please reply to GRO-C

30th December, 1980.

Dear Professor Bloom,

Thank you very much for your letters of 19th December and 11th December (which did cross mine in the post), and particularly for the information in the latter, which is very useful. We shall certainly treat the information as confidential.

I wonder if you would be kind enough to answer two further questions. The first, which I should have asked before, is whether there is any problem with the supply of Factor IX? Information from the Home Care Committee of the World Federation of Hemophilia indicates a U.K. usage of about 15 000 units per patient per year, putting us 9th of 13 countries they studied (although total usage was not stated). Is this in any way dictated by finance or limited supply?

The second question is whether it is possible to "break down" the predicted total demand for about 80million units per year of Factor VIII by about 1985? Is this figure obtained simply by extrapolation from the present trend (e.g. linear extrapolation of the totals since 1972 gives about 85 million units for 1985), or is it based on something more sophisticated? Is it possible, say, to estimate a need for x units for extra prophylaxis, y units extra for treating inhibitor patients, z units for more planned surgery, and so on?

Thank you again for your help. With best wishes for a happy new year,

Yours sincerely,

GRO-C

Kenneth E.Milne.

Professor A.L.Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park, Cardiff.

ALB/ENAI 5th January 1981

Mr. K.E. Milne,

GRO-C

Dear Mr. Milne,

Thank you very much for your letter of the 30th December and for your two queries. In the first place your question about factor IX is easy to answer. Because Christmas disease is so much less common than factor VIII deficiency and because the Fractionation Laboratory in Oxford and Edinburgh seem to cope very well with this more limited demand there is no shortage of factor IX in this country and indeed most of the Haemophilia Centre Directors consider that the quality of factor IX which we receive is extremely good indeed and the side effects have been less than that reported in other countries.

Your second question concerning the predicted demand is more difficult to answer. This is, as you have guessed, based on simple extrapolation from the present trend and not on something more sophisticated. However over the last few years patients have been entered on prophylaxis, more units have been used for inhibitor patients and there has been more planned surgery so that these factors have also accounted for the increased use in recent years and I think that any extrapolation is a reasonable way to estimate trends. In any case I doubt if we could come to a more sophisticated guesstimate without a crystal ball.

I can well understand the concern and comparisons which members of the Society view the usage of factor VIII in such countries as Germany. However, like many other Dierctors in the U.K. I am not convinced that the German experience is in the long-term interests of patients or blood donors. I think it quite likely that with present fractionation facilities in this country and America that our own extrapolating guess-work gives rise to a reasonable usage per patient per year. In other words, I think that we are perhaps slightly undertreating in this country at the moment and that we will no doubt climb to the American figures. However I am not at all convinced of the ethics or long-term effectiveness or safety of the practice in Germany and I know that my views are shared by very many haematologists in other countries. I do not therefore personally subscribe to the validity of making international league tables of factor VIII usage and would prefer to base our treatment programmes on the results of clinical and long-term studies.

These are of course my own personal views and do not represent the distillation of the views of the Haemophilia Centre Directors.

With best wishes for the New Year.

Yours sincerely, A.L. Bloom

EAC-A Schools

19th September, 1985.

Dr. E.D. Acheson,
Chief Medical Officer &
Chairman of EAGA,
Department of Health &Social Security,
Alexander Fleming House,
London SE1 6BY.

Dear Dr. Acheson,

I am writing to you in your capacity as Chairman of the EAGA. Following publicity in the Press recently concerning a haemophilic child and his attendance at school in the Bournemouth area, some Haemophilia Centre Directors are experiencing problems with parents. The latter are worried concerning the possibility that head-teachers may take steps to exclude haemophilic children from their schools or to attempt to elucidate their HTLV III sero-status. Although it is possible to counsel parents and teachers in a reassuring manner on an ad hoc basis, I wonder if you feel it appropriate that such advice be given in a more formal manner. It may help for instance if official guidelines to schools were made available by the Education Departments indicating that these pupils pose negligible risks. No doubt such guidelines could be formulated following discussion with the EAGA.

I think that the haemophilic community and Centre Directors would be helped by such a development.

Yours sincerely,

A.L. Bloom.

Mr. D.G. Watters,
The Haemophilia Centre,
P.O. Box 9,
16 Trinity St.,
London SE1 1DE.

20th January, 1983

Dear Mr. Watters,

Thank you very much for your letter of 19th January and for the cutting from the Observer. This cutting does seem to have caused some concern amongst the patients and indeed some medical administrators and physicians.

There may be a modicum of justification for this concern. You are no doubt aware of the background that a rather serious "new" disease began to be recognised towards the end of 1981 particularly amongst homosexuals in the U.S.A. The disease was characterised by a failure of normal immunity processes so that sufferers became susceptible to infections that most of us would just shrug off. In addition they became chronically unwell and the condition has quite a high mortality rate. At first it was thought possibly that the condition was due to a reaction to drugs etc or to some virus or other agent to which homosexuals were exposed. However, later, as detailed in the Observer article, several groups of people who are clearly not homosexuals including various immigrant groups in the U.S.A. as well as the ten haemophiliacs, were identified as suffering from the disease. Clearly at the present time the cause is quite unknown and neither has it been proven that it is transmitted through contaminated blood products. The incidence of the condition in America is not known but seems to be about one per thousand of the severely affected treated patients. On this basis if the disease exists in the U.K. we could reasonably expect two or three cases amongst British haemophiliacs. So far none have been reported. Various laboratory changes concerning immunity were reported in the American patients but nevertheless these changes are by no means specific for this particular condition and the tests most easily undertaken and hence reported often give similar results in many other conditions including hepatitis or even stress.

The Haemophilia Centre Director's organisation is closely monitoring the possibility of this condition in the U.K. At the meeting of our Hepatitis Working Party this week, the meeting referred to in the Observer, it was decided to institute a retrospective survey to all Haemophilia Centre Directors and also a prospective survey in order to try to detect any possible emergence of this syndrome in this country. We do not know at the moment if the condition exists in lesser degrees of severity but we shall clearly have to keep on the look out for this. As the full blown condition has not yet been reported amongst British haemophiliacs it is not possible to state if the coagulation concentrations produced in this country are safer

/continued ...

in this respect than the concentrates produced in the U.S.A. Indeed there is no evidence yet in fact to implicate the latter. However the Directors of several individual Centres are investigating possible markers of the condition in patients who receive various types of blood products. In the meanwhile there is certainly no need for the haemophilic community to be unduly concerned about this 'new" syndrome. They can rest assured that every effort is being made to monitor the situation in this country and to collaborate with the Centre for Disease Control in the U.S.A. Although no cases have been reported in the U.S.A., as far as I know, in haemophilia B, we are monitoring the situation in all these related conditions. As you and your colleagues in the Society know, coagulation factor therapy is so essential for the safety and well being of patients that there is no doubt whatsoever that their advantages far outweigh this disadvantage which at the moment seems to be potential rather than real in the U.K. at any rate. Further developments will depend upon identifying the responsible agent or constituent of concentrates, if it exists, and no doubt then steps can be taken to attempt to eliminate them in much the same way as steps are being taken to reduce the risk of hepatitis.

Finally I agree that after this publicity it would be helpful if an article was written for the Bulletin. Dr. John Craske, a consultant virologist at the Publick Health Laboratories in Manchester, is Chairman of our ~~Haemophilia~~ HLD Working Party and I think that he would probably be the best person to contribute this. He works closely with Dr. Rizza to whom I am sending a copy of this letter.

Yours sincerely,

A.L. Bloom

c.c. Dr. C.R. Rizza

THE
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SOCIETY

P.O. Box 9
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DGW/IW
19th January 1983

Professor A.L. Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park,
Cardiff,
CF4 1XW

Dear Professor Bloom,

The Reverend Alan Tanner has asked that I write to you enclosing this article from The Observer of Sunday 16 January. We are writing to you in your capacity as Chairman of the Centre Directors Meeting and our own Medical Advisory Panel to seek some clarification on current thinking in the U.K. on this matter which has, naturally, raised some anxiety, with calls coming from as far away as The Hague!

It would be most helpful to us if you could offer guidance at this stage, with the possibility of an early-date article for The Bulletin so that we can keep our members in touch with the situation.

Yours sincerely,

GRO-C

David G. Watters
Co-ordinator

APPENDIX 37

THE HAEMOPHILIA SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone 01-407 1010

In view of the unduly alarmist reports on AIDS which appeared in the press over the weekend, we are writing to reassure members of the Society about the true position. We have been in touch with PROFESSOR ARTHUR BLOOM, Chairman of the Haemophilia Centre Directors, senior member of our own Medical Advisory Panel and a member of the Central Blood Laboratories Authority, who has kindly written to us all as follows:-

Reports from America of the acquired immune deficiency syndrome (AIDS) in persons with haemophilia are causing anxiety to members of this Society and to their relatives. Haemophiliacs, their parents and doctors have always balanced the quality of life and the dangers from bleeding against the risks of treatment. We are no strangers to infective diseases, such as hepatitis, which can be transmitted by factor concentrates. Recent evidence indicates that in this respect at any rate concentrates prepared from British blood are not necessarily safer than those prepared in the United States. Even so we welcome the fact that the government is investing over twenty million pounds in the Blood Products Laboratory (i.e. factory) at Elstree so that this country shall become self-sufficient in blood products. Bearing this in mind it is important to consider the facts concerning AIDS and haemophilia. The cause of AIDS is quite unknown and it has not been proven to result from transmission of a specific infective agent in blood products. The number of cases reported in American haemophiliacs is small and in spite of inaccurate statements in the press we are unaware of any proven case in our own haemophilic population. Neither have any cases been reported from Germany where massive amounts of American concentrates have been used for many years. Nevertheless the situation is being closely monitored by the Haemophilia Centre Directors and in a more general way by the Communicable Disease Surveillance Centre in London. In addition the importation of licensed blood products has always been strictly monitored and controlled. Thus whilst it would be wrong to be complacent it would equally be counter-productive to alter our treatment programmes radically. We should avoid precipitate action and give those experts who are responsible a chance continually to assess the situation.

We are most grateful to Professor Bloom for this statement. If you have any further questions about AIDS and your own treatment programme then, of course, your Centre Director will be able to help you.

The Revd. Alan J. Tanner, MA
Chairman

4 May 1983

CONFIDENTIAL

The Rev. A. J. Tanner,
Chairman,
The Haemophilia Society,
c/o Mr. D. Watters,
P.O Box 9,
16 Trinity Street,
London SE1 1DB

3rd May, 1983

Dear Alan,

In response to David's telephone call over the weekend I have drafted out a letter which is enclosed. I hope that this is what you are looking for. I am not too sure if David meant that it would be circulated to members above both our signatures or just above yours, but either procedure would be acceptable to me. Please feel free to modify it as you wish. I am sorry about the inaccurate reports particularly in the "Mail" and was shocked to learn of the lengths to which this reported had gone with the Society. I hope that you make headway with the Press Council.

With all best wishes,

Yours sincerely,

A.L. Bloom

DRAFT

Reports from America of the acquired immune deficiency syndrome (AIDS) in persons with haemophilia are causing anxiety to members of this Society and to their relatives. Haemophiliacs, their parents and doctors have always balanced the quality of life and the dangers from bleeding against the risks of treatment. We are no strangers to infective diseases, such as hepatitis, which can be transmitted by factor concentrates. Recent evidence indicates that in this respect at any rate concentrates prepared from British blood are not necessarily safer than those prepared in the United States. Even so we welcome the fact that the government is investing over twenty million pounds in the Blood Products Labpratory (i.e. Factory) at Elstree so that this country shall become self-sufficient in blood products. Bearing this in mind it is important to consider the facts concerning AIDS and haemophilia. The cause of AIDS is quite unknown and it has not been proven to result from transmission of a specific infective agent in blood products. The number of cases reported in American haemophiliacs is small and in spite of inaccurate statements in the press we are unaware of any proven case in our own haemophilic population. Neither have any cases been reported from Germany where massive amounts of American concentrates have been used for many years. Nevertheless the situation is being closely monitored by the Haemophilia Centre Directors and in a more general way by the Communicable Disease Surveillance Centre in London. In addition the importation of licensed blood products has always been strictly monitored and controlled. Thus whilst it would be wrong to be complacent it would equally be counter-productive to alter our treatment programmes radically. We should avoid precipitate action and give those experts who are responsible a chance continually to assess the situation.

Mr. D.G. Watters,
Co-ordinator,
The Haemophilia Society,
P.O. Box 9,
16 Trinity Street,
London.

12th May, 1983

Dear David,

Thank you for your letter about AIDS and I am glad to see that you will be meeting Geoffrey Finsberg on May 20th. I am sure that the present Government has made a definite commitment to U.K. self-sufficiency in blood products but I am equally sure that your strong representations about the other three points would be very appropriate. You could ask Mr. Finsberg if he could draw the attention of the MRC to AIDS and to the desirability for funding for AIDS related research projects.

One important thing to emphasise is the essential need for increased regional funding for blood transfusion centres so that they will be in a position to increase the supply of plasma for processing at Elstree. This will be even more necessary if there is any substantial demand for cryoprecipitate on the part of haemophiliacs. Such a demand could reduce the supply of available plasma at present funding levels and a considerable expansion of regional facilities will be needed in any case.

With all best wishes,

Yours sincerely,

A.L. Bloom

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
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Monday 9 May 1983

TO ALL MEMBERS OF THE MEDICAL ADVISORY PANEL

First of all I would like to say how greatly we appreciate your help at this time! It feels as if I have written to you every day for the past ten days or so.

A group of us will be meeting with Geoffrey Finsberg on May 20 in connexion with the current AIDS publicity. It is our intention to raise the follcwing matters at our meeting with him:-

(a) A definite commitment to UK self-sufficiency in blood products.
(b) An assurance that there will be no immediate ban on the importation of US blood products.
(c) The possibility of the work at Elstree being further assisted in such a way as to make self-sufficiency possible earlier than 1985/6.
(d) Government support for research into AIDS in the United Kingdom.

The Chairman has asked that obtain any view you may hold on those matters and also any other subjects which you feel we should raise at this time which relate specifically to AIDS.

With our warmest thanks and best wishes
Yours sincerely

GRO-C

David G Watters
Co-ordinator

APPENDIX 39

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

26 May 1983

Dear Arthur

I am sending the enclosed papers, which have been sent out by the World Federation, to all members of the Medical Advisory Panel. You may regard them as being 'for information only' or you may care to contact Shelby Dietrich with any relevant information which might assist her in the work she is undertaking for WFH.

I would once again thank all the members of the Medical Advisory Panel for all the assistance rendered to the Society over the past few months in particular, and apologise for the sometimes short notice I have given in relation to questions which require weighty consideration.

Yours sincerely

GRO-C

David G Watters
Co-ordinator

PS. Do you feel there would be any benefit in sending the attached to all Centre Directors? DW

No - see page 4 - Centre productivity.

WORLD FEDERATION OF HEMOPHILIA
FEDERATION MONDIALE DE L'HEMOPHILIE
FEDERACION MUNDIAL DE HEMOFILIA

Suite 2902 - 1155 Dorchester Blvd. W., Montreal, Que. H3B 2L3, Canad
Telephone: (514) 866-0442 Cable WORHEMO Telex: 055-61[illegible]

MEMORANDUM

May 18, 1983

To: National Member Organizations From: WFH President & Executive

Subject: AIDS (Acquired Immune Deficiency Syndrome)

The Federation's Medical Board, with invited medical observers, will meet in Stockholm on June 26, 1983, just before the opening of the Congress on June 27, 1983. The Board will submit a report on AIDS to the General Assembly.

Aware that AIDS is causing international confusion and apprehension

Recognizing that information is better than misinformation

Cognizant that a worldwide reaction has been conveyed to the WFH President

Convinced that responsibility requires action, now

The WFH Secretariat transmits to the National Member Organizations that the following initiatives have been undertaken:

First, that Dr. Shelby Dietrich, Chairman of the Federation's Medical Board has accepted to coordinate AIDS activities.

Second, that Dr. Dietrich will serve as Coordinator for the WFH AIDS Clearinghouse, Los Angeles.

Third, that Professor Klaus Schimpf in collaboration with Dr. Dietrich, will distribute an AIDS bibliography through the WFH Information Clearinghouse, Heidelberg.

Fourth, that the WFH Secretariat, benefitting from the fact that Montreal is a renowned immunological research centre (McGill University and Montreal General Hospital), will liaison closely with Los Angeles and Heidelberg.

The questions surrounding AIDS, have not, as yet, been answered. We are, however, beginning to understand the questions. For hemophiliacs we hope current observations will soon provide an antidote to the rampant anxiety caused by the sensational media coverage of AIDS.

We urge the National Member Organizations to communicate with Los Angeles, Heidelberg and Montreal.

Respectfully submitted,

GRO-C

Frank Schnabel
President

HEMOPHILIA REHABILITATION CENTRE
Orthopaedic Hospital
P.O. Box 60132, Terminal Annex
Los Angeles, Calif. 90060, U.S.A.
Director: Dr. Shelby L. DIETRICH

WORLD FEDERATION OF HEMOPHILIA
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Suite 2902 - 1155 Dorchester Blvd. W., Montreal, Que. H3B 2L3, Can
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May 13, 1983

Mr. Frank Schnabel, President
World Federation of Hemophilia
1155 Dorchester Blvd., West, Suite 2902
Montreal H3B 2L3, Quebec
CANADA

Dear Mr. Schnabel:

The acquired immune deficiency syndrome (AIDS) is of great concern to all those involved with hemophilia. The enclosed background information has been prepared for the coming meeting of the Medical Advisory Board of the World Federation of Hemophilia in Stockholm. WFH members will probably find this AIDS summary of great interest, and so I am requesting that the WFH office distribute the statement as widely as possible.

Following the scheduled Stockholm meeting of the WFH Medical Advisory Board a statement regarding AIDS will be presented to the General Assembly. I shall be available throughout the Stockholm meeting to respond to questions and inquiries regarding AIDS.

Sincerely,

GRO-C

Shelby L. Dietrich, M.D.
Chairman
Medical Advisory Board
World Federation of Hemophilia

SLD:as

Enclosures

I. DEFINITION AND DESCRIPTION - Acquired immune deficiency syndrome (AIDS), as defined by the Centers for Disease Control (CDC) of the United States Public Health Service is the occurrence of Kaposi's sarcoma and/or an infection, moderately to highly predictive, of a defect in cell-mediated immunity in a person without a known predisposing cause. Although the present U.S. epidemic seems to have begun in 1979, the first report on AIDS appeared in the Mortality and Morbidity Weekly Report of the CDC (MMWR) on June 5, 1981, listing five cases of pneumocystis carinii pneumonia (PCP) in homosexual males. Since the initial report in MMWR, new cases of PCP as well as Kaposi's sarcoma and other rare infections and malignancies have been reported in certain high-risk groups and are summarized in Table 1. The first cases in patients with hemophilia were reported in the July 16, 1982, issue of MMWR, and currently total 12. All AIDS cases in hemophiliacs have been associated with opportunistic infections.

A number of hemophilia patients have manifested prodromal (or "incomplete") AIDS signs and symptoms which may include one or more of the following: generalized lymphadenopathy, fever, unusual fatigue, nightsweats, prolonged diarrhea, prolonged cough, unexplained weight loss, idiopathic thrombocytopenic purpura, and Coomb's positive hemolytic anemia. Some patients are anergic to all skin tests. The CDC has conducted a survey of the United States hemophilia treatment centers for patients with these possible AIDS-associated findings (results pending), and the complete description of the clinical spectrum (Table 2) is attached.

The prognostic significance of these findings is unclear; in many patients the clinical course is marked by waxing and waning of the generalized lymphadenopathy. Lymph node biopsies performed on hemophilia patients with generalized lymphadenopathy have generally shown changes characteristic of reactive hyperplasia.

II. ETIOLOGIC THEORIES

A. It must be emphasized that as yet no scientific evidence of the putative transmissible agent causing AIDS, whether a new or known viral agent, has yet been identified in the laboratory or clinically. Some researchers believe evidence points strongly to the acquired immune deficiency state arising as a result of multiple antigenic exposure which is high in the male homosexual or bisexual populations because of sexual practices by which semen and sperm enter the blood stream through breaks in the mucosal barrier. Still others involved in this mystery hold that both the above theories are tenable, and that a two-step process combined with genetic susceptibility may result in the onset of AIDS.

B. Dr. Carol Kasper has summarized the CDC position as follows:

"The CDC's working hypothesis of the etiology of AIDS is that it is caused by a virus, which may be a new hybrid virus, a new strain of a common virus, or an unusual reaction to a common virus. They strongly suspect that many more persons are exposed to this virus than show signs of infection with it. The virus may cause injury to

T-lymphocytes leading to immune deficiency. This immune deficiency may make the patient more susceptible to opportunistic infections, including perhaps infection with a virus which, in vulnerable hosts (which may include those with HLA type DR5), may induce malignant transformation of endothelial cells into Kaposi's sarcoma. Immunologists hypothesize that in the early stages of infection with the mystery virus, the number of helper lymphocytes is depressed while the number of suppressor lymphocytes remains normal, and as the disease progresses, the number of helper lymphocytes becomes even more depressed while the number of suppressor cells also is somewhat depressed. The absolute number of lymphocytes is low, and the ratio of helper to suppressor cells (usually in the range of 1:1 or 2:1 or higher) reverses, so that there are fewer helper than suppressor cells, i.e., ratios of 0.7 or below."

Several studies have confirmed immunologic abnormalities in a substantial percentage of hemophilia patients who use concentrate, yet most of these individuals appear healthy. Therefore, the significance of these findings will be determined by prospective, serial studies. Immunologic changes of a lesser degree and frequency have been reported in hemophilia patients on cryoprecipitate.

Theories of pathogenesis include:

? Multiple antigenic exposure
? Specific transmitted agent (e.g., virus)
? Chronic exposure to immune complexes
? Genetic susceptibility
? Combination of the above

Laboratory findings include the following immunoregulation disturbances:

Cellular (T cell) immunodepression - characterized by:

1. Lymphopenia
2. Skin-test anergy
3. Depressed <u>in vitro</u> T-cell responsiveness to mitogen
4. Reduction in T-helper subset with reduction in T-helper/T-suppressor ratio
5. Increase in absolute T-suppressor subset

Humoral (B cell) immunity

1. Generally remains intact
2. <u>Hypergammaglobulinemia</u> is often found

III. BLOOD/PLASMA DONATION - Because the possibility of acquiring AIDS through blood components or blood exists, there is intense concern about donation of blood or plasma by person belonging to the high-risk groups.

Recommendations are summarized in MMWR (March 4, 1983, Vol.32, No.8):

"As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma and/or blood. This recommendation

includes all individuals belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma and/or blood should inform potential donors of this recommendation. The Food and Drug Administration (FDA) is preparing new recommendations for manufacturers of plasma derivatives and for establishments collecting plasma or blood. This is an interim measure to protect recipients of blood products and blood until specific laboratory tests are available.

"Studies should be conducted to evaluate screening procedures for their effectiveness in identifying and excluding plasma and blood with high probability of transmitting AIDS. These procedures should include specific laboratory tests as well as careful histories and physical examinations.

"Physicians should adhere strictly to medical indications for transfusions, and autologous blood transfusions are encouraged.

"Work should continue toward development of safer blood products for use by hemophilia patients."

The interim recommendation requesting that persons in high-risk groups refrain from donating plasma and/or blood is especially important for donors whose plasma is recovered from plasmapheresis centers or other sources and pooled to make products that are not inactivated and may transmit infections, such as hepatitis B. The clear intent of this recommendation is to eliminate plasma and blood potentially containing the putative AIDS agent from the supply. Since no specific test is known to detect AIDS at an early stage in a potential donor, the recommendation to discourage donation must encompass all members of groups at increased risk for AIDS, even though it includes many individuals who may be at little risk of transmitting AIDS."

The pharmaceutical industry has been extremely concerned and cooperative in attempts to exclude plasma donors at high risk for AIDS. These efforts are summarized in a public service brochure recently issued by Alpha Therapeutic Corporation.

"Q: What are manufacturers doing to diminish our risk?

"A: All commerical producers of concentrate, following Alpha's lead, have taken steps to eliminate members of high-risk groups from their donor pools. Alpha now educates donors about the risk of AIDS and specifically indentifies high-risk donors such as male homosexuals, intravenous drug users, and travellers from Haiti. Staff personnel back up a self-exclusion option with questions designed to identify and exclude high-risk donors. All donors are screened via medical history, physical examinations, and questionnaires for early signs of AIDS, such as unexplained weight loss and swollen glands. Alpha does not accept plasma from any suspect donor.

"Many Community Blood Banks like the New York Blood Center, which provide some 20% of raw material for concentrates, also are instituting policies to exclude high-risk donors."

Community and volunteer blood banks are instituting educational and self-exclusion systems. Persons who have had symptoms of AIDS, persons who consider themselves at high risk for AIDS, and persons who have had intimate contact with someone who may have had AIDS are asked to refrain from donating blood.

IV. AIDS AND THE USE OF BLOOD PRODUCTS FOR THE TREATMENT OF HEMOPHILIA

The patient with hemophilia and the patient's physician is presently faced with the necessity for immediate decision regarding treatment of hemophilia and use of blood products, decisions which cannot be deferred until further scientific data is available.

The National Hemophilia Foundation in the United States and its Medical and Scientific Advisory Council (MASAC) has issued recommendations regarding AIDS in patients with hemophilia which are summarized below:

"A. It is recommended that cryoprecipitate be used to treat patients in the following groups except when there is an overriding medical indication:

* new born infants and children under 4
* newly identified patients never treated with Factor VIII concentrate
* patients with clinically mild hemophilia who require infrequent treatment

"B. The potential advantages and disadvantages of cryoprecipitate versus Factor VIII concentrate therapy for severe hemophilia A are not clear at the present time and are controversial. The Medical and Scientific Advisory Council does not offer a specific recommendation at this time, but will continue to review the data.

"C. DDAVP (synthetic vasopressin analogue) should be used whenever possible in patients with mild or moderate hemophilia A. (Editorial note: Licensure of DDAVP in the U.S. is expected shortly.)

"D. All elective surgical procedures should be evaluated with respect to the possible advantages or disadvantages of a delay."

It is painfully evident that hemophilia is a chronic, life-long disease with well documented morbidity and mortality. Treatment of hemophilia rests basically in replacement of the missing coagulation factors, Factor VIII or IX, from human source blood or plasma products.

The next table lists currently available coagulation factor replacement products.

BLOOD/PLASMA PRODUCTS USED IN TREATMENT OF HEMOPHILIA

1. Whole Blood - Effective in Factor VIII or IX replacement only if fresh and use limited by volume.
   Indicated principally for red cell and volume replacement.

2. Fresh plasma and fresh frozen plasma - Use limited by volume.
   Indicated for replacement of Factors I, II, V, VII, VIII, IX, X, and XI, and von Willebrand's disease.

3. Cryoprecipitate - Indicated for replacement of Factors I and VIII and von Willebrand's disease.

   a. Single donor
   b. Pooled lots - 12 donors or less
   c. Pooled cryoprecipitate from greater than 12 donor lots.
   d. Lyophilized cryoprecipitate

4. Lyophilized Factor VIII concentrates (from large-donor pools)
   Trade names: Alpha (Profilate), Armour (Factorate & Generation II), Cutter (Koate), and Hyland (Hemofil)

   a. Intermediate purity
   b. High purity
   c. Heat-treated

   Manufacturers offer various ranges of protein content as well as volume and number of AHF units per ml.

5. Factor IX concentrates

   a. Regular - Trade names: Cutter (Konyne), Hyland (Proplex), and Alpha (Profilnine)
   b. "Activated" - Trade names: FEIBA and Autoplex used in Factor VIII inhibitor patients.

6. Porcine Factor VIII - Trade name: Hyate
   Indicated for Factor VIII inhibitor patients.

7. DDAVP - Synthetic vasopressin analogue
   Indication: Von Willebrand's or mild Factor VIII deficient patients.

The patient and physician must weigh and balance various modes of treatment including choice of factor replacement product and intensity of use against potential risks/problems as opposed to medical and psychologic benefits. Table 3 outlines various modes of treatment and the risks/problems and benefits/positives associated with each.

The recognition and description of the acquired immune deficiency syndrome in the hemophiliac population is a major challenge for all those involved in the professional and personal aspects of this disease. Because modern treatment has revolutionized the life quality as well as life expectancy of most persons with hemophilia, the implied threat to the safety and purity of blood and plasma products is causing deep distress. All segments of the blood banking system and plasma product producers are challenged to assure as safe a product as possible in the light of present incomplete knowledge. In the best of circumstances physicians and patients together will weigh the relative benefits/assets and risks/problems of various modes of treatment and reach a decision beset with ambiguities and uncertainties. Hemophilia per se is a

life-threatening and crippling disease and will remain that way until genetic prevention or engineering becomes a reality. Adult patients with hemophilia have already experienced in their lifetimes the range of minimal treatment to inadequate treatment to modern treatment. The threat of complications and potential side effects (real or not) of inhibitor stimulation, hepatitis, and now AIDS has been part of that experience. Members of the medical profession more than ever before need to establish and maintain close patient-physician relationships and cooperate in the scientific community by discussion, data collection, and sharing of information.

The Medical Advisory Board is asked to consider the following questions or situations:

1. Impact of AIDS on volunteer blood donations and commercial plasmapheresis and fractionation.

2. Impact of AIDS on hemophilia treatment.

3. Impact of AIDS on international hemophilia data collection efforts.

    a. Identification and tabulation of number of hemophilia cases per country.
    b. Identification and tabulation of number of deaths annually from hemophilia per country by cause.
    c. Treatment modes available by country.
    d. Reporting mechanisms of actual or suspected AIDS cases.

TABLE 2

Acquired Immune Deficiency Survey
Hemophilia Treatment Centers

Attachment 5

SPECTRUM OF DISEASE PRESENTATION IN THE
ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Please report to the Centers for Disease Control (CDC) all hemophilia patients visiting your Center who fulfill any of the following criteria. Although some patients meeting the following criteria may have other underlying conditions and/or immunosuppressive therapy accounting for AIDS-related findings, please report these patients anyway. Use the ILL OR DEAD PATIENT SURVEY/SURVEILLANCE REPORT to report these AIDS-suspect patients to the CDC address provided in the instructions.

1. Diseases Specific for AIDS
   The following diseases may be specific manifestations of or associated with AIDS. Report all patients with these diseases:

   Malignancies
   - Kaposi's sarcoma
   - Lymphocytic leukemia
   - Lymphoma
   - Other lymphoreticular neoplasms

   Infections

   Parasitic
   - Pneumocystis carinii pneumonia
   - Toxoplasmosis (CNS or pulmonary)
   - Strongyloidosis (CNS or pulmonary)
   - Cryptosporidiosis (intestinal disease lasting longer than one month)

   Fungal
   - Candidiasis - "thrush" (oral, pharyngeal, esophageal or systemic)
   - Cryptococcosis (CNS or pulmonary)
   - Zygomycosis (CNS or pulmonary)
   - Aspergillosis (CNS or pulmonary)
   - Nocardiosis (CNS or pulmonary)

   Viral
   - Cytomegalovirus disease (CNS, pulmonary or esophageal)
   - Herpes simplex virus (extensive oral or genital disease or persisting longer than one month)
   - Varicella zoster virus- herpes zoster, "shingles" (involving more than one dermatome or persisting longer than one month)

TABLE 1

AIDS DIAGNOSED CASES

Total Cases 1,300* to date **Overall Mortality Rate 37.6%**

Homosexual or Bisexual Men: **933 Cases, 35% Mortality**

AIDS first struck extremely promiscuous "fast-lane" gays. Many of the early victims had had more than 1,000 different sex partners, were frequent users of recreational drugs and had long histories of sexually transmitted diseases. The epidemic has now spread to include more conservative, even monogamous gays.

Intravenous Drug Users: **217 Cases, 40% Mortality**

Both male and female drug users have developed AIDS. Researchers suspect an infectious agent is getting into the victims' blood through the use of shared needles in "shooting galleries." The majority of cases have been diagnosed in New York City.

Haitians: **64 Cases, 55% Mortality**

The outbreak of opportunistic infections among recent Haitian immigrants of both sexes in New York and Miami is one of the biggest mysteries puzzling AIDS researchers. Nearly all of the victims deny IV drug use and are vehement about their heterosexuality, but a deep-rooted anti-homosexual bias in Haitian culture makes sexual orientation difficult to determine. Early theories linking AIDS to Haitian animal sacrifice and voodoo rituals have been discarded.

Hemophiliacs: **11 Cases, 73% Mortality**

AIDS poses a serious threat to the nation's 20,000 hemophiliacs, some of whom require 30 to 40 transfusions of blood-clotting concentrates each year. Because a single dose of clotting agent may be drawn from thousands of donors, hemophiliacs are extremely susceptible to blood-borne infections. To reduce the likelihood of AIDS transmission by this route, major blood-collecting organizations have urged people who are at high risk for the disease to refrain from donating blood.

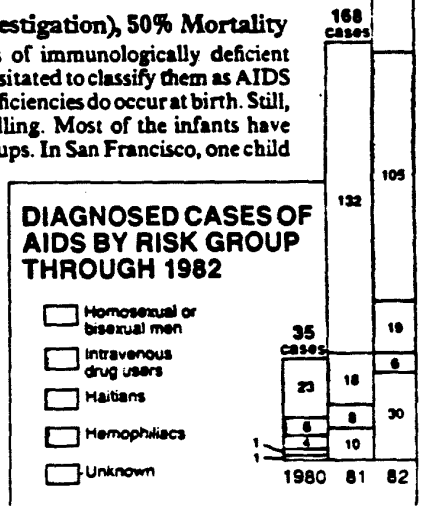
Children: **20 Cases (under investigation), 50% Mortality**

The CDC has been receiving reports of immunologically deficient children for the last six months, but has hesitated to classify them as AIDS victims because certain immunological deficiencies do occur at birth. Still, the evidence suggesting AIDS is compelling. Most of the infants have parents who are members of high-risk groups. In San Francisco, one child developed opportunistic infections after receiving a blood transfusion from a man who later died of AIDS.

Others: 75 Cases, 43% Mortality

While still under investigation, these cases do not now belong to any of the above risk groups. They include other transfusion cases, female sex partners of IV drug users and Haitians, and a group of 36 seemingly risk-free heterosexual men.

*Figures as of April 7, 1983



Bacterial

Tuberculosis (active, reactivated, and/or disseminated)
Non-tuberculosis mycobacterial disease (e.g., M. avium [intracellulare]/Battey bacillus)

2. AIDS-Related Diseases: Nonspecific Diagnoses

The following "diseases" are non-specific diagnoses for which AIDS-specific diagnoses must be considered until a specific diagnosis is made.

Pneumonia
Central nervous system dysfunction

3. AIDS-Related Prodromal Symptoms and Signs

The following symptoms and signs have been common among AIDS cases prior to the diagnosis of the specific diseases listed above. Report all patients with any of these symptoms or signs:

Throat pain and difficulty swallowing (lasting more than a week)
Shortness of breath
Fever (lasting more than a week)
Diarrhea (lasting more than a week)
Swollen lymph glands (lasting more than a month)
Cough (lasting more than two weeks)
Unexplained weight loss

4. Hematologic/Immunologic Abnormalities

The underlying defect leading to AIDS appears to be a loss of the "helper" subset of the T cell population of lymphocytes. The following laboratory test abnormalities are seen in a variable (depending on the test) proportion of AIDS cases. Please report all patients with the following abnormalities:

Lymphopenia (WBC x % lymphs in differential e.g., 4500 x .20 = 800) (consistently less than 1,000 lymphocytes per mm^3 on at least two occasions at least two weeks apart)
In vitro lymphocyte stimulation test responses abnormally low
Skin test anergy to delayed type hypersensitivity antigens
T lymphocytes percent or absolute number abnormally low
T-helper lymphocytes percent or absolute number abnormally low
T-helper:T-suppressor lymphocyte ratio abnormally low (below 1.0)

5. Autoimmune Disorders

Idiopathic thrombocytopenia purpura
Coombs positive hemolytic anemia
Demyelinating neuropathy (recent onset, unexplained)

H[illegible]OPHILIA TREATMENT - MODES AND PROD[illegible]S

TYPE	RISKS/PROBLEMS	BENEFITS/ASSETS
No Treatment or Minimal		
Indication: Life-saving, severe pain, prolonged bleeding Products Used: Blood, FFP, very limited cryo & concentrates	1. Death, severe pain & disability 2. "Invalid" life-style 3. Shortened life-span 4. Economic & physical dependence on others 5. Nonproductive member of society	1. Cost: None to low 2. Exposure to blood products is minimal as is exposure to hepatitis & AIDS 3. Other iatrogenic treatment complications nil to minimal
Crisis Treatment		
Indication: Significant pain, joint swelling, bleeding Treatment usually hospital or M.D. based Products Used: Whole blood, FFP (cryo, concentrate in limited degree)	1. Same as above but less intense & severe 2. Productivity problematic	1. Moderate cost 2. Some decrease in morbidity & mortality 3. Moderate exposure to blood products 4. ? lower incidence of hepatitis, etc.
Early "p.r.n." Rx or Prophylactic		
Usually on SST	1. High $$$ 2. Intense exposure to plasma products 3. ? increase in hepatitis, cirrhosis	1. Normal life-style 2. Normal vocational/professional opportunities 3. Prevention of arthropathy 4. Productive member of society
Elective Orthopedic Surgery		
	1. Usual surgical & anesthetic risks 2. Bleeding & infection 3. Failure of surgical procedure 4. High cost $$$ Dollar days hospitalized & missed days from school/work 5. Intense concentrate exposure	1. Relief of pain 2. Improvement of physical functioning 3. Decreased need for analgesic & anti-inflammatory medication 4. Potential long-term decrease in concentrate/cryoprecipitate use

Appendix

"Summary of Haemophilia Newsnotes"

Issued by National Haemophilia Foundation, New York 1982 - 1985

July 14th 1982	"Risk of contracting this immunosuppres-servation is minimal and CDC is hot recommending any change in blood product used."
9th December 1982	CDC recommends that patients should be advised of risks of AIDS. Concern expressed that AIDS may be spread by concentrate but insufficient data to directly link AIDS with concentrate use.
21st December 1982	No conclusive evidence that cryo/fresh frozen plasma reduced risk of AIDS but factor VIII should not be given to patients not previously exposed to concentrate..
14th January 1983	Cryo should be used for newborns, new patients with severe haemophilia not previously in receipt of concentrate and mild haemophiliacs. The disadvantages of cryo versus concentrate unclear for severe haemophilia. MSAC makes no recommendation. Review the necessity for surgical operations.
	Manufactures requested to exclude members of high risk groups, evaluate surrogate testing, cease collection of plasma from donor centres situated in populations with high incidence of AIDS, increase reasearch to inactivate potential virus, consider DDAVP to plasmaphoresis donors or consider feasibility of producing small pool of lyophilised products. Regional and community blood centres in regions of low incidence of AIDS should increase capacity for cryo production and small pool concentrates.
11th May 1983	NHF urges haemophiliacs continue to use factor VIII concentrate. Emphasises that the number of AIDS cases very low (12/20,000)
7th September 1983	NHF again urges haemophiliacs to use concentrate.
22nd October 1983	Recommendations similar to those of the 14th January 1983 for patient treatment. The

	manufactures of concentrate (in addition to recommendations of the 14th January 1983) exclude donors with symptoms associated with AIDS and evaluate surrogate tests. Heat treatment process offers theoretical advantages but data insufficient to assess efficacy or recommend their license.
2nd November 1983	NHF recommends patients to use factor VIII and cryo.
24th January 1984	NHF recommends patients use factor VIII or cryo.
January 1984	In response to article Annals of Internal Medicine describing a case of sexual transmission from haemophiliac to spouse the view is expressed that the risk of transmission to a sexual partner is "remote" but preliminary precautionary advice is to use condoms.
16th April 1984	NHF continues to recommend factor VIII/ cryo use. DDAVP approved by FDA.
6th September 1984	NHF reaffirms position that product withdrawal should not change use of clotting factor.
13th October 1984	NHF recommends changing to heat treated concentrates although protection against transmitting AIDS is unproven. Urges research to evaluate anti-HTLV-III tests.
5th November 1984	Concern about 70 - 90% haemophiliacs anti-HIV positive. Dr. Levine quoted "that it is important to remember that testing positive for HTLV-III establishes the presence of antibodies against the virus. It does not suggest diagnosis of AIDS."
12th December 1984	Heat treated factor IX available in U.S.
29th March 1985	No justification for routine anti-HTLV-III testing of all haemophiliacs.
March 1985	NHF "AIDS and Haemophilia - Your questions answered" published.
12th April 1985	Recommends all patients to be treated with heat treated factor VIII concentrate rather than cryoprecipitate althoug cryo could be used in areas of low incidence of AIDS. Except that factor VIII may transmit non A non B hepatitis but this is prefereable to

	HIV. Recommends hepatitis B vaccine. Manufactures recommended to anti-HTLV-III test all donors.
8th May 1985	NHF no longer recommends withdrawal of heat treated factor VIII if donor is found subsequently to be anti-HTLV-III positive. Because of possibility of HTLV-III infection of wives, delay of pregnancy is advised.
18th June 1985	MASC of NHF considered further the use of heat treated factor VIII in preference to cryoprecipitate as recommended on April 12th 1985 - some members concerned because of the risk of non A non B hepatitis transmission.
25th July 1985	NHF issues "Haemophilia and AIDS - Intimacy and sexual behaviour"
1st November 1985	NHF issues "Recommendations for providing education for students with AIDS"
November 1985	NHF recommends that only heat treated concentrates should be used.
13th December 1985	Risk of transmission of HTLV-III heterosexually 1 - 5% per year. Recommends regular use of condoms.

RESOLUTIONS BY THE WORLD FEDERATION OF HEMOPHILIA GENERAL ASSEMBLY REGARDING ACQUIRED IMMUNE DEFICIENCY SYNDROME(AIDS) 29 JUNE 1983

DISCUSSION

Medical Board - Report on AIDS

Mr. Chairman I will introduce this report by quoting a portion of the Administration Report presented to the General Assembly.

> Last summer AIDS began to cause alarm amongst hemophiliacs and physicians in North America. Early in 1983 the media in Europe subjected the public to sensational coverage on AIDS. Societies in Australia, Japan and Latin America have recently expressed concern. In anticipation, Montreal has become an AIDS OPERATIONS CENTRE. Every day, evenings, weekends, the Federation's President responded to communications: telephone, telex, correspondence, publications, medical journals, radio and television. The WFH AIDS Operations Centre has been in liaison with government agencies, national hemophilia organizations, hematologists, research immunologists, universities, hospitals, plasma derivative companies, blood banks, blood associations and the Red Cross.

The actions taken to date by the WFH and its Executive include:

1) Distribution of a background statement and information on AIDS to the National Member Organizations and Council and Medical Board Members.

2) Distribution of an AIDS computerized bibliography by the WFH Information Clearinghouse in Heidelberg, prepared by Professor Klaus Schimpf.

3) Decision to request consideration of AIDS issues at the Stockholm meeting by the Medical Board.

Before giving the Board's recommendations several points regarding AIDS and also the Medical Board's status are appropriate.

1) The Medical Board is an advisory body to the WFH Council.

2) Further AIDS topics are scheduled for presentation Thursday and Firday afternoon, including an opportunity for free discussion.

For clarity and consistancy in this discussion, the definitions and terms used by the Center for Disease Control of the United States Public Health Service are employed throughout.

The Center for Disease Control conducted a survey in 1982 of United States hemophilia centers to tabulate AIDS cases, hemophiliacs with opportunistic infections and those with "incomplete" or "prodomal" AIDS signs and symptoms. The most consistant of these "incomplete" signs is generalized lymphodenopathy. It must be emphasised

that these patients are not AIDS "victims" or "cases", the prognostic significance of "incomplete" signs and symptoms remains undetermined as does the precise cause of etiology of AIDS.

Following the recognition of AIDS in hemophiliacs steps were taken to exclude high risk donors from the US blood and plasma supply. The commercial producers of concentrate acted swiftly to eliminate members of high risk groups by, 1) Closing plasmapheresis centers in high risk areas, and 2) Providing for self-exclusion by educational materials supplemented by medical screening and physical examination. Donors maybe excluded at the discretion of plasmapheresis personnel.

Similarly community and voluntary blood collection agencies have been mandated by FDA regulation to initiate educational and self-exclusion systems.

Research

Since the recognition of AIDS approximately 2 years ago, research efforts have greatly intensified. As yet efforts to develop "surrogate" donor blood tests as highly specific or sensitive markers for Aids have not been successful. Additionally intense research efforts are under way to identify the etiologic agent or agents. For the present US fiscal year the federal AIDS research budget is $14,532,000, which will increase to $17,691,000 in the coming year. The National Heart and Lung and Blood Institute will soon solicit applications for a multi-center international 5 year study on the long-term effects of blood and blood products on multi-transfused chronic anemia patients and hemophiliac patients.

WFH Medical Board Actions

The Medical Board meeting on June 26, 1983 was attended by more than 25 physician members and invited observers from 18 countries in North America, Central and South America, Europe, the Middle East, Asia, including Japan and the People's Republic of China, and Africa. During a mini-medical-epidemiologic symposium data on AIDS in hemophiliacs in these areas was presented.

Using the Center for Disease Control definition(opportunistic infection or malignancy) the current tabulation is:

United States:	16 cases
Canada:	2 (1 homosexual)
Europe:	3
Total	21 - all with opportunistic infections

Many participants also reported preliminary results of clinical and immunological studies in progress, which indicate laboratory identified immune changes are frequent in hemophiliacs irrespective of the source of blood product.

Medical Board discussion focused on questions of choice of clood products and intensity of treatment. No concensus could be reached in these arease.

RECOMMENDATIONS

The Medical Board reached agreement on 2 issues and wish to adivse the Council and General Assembly accordingly:

1) There is insufficient evidence to recommend at the present, any change in treatment; therefore present treatment, of hemophilia should continue with whatever blood products are available, according to the judgement of the individual physician.

2) Longitudinal studies are urgently needed on the questions already mentioned, as well as better definition of the relative risk/benefit ratios of various treatment regimens.

ACTIONS

The WFH actions in response to AIDS now include:

1) Planning for a major plenary AIDS symposium on AIDS at the Rio de Janeiro meeting in 1984.

2) Establishment of the WFH AIDS Operations Center at the Orthopedic Hospital, Los Angeles, United States, whose objectives will include:
   a) Communications with patients, physicians and the public to answer questions, dispel myths and prevent rumors.
   b) Dissemination of information to all WFH member organizations and concerned professionals at regular intervals.
   c) Initiation of AIDS case finding and reporting using Center for Disease Control definitions and standardized forms.
   d) Establishment of a public relations program to provide information on hemophilia and AIDS and counter the current media hysteria.
   e) Establish WFH medical liaison with Centre for Disease Coontrol, World Health Organization, voluntary blood collection agencies and the plasma fractionation companies.

f) Continue close collaboration and cooperation with the WFH Information Clearinghouse in Heidelberg.

It should be noted that both the voluntary and commercial institutions involved in blood and blood products are deeply concerned over the present situation and with the copperation and support of industry the WFH AIDS Operations Center will open lines of communications to all parties concerned.

Your help and involvement as individuals and National Member Organizations is crucial. You are requested to cooperate in case reporting, in clarifing misinformation, in preventing rumors and hysteria, and to continue active support of the goals of improving diagnosis and treatment of persons with hemophilia.

Mr. D.G. Watters,
The Haemophilia Society,
P.O. Box 9,
16 Trinity Street,
London SE1 1DE

25th July, 1983

Dear David,

Many thanks for your letter. With regard to the status of AIDS in the U.K. I agree with you that there hasn't been any major change. The recommendations of the World Federation of Haemophilia Medical Board has set out on page 3 of their document seem to me to be clearly benign and not very conscientious. If anything it errs in recommending too little but I don't think that we need emphasise this to the Society members and I am not convinced that much is to be gained by circulating them again at the present time. For your information I am enclosing a copy of a letter which Dr. Rizza and I have circulated to Haemophilia Centre Directors. This is for the information of Society Officers when formulating their own advice to members and I do not think it would be appropriate to circulate this letter to the membership at large. If you have any specific point that I may have missed please don't hesitate to let me know.

Yours sincerely,

A.L. Bloom

enc

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

DGW/IH

19th July 1983

Professor A L Bloom
Department of Haematology
Unversity Hospital of Wales
Heath Park
Cardiff
CF4 4XN

Dear Arthur,

I write further to your letter of 23rd May 1983, the contents of which have now been discussed fully by the Executive Committee of the Haemophilia Society.

First of all we want to thank you for the trouble you have gone to in replying to my letter of the 20th May and it is the Executive Committee's wish that I go on to express their appreciation of the distinction between true Haemophilia Centres and places where treatment may be available.

While in the past this Society may have expressed reservations on the subject of the redefinition of real Haemophilia Centres those reservations would not necessarily apply any longer and we would hope to have an opportunity to peruse the draft proposals which you hope to submit to the next meeting of the Centre Directors.

I would like to continue on the subject of AIDS. You will recall that early in May you were kind enough to provide us with the gist of our statement which was issued to all members of the Haemophilia Society. While we do not believe that the situation has changed to any extent in the UK since that time, we did however wish to give you an opportunity to issue any amending statement which you may care to let us have particularly in view of the World Federation of Haemophilia Medical Board report on AIDS which was presented by Doctor Shelby Dietrich in Stockholm.

I do hope you are having a pleasant summer and some where in the mids of it all you will be able to have a holiday.

/2.....

With best wishes from the Haemophilia Society,

Yours sincerely

GRO-C

David G Watters

Personally dictated by Mr.Watters but sent in his absence.

APPENDIX 43

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

Please Reply to:-

GRO-C

22nd August, 1983.

..ofessor A. L. Bloom,
Welsh National School of Medicine,
-partment of Haematology,
University Hospital of Wales,
Heath Park, Cardiff CF4 4XN.

Dear Professor Bloom,

In Stockholm I discussed with several of the drug company representatives and one or two doctors the new "reduced hepatitis risk" concentrates which are now commercially available (and to which you refered in your AIDS circular dated 24th June). I understand from Dr. Savidge that the trial of these materials is still in its early stages, but it seems appropriate to at least speculate on the effect these materials might have. It seems clear that these commercial materials are more expensive than "conventional" concentrates, because of lower yield. If their use were to become widespread, the following questions seem to arise:-

1. What would be the effect on Haemophilia Centre budgets

of having to buy concentrates at an increased price?

2. In the longer term, could such concentrates be produced by NHS laboratories, e.g. BPL, Elstree?

3. If the answer to 2 is yes, what would be the effect on progress towards self-sufficiency in Factor VIII, given that the yield is lower?

We would appreciate your thoughts on such topics as these, and your advice on whether these are issues we could usefully raise with the Minister of Health at one of our periodic meetings.

My apologies for writing in manuscript, but my typing is painfully slow.

I look forward to hearing from you,

Yours sincerely,

GRO-C: Ken Milne

ALB/CE

31st August, 1983

Mr. Ken Milne,

GRO-C

Dear Mr. Milne,

Thank you very much for your letter about the "new" factor VIII concentrate. I have briefly read your letter in the one or two days between returning from vacation and departing for a Haematology Congress. I will return to the U.K. at the end of next week (September 8th) and I will then give a more detailed consideration and reply to your very important letter. However, in the meanwhile rest assured that these points are under active consideration and I do not think that we need be unduly pessimistic about the financial constraints althought I am afraid we may be over optimistic about the actual effectiveness of these concentrates in preventing hepatitis. This is a complicated subject and I will write you more fully when I return

Yours sincerely,

A.L.BLOOM

Mr. K. Milne,

GRO-C

13th September, 1983

Dear Mr. Milne,

Thank you very much for your letter about hepatitis reduced concentrates and I am sorry about the delay but I have been out of the country last week.

I think that we must look at these concentrates in perspective. There are three types :-

Type 1 : Factor VIII concentrates heated for a length of time know only to reduce the activity of factor VIII by an acceptable amount in the hope that the viruses of hepatitis will be inactivated. These productst are the ones currently abailable but present evidence suggests than in fact the viruses are not inactivated, at least not completely. Even so these concentrates (Hemofil T and Factorate HT) are significaintly more expensive than unheated concentrates.

Type 2 : Chemically treated concentrates, mainly prioduced 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 virus but this leads to about a 50% loss of factor VIII activity and the cost would be very high.

Types 2 and 3 are not abailable yet for therapy and I known nothing about the degree of denaturation of the factor VIII and other proteins which these more extensive processes involve.

All in all therefore things are only at an early stage in the production of hepatitis reduced factor VIII concentrates. Only type 1 is available in this country for clinical trial and current evidence suggests that it may not be dll that effective.

In the short term therefore there seems to be little point in turning over to these concentrates. In the longer term you may rest assured that research is going on at the Blood Products Laboratory and in the Scottish Factory and I do not think that progress towards self-sufficiency should be hindered. The main requirements will be for the production of sufficient plasma at local level in order to take account of the reduced yields and this may require increased financial input to regional blood transfusion centres. There should be no shortage of donors as only 4% of the population donate blood anyway and this could obviously be improved by sufficient publicity. I think therefore that a good discussion point with the Minis

/cor

Health would be for him to ensure that there is adequate input to regional blood transfusion centres to increase their plasma separating capacity and, if necessary, establish plasmapheresis programmes.

I do not think at the moment that there is any evidence that type 1 concentrates have reduced risk of transmitting AIDS and in the lack of any firm data on this disease I do not see how we can consider the possible effect of heat treatment etc. on the transmission of these diseases by factor VIII concentrates.

The Haemophilia Centre Directors and the Hepatitis Working Party are reviewing these aspects frequently and no dout there will be discussion on these in the forthcoming meeting.

With all best wishes,

Yours sincerely,

A.L. Bloom

The Rev. A. J. Tanner,
Chariman,
The Haemophilia Society, P
P.O. Box 9,
16 Trinity Street,
Loddon SE1 1DE.

2nd August, 1983

Dear Alan,

Thank you very much for your letter and I was also sorry not to see more of you in Stockholm for discussions however I quite understood your problem and thought that you deputised magnificently for Frank Schnabel as the occasion demanded.

With regard to a further circular on AIDS, I doubt if anything is needed at the present time since there has been little development, however I would be delighted to join you and the Council on Saturday October 8th and perhaps we can discuss things in further detail then. By all means if you would like to ask a small panel of other physicians please don't hesitate to do so. For this sort of discussion may I take the liberty of suggesting that you recruit persons with mature experience. I hesitate to suggest names but the two Charles, Forbes and Rizza, spring readily to mind. In the meanwhile if there are any more specific points please don't hesitate to contact me and I assume that someone will let me know in due course the time and venue of the meeting on October 8th.

With all best wishes,

Yours sincerely,

A.L. Bloom

enc.

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

AJT/RJM/NSAg

26 July, 1983

My dear Arthur,

I was very heavily pressed with World Federation business during the last few days in Stockholm, due to the President's being unwell. so I missed the opportunity to speak to you about one or two matters.

To begin with, I intended to apologise for not having been in contact with you directly when we were seeking your advice about the statement we made regarding AIDS. We were very grateful indeed for your preparing a statement for us so quickly because that gave us a definite Society policy regarding AIDS and helped to allay a good deal of anxiety among our members.

At the next meeting of the Council on Saturday, October 8 we intend to have as the main subject a discussion about AIDS. The Executive Committee would find it most helpful if you were free to be with us on that occasion to introduce the subject and deal with the medical aspects which arise in the course of the discussion.

If you are free to come to this meeting in London, I will be very much open to advice from you about the way in which we should conduct the session, especially whether you would prefer to be the one Medical Adviser involved or have a small panel of other doctors with you. I will write further about the session when I hear whether or not you can join us.

We have circulated to the Groups the paper presented by Dr Shelby Dietric but I wonder whether, following any conversation you may have had in Stockholm, you would wish to add anything to the statement which you prepared for us, or whether you think that this is still sufficient without any amendment?

I do hope that we are not overburdening you with the demands that we are making upon you at the present time but, as you know, we are very grateful indeed for your advice and support.

With warm greetings,

GRO-C: Rev Alan Tanner

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

DGW/IH

10th October 1983

Professor A.Bloom
Department of Haematology
University Hospital of Wales
Heath Park
Cardiff
CF4 1XW

Dear Arthur,

I have been asked by the Chairman, on behalf of the Council, to write expressing our deep thanks to you for your excellent talk on AIDS at our Council Meeting on Saturday 8th October.

As I am sure you have gathered, this was a most useful session and did help us considerably to allay unfounded fears held by a large number of our members. I happen to know that people arrived at the meeting quite prepared to take up cudgels and create war within and against the Executive Committee! Happily, in the event, this did not happen since people had AIDS put in to a helpful prospective which can only benefit relationships between the Society, its Groups, and its members.

With our grateful thanks and best wishes

Yours sincerely

GRO-C

David G Watters
Co-ordinator

THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
16 Trinity Street
London SE1 1DE
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DGW/IH 10th October 1983

Professor A.Bloom
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With our grateful thanks and best wishes

Yours sincerely

GRO-C

David G Watters
Co-ordinator

APPENDIX 46

THE HAEMOPHILIA SOCIETY

P.O. Box 9
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London SE1 1DE
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To: Medical Advisory Panel 17 February 1984

I enclose a discussion document on blood products which was discussed at the February meeting of the Executive Committee.

We would be glad to receive any comments you feel you want to make on the paper. We are particularly anxious about how the supply of blood products may be affected by regional health authority cuts and any comments you have to make in that connection would be most welcome.

Yours sincerely,

GRO-C

David G. Watters
Co-ordinator

THE HAEMOPHILIA SOCIETY

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Telephone : 01 407 1010

Blood Products Sub-committee

"Discussion Document"

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 cppropriate 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./
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 Dr. Lane (Director of B.P.L.) 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 "Biggs/Cash" calculations did for the post 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).

OK.

(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.

OK. but this argument does not apply.

(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).

Now it can't be clear-

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.

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 (B 86), 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.

K.E. Milne
Blood Products Sub-committee
9 January 1984

GRO-C: Jon Fig

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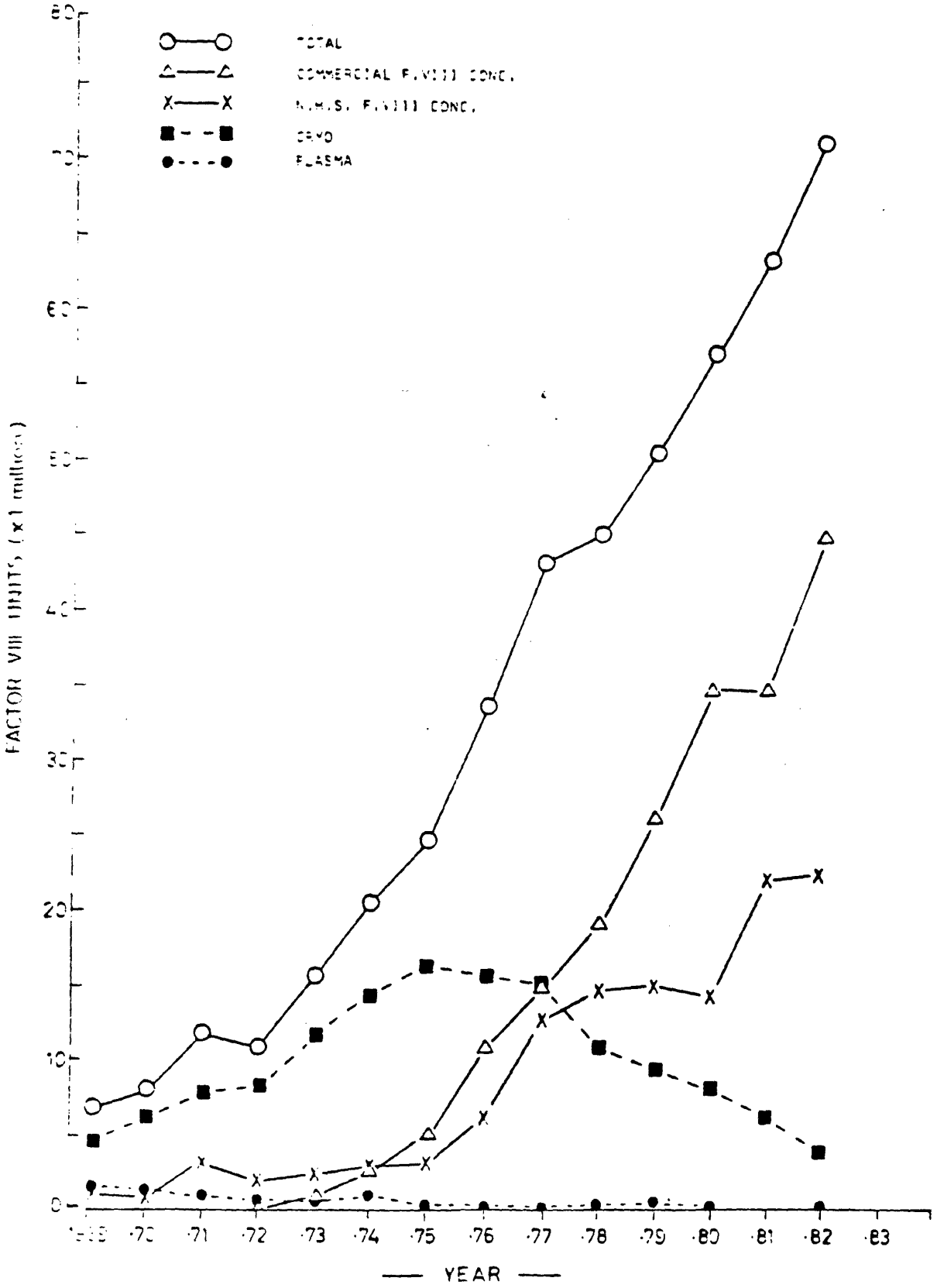

File Haemophilia Soc

Mr. D. Watters,
The Haemophilia Society,
16 Trinity Street,
London SE1 1DE

28th Febauary, 1984

Dear David,

Thank you very much for letting me see Ken Milne's discussion document on factor VIII concentrates. In general I think this is an admirable document although obviously I do have one or two comments. I shall take these one by one :-

1. Para 2 - Although the use of factor VIII concentrates per patient has risen over the years the effect of the AIDS scare in 1983 has yet to be assessed.

2. Para 7 - There are a number of assumptions which are not quite valid in this paragraph :-
   a) I do not understand how the figure 1.75 was calculated.
   b) There is no evidence that 70 patients need factor VIII treatment per million of the population per year. Currently the prevalence of treated haemophilia A in the U.K. is about 6 patients per million of the population per year. The prevalence of vWd etc. treated is only about 6 patients per million per year.
   c) The current usage of about 30,000 units per patient per year covers treatment of inhibitors and surgery etc. so I don't see why these are included as an additional therapeutic need.
   d) The requirements given for increased longevity suggests an additional treated haemophiliac per million per year or a rise of 25 patients in the next 25 years. I am not sure that this assumption is correct even allowing for increased fertility and the figure takes no account of possible eugenics.

   All in all therefore, I would calculate that the assessment based on 50,000 units per patient per year is considerably exagerrated. Although I accept that if side effects had not overtaken us then the use per patient could rise to this figure. Nevertheless over all I still think that the original estimates were realistic and that we shall probably rise to a usage of about 100 million units by the middle of the decade.

3. Para 9 - I agree with the ethical considerations which I think is a good point. I also agree with what Mr. Milne says about the pricing but I think it worth bearing in mind that the BPL (not the BNBTS) has enabled us to compete effectively in the commercial sector resulting in the comparatively low prices paid for commercial concentrates in

/continued .....

the U.K. With regard to hepatitis I think that Mr. Milne is somewhat complacent. Hepatitis is now the second commonest cause of death in haemophilia after bleeding. Since the ill effects of liver disease may take 20-20 years to manifest themselves we may we well be in for progressive problems from this disease. In this respect by the way, although British material may be no better than imported material I know of not the slightest evidence that it is worse. In this section also reference 11 (to me) is not strictly correct since I am afraid that I 'lifted' this information from Dr. Craske's circular to Haemophilia Centre Directors. He should therefore be given the credit.

4. Para 11 - The BPL is in fact looking into the marginals of convenient presentation etc.

Although I can see a great deal of common sense in Mr. Milne's document, personally I am not quite so complacent about importing American blood products as he and presumably the Subcommittee feel. We must bear in mind that we may not have had the AIDS problem in the U.K. had we been self-sufficient in blood products. At least we certainly wouldn't have this niggling worry about the importation of a hypothetical AIDS virus or other unknown viruses from the New World in the future. Thus, although we must still use imported materials I would not be happy about accepting this situation for ever and I think that it would be nice if the Society could continue to press for an increase in facilities for producing all the necessary factor VIII concentrates within the U.K. It is impossible to look too far into the future and to guess the long-term effects of heated factor VIII concentrates or the future impact of biogenetic material. I hope that these remarks will be of some help to the Subcommittee.

All best wishes,

Yours sincerely,

A.L. Bloom

The Haemophilia Society

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

TO: ALL Centre Directors/Transfusion Centre Directors

Dear Director

I am enclosing a copy of a special report from the Centers for Disease Control:'Update: AIDS in persons wil haemophilia - this was published in its MORBIDITY & MORTALITY WEEKLY REPORT and is concerned with the use of heat-treated product and its role in reducing the potential for transmission of the AIDS virus in factor concentrate products.

I would be grateful if all recipients of this paper could let me have their response to it as soon as possible. It may be that representations should be made to the authorities in the UK so that thought can be given to the introduction of heat-treatment in the Elstree development and the wider use of heat-treated commercial product in the meantime.

Yours faithfully

GRO-C

David G Watters
Co-ordinator

14 November 1984

Mr. D.G. Watters,
Co-ordinator,
The Haemophilai Society,
P.O. Box 9,
10 Trinity Street,
London

21st November, 1984

Dear David,

Thank you very much for sending me a copy of the MMWR concerning AIDS. As you have probably realised CBLA had already decided to heat treat factor VIII concentrates before the recent explosion of publicity in Australia and Newcastle incidents. I think that the public should be aware however of the draw backs of these procedures in that the dry heat treatment method does not kill nonA-non B hepatitis viruses so that this heat treated product will certainly not be sterile. With regard to AIDS the evidence so far published is available from small scale laboratory tests and there is no clinical data available. Unless we are careful the wide spread use of heat treated products could mean that we will not obtain the necessary information. However I think that in the light of the evidence that has become available only in the last two or three weeks it is reasonable now to use the heat treated product.

Bearing in mind the last fact that the evidence concerning HTLV III, its relationship to AIDS and the effect of heat are very recent developments indeed, I cannot help feeling that the statements attributed to you in the Daily Telegraph were a little hard on the Blood Transfusion Services. It is virtually impossible to ensure exclusion of homosexual donations in either a voluntary or a paid donor system. The CBLA new factory is being rapidly built and is well on time so that we should be self sufficient in 1986. In addition until now the evidence was that dry heat did not kill hepatitis viruses and the esixtance of HTLV III was unknown. Therefore I do not really think that the Blood Transfusion Services in the U.K. deserve severe criticism and this could well be counter-productive by inhibiting voluntary donation. What the Society could push for specifically is extra funding for plasmapheresis and to ensure sufficient supplies of plasma by additional Regional funding as well as for equipment for HTLV III serological studies. In this way the NBTS could be encouraged in a positive rather than a negative way.

With all best wishes,

Yours sincerely,

A.L. Bloom

APPENDIX 48

The Haemophilia Society

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

KM/IH 30th November 1984

Professor A L Bloom
Department of Haematology,
University Hospital of Wales
Heath Park
Cardiff
CF4 1XW

Dear Professor Bloom,

I enclose a copy of a "background paper" on Factor VIII supply which we recently produced (before the latest AIDS publicity and its consequences) to help us prepare for a meeting with the Minister of Health. As we have now been given a much earlier date for this meeting than we had originally anticipated (Friday 7th December), it will not be possible to circulate the paper for comment as widely as we had intended. We would appreciate your views on the matter, however, if you have time to consider it before next Friday.

You will see from the paper that we certainly intend to press for the allocation of funds to allow for increased plasma collection (e.g. by plasmapheresis), as you suggest in your letter to David Watters dated 21st November. In connection with your comments on the remarks attributed to David in the Daily Telegraph, we certainly do not suggest that employment of heat treatment or possible HTLV-III testing could have been decided upon any earlier. Nor do we have any criticism of progress in building the Elstree factory (other than that the DHSS should have undertaken the project years ago!). We do, however, feel strongly that donor screening has been totally inadequate, particularly in mobile collection facilities, and David's remarks were, I think, directed to this. To illustrate this, for a period of several months after the introduction of the leaflet on AIDS for blood donors (in about September last year, if I remember correctly) I made a point of asking family members, friends, colleagues and fellow members of the Haemophilia Society if they were blood donors and, if so, what information they had been given about AIDS.

/2..

Over this period I talked in fact to 15 donors who had donated blood at different centres throughout Great Britain (in 6 or 7 different NBTS regions). All but one had donated blood at a mobile collection unit. None had seen any AIDS information on display, none had been asked if they might be in one of the risk groups. 2 Society members had asked about the AIDS literature. In one case the NBTS staff had not heard of it; in the other some leaflets were eventually found in the van. Whilst I would not suggest that these findings above are statistically significant, coupled with other anecdotal evidence we have heard they lead us to believe that no serious attempt has been made to screen donors in many areas, at least at the "grass roots level". The NBTS efforts seem to compare poorly with those of Commercial Companies in this respect, if the Companies' information is to be believed.

I hope this helps to clarify the matter.

With warmest regards,

GRO-C

Ken Milne
Blood Products Sub-Committee

Dr. K. Milne,
The Haemophilia Society,
P.O. Box 9,
16 Trinity Street,
London

4th December, 1984

Dear Ken,

Thank you very much for your letter of 30th November and I was pleased to note that your only criticisms concerning the Blood Transfusion Services were related to their questionnaire and screening [illegible]. I am quite disturbed to learn of the results of [illegible]. In all honesty I think that even with the [illegible] of [illegible] the exclusion of homosexual donors [illegible] however conscientiously the questionnaire is [illegible]. These points have been discussed in detail by a [illegible] of the Blood Transfusion Services at the [illegible] and [illegible]. [illegible] I am sure that the situation [illegible] HTLV III testing. One point which [illegible] in the past spouses and relatives of haemophiliacs had been encouraged to donate blood. Until we are certain about the domestic incidence of HTLV III positivity in the current circumstances house contacts and spouses of patients should really be discouraged from donating. I would be interested to learn your reactions to this suggestion.

Please rest assured that I am only too anxious to help [illegible] that I can to improve the tretment for haemophiliacs and to support [illegible] representation for increased funding for the supply of plasma. [illegible] I am continually making this point.

With all best wishes,

Yours sincerely,

A.L. Bloom

c.c. Mr. David Watters
Dr. H. Gunson

CONFIDENTIAL

THE HAEMOPHILIA SOCIETY

BLOOD PRODUCTS SUB-COMMITTEE

Future plasma supplies in the U.K.

1. The report of the Blood Products Sub-Committee produced in January 1981 explored some aspects of plasma supply and their effect on Factor VIII supply, but the question was to some extent academic in the absence of adequate plasma fractionation capacity. Now that greatly increased capacity is to be provided, it seems appropriate to consider again the problems of supplying plasma for fractionation at the Blood Products Laboratory, Elstree. This paper concentrates on meeting the requirements for Factor VIII. Factor IX is not in short supply, and will be produced in large surplus when Elstree is fully re-developed. Much of the information for this paper has been obtained from a "Report on evaluation of plasma procurement and use" produced by the Health Economics Research Unit of the University of Aberdeen for the West Midlands Regional Blood Transfusion Service. A copy of the report has been made available to us through the generosity of the Director of the West Midlands B.T.S., Dr Fereydoun Ala.

2. The U.K.Haemophilia Centre Directors have concluded that demand for Factor VIII in the U.K. will reach about 100 million units per year by about 1986. B.P.L. is being redeveloped to increase its fractionation capacity from 150,000L. of plasma to about 450,000L. The Increased capacity should enable it to increase Factor VIII production from 30 million to over 90 million units, and to produce about 10,000 kg of Albumin, per year. So as to avoid the problems of a very rapid increase in the amount of plasma sent to B.P.L. when the new plant becomes operational, B.P.L. are asking that plasma supplies be gradually increased from now on, excess plasma being stockpiled.

3. The West Midlands B.T.S. at present handles about 195000 blood donations from a population of about 5.2.million (both figures being about 10% of the national total). Socially and geographically the region is typical of Britain as a whole, including both large city and rural areas. About 230 Haemophilia A patients were treated in the region in 1983 (also about 10% of the national total), using about 6 million units of Factor VIII.

4. Usage of Factor VIII in the West Midlands is at present equivalent to approximately 30,000 L. of plasma. Usage is expected to rise to approximately 9 million units per year, equivalent to approximately 45,000 L. of plasma. At present only about 14,300 L. are sent to B.P.L. for fractionation, but B.P.L. have set a "target" for the region of more than 47000L. from 1987-8 onwards. B.P.L. issues blood products to regions in direct proportion to the amount of plasma sent for fractionation. This system may create difficulties for Haemophilia Centres in B.T.S. regions, which will find it difficult to increase plasma production, as such regions will receive a decreasing proportion of Factor VIII issued from Elstree.

5. Nationally, somewhat less than 40% of blood donations are processed and the resulting plasma sent to B.P.L. (yielding about 150,000 L. of plasma). In order to make plasma available for fractionation there has to be a demand for the red cell concentrate (R.C.C.) also obtained. British clinicians have had a traditional preference for the use of whole blood for transfusion, over 60% of donations being so employed at present. If the demand for R.C.C. could be increased more plasma could be made available for fractionation. Other countries have achieved much higher usage of R.C.C., e.g. Canada (72% of total donations) and W.Germany (65%).

6. A related aspect of plasma supply is the amount of plasma removed from each donation. At present, using CPD-A additive, only about 200ml of plasma can be removed. Removing larger volumes of plasma gives R.C.C which is too viscous to be easily transfused. However, it is possible now to collect blood in "SAG.M" bags, the "SAG.M" being an additive solution in which red cells can be re-suspended after removal of plasma. The SAG.M technique enables more plasma to be removed from each donation (about 290 ml) and gives a superior quality R.C.C of viscosity equivalent to whole blood.

7. The improved R.C.C. obtained using SAG.M should help to overcome clinical resistance to use of R.C.C., and it is thought that 70% of donations could be processed, and possibly even as much as 85%. In West Midlands, processing 70% of donations, all in SAG.M.bags, would yield approximately 33,600 L. of plasma (if 85% could be achieved, 41, 000 L. of plasma would be made available - however, 70% is regarded as a more realistic target). The approximate cost to West Midlands B.T.S. of increasing donations processed to 70% and switching to SAG.M.collection is estimated as:-

Capital	£78,000
Recurring	£430,000

8. In order to increase plasma supply beyond the above presumed limit of approximately 33,600 L., other techniques have to be considered. The first possibility is simply to collect more blood (so called "over bleeding"). This option is used in Switzerland, where enough plasma to meet the needs of Factor VIII and Albumin production is thereby obtained. The problem with this option, however, is that red cells in quantities far in excess of what are required are obtained. In Switzerland about 60% of red cells donated are surplus to Swiss requirements. These red cells have either to be discarded or sold. Switzerland exports substantial quantities of R.C.C. to the United States. It is widely thought that it would be unacceptable in Britain to discard or sell voluntarily donated blood components in this way. In financial terms, moreover, it is a relatively expensive way of obtaining extra plasma unless a demand exists for the extra red cells generated. The West Midlands study suggests that the cost of providing a further approx. 10,400 L.of plasma (beyond the approx. 33,600 L. obtained by changing collection techniques) would be:-

With 70% of present donations processed and "overbleeding" £440,000
With 80% of present donations processed and "overbleeding" £340,000

8. If 80% of present donations could be processed and an increased demand created for R.C.C., then the cost of providing this additional plasma would be £250,000. A further difficulty of "overbleeding" would be that nearly 40,000 new donors in West Midlands would have to be found.

9. The second possibility is to establish a plasmapheresis programme employing manual plasmapheresis (in which blood is collected from a donor, plasma manually seperated and the red cells then returned to the donor). Because red cells are not lost in plasmapheresis, donors can donate more often (e.g. monthly) and in greater amounts (typically 500 ml.) Although manual plasmapheresis is employed by commercial companies (being the cheaper form of plasmapheresis), it is thought that the risk of returning red cells to the wrong donor makes this option unacceptable in Britain. In any case, manual plasmapheresis takes about 90 minutes compared with about 40 minutes for machine plasmapheresis. This time difference would cause difficulties for volunteer donors which it presumably does not for paid donors.

10. The most likely option for collecting further plasma seems to be machine plasmapheresis (in which blood is drawn from a donor into a machine in which plasma is separated and red cells returned to the donor in a continuous operation). A plasmapheresis centre with 8 machines could collect 12-16000 plasma donations per year (6-8000 litres). To enable West Midlands to reach "self-sufficiency" in Factor VIII two such centres would be needed. The costs of producing 11,000 L. of plasma by machine plasmapheresis are estimated as:

Capital	approx £470,000
Recurring	approx.£480,000

Further, it would be necessary to recruit and maintain a special panel of additional donors. If each donor attended 4-5 times a year a panel of about 6000 donors would be needed.

11. The West Midlands study indicated that the costs of producing additional plasma by the main options are as given in the Table. Also shown in the Table are the potential savings consequent on increasing NHS production instead of purchasing commercial material. It is emphasised that these figures relate only to Regional budgets,and do not include the cost of fractionation at B.P.L. Figures are given based on the current commercial price for Factor VIII of 8p per unit, and also on a price of 14p per unit (to which the price of Factor VIII is expected by some observers to rise over the next few years). The savings indicated for Albumin production are the maximum that could be achieved if a demand exists for all Albumin produced (the future demand for Albumin is much more uncertain than that for Factor VIII). The approximate costs of increasing plasma supplies in West Midlands to 44,000 L. are thus:-

	CAPITAL	RECURRING
(a) By "overbleeding"	£78,000	£760,000
(b) By plasmapheresis	£550,000	£910,000

12. The tentative conclusion of the West Midlands study is that plasma supplies should initially be increased by increasing R.C.C. usage to about 70% of donations, progressively switching from CPD-A to SAG.M collection,until the maximum of about 34 000 L. of plasma is reached. No definite recommendations have been made about increasing plasma suppy above that level, further study being recommended when future demand for blood products is clearer.

13. If one multiplies the West Midlands figures by 10 to try to obtain a national figure, it can be seen that to increase plasma supplies (by plasmapheresis) to 450 000 L. per year a capital expenditure of about £5.5 million and a recurring expenditure of about £9. million per year would be necessary. No great reliance can be placed on these figures, as the extrapolation could be grossly inaccurate and misleading. They may, however, indicate the order of magnitude of the expenditure needed. Clearly it will be necessary for us to press the D.H.S.S., through the Minister, to ensure that adequate funding is made available to Regional Blood Transfusion Centres as well as to B.P.L.

K.E. Milne
October, 1984

ANNEX

Table

Method	(1)	(2)	(3)
Plasma produced (L.)	33600	44000	44000
Cost of increasing producation from 14300 L. :-			
Capital	£78,000	£78,000?(4)	£550,000
Recurring	£430,000	£760,000 (5)	£910,000
Products obtained:-			
Factor VIII	3957000 i.u.	6089000 i.u.	6089000 i.u.
Albumin	386 kg	594 kg	594 kg
Equivalent commercial cost:-			
Factor VIII (8p/i.u.)	£316,600	£487,100	£487,100
Factor VIII (14p/i.u.)	£554,000	£852,500	£852,500
Albumin (£25/400ml)	£536,100	£825,000	£825,000
Potential saving on NHS production:-			
Factor VIII (8p)	-£113,400	-£272,900	-£422,900
Factor VIII (14p)	£124,000	£92,500	£57,500
Net potential saving if demand exists for Albumin:-			
Factor VIII at 8p	£422,700	£552,100	£402,100
Factor VIII at 14p	£660,100	£917,500	£882,500

NOTES

(1) Increase in R.C.C. usage to 70% ; change in collection method
(2) As(1), + "overbleeding"
(3) As(1), + machine phasmapheresis
(4) No capital expenditure figures given for this option
(5) This is a crude estimate based on assumed demand for R.C.C.

NORTH WESTERN REGIONAL HEALTH AUTHORITY

NATIONAL BLOOD TRANSFUSION SERVICE

Director:
H.H. GUNSON, DSc MD MRCP FRCPath.

Telephone:
061-273 7181 Ext. 276

REGIONAL TRANSFUSION CENTRE,
PLYMOUTH GROVE,
MANCHESTER,
M13 9LL.

HHG/LM

7th December, 1984

Professor A.L. Bloom,
University of Wales College of Medicine,
Department of Haematology,
Heath Park,
CARDIFF,
CF4 4XN.

Dear Arthur,

Thank you for sending me the correspondence with Mr. K. Milne of the Haemophilia Society.

I think there is no doubt that the previous leaflet on A.I.D.S. was not handled in the most advantageous manner. I did press more hard at the time for a positive distribution of this leaflet amongst donors, but some of my colleagues were unwilling to do this thinking at the time that it was an over-reaction. I think events have proved otherwise, but I do not think that a survey of 15 donors out of some 1.2 million bled each year is a fair reflection on the Transfusion Service. Certainly in the North Western and Trent regions well over 100,000 leaflets were sent to donors being called to sessions so that they received the leaflet with the call-up card, and the only reason for having to stop this was the fact that the supply of leaflets ran out and we are waiting for the new ones to come.

I share your view that things should be improved with tests on anti-HTLV III, but even that I think will bring along its own problems.

I would be grateful if you could assure the Haemophilia Society that the Blood Transfusion Service will make every effort to minimise the affect of this unfortunate disease on their members.

With kind regards and best wishes for Christmas and the New Year.

Yours sincerely,

GRO-C

H.H. GUNSON,
Director.

Dr. K.R. Gunson,
Director
National Blood Transfusion Centre
Jean Street
Manchester M1 3BP

4th December, 1984

Dear Arnold,

I am enclosing a copy of a letter that I received from Mr [illegible] Haemophilia Society. Since it refers to the FEIBA [illegible] you may be interested in reading it. I also enclose [illegible].

Yours sincerely,

A.L. Bloom

enc.

APPENDIX 49

The Haemophi... Society

P.O. Box 9
16 Trinity Street
London SE1 1DE
Telephone: 01-407 1010

DGW/IH 20th December 1984

Professor A L Bloom
University of Wales College of Medicine
Department of Haematology
Heath Park
Cardiff CF4 4XN

Dear Arthur,

Thank you for your letter of the 7th December 1984.

Unfortunately you letter did not arrive until Monday 17th December but the Executive Committee were, in any case, represented by Diane Lewis. I have heard glowing reports about the meeting and I think in the light of todays news it was a very good idea to hold it then!

Please accept the warmest best wishes of us all at Christmas and the New Year.

Yours sincerely

GRO-C

David G Watters
Co-ordinator

Coleg Meddygaeth Prifysgol Cymru

University of Wales College of Medicine

Department of Haematology,
Heath Park, Cardiff CF4 4XN
Tel. 0222-755944

Professor A. L. Bloom

2nd January 1985.

Mr. D.G. Watters
Co-ordinator
The Haemophilia Society
P.O. Box 9
16, Trinity Street
London SE1 1DE.

Dear David,

Thank you for your letter of 20th December, 1984. I think that our meeting went reasonably well although some patients and families may have had their worries increased. I can't see any realistic way of avoiding this. However like you I am glad that the meeting was held before all the publicity.

I was also glad to receive the copy of HN (83) 36 regarding supraregional services. In point of fact this possibility has been discussed in detail at the last meeting of the Reference Centre Directors in September in the presence of Dr. Alison Smithies of DHSS. It was decided that each Reference Centre Director would write to me setting out his/her ideas for the case for supraregional funding so that a general case could be put forward under the terms of the above HN. Copies of individual specific applications were also to be sent to me. So far however no proposals have been received by me even from the most vociferous Directors, probably because everyone is so overworked by the AIDS crisis. However your letter and enclosures will certainly come as a timely reminder and I will make sure that this is discussed at an extra January meeting as well as at our normal meeting in February.

With regard to the general situation regarding AIDS the whole thing is worrying. We are in a catch 22 situation. In the past my committee has always been under pressure from patients and from the Society to seek increased funding for the purchase of commercial factor VIII. It is perhaps natural that the useage of factor VIII for patients in the UK was compared unfavourably with the greater useage in some other countries. Some more conservative UK haemophilia specialists felt themselves under criticism even from some of their colleagues in spite of a feeling that it would be unwise to increase treatment levels ad lib with potentially dangerous concentrates. These considerations of course predated the AIDS crisis.

Contined.....

We are now in a situation in which we are being driven to administer large volumes of heat treated factor VIII without adequate clinical trial. We do not know the short or medium term effects leave alone the long term effects of such treatment. For instance, immunological effects on inhibitor development, immune complex disease, liver and kidney impairment. We do not know if these effects, or indeed protection from AIDS, may be dose-related. I am therefore writing in my private capacity, not as Chairman of the haemophilia directors organisation, to ask you to draw the attention of your colleagues to my fears. Perhaps you could consider the advisability of introducing a note of caution concerning doseages of factor VIII and free useage of heated materials until more experience is obtained with their use. You may like to solicit the views of your other Medical Advisors on these aspects.

It is salutory to note that problems have recently been encountered with biogenetically synthesised growth hormone. This is a much more simple molecule than factor VIII but it appears that a slight difference in its structural analyses has resulted in the synthesis of a product which stimulated the development of growth hormone inhibitors in patients. The possible analogies with factor VIII are obvious and as with heated products counsel the need for caution in the mass introduction and "consumer" demand for these new materials even when they are available.

As a haemophilia physician I feel somewhat guilty that my therapeutic endeavours have resulted in exposure of patients to this newly discovered HTLV III virus. I do not wish to see this type of process repeated in the future albeit with a different hazard. For this reason I wish to draw your attention to the need for caution. I realise the desire of haemophiliacs to lead a normal life but at the same time one must realistically conclude that ideal treatment is not available. If I were to act as devils advocate I would suggest that it is reasonable to steady out at levels of treatment attained during the last five years, say at an average of 25,000 units per patient per year giving overall useage of 50 to 60 million units per annum. In the light of present knowledge I am not convinced that it is wise to push for steady increase to 100 million units per year, although we are right to ensure that the necessary potential is available. Expectations must be balanced against informed reality. I leave it to you and your colleages to consider the best ways by which this particular nettle may be grasped; always accepting that, there is in fact a nettle.

With all best wishes for the New Year.

Yours sincerely,

A.L. BLOOM

[illegible] Peters
[illegible]-ordinator
Haemophilia Society
[illegible] 9,
[illegible] Trinity Street
[illegible] SE1 1DT

7th December, 1984

[illegible] out of Peter Jones' text and holding
[illegible] and the [illegible] facilities on Sunday next,
[illegible] of this notice is enclosed.
[illegible] executive would be very welcome
[illegible] any collation.

[illegible] sincerely,

A.I. Bloor

[illegible]/

14th January, 1985.

Mr. David Watters,
The Haemophilia Society,
P.O. Box 9,
16, Trinity Street,
London SE1 1DE.

Dear David,

We have had two recent meetings of Haemophilia Reference Centre Directors. The first in December was held together with virologists, blood transfusionists and the CBLA (BPL) Director et al. After consultation, I put together very rapidly a draft document, circulated it only to the Reference Centre Directors for comments and after incorporation of these, a final document was sent out to all Centres last week. Of course the Christmas and New Year period did not accellerate the process. A copy is enclosed for your information. On 11th January we held a meeting of our AIDS group chaired by Dr. Charles Forbes. No doubt you will learn of only relevant recommendations directly from him. In the meanwhile I am writing to keep you, and the Society, informed of our more general plans.

With regard to Supraregional Funding, I have had several telephone conversations with DHSS representatives. The Under Secretary of State is well aware of the financial problems related to the AIDS crisis. Nevertheless, we plan in the first place to write to him. I hope to set down our requirements in brief logical form following receipt of advice from my colleagues. Hopefully this letter will go out shortly. When we have the response to this and when, and if, we can put forward a detailed general case for Supragegional Funding then we think that we would be in a better position to see him in person. I understand that two Regions have in fact made approaches for Supraregional Funding but were not encouraged. One of our problems is that our case for designation of Supraregional Centres is not as clear-cut and is more contentious than that for some other specialities. What we really need is central help to Regions and Districts for funding not only for the supply of concentrates but for all the other increased requirements for laboratory investigation, care and documentation of patients. We are taking on this problem as quickly as we can.

The other important point in the AIDS scene is the laboratory facilities for HTLV III antibody testing. As you know the two laboratories of Dr. Tedder at the Middlesex Hospital and Dr. Mortimer at PHLS are hard pressed for lack of staff. In the short-term they therefore need additional financial support. I understand that the Society would be prepared to look sympathetically at a request for funding at least one

technical assistant. I am writing to urge the Society to give proposals along these lines highest priority. My colleagues and I feel that both Dr. Tedder and Dr. Mortimer are already supplying a research and routine service to haemophiliacs above and beyond the normal call of duty. I think that this would be with some element of personal risk if laboratory staff are over-stretched. I therefore urge you to consider favourably a request say for one technician for both of these laboratories for a period of one year. I realise that your finances are strained but possibly groups could be encouraged to launch special AIDS-related fundraising drives.

I will continue to keep you regularly informed of the Reference Centre Directors' deliberations. We are holding monthly meetings for the time being.

All best wishes,

Yours sincerely,

A.L. Bloom.

c.c. Dr. C. Rizza,
Director,
Oxford Haemophilia Centre,
Churchill Hospital,
Headington, Oxford, OX3 7LJ.

Dr. C.D. Forbes,
Department of Medicine,
Royal Infirmary,
Glasgow G4 OSF.

AND NOW.....We will continue to keep you informed as and when there are items of value to report to you.

IN THE MEANTIME please continue to discuss your personal position with your Centre Director. While we would urge you to remain on treatment, the final decision lies with you and your medical advisers. Their advice must always be given priority over any general advice which we may give.

Please feel free to contact the Society if you wish to have more information, to check on 'rumours' or put forward ideas or criticisms to the Executive Commitee.

FINALLY - as we have already stated, £25,000 has been made available to assist with AIDS research relevant to haemophilia. If there is anything you can do to replenish our RESEARCH FUND, all donations will be gratefully received!!

HAEMOFACT is a new leaflet series produced by the Haemophilia Society. They will be issued from time to time on topics of interest or concern to people with haemophilia.

The Haemophilia Society

HAEMOFACT

A.I.D.S.

RELEASE No 2.

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

22 September 1983

P.O. Box 9 16 Trinity Street London SE1 1DE

APPENDIX 51

FACTS We last wrote to you in May and we now send this leaflet to bring you up to date about the present situation. We have to report that there has been one death recorded in a person with haemophilia. This has been confirmed within the past few days. There remains one other suspected case in Cardiff. There have been no other cases relevant to haemophilia reported to the Public Health Laboratory Service.

UPDATE Media-reaction to AIDS has kept the Society's office very busy with enquiries, in addition to the standard activities created by the presence of AIDS in the United Kingdom. We thought that you would like to know some of the things we have done:

<> **A meeting has been held with Lord Glenarthur, Under-Secretary of State at the Department of Health, and his officials.** The Society was represented by the Officers and the Co-ordinator and at the meeting we strongly emphasised our members' views about AIDS in this country.

<> Regular liaison has been established with the Centre for Disease Surveillance and Control, which monitors AIDS in the United Kingdom as well as liaising with the situation in the United States. Constant contact has also been maintained with officials of our own DHSS, the Public Health Laboratory Service and members of the Society's Medical Advisory Panel.

<> Close contact has been maintained with the Pharmaceutical companies involved in the importation of concentrates from America and their improved methods of blood collection have been noted.

<> **RESEARCH GRANTS from the Society totalling some £25,000 have been approved to enable research directly benefitting people with haemophilia, in relation to AIDS, to go ahead.**

<> Members of the Society attended the World Federation of Hemophilia Congress in Stockholm in late June and discussed the international AIDS situation as it affects people with haemophila. *The Medical Board of WFH in their report (copies available from the office, please send an s.a.e.) EMPHASISED and CONFIRMED the points made in our last letter sent in May.*

<> Every meeting of the Executive Committee has been briefed about developments in detail and discussed AIDS at length.

TO SUM UP.....

[] The Society has established and maintained close liaison with all relevant personnel and departments of government in order to keep all our members informed of developments and, of equal importance, to ensure that the Society's views are known to decision makers in the public health services.

[] Blood collection in the USA has been improved to the satisfaction of Federal Health Authorities and our own DHSS. Assuming blood to be a transmission agent, it is not yet possible to state that imported blood products are AIDS-free (nor indeed that UK product is so), the chances are that the risk involved in imported concentrates has been reduced considerably. It is also important to remember that we have not seen the massive increases in reported cases of AIDS either in this country, nor in the USA, which were being predicted earlier in the year. ***Our message remains unchanged: THE ADVANTAGES OF TREATMENT FAR OUTWEIGH ANY POSSIBLE RISK.*** *BALANCE THE RISKS for yourself, but we would state again that the risk of AIDS is tiny compared to the risks from untreated bleeding episodes. By refusing treatment or not following your Centre Director's advice you are probably exposing yourself to even greater risk. RISK has always been a feature of haemophilia and in time this risk too will diminish, especially given the volume of research being conducted around the world.* Research in the UK has received substantial support from the Society - that is support from YOU and your local Group. Elsewhere in the world support has come from other members of the World Federation of Hemophilia.

1984 SUBSCRIPTIONS: Have YOU paid your subscription yet? We realise that it is a small amount we ask - that may be why some 40% of members didn't pay it in 1983 - BUT do try to pay or at least return your form!! If you can add a donation this will be gratefull received - your £1 pays for about 1½ Bulletins!!
.....and if you can, it will help us to help you if you can pay by standing order and under a Deed of Covenant - that adds 43p to every pound you give us!!

MRS IRENE WATSON finished her employment here at the end of April. However, she will be back from time to time to cover for holidays. IF you had intended to donate to her farewell presentation but never got round to it, there is still a chance. Send it to David Rosenblatt, at the Society's office, marked CONFIDENTIAL.

HAEMOFACT is a leaflet series produced by the Haemophilia Society. They are issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE Tel:01-407 1010.

The Haemophilia Society

HAEMOFACT

A.I.D.S.

RELEASE NO 3

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

11 May 1984

P.O. Box 9 16 Trinity Street London SE1 1DE

ACQUIRED IMMUNODEFICIENCY SYNDROME: AN UPDATE

The occurrence of acquired immunodeficiency syndrome (AIDS) in haemophilic patients has strongly suggested transmission of the order by blood products and epidemiological studies have suggested it may be related to a transmissible agent. Recntly it has been reported that a retrovirus, which may be associated with AIDS, has been isolated at the US National Cancer Institute. Similarly, in Paris, a retrovirus has been isolated from the lymphocytes of a patient with haemophilia B who had AIDS. These reports should be received with optimism. The obvious benefits from such findings would be the provision of a blood test for both affected persons and donated blood - and in the long-term, the development of a vaccine.

In Great Britain the number of haemophiliacs who have been reported with AIDS remain at 2. Thus the incidence is less than 1 in 1,000 patients at risk. The relationship of the immunological abnormalities found in many heavily treated haemophiliacs at centres throughout the world is uncertain. However, it is now clear from studies in Scotland, Australia and America that these changes occur whether the plasma source used for the concentrate manufacture is volunteer or commercial.

It is possible that the immune suppression produced by repeated exposure to clotting factor concentrates lowers the threshold for infection with the putative AIDS agent. There is evidence that different clotting factor concentrates have a correspondingly different propensity to induce these changes. This is a function of the characteristics of the final product and the fractionation methods used to make it. Thus prospects for resolving these problems are brighter for haemophiliacs than for other high-risk populations since improvements in plasma fractionation are likely to make it possible to remove or inactivate causal agents from therapeutic products. The heat-treated clotting factor concentrates which have been manufactured by many commercial companies and the NHS may be an advantage in this respect.

Finally, THE REALLY GOOD NEWS is the announcement from the Royal Free Hospital, Speywood Laboratories and Genentech, San Francisco, that the gene for factor VIII has been cloned and that factor VIII has been synthesised in mammalian cell culture. Provided this can be successfully scaled up, which may take several years, synthetic factor VIII would be available for use by haemophiliacs. Clearly this would provide a hepatitis and AIDS-free therapeutic produc

C.A. Lee MA MRCP MRCPath
Senior Registrar
The Katharine Dormandy Haemophilia Centre
The Royal Free Hospital, LONDON, NW3 2QG

The Editor writes:-

A Special Edition of The Bulletin on the subject of the synthetic production of factor VIII is in preparation. Members will recall Special Edition No 2, August 1981, in which Dr Tuddenham described the problems associated with factor VIII synthesis.

It is estimated that the total cost of the work to date on cloning the factor VIII gene and the synthesis of factor VIII is some £11,000,000. The Society donated something like £8,000 to this process, mainly in the support of manpower.

---

chronic carrier of HBV. Although the agent seems to occur most frequently in Italy, it can be transmitted by blood products of non-italian origin. Prevention of delta infection is achieved in the same way as prevention of HBV - by effective screening of blood donors for HBV. Hopefully, further technical advances in screening will eliminate all transfusion-transmitted HBV and delta infections. For the small minority unlucky enough to be carriers of HBV, and therefore at risk of delta infection, anti-viral drugs now undergoing clinical trial look a promising approach.

Although currently the subject of a great deal of interest, LAV/HTLV-3 and delta agent are of course only two of the many infective agents, both known and unknown, which may contaminate blood products. Improved donor screening will help to reduce risk, but it won't entirely remove it. Major efforts are now being made to sterilize clotting factor concentrates, most commonly by heat treatment, and products made both by commercial companies and the NHS are now being clinically assessed. Preliminary results suggest improvement but not perfection. In the longer term, we hope that risk-free 'synthetic' concentrates will become available. This is unlikely to be achieved for several years.

14th September 1984

HAEMOFACT is a leaflet series produced by the Haemophilia Society. They are issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE.
Tel: 01 407 1010.

The Haemophilia Society

HAEMOFACT

A.I.D.S.

RELEASE No 4

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

<<<<<<<<<<<<<<<<<<<<<<>>>>>>>>>>>>>>>>>>>>

24 September 1984

P.O. Box 9 16 Trinity Street London SE1 1DE

...w VIRUSES IN AIDS AND HEPATITIS: LAV/HTLV-3 AND DELTA AGEN...

Peter B.A.Kernoff

Haemophilia Reference Centre,
The Royal Free Hospital, London.

The possibility that the acquired immunodeficiency syndrome (AIDS) might be caused by an unusual virus has always been a strong one. Two groups of workers, in Paris and the USA, have isolated viruses which seem likely candidates. Called LAV (lymphadenopathy associated virus) by the French group, and HTLV-3 (human T-cell lymphoma-leukaemia virus 3) by the Americans, the viruses are probably the same. The virus doesn't cause leukaemia - the HTLV designation arose because it belongs to the same family as a different agent (HTLV-1), which may rarely do so.

There's no doubt that identification of the LAV/HTLV-3 virus is a major step forward. Although tests for the virus itself may take some while to be developed, tests for antibodies to it have now been established in this country and will become widely available in the very near future. We can expect these tests to be rapidly applied to blood donor and blood product screening. It should also be possible, although this will take longer, to develop a vaccine which may help protect against AIDS.

Using these new tests,antibodies to LAV/HTLV-3 have been found in the blood of about a third of a group of English haemophiliacs. What does this mean,and how does the presence of antibodies relate to the T-lymphocyte abnormalities detedtable in many haemophiliacs, and the risk of contracting AIDS? We don't yet know. The presence of antibodies implies past exposure to LAV/HTLV-3, but this in itself isn't too surprising. Most haemophiliacs have antibodies to a variety of different viruses in their blood, probably as a result of repeated exposure to small amounts of these viruses in tre...used b...d products. The presence of antibodies is usually taken as evidence of immunity to infection, and perhaps one reason why the risk of AIDS in haemophilia is so low (around 1 in 1000) is that many patients are immune to it. There are probably other reasons too, and LAV/HTLV-3 may not be the whole answer to the problem of immune deficiency (see Haemofact No.3). Nevertheless, important progress has been made.

Whilst AIDS is a relatively new problem for haemophiliacs, infection with hepatitis B virus (HBV) is an old one, which is fast on the way to being solved. In the Western World, very sensitive 'third generation' tests for HBV have been routinely applied to blood donor screening for several years, and the risk of acquiring HBV infection from blood products has fallen dramatically. Most haemophiliacs have antibodies to HBV in their blood, implying past exposure and immunity to HBV. For those who haven't been exposed, *vaccination is now available*. For reasons which are not understood,a small proportion (perhaps 5-10%) of people who contract acute hepatitis B don't subsequently develop antibodies, but become 'chronic carriers' of the virus. HBV which is present in their blood during the initial acute attack is not cleared as it usually is, and can persist for many years. Such carriers of HBV can remain completely well. In others, however, there may be exacerbations of hepatitis, and sometimes progressive liver damage. Why the course of the infection should differ so much between different individuals is unclear, but one possible explanation has recently emerged. This is that some carriers of HBV can acquire a 'superinfection' with another virus called delta agent (hepatitis D virus), which seems to have the capability to cause recurrences of hepatitis and, probably, to accelerate liver disease.

Delta agent can't exist in the body without HBV, so the possibility of infection with the virus only arises in the course of acute HBV infection or, more commonly, in a

CURRENT PRACTICE at major Haemophilia Centres [illegible]he UK [illegible]hat *cryoprecipitate* is used in factor VIII deficient newborn infants and chi[illegible]en under 4 years of age and in newly identified patients never treated with factor VIII concentrates; whenever possible *fresh frozen plasma* is used in factor IX deficient patients in the same categories, and *desmopressin* (*DDAVP*) wherever possible, is used in patients with moderate or mild haemophilia and von Willebrand's Syndrome. It is, as already stated, the Society's recommendation that heat-treated product be made available as quickly as possible for all other groups of people with haemophilia.

IF YOU HAVE ANY ENQUIRES ABOUT YOUR OWN POSITION YOU SHOULD SPEAK TO YOUR CENTRE DIRECTOR WHO WILL BE ONLY TOO ANXIOUS TO ASSIST YOU.

HAEMOFACT is a leaflet series produced by the Haemophilia Society. They are issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE.

Tel: 01 407 1010

The Haemophilia Society

HÆMOFACT

A.I.D.S.

RELEASE No 5.

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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3rd December 1984

P.O. Box 9 16 Trinity Street London SE1 1DE

HAEMOFACT is produced regularly to keep people with haemophilia up-to-date on matters such as AIDS.

In view of the widespread publicity about AIDS arising from the tragic death of Mr T McStay, a patient at the Haemophilia Centre, Royal Victoria Infirmary Newcastle upon Tyne and elsewhere, the Society wishes to give members a factual update on AIDS, on the responses to the current publicity of the DHSS and the NBTS and to outline the action which the Society has taken. IT IS ESSENTIAL TO NOTE THAT, DESPITE THE CURRENT PUBLICITY, LITTLE HAS CHANGED. In fact the position on AIDS remains substantially as outlined in HAEMOFACT 4, namely:-

(1) *that the probable causative agent for AIDS is a virus known as HTLV-III or LAV.*
(2) *that tests to establish the presence of antibodies to HTLV-III have been developed.*
(3) *that about one third of a group of english haemophilic patients studied were found to have antibodies to HTLV-III.*
(4) *that the presence of antibodies is usually taken as evidence of immunity to infection, although in the case of AIDS this is not yet certain.*
(5) *the level of publicity about AIDS is new but the known facts remain as outlined in HAEMOFACT over the past year or so (changes have been and will be noted in HAEMOFACT when necessary).*
(6) *DHSS guidance to blood donors indicating the 'at risk' groups who should not donate blood do not currently include the sexual partners of people with haemophilia. Blood donors in this situation should contact their Blood Transfusion Centre for advice about this and their Centre Director about all matters concerning their treatment.*
(7) *Heat treatment appears to destroy the HTLV-III (AIDS) virus. Heat-treated factor VIII has become available in the United States over the past few months and is now in universal use there.*

The Minister, Mr John Patten and the DHSS have issued the following statements on AIDS:-

Heat treated products will be available from Elstree in April 1985.
The UK will be self-sufficient in blood products from 1986.

The NBTS has issued the following statements on AIDS:-

The Elstree plant will produce heat-treated products by April 1985.

THE SOCIETY HAS TAKEN ACTION AS FOLLOWS:-

(1) A meeting has been arranged with Lord Glenarthur, Parliamentary Under Secretary of State on December 7th at which we shall press for the following measures:-

(a) The IMMEDIATE introduction of heat-treated product by importing this from the United States and the release of additional funding to the regions to enable this to happen forthwith.
(b) Immediate consideration be given to the introduction of plasmapheresis programmes on such a scale that the UK may become self-sufficient in factor VIII by 1986.
(c) More stringent measures be taken by the Blood Transfusion Service to ensure that 'at risk' donors are made fully aware of their position.
(d) That no financial constraints be allowed to stand in the way of developing HTLV-III tests in both donors and donated blood.
(e) That all Supra-Regional Centres be given adequate staffing and resources to cope with the AIDS situation.

(2) **WE HAVE** (a) kept in close touch with our own Medical Advisors, other health care professionals, the DHSS, the NBTS and other charities and organisations with interests in the problem of AIDS.
(b) continued to monitor AIDS developments overseas especially through the World Federation of Haemophilia and World Haemophilia AIDS Centre in Los Angeles.
(c) launched a major fund raising initiative to enable us to continue the provision of our information services which have been seriously strained by the AIDS problem.
(d) made a major effort to provide the media with the facts about AIDS.
(e) dealt with literally hundreds of phone calls received from members and others concerned about AIDS.

We ENDORSE our earlier advice to everyone with haemophilia, however mildly affected, to continue to accept medication as prescribed by medical staff. However, we make the following additional RECOMMENDATIONS:-

(a) That you ask your Centre Director to make heat-treated product available as soon as possible.
(b) That you write to your MP (and to Norman Fowler) pointing out your anxieties and urging them to take all the steps which are set out above at (2) a-e.
(c) We also suggest that you monitor the advice being given to donors at your local Blood Transfusion Service - let the Co-ordinator know if you find that there are no AIDS leaflets, etc,on display.

The Haemophilia Society

HÆMOFACT

RELEASE No 6

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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22 April 1985

P.O. Box 9 16 Trinity Street London SE1 1DE

WE ENDORSE OUR EARLIER ADVICE TO EVERYONE WITH HAEMOPHILIA - HOWEVER MILDLY AFFECTED - TO CONTINUE TO ACCEPT MEDICATION AS PRESCRIBED BY MEDICAL STAFF.

WE REPEAT OUR ADVICE REGARDING ENQUIRIES ABOUT YOUR OWN POSITION: YOU SHOULD SPEAK TO YOUR CENTRE DIRECTOR - WHO WILL BE ONLY TOO GLAD TO ASSIST YOU WITH ANY MATTER WHICH IS WORRYING YOU.

CURRENT PRACTICE at major Haemophilia Centres in the UK is that *cryoprecipitate* is used in factor VIII deficient newborn infants and children under 4 years of age and in newly identified patients never treated with factor VIII concentrates; whenever possible *fresh frozen plasma* is used in factor IX deficient patients in the same categories and *desmopressin (DDAVP)* whenever possible, is used in patients with moderate or mild haemophilia and von Willebrand's Syndrome. It is, as already stated, the Society's recommendation that heat-treated product be made available as quickly as possible for all other groups of people with haemophilia.

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HAEMOFACT is a leaflet produced by the Haemophilia Society. They are issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE.

HAVE YOU paid your 1985 Annual Subscription? - or applied for free membership if you cannot afford the £5 subscription?

HAVE YOU thought about paying your subscription by Bankers Order - and under a Deed of Covenant? If you do not have the necessary forms, ask for them from 16 Trinity St!

As members will have noticed since the last issue, media coverage of AIDS has increased in volume if not quality. There have been honourable and influential exceptions to this for which we are very grateful.

Because AIDS is a relatively new problem to which great research and medical resources are being applied our knowledge of the disease has grown at a furious pace. This has made our aim of bringing you the facts about AIDS very difficult to achieve as, at any one time, there are several versions of the facts available. In light of this our policy is to publish HAEMOFACT whenever a reasonably clear consensus emerges but we must all realise that many of the conclusions reached are "probable" not "certain". IN THE MEANTIME the position as far as it is known is that:-

(a) *the causative agent of AIDS is a virus known as HTLV-III or LAV, which may or may not be one and the same*

(b) *tests to establish the presence of antibodies to HTLV-III have been introduced but the precise meaning of the presence or absence of those antibodies is not yet known. Moreover, the accuracy of the test has not yet been established.*

(c) *as reported in HAEMOFACT 5, one third of a group of English haemophilic patients were shown to have antibodies to HTLV-III. Current predictions are that this figure seems low and it may be that the majority of people with haemophilia will have antibodies to HTLV-III.*

(d) *DHSS guidance to blood donors does not yet include the sexual partners of people with haemophilia; in the light of recent developments, we must now suggest that it would be inappropriate for such sexual partners to continue to donate blood.* (see **AIDS AND THE BLOOD** p59)

(e) *heat-treatment of concentrates* - **BOTH FACTOR VIII AND IX** - *has been shown to destroy the HTLV-III virus in laboratory conditions. On this basis we continue to recommend that the case for use of heat-treated concentrates is a strong one.* **IN ANY CASE,** *as recently as Monday 18 March, Lord Glenarthur, speaking in the Lords, made it clear that ALL home-produced factor VIII will be heat-treated from April 1985.*

SELF-SUFFICIENCY IN BLOOD PRODUCTS.

The Government has promised self-sufficiency in blood products by the end of 1985 but Kenneth Clarke has recently acknowledged on TV that there will be a problem of obtaining sufficient plasma to achieve this. (*It has been estimated that plasma collection would have to increase fourfold to achieve self-sufficiency*). The good news about blood products is that the Blood Products Laboratory Elstree (BPL) is on target for completion in 1986. It seems inconceivable that the Government, which has invested so heavily in creating a modern blood products plant at Elstree, will then fail to ensure sufficient plasma supplies for the plant to operate efficiently.

THE SOCIETY HAS TAKEN ACTION AS FOLLOWS:-

(1) Since HAEMOFACT 5 was issued, the Haemophilia Society has had a long meeting with Lord Glenarthur and his officials. We are pleased to report that:

(a) Heat-treated concentrates - both factor VIII and IX - have been widely introduced at many Centres, despite the increased costs. We welcome this development and would encourage ALL Centres to follow suit.

(b) New guidelines for blood donors have been issued on an individual basis to all blood donors.

(c) The DHSS hope that donor-screening will be introduced soon.

(d) As reported in the national press, the Society has received a DHSS grant of £15,000 for 1984/1985 to help with the extra workload arising from AIDS.

HOWEVER, Lord Glenarthur was unable to reassure us regarding the widespread introduction of plasmapheresis programmes in order to increase the plasma available to BPL, **NOR** was he able to promise any further finance to Supra-Regional Centres to enable them to ensure adequate staffing to cope with the AIDS situation. In connection with both of those matters we were reminded that the Department provides funds to Regional Health Authorities and the allocation of resources lies with those Regions.

(2) **WE HAVE:-**

(a) **CIRCULATED ALL SOCIETY MEMBERS** with a free copy of Dr Peter Jones' excellent new booklet **'AIDS AND THE BLOOD'**. This is the ONLY book in the English language dealing with AIDS and there has been an enormous demand for copies from all over the world. We are most grateful to Dr Jones, not only for producing the book so speedily, but also for donating all profits to the Society.

(b) **DONATED** a grant of approximately £25,000 to Dr Richard Tedder and Dr Philip Mortimer to enable them to handle samples from people with haemophilia for HTLV-III testing more speedily and also to evaluate the meaning of the HTLV-III test.

(c) **We have continued the activities listed in HAEMOFACT 5.**

(d) **Undertaken innumerable media briefing sessions for all the television, radio and quality daily newspaper articles on AIDS.**

WE MUST THANK ALL THOSE MEMBERS who wrote to their MP and to the Minister. Those letters have been most effective in keeping the problem in the public - and political - eye! We would ask that you continue to write with particular reference to the introduction of plasmapheresis programmes!

IF YOU HAVE PROBLEMS OR ANXIETIES CONCERNING AIDS PLEASE DISCUSS THEM WITH YOUR CENTRE STAFF who should be only too happy to discuss them with you.

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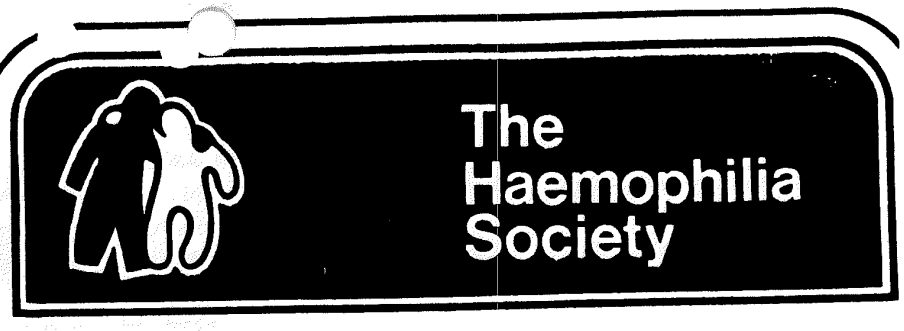
HAEMOFACT is a leaflet produced by the Haemophilia Society. They are issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE



HÆMOFACT

A.I.D.S.

RELEASE No 7

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

22 May 1985

P.O. Box 9 16 Trinity Street London SE1 1DE

The content of this issue of HAEMOFACT is based on the April 1985 AIDS Centre News, published by the World Hemophilia AIDS Centre (WHAC) in Los Angeles. The Director of WHAC is Dr Shelby Dietrich, MD.

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All the evidence now points to the fact that virtually all Haemophilia patients who have received large-pool plasma products (eg concentrates) within the past five years have been exposed to the putative agent of AIDS, HTLV-III.

Individual interpretation of the results of the anti-body test on any given patient is NOT an indication of AIDS or any AIDS-related condition. At the moment the potential value is scientific and we would urge those who feel able to do so to continue to co-operate with their doctors in such tests.

IT CANNOT BE STRESSED ENOUGH that the results of antibody tests will not answer any of the pressing questions regarding an individuals infectivity to others, the future clinical course, or any other concurrent perplexing problem.

Until such time that further studies similar to the hepatitis B antigen test become available we recommend as follows:-

CONTINUE TO TREAT BLEEDING EPISODES, wherever possible with heat-treated material, be that imported or British.

LEAD A HEALTHY LIFESTYLE - get plenty of wholesome food, exercise, rest and sleep, avoid excesses of alcohol or other drugs which lower immunity; maintain a high standard of hygiene and do not share razors or toothbrushes - see your dentist regularly! Above all, talk about your fears and anxieties about the condition and share those thoughts with those closest to you: relax and reduce the stress.

INFUSION SAFETY:- Wash hands with soap and water before infusion and practice proper infusion techniques as they have been taught to you. This is for *YOUR OWN BENEFIT.*

For the benefit of others, wash your hands with soap and water at the end of the infusion: clean the work area: *DO NOT INFUSE NEAR FOOD PREPARATION AREAS.* If blood or concentrate is spilled on the work area, wash the area with household liquid bleach.

Dispose of your equipment properly by placing used needles in a used needle box; syringes, bottles and gloves should be placed in a plastic bag and sealed for safe disposal at your Centre, or in the containers provided by your Centre.

If a member of your household has a needle-stick accident, encourage bleeding from the puncture site. Wash the affected area with soap and water and contact the Centre within 24 hours.

SAFE SEXUAL PRACTICES: All evidence to date indicates that AIDS may be transmitted by close sexual contact involving the exchange of body fluids, especially through breaks in the skin or mucous membranes. Therefore it is recommended that condoms are used, even if your partner is pregnant or male.

REMEMBER: No one knows the precise meaning of HTLV-III antibody tests: their value is scientific and for this reason we recommend that you continue to co-operate with your doctor. These tests may carry greater meaning in the future.

IF YOU HAVE ANY PROBLEMS OR ANXIETIES CONCERNING AIDS PLEASE DISCUSS THEM WITH YOUR CENTRE STAFF who should be only too happy to discuss them with you.

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HAEMOFACT is a leaflet produced by the Haemophilia Society. They are issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE

The Haemophilia Society

HÆMOFACT

A.I.D.S.

RELEASE No 8.

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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29th August 1985

P.O. Box 9 16 Trinity Street London SE1 1DE

HTLV-III antibody testing has been in the news during the last month and many innacurate things have been said about it. For example, it has been presented as a test for AIDS. It is not: as far as is known it only indicates exposure to the most probable causative agent for AIDS namely HTLV-III. The meaning of positive or negative test results is not yet clear.

In view of the above uncertainty many Haemophilia Centres and the Haemophilia Society recommend that people with haemophilia should behave as though they are potential carriers of HTLV-III virus. Our advice is as follows:-

CONTINUE TO TREAT BLEEDING EPISODES,

wherever possible with heat-treated material, be that imported or British.

LEAD A HEALTHY LIFESTYLE - get plenty of wholesome food, exercise, rest and sleep, avoid excesses of alcohol or other drugs which lower immunity; maintain a high standard of hygiene and do not share razors or toothbrushes - see your dentist regularly! Above all, talk about your fears and anxieties about the condition and share those thoughts with those closest to you: relax and reduce the stress.

INFUSION SAFETY:- Wash hands with soap and water before infusion and practice proper infusion techniques as they have been taught to you. This is for ***YOUR OWN BENEFIT***

For the benefit of others, wash hands with soap and water at the end of the infusion: clean the work area: ***DO NOT INFUSE NEAR FOOD PREPARATION AREAS.*** If blood or concentrate is spilled on the work area, wash the area with household liquid bleach.

Dispose of your equipment properly by placing used needles in a used needle box; syringes, bottles and gloves should be placed in a plastic bag and sealed for safe disposal at your Centre, or in the containers provided by your Centres.

If a member of your household has a needle-stick accident, encourage bleeding from the puncture site. Wash the affected area with soap and water and contact your Centre within 24 hours.

SAFE SEXUAL PRACTICES: All evidence to date indicates that AIDS is transmitted by close sexual contact involving the exchange of body fluids, especially through breaks in the skin or mucous membranes. Therefore it is recommended that condoms are used, even if your partner is pregnant or male.

IT IS IMPORTANT THAT THERE BE NO EXCHANGE OF SEMEN OR BLOOD BETWEEN SEXUAL PARTNERS. *For this reason a sheath/condom should be used as a barrier (not as a contraceptive). Current medical advice is that pregnancy should be avoided because the foetus may be at risk. In view of this it is most important not to rely on the sheath as a form of contraception.*

We recommend that you discuss these difficult and personal problems with your Centre Director as soon as possible if you have not already done so.

The Haemophilia Society has prepared a detailed guide to a safe sex life, which will be available either from your Haemophilia Centre or by post from the Haemophilia Society.

REMEMBER: No one knows the precise meaning of HTLV-III antibody tests: their value is scientific and for this reason we recommend that you continue to co-operate with your doctors. These tests may carry greater meaning in the future.

We would stress that if you have worries or problems about anything relating to haemophilia, we are hear to listen, advise and, where necessary, take action on your behalf. Please telephone us or write and we will do whatever we can to help you and your family at this difficult time.

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HAEMOFACT is a leaflet series produced by the Haemophilia Society. HAEMOFACT is issued from time to time on topics of interest and concern to people with haemophilia.

For further details of Society membership please write to us at 16 Trinity Street, London, SE1 1DE

The Haemophilia Society

HÆMOFACT

A.I.D.S.

RELEASE No 9.

THIS FACTSHEET CONTAINS IMPORTANT INFORMATION

concerning

ACQUIRED IMMUNE DEFICIENCY SYNDROME

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24 September 1985

P.O. Box 9 16 Trinity Street London SE1 1DE

THE STORY SO FAR.....

Action to panic

Parents seek help to quell Aids panic

'We shall kiss and cuddle him like before...it's just another p

Facing the AIDS scare, par

Pupils stay away

vir in AIDS scare

Carrier pupils at the centre of a nationwide 'witch-hunt'

Boycott threat for schools over AIDS

TERRIFIED parents are set to boycott six schools this week as fears of an AIDS outbreak among pupils sweeps

By BARBARA HINES Medical Correspondent

NEWS

Urgent talks on AIDS scare in schools

Parents of AIDS by: Why we may be to blame

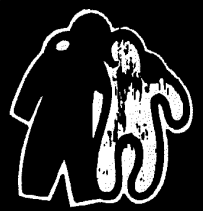
We feel that the recent publicity in Hampshire must have caused the parents of children with haemophilia very great concern.

We are awaiting a Ministerial Statement about boys with haemophilia, education and the question of disclosure of antibody status. In the meantime we want to let you know our position on the question of HTLV-III antibody status as it affects both children and adults with haemophilia.

1. Your antibody status is private and confidential medical information and no business of anyone else other than your family, your Centre Director and, with your permission, your family doctor. We would also suggest that you inform your dentist in advance of your next treatment.

2. If you are antibody positive you pose absolutely no risk to anyone - apart from your sexual partner. (For fuller information see HAEMOFACT 8 or request our ADVICE ON SAFER SEX from your Centre or direct from this office - publication date: 7 October 1985.

3. While the decision about disclosing your antibody status is entirely up to you, we advise against sharing this information about your child's antibody status (or your own) with anyone outside your immediate family apart from your local authority medical staff or, at your own discretion and in absolute confidence, the head teacher at your child's school.



The Haemophilia Society

HÆMOFACT

ADVICE ON SAFER SEX

SPECIAL ISSUE

FIRST EDITION OCTOBER 1988

P.O. Box 9 15 Trinity Street London SE1 1DE

This pamphlet is supplied free of charge to members of the Haemophilia Society.

This guide to a responsible sex life has been written for a heterosexual audience. For the gay community the Terrence Higgins Trust. (BM AIDS, London, WC1N 3XX) has produced a well informed booklet "AIDS Medical Briefing" which includes a comprehensive section on gay sexual practices and the reduction of the risks of transmission of HTLV-III.

Acknowledgments
The Society is indebted to the following for their help and guidance in preparing this pamphlet:—

Dr Peter Jones; Dr Richard Tedder; Mrs Riva Miller; Mrs Jean Lovie; Mrs Kate Parkin; Sister Maureen Fearns

HTLV-... AND AIDS

As we now know people with haemophilia and von Willebrand's syndrome are in the 'at risk' groups for exposure to HTLV-III. Consequently, we must adapt and make changes if we are to protect our sexual partners from exposure to HTLV-III.

HTLV-III virus is not AIDS but the most probable causative agent for the development of AIDS. Only a very small number of those who are exposed to the virus (HTLV-III) go on to develop further symptoms of AIDS itself.

AIDS is a new viral disease in which the body's defence mechanisms are altered in such a way that uncommon infections can occur. HTLV-III is simply the name given to the virus believed to be responsible for AIDS and the anitbody is simply a marker of the presence or former presence of the virus. The virus (HTLV-III) is transmitted in blood and semen and found in other body fluids.

Probably the most significant threat that AIDS poses is the fear and uncertainty which it creates. Because HTLV-III and AIDS are sexually transmitted the emotions which they arouse touch on the most private and vulnerable areas of our lives. This not only affects us as individuals in an 'at risk' group but also the people who staff haemophilia centres — none of us volunteered to be in the front line fight against AIDS.

Remember that you are not alone — thousands of other people now share your fears, anxieties and dilemmas. Like you they have had the experience of overcoming many medical and social problems which others never have to face. You belong to a community of survivors; you already have the expertise — you just need to apply it to a new situation. Don't let a virus kick you around — fight back by taking sensible precautions and protecting your partner and so your family. If you need to talk things over go to your centre to get in touch with the Haemophilia Society and when you need support don't forget your listener probably needs your support too!

Above all, try to keep well informed about AIDS, To help you do this the Haemophilia Society regularly produces HAEMOFACT with news updates and advice, and of course your Haemophilia Centre should always be able to give advice to you if you ask for it.

GENERAL ADVICE

Continue to Treat Bleeding Episodes to avoid long term joint damage etc. *By now you should ONLY be receiving heat-treated materials, whether imported or British, IF THIS IS NOT SO, raise the matter with your Centre Director.*

All evidence to date indicates that HTLV-III is found in body fluids so if the need arises great care should be taken in handling blood, semen, urine, faeces and vomit.

Lead a Healthy Lifestyle because this will help your immune system to protect you. Get plenty of wholesome food, exercise, rest and sleep, avoid excesses of alcohol or other drugs which lower immunity; maintain a high standard of hygiene and do not share razors or toothbrushes (both of which may be contaminated with blood) and see you dentist regularly because oral hygiene, which is important at any time, is even more so now. Above all, talk over your fears and anxieties about HTLV-III with those closest to you and try to reduce the stress.

MATERNAL TRANSMISSION

Because there is evidence of transmission from mother to baby, pregancy should be avoided at present. If you are already pregnant you will obviously want to discuss this with your partner's Centre Director. It is not yet known if the virus (HTLV-III) is transmitted by breast milk but your Centre Director will be able to give you advice on your own position.

SEXUAL TRANSMISSION

Just as there is no test for AIDS — so there is no test for HTVL-III infectivity. *Until there is such a test the only safe course is to behave as though you may be infectious. Because exposure to HTVL-III may have a cumulative effect the fact that you have not taken precautions before does not mean that you need not take them from now one.*

The advice given below may mean making unwelcome, but necessary, changes in your life but please read on .....

Because the majority, if not all, haemophilia centres are now using heat treated blood products, sexual transmission of HTLV-III virus is the main risk factor. Testing of the sexual partners of people with haemophilia for HTLV-III antibody is being carried out and, although results so far are encouraging, there are cases in which sexual transmission has occurred. *It is most important to realise that the need to modify sexual behaviour applies to all those who are sexually active whatever their HTLV-III antibody or antigen (virus) status may be. This is so because the precise significance of HTLV-III antibody positivity or negativity is not yet understood.*

For sexual transmission to occur, body fluids containing HTLV-III (especially blood and semen) must enter your partners' body through the vagina, anus, mouth, eyes or breaks in the skin (cuts, grazes, open wounds etc). A sheath or condom should therefore be used as a barrier in any penetrative sexual activity.

Do not rely on this barrier as a method of birth control. Any sexual activity **NOT** involving penetration or internal exchange of body fluid ought to be of low or no risk assuming that your partner's body surfaces are uninjured. Any sexual activity which tends to break the skin or mucous membranes will increase risk and for this reason *anal intercourse in particular is considered a high risk activity.*

Blood and semen are the main 'culprit' fluids identified so far, but all body fluids and products *may* contain an element of risk if they are exchanged *frequently.* It is though that saliva is not a significant risk factor unless it contains some blood (from bleeding gums or other lesions in the mouth or throat).

To summarise the above we give the following estimated risk categories:

HIGH RISK
Vaginal intercourse **without** the use of a sheath or condom or any act which draws blood or which causes semen or blood to enter a sexual partner's body. Anal intercourse should be regarded as a high risk even when a sheath is used as a barrier.

MEDIUM RISK
Oral sex by the woman to the man is in this category, even if withdrawal before orgasm is practised.

LOW RISK
Vaginal intercourse with condom or sheath, oral sex by the man to the woman when no blood is present in saliva.

NO RISK
Mutual or solo masturbation. General body contact, stroking, caressing, body kissing. Although orgasm on your partners' body is safe (providing you have avoided body openings or any injury site) remember that semen can transfer from one place to another with or without your help. Don't let it because the virus will survive as long a fluid stays fluid.

ACCIDENTAL RISK
If an accident occurs, you should wash as thoroughly as possible with copious amounts of water and, if practicable, soap and water.
NEVER use bleach — or any other fluid apart from soapy water — on your own body or that of your partner.
There is no need to panic but if you are concerned do not hesitate to contact your local Haemophilia Centre Director who will, in due course, arrange for you to be tested.

ADDITIONAL SOURCES OF INFORMATION AND ADVICE

Your Centre will be able to refer you to specialist counsellors if you are having sexual problems and your General Practitioner can often be very helpful in discussing sexual matters.

The Marriage Guidance Council are training counsellors especially to deal with worries about AIDS and sexual relationships. Local addresses for these counsellors can be obtained from the Marriage Guidance Council:—

For England, Wales and Northern Ireland
Herbert Gray College
Little Church Street
Rugby
Warwickshire, CV21 3AP
Tel: 0788 73241

Or from the Scottish Marriage Guidance Council
26 Frederick Street
Edinburgh
EH2 2JR
Tel: 031 225 5006

In addition most good bookshops stock reliable and authorative books and publications dealing with sex, its pleasures and problems.

BOOKS AND PUBLICATIONS ON HTLV-III, AIDS AND SEX

AIDS AND THE BLOOD: A Practical Guide-by Dr Peter Jones (free to membrs or £2.00 post paid).

HAEMOFACT — an information series on AIDS, frequently updated and free to members.

THE BULLETIN — the Society magazine, issued three times a year.

The Marriage Guidance Council General List of Books and Booklets contains many appropriate titles about sexual relationships and their problems. This may be obtained by writing to the above addresses.

THE HAEMOPHILIA SOCIETY AND YOU

If you are **not** already a member of the Haemophilia Society we feel you should know more about us . . . . . .

The Society has been in existence for over thirty-five years and its main function is to protect the interest of people with haemophilia and their families by: making represenations to the Government; securing high standards of treatment; making publications available to members, doctors, nurses, social workers, physiotherapists and other health care professionals; providing help to people with haemophilia; limited support to vital research projects.

More especially the Society can help you by: keeping you up to date on developments in treatment and care through our literature — this applies particularly to the problems of HTLV-III and AIDS, answering any questions you have by letter or telephone; advising teachers, social workers, health visitors, employment workers and employers on the implications of haemophilia; giving grants for certain financial problems; through local groups, giving you an opportunity to discuss problems and share difficulties; directing you to other sources of help.

We provide many other services to our members but probably the most important now is supplying them with accurate, up-to-date information about HTLV-III and AIDS. We are the only organisation committed to providing this service to people with haemophilia.

MEMBERSHIP

This is available to anyone. People with haemophilia may become members without payment but in the normal course of events there is an annual subscription (currently £5).

THE MAIN HAEMOPHILIA CENTRES ARE:

AREA	NAME & ADDRESS	TEL No.	EXTENSION
London	Royal Free Hospital Pond Street, London NW3 2QG	01 794 0500	
London	St Thomas' Hospital London, SE1 7EH	01 928 9292	2268
Manchester	The Royal Infirmary Manchester, M13 9WL	(Manchester) 276 1234	
Newcastle	Royal Victoria Infirmary Newcastle upon Tyne Tyne & Wear, NE1 4LP	(Newcastle.U.Tyne) 325131	773
Oxford	Churchill Hospital Headington, Oxford OX3 7LJ	(Oxford) 64841	532, 552, 569 & 584
Sheffield	Royal Hallamshire Hospital, Glossop Road Sheffield, S10 2JF	(Sheffield) 26484	
Northern Ireland	Royal Victoria Hospital Grosvenor Road, Belfast BT12 6BA	(Belfast) 40503	
Scotland			
Edinburgh	The Royal Infirmary Edinburg, EH3 9YW	(Edinburgh) 2292477	2099
Glasgow	Royal Infirmary Glasgow, G4 0SF	(Glasgow) 552 3535	203
Wales			
Cardiff	University Hospital of Wales, Heath Park Cardiff, CF4 1XW	(Cardiff) 755944	

HEMOPHILIA INFORMATION EXCHANGE

AIDS UPDATE

MEDICAL BULLETIN # 9
CHAPTER ADVISORY #12

THE NATIONAL HEMOPHILIA FOUNDATION
MEDICAL AND SCIENTIFIC ADVISORY COUNCIL
(Revised -- October 22, 1983)

RECOMMENDATIONS TO PREVENT AIDS IN PATIENTS WITH HEMOPHILIA

Recommendations for physicians treating patients with hemophilia.

A. It is recommended that cryoprecipitate be used to treat patients in the following groups except when there is an overriding medical indication:

- newborn infants and children under 4;
- newly identified patients never treated with factor VIII concentrate;
- patients with clinically mild hemophilia who require infrequent treatment;

Similar guidelines should be applied to factor IX deficiency patients where fresh frozen plasma can be used instead of concentrate.

B. The potential advantages and disadvantages of cryoprecipitate versus factor VIII concentrate therapy for severe hemophilia A are not clear at the present time and are controversial. The Medical and Scientific Advisory Council does not offer a specific recommendation at this time, but will continue to review the data.

C. DDAVP should be used whenever possible in patients with mild or moderate hemophilia A.

D. All elective surgical procedures should be evaluated with respect to the possible advantages or disadvantages of a delay.

Recommendations to factor VIII concentrate manufacturers:

A. Serious efforts should be made to exclude donors that might transmit AIDS.

1. Blood and plasma donation should not be obtained from prospective donors who are members of groups who are at higher risk of contracting AIDS. Such groups include: male homosexuals; intravenous drug users; those who have recently resided in Haiti; and sexual partners of members of those groups who are at higher risk. This effort should make use of educational materials and questionnaires in a discreet and sensitive manner.

2. Prospective blood donors should be excluded if they have symptoms associated with AIDS. This should be done by direct questioning and physical examinations as recommended by the Food and Drug Administration, Office of Biologics (March 24, 1983).

3. Research is encouraged in the evaluation and implementation (if verified) of surrogate laboratory tests that would identify individuals at high risk of AIDS transmission.

4. In addition, the manufacturers should cease using plasma obtained from donor centers that draw from population groups in which there is a significant AIDS incidence. It is clear from the epidemiologic data that the pool of individuals at risk for AIDS transmission is not uniform throughout the country and that a great deal could be achieved by excluding donors from the "hot spots".

B. Efforts should be continued to expedite the development of processing methods that will inactivate viruses potentially present in factor VIII concentrates.

While heat treated products offer certain theoretical advantages, the data are insufficient at this time to assess their efficacy or to recommend that the presently licensed heat treated products be used instead of standard factor VIII concentrate, either for modification of the risk of hepatitis or AIDS. For this reason, prospective studies of the efficacy and safety of modified products are strongly encouraged.

C. There should be an evaluation of the possibility that the yield of factor VIII in pheresis donors could be increased using DDAVP or exercise to maximize yield. This would permit a reduction in the size of the donor pool and would compensate for losses in plasma that might occur due to steps noted above.

D. There should be an evaluation of the feasibility of fractionating and processing plasma so that lyophilized small pool products are available.

E. Concentrate manufacturers should immediately cease purchase of recovered plasma for factor VIII concentrate from blood centers that do not meet the criteria listed in II.A above. These criteria should also apply to the production of cryoprecipitate.

F. Manufacturers should recall any lot of concentrate if it includes material from an individual that has been identified as having AIDS, or from an individual that, in the best medical judgement of the manufacturers, has characteristics strongly suggestive of AIDS.

G. Manufacturers should accelerate efforts towards the production of coagulation factor concentrates by recombinant DNA technology.

Recommendations to regional and community blood centers:

A. Those centers that are in regions in which there is a very low incidence of AIDS should increase capacity for cryoprecipitate production to be used locally and in other regions.

B. These centers should evaluate the feasibility of preparing small pool lyophilized cryoprecipitate for hemophilia treatment.

C. The production of cryoprecipitate should also adhere to criteria detailed in II.A above.

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HEMOPHILIA INFORMATION EXCHANGE

AIDS UPDATE

October 13, 1984
MEDICAL BULLETIN #15
CHAPTER ADVISORY #20

THE NATIONAL HEMOPHILIA FOUNDATION
MEDICAL AND SCIENTIFIC ADVISORY COUNCIL

RECOMMENDATIONS CONCERNING AIDS AND THE TREATMENT OF HEMOPHILIA

(Revised — October 13, 1984)

Recommendations for physicians treating patients with hemophilia:

A. For patients with factor VIII deficiency, it is recommended that cryoprecipitate be used to treat patients in the following groups, with the recognition that there are some circumstances where viral attenuated (heat-treated) factor VIII concentrate may be appropriate therapy:

- newborn infants and children under 4;
- newly identified patients never treated with factor VIII concentrates.

Similar guidelines should be applied to factor IX deficiency patients where fresh frozen plasma can be used.

B. Desmopressin (DDAVP) should be used whenever possible in patients with mild or moderate hemophilia A. When desmopressin does not provide adequate treatment, these patients should be treated as specified in A.

C. We do not yet have sufficient data of scientific nature to know with certainty that viral attenuated (heat-treated) coagulation factor concentrates should now be universally adopted. However, very preliminary data do suggest that HTLV-III is heat sensitive. Further, we do not know whether hemophiliacs who are positive for antibody to HTLV-III have been exposed to living virus capable of causing AIDS, or have developed effective immunity against AIDS.

Because heat-treated products appear to have no increase in untoward effects attributable to the heat treatment, we now recommend that treaters using coagulation factor concentrates should strongly consider changing to heat-treated products with the understanding that the protection against AIDS is yet to be proven. We again urge a prospective national study of the use of these and other materials in patients not previously exposed to pooled blood products. In addition, further basic studies on the efficacy of viral attenuation procedures are urged. The Medical and Scientific Advisory Council will continue to review its position on heat-treated products as more complete studies become available.

D. All elective surgical procedures should be evaluated with respect to the possible advantages or disadvantages of a delay.

E. We reaffirm our position that patients continue treating bleeding episodes with clotting factor as prescribed by their physicians, as the risks of withholding treatment far outweigh the risks of treatment. Therefore, it is important that patient education and psychosocial support be provided.

(over)

II. Recommendations to factor VIII concentrate manufacturers:

A. Serious efforts should be continued to exclude donors that might transmit AIDS.

1. Blood and plasma donation should not be obtained from prospective donors who are members of groups who are at higher risk of contracting AIDS. Such groups include: male homosexuals; intravenous drug users; those who have recently resided in Haiti; and sexual partners of members of those groups who are at higher risk. This effort should make use of educational materials and questionnaires in a discreet and sensitive manner.

2. Prospective blood donors should be excluded if they have symptoms associated with AIDS. This should be done by direct questioning and physical examinations as recommended by the Food and Drug Administration, Office of Biologics (March 24, 1983).

3. Research is encouraged in the evaluation and implementation (if verified) of surrogate laboratory tests that would identify individuals at high risk of AIDS transmission. With regard to HTLV-III testing, we urge the continued rapid development and study of this and other laboratory tests which can identify blood donors at risk of transmitting AIDS. When the sensitivity and specificity of HTLV-III antibody testing or other such tests are found to be sufficient, verified by clinical trials, these tests should be then applied to all blood and plasma donors as soon as feasible.

4. Until effective blood donor screening methods are available, manufacturers should continue to avoid using plasma obtained from donor centers that draw from population groups in which there is a relatively high AIDS incidence.

B. Efforts should be continued to expedite the development of processing methods that will inactivate viruses potentially present in all clotting factor concentrates.

C. There should be an evaluation of the possibility that the yield of factor VIII in pheresis donors could be increased using DDAVP or exercise to maximize yield. This would permit a reduction in the size of the donor pool and would compensate for losses in plasma that might occur due to steps noted above.

D. Concentrate manufacturers should immediately cease purchase of recovered plasma for factor VIII concentrate from blood centers that do not meet criteria listed in II. A above. These criteria should also apply to the production of cryoprecipitate.

E. Manufacturers should withdraw any lot of concentrate if it includes material from an individual that has been identified as having AIDS, or from an individual that, in the best medical judgement of the manufacturers, has characteristics strongly suggestive of AIDS.

F. Manufacturers should accelerate efforts towards the production of coagulation factor concentrates by recombinant DNA technology. When such materials are ready for clinical trials and for introduction into clinical use, the necessary review processes should be carried out as expeditiously as possible.

I. Recommendations to regional and community blood centers:

The production of cryoprecipitate should also adhere to criteria detailed in II. A above.

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HEMOPHILIA
INFORMATION EXCHANGE

AIDS UPDATE

April 12, 1985

Medical Bulletin #21
Chapter Advisory #26

REVISED
MEDICAL AND SCIENTIFIC ADVISORY COUNCIL
RECOMMENDATIONS CONCERNING AIDS AND THE TREATMENT OF HEMOPHILIA

Attached please find a copy of the revised "Recommendations Concerning AIDS and the Treatment of Hemophilia." These revisions are based on actions taken by the NHF Medical and Scientific Advisory Council at a meeting held on February 14, 1985, and finalized on April 5, 1985.

The major changes to the previous recommendations are as follows:

1. Treatment of patients with severe hemophilia

   Recommendations were modified concerning the treatment of newborn infants and children under 4 with severe hemophilia as well as newly identified patients with severe hemophilia never treated with Factor VIII or Factor IX concentrate (see Section I. B.). These revisions are due to the accumulating evidence concerning the effectiveness and safety associated with heat treated concentrates.

2. Treatment of patients with mild and moderate hemophilia

   Recommendations were modified for mild and moderate patients with hemophilia (see Section I. C.).

3. The NHF Medical and Scientific Advisory Council (MASAC) recommended the adoption of HTLV-III testing of all blood and plasma donors, as well as provisions for alternate site testing for members of other high risk groups (see II. A. 1.).

The above are the highlights of the changes introduced into the MASAC Recommendations. While a few additional changes were made, the remaining text is essentially the same as the recommendations that were issued on October 13, 1984.

Recognizing that there are a number of complex issues that must be considered in regard to the impact of AIDS transmission on the lifestyles of hemophiliacs, health care providers and patients are referred to "AIDS & Hemophilia: Your Questions Answered" for more detailed background on these matters.

The MASAC reaffirms its position that **PATIENTS CONTINUE TREATING BLEEDING EPISODES WITH CLOTTING FACTOR AS PRESCRIBED BY THEIR PHYSICIANS AS THE RISKS OF WITHHOLDING TREATMENT FAR OUTWEIGH THE RISKS OF TREATMENT.**

Any questions you may have concerning these revised recommendations should be referred to your treating physician or member of the treatment center team.

Chapters: Please distribute this information to all chapter members.

Physicians: Please distribute this information to all providers who treat patients with hemophilia in your area.

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HEMOPHILIA
INFORMATION EXCHANGE

AIDS UPDATE

THE NATIONAL HEMOPHILIA FOUNDATION
MEDICAL AND SCIENTIFIC ADVISORY COUNCIL

RECOMMENDATIONS CONCERNING AIDS AND THE TREATMENT OF HEMOPHILIA

(Revised — February 14, 1985)

I. Recommendations for physicians treating patients with hemophilia:

A. In view of the accumulating evidence for the heat sensitivity of HTLV-III, and the apparent lack of untoward effects attributable to the heat treatment, we recommend that physicians should strongly consider prescribing heat treated coagulation factor concentrates for the treatment of patients with severe hemophilia, with the understanding that protection against AIDS is yet to be proven. It is recognized that we do not know whether hemophiliacs who are positive for antibody to HTLV-III have been exposed to living virus capable of causing AIDS, or if they have developed effective immunity against AIDS.

In order to develop a secure scientific basis for such practice, we again urge a prospective national study of the use of heat treated materials in patients not previously exposed to pooled blood products. The Medical and Scientific Advisory Council will continue to review its position on heat treated products as more complete studies become available.

B. The accumulating evidence for the heat sensitivity of HTLV-III suggests that heat treated factor VIII and factor IX are the preferred products for the treatment of patients in groups for which it was previously recommended that cryoprecipitate or plasma be used:

- newborn infants and children under 4 with severe hemophilia;
- newly identified patients with severe hemophilia never treated with factor VIII or factor IX concentrates.

It is emphasized that hepatitis B vaccination is essential when these patients are treated in this way, and it is recommended that this be administered shortly after birth. Moreover, as the transmission of non-A, non-B hepatitis may be greater with these products, even if heat treated, it may be preferable in some cases to treat patients in these groups with cryoprecipitate (hemophilia A) or fresh frozen plasma (hemophilia B), especially in those areas in which there is a low incidence of patients with AIDS in the general population.

C. Desmopressin (DDAVP) should be used whenever possible in patients with mild or moderate hemophilia A. When desmopressin does not provide adequate treatment, these patients should usually be treated with cryoprecipitate. Similarly, for patients with mild or moderate factor IX deficiency, plasma is usually the preferred product. It is recognized, however, that there are some circumstances in which viral attenuated (heat treated) factor VIII or factor IX may be the more appropriate therapy.

D. All elective surgical procedures should be evaluated with respect to the possible advantages or disadvantages of a delay.

E. We reaffirm our position that patients continue treating bleeding episodes with clotting factor as prescribed by their physicians, as the risks of withholding treatment far outweigh the risks of treatment. Therefore, it is important that patient education and psychosocial support be provided.

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F. There are a number of complex issues that must be considered in regard to the impact of possible AIDS transmission on the lifestyles of hemophiliacs. For a detailed consideration of these issues, the physician is referred to the NHF publication "AIDS & Hemophilia: Your Questions Answered." This publication is endorsed by MASAC and by the Centers for Disease Control.

II. Recommendations to factor VIII concentrate manufacturers:

A. Every effort should be made to exclude donors who might transmit AIDS.

1. We recommend the adoption of HTLV-III testing of all blood and plasma donors. At the same time, we urge that actions be taken by blood and plasma collection facilities and other agencies so that HTLV-III testing is available to members of high risk groups apart from that carried out for blood and plasma donors.

2. Blood and plasma donation should not be obtained from prospective donors who are members of groups who are at higher risk of contracting AIDS. Such groups include: male homosexuals; intravenous drug users; those who have recently resided in Haiti; and sexual partners of members of those groups who are at higher risk. This effort should make use of educational materials and questionnaires in a discreet and sensitive manner.

3. Prospective blood donors should be excluded if they have symptoms associated with AIDS. This should be done by direct questioning and physical examinations as recommended by the Food and Drug Administration, Office of Biologics (December 14, 1984).

4. Until blood donor screening methods have been shown to be effective, manufacturers should continue to avoid using plasma obtained from donor centers that draw from population groups in which there is a relatively high AIDS incidence.

B. Concentrate manufacturers should not purchase recovered plasma for coagulation factor production from blood centers that do not meet criteria listed in II.A. above.

C. Manufacturers should withdraw any lot of concentrate if it includes material from an individual that has been identified as having AIDS, or from an individual that, in the best medical judgment of the manufacturers, has characteristics strongly suggestive of AIDS. MASAC will review this position as more information becomes available about the effect of heat treatment on the possibility that these lots might transmit AIDS.

D. Manufacturers should continue efforts towards the production of coagulation factor concentrates by recombinant DNA technology. When such materials are ready for clinical trials and for introduction into clinical use, the necessary review processes should be carried out as expeditiously as possible.

III. Recommendations to regional and community blood centers:

The production of cryoprecipitate should also adhere to criteria detailed in II. A above.

4/85

May 8, 1985

HEMOPHILIA INFORMATION EXCHANGE

AIDS UPDATE

MEDICAL BULLETIN #22
CHAPTER ADVISORY #27

- MASAC REVISES PRODUCT WITHDRAWAL POLICY IN RESPONSE TO NEW DATA ON HEAT TREATMENT
- PRODUCT WITHDRAWAL ANNOUNCED

MASAC No Longer Recommends Withdrawal of Heat Treated Products

On April 26, 1985, The National Hemophilia Foundation's Medical and Scientific Advisory Council unanimously revised its position on product withdrawal, which was subsequently endorsed by the NHF's Board of Directors on April 27, 1985. The new policy is as follows:

> Based on current information on the issue of heat treatment and HTLV-III, and on the recall of lots of factor VIII and factor IX concentrates to which a person subsequently found to have AIDS had donated, the MASAC no longer recommends that heat treated product be withdrawn. Where product that has not been heat treated is involved and contains material from an individual that has been identified as having AIDS or from an individual in the best medical judgment of the manufacturer has characteristics strongly suggestive of AIDS, the NHF MASAC recommends that associated lots of concentrate continue to be withdrawn. (This replaces Section II C. of February 14, 1985 MASAC Recommendations Concerning AIDS and The Treatment of Hemophilia).

The reason that MASAC revised its position concerning the withdrawal of heat treated product is because HTLV-III appears to be adequately killed under currently licensed heat treatment procedures at the number of infectious doses likely to be present in the final blood product.

Product Withdrawal Announced

Friday, May 3, 1985, the Armour Pharmaceutical Company initiated a voluntary market withdrawal of ten lots of AHF (not heat treated) in the United States. The withdrawal was based on identification of a donor who was confirmed as having AIDS. The lot numbers being withdrawn by Armour Pharmaceutical Company involve donations from a single donor, who did not present symptoms until after his last donation.

The Armour Pharmaceutical Company has consulted with The National Hemophilia Foundation on this matter, and we have been assured that all efforts have been made to contact the points of distribution that may have distributed vials from these lots.

The lots that are being voluntarily withdrawn are only those that have not been heat treated. There are also three (3) lots of AHF that are not being withdrawn because they have been heat treated. On May 8, 1985, Armour contacted their customers to inform them of those lots of heat treated AHF associated with the same donor that are not being withdrawn.

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Not withdrawing the heat treated lots is in keeping with the new NHF-MASAC policy indicated above. We anticipate that our conservative policy regarding product withdrawal may lead to further voluntary product withdrawals in the future on the part of the industry. It should be added that this product withdrawal action was taken as a strictly precautionary measure.

AND MOST IMPORTANT, DESPITE THE CONCERN THAT MAY BE RAISED BY THE WITHDRAWAL OF PLASMA PRODUCTS, THE NHF REAFFIRMS ITS RECOMMENDATION THAT PATIENTS MAINTAIN THE USE OF CONCENTRATE, OR CRYOPRECIPITATE AS PRESCRIBED BY THEIR PHYSICIANS. THE LIFE AND HEALTH OF HEMOPHILIACS DEPENDS UPON THE APPROPRIATE USE OF BLOOD PRODUCTS.

If you have any questions regarding this matter, they should be directed to your treating physician, Chapter Medical Advisory Board Chairman, NHF Medical and Scientific Advisory Council Regional Representative or The NHF.

The lots of clotting factor withdrawn by Armour Pharmaceutical Company (May 3, 1985) were filled into different vial sizes bearing the following lot numbers:

Product	Lot #	Expiration Date
FACTORATE	X 54809 -	October 18, 1985
FACTORATE	X 58010 -	November 2, 1985
FACTORATE	X 63111 -	December 22, 1985
FACTORATE	X 63211 -	January 6, 1986
FACTORATE	Y105103 -	April 16, 1986
FACTORATE	Y 75904 -	May 10, 1986
FACTORATE	Y 82306 -	June 27, 1986
FACTORATE	Y 82406 -	July 9, 1986
FACTORATE Generation II	Y 68702 -	March 5, 1986
FACTORATE Generation II	Y105508 -	September 14, 1986

Chapters: Please distribute this information to all chapter members.

Physicians: Please distribute this information to all providers who treat patients with hemophilia in your area.

July 25, 1985

HEMOPHILIA INFORMATION EXCHANGE

AIDS UPDATE

HEMOPHILIA AND ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS): INTIMACY AND SEXUAL BEHAVIOR

by: Stephen B. Levine, M.D.
Case Western Reserve University
Cleveland, Ohio

The appearance of AIDS in the hemophilia population has caused considerable emotional distress. A major focus of the AIDS concern has been the sexual activity of men and adolescents with hemophilia. The following questions and answers address the concerns of patients, parents, and sexual partners. Because of the rapid development of medical knowledge in this area the current, most reasonable recommendations to prevent the transmission of the AIDS virus are considered tentative. The National Hemophilia Foundation (NHF) is concerned with preventing the transmission and development of AIDS while at the same time maintaining a psychologically comfortable intimacy between men with hemophilia and their loved ones. Some of these issues may raise further questions and concerns. It is strongly encouraged that further dialogue about these matters take place with your physician and other health care providers.

SECTIONS

A. Sexual Intimacy and AIDS: Who is at Risk?
B. Sexual Intimacy and Risk of AIDS: Advice for Prevention.
C. AIDS and Pregnancy
D. Sexual Intimacy and the Risk of AIDS: Additional Advice for Teenagers and Their Parents.
E. Sexual Intimacy and the Risk of AIDS: Other Considerations.

* * * * *

A. SEXUAL INTIMACY AND AIDS: WHO IS AT RISK?

1. Are all persons with hemophilia and von Willebrand's Disease at risk?

During the past year it has become clear that heterosexual transmission of HTLV-III virus is possible. Until we know more about the possibility of AIDS occurring in sexual partners of persons with hemophilia, the recommendations included in this document are intended for all persons with hemophilia and von Willebrand's Disease regardless of their antibody status or antigen (virus) status.

2. Exactly how is the HTLV-III virus transmitted during sexual behavior?

The HTLV-III virus is found in certain body fluids including the male ejaculate or semen. It is possible that the virus may be absorbed through the sexual partner's mucous membranes, the tissues which line the vagina, the anus or the rectum. This may occur directly or through small injuries of the mucous membranes, or through raw or bleeding areas such as may develop during rectal intercourse.

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3. If I don't have evidence of AIDS, do I still have to be concerned about transmitting the AIDS risk to my sexual partner?

Yes. Even though the chance of disease transmission in men with hemophilia to their sexual partners is rare, approximately 90% of the persons with hemophilia have HTLV-III antibodies. It has been suggested by some treaters that repeated exposure to antibody positive semen increases the risk of female partners developing HTLV-III antibodies. NHF recommends the use of condoms because they provide the most effective barrier for semen.

4. If I don't have evidence of antibody to the HTLV-III virus, do I still have to worry about transmitting the AIDS risk to my sexual partner?

It is uncertain. In only rare instances have men with hemophilia had the virus without the antibody to it being present, but a recent exposure to the virus through a blood product could have occurred without the antibody having yet developed, due to the long incubation period of the virus. For this reason, the use of condoms is recommended until more information is available.

5. If I am the sexual partner of a person with hemophilia who has a positive HTLV-III antibody test, what should I do?

Until more information is available, NHF is recommending the use of condoms. Many persons with hemophilia have been exposed to this virus without developing any evidence of AIDS. Having antibodies simply indicates the individual has had an immune response. Recent research, however, has shown that in some instances the virus has been transmitted to sexual partners of otherwise healthy persons with hemophilia, and only in extremely rare instances, has the disease been transmitted. But it is important to remember that preventive measures can be taken (see section B, below).

6. I am a sexually active man with hemophilia who is worried about contracting AIDS through sexual behavior. What do I need to know?

Heterosexually active men do not generally have to be concerned about contracting AIDS through sexual behavior. Men with hemophilia, however, who have had sexual contact with women who are antibody positive to the HTLV-III virus may be at an increased risk of contracting AIDS. Women who may be antibody positive to the HTLV-III virus include women who have had sexual contact with IV drug users, bisexual men or antibody positive men. A high percentage of prostitutes have also been found to be antibody positive.

For the vast majority of men with hemophilia, the major concern is that they might transmit the virus through sexual behavior to their sexual partner. Men with hemophilia typically acquire the virus through blood products, not sexual behavior.

B. SEXUAL INTIMACY AND THE RISK OF AIDS: ADVICE FOR PREVENTION.

7. What can be done to minimize the transmission of HTLV-III virus to a partner?

It seems likely that condoms will prevent the transmission of the virus to the mucous membranes of the partner's vagina, anus or rectum. It also seems wise to avoid rectal intercourse and ejaculation into the partner's mouth even though oral spread of virus seems a remote possibility. It is vital to remember that other things can be done to enhance sexual pleasure. The hand is often overlooked as a means of generating your own and your partner's orgasm. Men and women are capable of giving and receiving sexual pleasure with combinations of caresses, massages, lotions, body rubbing and vibrators. Sex manuals from all parts of the world depict the skillful innovative use of the hands in producing male and female orgasms.

Orgasm in the vagina is the most efficient means of achieving the male's orgasm, but not the only one. Hand stimulation, not intercourse, is the way most women achieve orgasm.

8. **Rather than using a condom, why not just have intercourse until I am ready to achieve orgasm and withdraw the penis from the vagina?**

Commonly there is a little seepage of semen or sperm prior to the actual orgasm. This has led to pregnancies even when couples disciplined themselves to withdraw prior to orgasm. HTLV-III virus could be in the few drops of seepage. In addition, knowing that the man must withdraw keeps him and his partner preoccupied with withdrawing rather than with getting lost in the sensations of sexual arousal. This tends to ruin the experience for both of them and makes male and female orgasm more difficult to achieve. The result may be often a gradual cessation of sexual intercourse.

9. **If I have not used condoms with my spouse of ten years why should I start now if I am using heat treated product?**

A high percentage (90%) of persons with hemophilia have developed and continue to have HTLV-III antibodies as a result of blood product usage previous to the use of heat treated products. The use of condoms is recommended to prevent the repeated exposure of the sexual partner to antibody positive semen. This is recognized as an extremely difficult and very personal area. Talking through your concerns with each other is the healthiest approach. Consult your treatment center staff if you feel the need of professional support.

10. **Is AIDS passed by kissing?**

While it cannot be absolutely guaranteed that it is not, the chances of transmission by kissing is remote. If AIDS were transmitted by saliva, it would be found that many family members of persons with HTLV-III infection would also develop HTLV-III infections. This has not occurred. A total of several hundred family members of persons with hemophilia have now been surveyed for HTLV-III infection at various centers; only a few sexually active partners of hemophiliacs were positive for antibody. The spread of AIDS is thus believed to occur very infrequently, and to happen by intimate sexual activity, rather than by kissing, touching, coughing or sneezing, etc.

11. **How am I and my partner to cope with the AIDS risk?**

AIDS is not an invariable consequence of multiple transfusions. Even though a person is exposed to the virus the chances of him or her developing AIDS are low. Some people exposed to the virus: will develop AIDS (less than 1%); some may develop symptoms of mild immune deficiency which does not progress to AIDS; others may carry the virus without any symptoms of illness; some may develop antibodies to the virus; the rest will not carry the virus. It is the uncertainty of outcome that creates emotional discomfort.

The answer to "how am I to cope?" is, "in the same way you have successfully dealt with other troublesome life circumstances that you have had to master.". NHF and the medical community are hard at work on the problem; the rate of new useful knowledge generated is impressively high. After a brief period of alarm and taking prudent precautions, one simply has to lead one's life - dating, forming new attachments, experiencing safe sexual behavior with one's partner when the relationship is ready. If married, after discussing fears and risks and understanding the need for temporary condom usage, behave sexually within the limits.

Sexually, the current uncertainties about AIDS have at least one "silver lining", that is, the opportunity to increase one's sexual behavioral repertoire, to go beyond the standard intercourse and discover the many means of giving sexual pleasure without depending solely upon intercourse.

12. Do "normal" people really make love without having intercourse?

Yes. Here are some reasons: variety; menstruation; vaginal infection; recent vaginal delivery; spontaneous discovery during foreplay leading to orgasm; intimacy before marriage or prior to having effective contraception. There are a number of alternatives to having intercourse. However, there seems to be no reason to stop having intercourse at this point; just use a condom.

13. Specifically, what can I do to bring my partner to orgasm besides manual clitoral stimulation?

The woman or the man can use the penis, with a condom, to stimulate the clitoris. The opening to the vagina and the vaginal walls are very sensitive to a slight lateral distention. Depending on the exact location of the vaginal stimulation a slightly different but intensely voluptuous sensation leading to female orgasm can result.

14. What about oral stimulation of the penis?

There seems to be no risk in the behavior as long as the pre-ejaculatory seepage of the semen and sperm do not contact the inside of the mouth during oral stimulation. The penis does not need to be taken fully into the mouth. The shaft of the penis or the testicles can be caressed with the lips or tongue.

15. Can AIDS be transmitted through oral stimulation of the female genitals in order to arouse the partner or bring her to orgasm?

As with kissing (see Question #10), it cannot be absolutely guaranteed that it is not, but the chances are remote, as the transmission of AIDS through saliva appears to be quite unlikely.

C. AIDS AND PREGNANCY

16. My wife and I are hoping to conceive a child in the next few months. Since I have hemophilia, is the pregnancy or the child at risk?

A baby recently born to a couple with a hemophilic father, who later developed AIDS, was diagnosed with AIDS shortly after birth. Although this is the only such case, it suggests the heterosexual transmission of the HTLV-III virus to the mother, who then transmitted the virus to her newborn child. As a new precaution, we are urging that serious consideration be given to deferring pregnancy until better data is available. The potential risk of intra-uterine passage of HTLV-III from a mother to the fetus is real, and infants so infected appear to run a relatively high risk of AIDS. Discuss this matter with your treatment center staff. We recognize this to be an extremely anguishing personal dilemma, which will again raise the level of concern for persons with hemophilia and their sexual partners. We hope to have more medical knowledge soon on the risk to the child. In the meantime, discussing the risk of pregnancy with your partner and treatment center staff is recommended.

D. SEXUAL INTIMACY AND THE RISK OF AIDS: ADDITIONAL ADVICE FOR TEENAGERS AND THEIR PARENTS.

17. What should a parent of a teenager with hemophilia do about the AIDS risk?

You may be concerned about the impact of AIDS on the development of your teenage son's social interactions and relationships. Social interactions that often lead to intimate physical contact up to (and sometimes including) intercourse between teenagers are an important step in the emotional development of young people. On the other hand, there are many medical uncertainties about the transmission of the AIDS virus. The conflict between the need to encourage teenage social interactions and the medical anxiety of genital viral transmission causes serious dilemmas. At this point (July 1985) it is reasonable to assure teenagers and their parents that the hand-holding, hugging, kissing, and petting that usually appears as teenagers become more psychologically intimate with one another, should not be discouraged.

It is a concern that as teenagers get older and feel ready for sexual intercourse they pay careful attention to three things: 1) contraception, 2) the prevention of transmission of the AIDS virus through semen and sperm , and 3) sharing information about the AIDS risk with the prospective sexual partner. The recommended solution for the first two of these problems among teenagers is the use of a condom, prophylactic or "rubber." The teenager who already is having intercourse, or those who are contemplating it, are strongly encouraged to obtain prophylactics and use them.

Commonly, parents and their teenagers find they are unable and uncomfortable with discussing sexual intimacy. Most teenagers have a natural need to separate their sexual experiences from the perspective of their parents. But hemophilia and AIDS require some exception to this general pattern. If the parent or the teenager feels uncomfortable, parents may want to indicate their concern about this and urge the health care provider and the teenager to discuss this in a medical setting. This topic should not be swept under the rug. Even if AIDS were not the issue, it is important for parents to articulate that if a teenager is mature enough to have sexual intercourse, he has to be mature enough to do so responsibly.

In essence recommendations concerning AIDS for teenagers with hemophilia, are quite similar to recommendations that have existed before AIDS became a problem.

18. What can the teenager with hemophilia do about being teased about becoming homosexual?

Because of the widespread publicity about AIDS in the media, the public associates AIDS with homosexuality. A number of teenage boys with hemophilia have been teased by their friends about getting transfusions. For example, one young man was teased: "I don't know if I would get a transfusion. You might go from hemo- to homo-!" Obviously such a remark about the relationship between hemophilia and homosexuality is based upon ignorance and misunderstanding - hemophilia and homosexuality are quite separate. The vast majority of hemophilic men are not, nor will ever become homosexual or interested in a homosexual experience. There is no way a transfusion can have anything to do with the development of homosexuality. The issue becomes how to handle the misunderstanding and ignorance of one's friends and acquaintances. In general, hemophilic teenagers are probably quite used to jokes about hemophilia that disguise other people's lack of understanding and knowledge. These things are best dealt with simply and directly. "The joke may be funny, but it isn't true." The person who made the joke must simply be educated in a direct, simple fashion. "If that were true I'd have a lot to worry about, but I've had hundreds of transfusions and not once have I become gay." You may want to discuss some of your thoughts further with your parents, friends, or a health care provider at your hemophilia treatment center.

E. SEXUAL INTIMACY AND THE RISK OF AIDS: OTHER CONSIDERATIONS.

9. How can I feel comfortable and open about starting a new relationship at this time?

Some single men with hemophilia are hesitant to become involved intimately with another person. There are many reasons for this pattern. Fear of rejection, unwillingness to burden another person with the illness that goes along with the loving relationship, and fear of sexual inadequacy are common reasons for hesitation. The concern about transmitting the AIDS virus through sexual behavior can further discourage some men from starting psychologically intimate relationships. This is quite unfortunate; a great deal of life's richness comes from being able to share intimacy with another person.

The burden of the AIDS risk may be much greater in the man's mind than in the mind of the informed partner. Many women when fully informed of the consequences and the meaning of hemophilia, still find that the human relationship transcends the fact that the particular man has an illness. The AIDS risk then is an added dilemma for both the already hesitant man and the interested woman. Close relationships which might otherwise have formed may remain undeveloped.

20 How are we to understand the withdrawal from sexual behavior when a person discovers he is antibody positive for the AIDS virus?

Stopping sexual behavior when one discovers the risk of being an AIDS's carrier is a perfectly understandable reaction.

The antibody positive individual feels, for a while at least, that he has become infectious and may withdraw from intimate relationships. The greater worry is that "Oh no, I could be giving this thing to my partner. I don't want to do that! It is better not to have sex at all or to simply return to masturbation!" As in other stresses in life, the way a person feels about a problem one day is often quite different than a week, two weeks, and a month later. It is important to respect one's emotions - one's natural reactions - to understand the array of feelings and thoughts that come with any particular new life circumstance. There is a tension between the sense that "I am contagious," and "I need another person."

This tension fluctuates over time; a person may logically feel at one moment the best thing to do is to stay away, and at another, the best thing to do is to have sex. At one time, the fear will win out and yet, a day or two later, the need will win out. This inconsistency, this tendency to resolve the dilemma in different ways depending on mood, or the partner's needs, is the usual way humans cope with dilemmas. People are not entirely consistent. Our feelings, dilemmas, and conflicts have a different power from day to day. It is important to feel comfortable sharing these concerns with your partner, a close friend or health care professional.

21. Why not just give up all partner sexual contact and content oneself with masturbation?

Masturbation certainly is safe but withdrawal from partner sexual behavior is not psychologically risk free. Sexual contacts, for those who emotionally want it, is usually a rewarding experience that helps to form and maintain emotional closeness to others.

Sexual intimacy tends to enhance self-esteem and the sense of masculinity and your partner's femininity. It is widely regarded as generating emotional health. These important psychological uses of sex may be a lot for you and your partner to give up. Very likely a compromise (using a condom) is a more prudent temporary approach until more is learned about the virus.

22. What about homosexually active men with hemophilia?

The same principles apply, that is, steps should be taken to avoid the discharge of body fluids, rectal intercourse and fellatio with ejaculation in the mouth should be avoided, or if practiced, a condom should be used. Manual stimulation outside body cavities is medically safest.

SUMMARY: The AIDS risk has caused distress concerning sexual activity for many hemophilic men, teenagers, and their partners. The danger is that this distress will cripple the sexual development and sexual behavior of many young and adult men with hemophilia, or cause undue alarm for their sexual partners. While it is not denied that there are reasons for concern, it is important to realize that people with hemophilia are used to dealing with many medical and social problems that others do not have to confront, and have a long tradition of overcoming seemingly overwhelming obstacles. In fact, this hopefully temporary dilemma may be used to broaden a couple's sexual repertoire.

The National Hemophilia Foundation will continue to provide new information and recommendations as they are developed.

ACKNOWLEDGMENTS

"Intimacy and Sexual Behavior" was produced under the aegis of the NHF AIDS Task Force and Mental Health Committee. The NHF AIDS Task Force wishes to express its appreciation to Stephen B. Levine, M.D., for his leadership in authoring this document. The contributions of the Centers for Disease Control and NHF's Mental Health Committee were significant in assisting Dr. Stephen B. Levine in his efforts.

We wish to thank Armour Pharmaceutical Company. Their support of NHF's Mental Health Committee helped make the preparation of this document possible.

THE HEMOPHILIA INFORMATION EXCHANGE, under the aegis of The National Hemophilic Foundation, is made possible with funding from the Division of Maternal and Child Health, of the United States Department of Heatlh and Human Services.

HEMOPHILIA INFORMATION EXCHANGE

AIDS UPDATE

THE NATIONAL HEMOPHILIA FOUNDATION MEDICAL AND SCIENTIFIC ADVISORY COUNCIL

RECOMMENDATIONS CONCERNING AIDS AND THE TREATMENT OF HEMOPHILIA

(Revised -- November 1985)

I. Recommendations for physicians treating patients with hemophilia:

A. In view of the accumulating evidence for the heat sensitivity of HTLV-III, and the apparent lack of untoward effects attributable to the heat treatment, we recommend that physicians who prescribe clotting factor concentrates should prescribe only heat treated or otherwise viral-attenuated coagulation factor concentrates for the treatment of patients with severe hemophilia who do not have inhibitors, with the understanding that protection against AIDS is yet to be absolutely proven.

B. Heat treated, or otherwise viral-attenuated factor VIII and factor IX may be the preferred products for the treatment of patients in groups for which it was previously recommended that cryoprecipitate or plasma be used:

- newborn infants and children under 4 years of age with severe hemophilia;
- newly identified patients with severe hemophilia never treated with factor VIII or factor IX concentrates.

It is emphasized that hepatitis B vaccination is essential when these patients are treated in this way, and it is recommended that this be administered shortly after birth. Moreover, as the transmission of non-A, non-B hepatitis may be greater with these products, even if heat treated, it may be preferable in some cases to treat patients in these groups with cryoprecipitate (hemophilia A) or fresh frozen plasma (hemophilia B). A decision as to the risks and benefits of these alternatives will vary depending on the circumstances of the particular patient and the latest data on various blood products, and the treating physician's best judgement will be important in each case.

C. Desmopressin (DDAVP) should be used whenever possible in patients with mild or moderate hemophilia A. When desmopressin does not provide adequate treatment, these patients should usually be treated with cryoprecipitate. Similarly, for patients with mild or moderate factor IX deficiency, plasma is usually the preferred product. It is recognized, however, that there are some circumstances in which viral attenuated (heat treated) factor VIII or factor IX may be the more appropriate therapy.

D. All elective surgical procedures should be evaluated with respect to the advantages or disadvantages of a delay although recent developments in donor screening and in virus inactivation suggest that such surgery can be undertaken when indicated.

E. We reaffirm our position that patients continue treating bleeding episodes with clotting factor as prescribed by their physicians, as the risks of withholding treatment far outweigh the risks of treatment. Therefore, it is important that patient education and psychosocial support be provided.

(over)

The HEMOPHILIA INFORMATION EXCHANGE under the aegis of The National Hemophilia Foundation is made possible with funding from the Division of Maternal and Child Health, United States Department of Health and Human Services.

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F. There are other complex issues that must be considered in regard to the impact of possible AIDS transmission on the lifestyles of hemophiliacs. For detailed consideration of these issues, the physician is referred to the following NHF publications: "AIDS & Hemophilia: Your Questions Answered"; - "Hemophilia and AIDS: Intimacy and Sexual Behavior"; and "Recommendations For Providing Education to Students with AIDS".

II. Recommendations to factor VIII concentrate manufacturers:

A. Every effort should be made to exclude donors who might transmit AIDS.

1. We recommend the HTLV-III testing of all blood and plasma donors. At the same time, we urge that actions be taken by blood and plasma collection facilities and other agencies so that HTLV-III testing is available to members of high risk groups apart from that carried out for blood and plasma donors.

2. Blood and plasma donation should not be obtained from prospective donors who are members of groups who are at higher risk of contracting AIDS. Such groups include: male homosexuals; intravenous drug users; those who have resided in areas of the world where AIDS is endemic; and sexual partners of members of those groups who are at higher risk, including sexual partners of persons with hemophilia. This effort should make use of educational materials and questionnaires in a discreet and sensitive manner.

3. Prospective blood donors should be excluded if they have symptoms associated with AIDS. This should be done by direct questioning and physical examinations as recommended by the Food and Drug Administration, Office of Biologics (December 14, 1984).

4. Manufacturers should continue to avoid using plasma obtained from donor centers that draw from population groups in which there is a relatively high incidence of hepatitis and AIDS. This would include prison populations.

B. Concentrate manufacturers should not purchase recovered plasma for coagulation factor production from blood centers that do not meet criteria listed in II.A. above.

C. Manufacturers should continue efforts towards the production of coagulation factor concentrates by recombinant DNA technology. When such materials are ready for clinical trials and for introduction into clinical use, the necessary review processes should be carried out as expeditiously as possible.

III. Recommendations to regional and community blood centers:

The production of cryoprecipitate should also adhere to criteria detailed in II. A above.

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HEMOPHILIA
INFORMATION EXCHANGE

AIDS UPDATE

December 4, 1985

Medical Bulletin #32
Chapter Advisory #37

REVISED
MEDICAL AND SCIENTIFIC ADVISORY COUNCIL
RECOMMENDATIONS CONCERNING AIDS AND THE TREATMENT OF HEMOPHILIA

Attached please find a copy of the revised "Recommendations Concerning AIDS and the Treatment of Hemophilia". These revisions are based on actions taken by The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) at a meeting held on November 1, 1985 and approved by NHF's Executive Committee on November 21, 1985.

changes essentially represent an update of NHF's policy with respect to the significant improvement in the safety of blood products for people with hemophilia and related clotting disorders, and a response to the increasing data available in this regard.

address other concerns of patients and families The National Hemophilia Foundation has prepared the following publications that are available through your chapter or treatment center: "AIDS & Hemophilia: Your Questions Answered" and "Hemophilia and AIDS: Intimacy and Sexual Behavior".

The MASAC reaffirms its position that **PATIENTS CONTINUE TREATING BLEEDING EPISODES WITH CLOTTING FACTOR AS PRESCRIBED BY THEIR PHYSICIANS AS THE RISKS OF WITHHOLDING TREATMENT FAR OUTWEIGH THE RISKS OF TREATMENT.**

Any questions you may have concerning these revised recommendations should be referred to your treating physician or member of the treatment center team.

Chapters: Please distribute this information to all chapter members.

Physicians: Please distribute this information to all providers who treat patients with hemophilia in your area.

The HEMOPHILIA INFORMATION EXCHANGE, under the aegis of The National Hemophilia Foundation, is made possible with funding from the Division of Maternal and Child Health, United States Department of Health and Human Services.

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APPENDIX 58

Immuno Ltd

Arctic House, Rye Lane, Dunton Green,
Nr Sevenoaks, Kent TN14 5HB

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Telex: 95413

Professor A.L. Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XN.

13th October 1982
NB/BMC

Dear Arthur,

As I am sure you are aware, 3 cases of Pneumocystis carinii pneumonia (PCP) were reported in haemophiliacs receiving Factor VIII concentrate(a) This caused concern about the transmission of the disease by Factor VIII or possibly other blood products.

As far as Factor VIII is concerned we very much doubt the liklihood of this, as the organism would not pass through the bacterial filtration process. We do, however, wonder if there is some unknown entity in the product which causes an immuno deficiency which perhaps specifically enables the organism to invade a patient.

I do not know if it will be possible to discuss this problem at your next Haemophilia Directors meeting, but if you do we would welcome any information you acquire and we would be especially interested in any haemophiliac who has repeat occurrences of chest infection.

I look forward to hearing from you

(a) In USA

Yours sincerely,

GRO-C

Norman Berry

Mr. Norman Berry,
Managing Director,
Immuno Ltd.,
Arctic House,
Rye Lane,
Dunton Green,
Nr. Sevenoaks,
Kent.

15th October, 1982

Dear Norman,

Thank you very much for your letter about Pneumocystis and factor VIII concentrates. As a matter of fact we discussedtthis at the Manchester meeting of the Haemophi Haemophilia Directors and also at the Reference Centre Directors meeting. At the moment our advice from the virologists is not to panic but we will certainly a.l keep an eye out for this immuno deficiency syndrome. I am sure that if a case is discovered in the U.K. then all interested parties would be notified.

With all best wishes,

Yours sincerely,

A.L. Bloom

Immuno Ltd

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Professor A.L. Bloom
Department of Haematology.
University Hospital of Wales,
Heath Park,
Cardiff CF4 1XW.

18th March 1983

Dear Professor Bloom,

I have much pleasure in enclosing the summary of discussions of the meeting held at the Excelsior Hotel, Heathrow Airport, on Monday 24th January 1983.

Yours sincerely,
for IMMUNO LTD.

GRO-C

Managing Director

Enc.

Summary of discussions of the meeting held at Excelsior Hotel, Heathrow Airport, on 24th January 1983

Professor A.L. Bloom in the Chair.

Mr. Berry welcomed all who were present and outlined the arrangements made.

Dr. Eibl then explained that two methods were being studied whereby the risk of transmitting non A, non B hepatitis by Factor VIII or IX concentrates could be removed or at least very greatly reduced. Unfortunately, as patenting procedures were not complete, he could not reveal full details. This would be possible within three months by which time treated concentrates would be available.

Method I

This is carried out at 4°C and is suitable for use with Factor VIII concentrate. The substance used is frequently employed in the food industry. The process is applied to the final product so other products from the fractionation scheme are not affected.

There is a 25% loss in yield.

No significant change has been observed in Ristocetin co-factor, Cag or Rag.

There is no loss of protein as shown by immunoelectrophoresis and chromatography, and no change in proteins.

It can be shown by chemical tests that less than 1% of the additive remains.

It was not yet known if all other viruses would be destroyed but certain animal disease viruses had been inactivated.

Factor VIII concentrate known to have transmitted non A, non B hepatitis was treated by Method I and 250 units in 10 ml (>100 infective particles) given to each of four chimpanzees. No increase in transaminase level occurred during six months observation. The animals were then challenged with untreated material and non A, non B hepatitis occurred in each as shown by elevated transaminase level and biopsy samples.

Method II

This method had been shown to be more suitable for treating partial prothrombin complex, whereas Method I caused too great a loss of yield. The process is carried out at 37°C using substances which are present in normal body metabolism.

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Method II has been shown to be more powerful than Method I for inactivating animal disease viruses, but experiments with non A, non B hepatitis in chimpanzees have not yet been completed.

Dr. Eibl then said that guidance was required from the meeting as to the correct procedure as far as future use of these products were concerned and the following points were made:

1. Young children could not be used for trials as neither they nor their parents could give consent.

2. Adult haemophiliacs with an established immunity to non A, non B hepatitis would not benefit from a trial, but it was thought that they would be sufficiently public spirited to agree to these materials being used on them to shown haemostatic effect and absence of toxicity due to remnants of additives.

3. All batches of NHS and US commercial concentrates had been shown to be capable of transmitting non A, non B hepatitis. It is believed that a one in fifty chance of transmission from cryoprecipitate occurs.

4. Because of 3, many thought it would be difficult to justify carrying out a prospective controlled trial. However, it was generally agreed that sufficient susceptible adult patients needing high level treatment, e.g. for surgery, could be identified to warrant uncontrolled prospective trials of this and other virus inactivated products. It was agreed that such trials should be instituted.

5. Aggregates are not formed by processing.

6. It was not practical to test every batch in animals. In fact, it is hoped that the requirement to test batches of HB_s vaccine in chimpanzees will soon be discontinued. However, it is intended that three consecutive batches will be tested in animals.

7. Maximum effort so far had been to show clearance of non A, non B hepatitis which is regarded as the main problem. Later on tests will be made on the effect of both methods on hepatitis B and possibly other viruses.

   It will be necessary to show separately that B and non A, non B can be removed and then in practice remove them together.

8. Testing for effect on poliomyelitis and canine hepatitis could be done on tissue cultures without resorting to chimpanzees.

../3

9. Residual additive will be minimal but the amount will be declared.

10. Test concentrate will be made from infected chimpanzees treated and re-injected to indicate absence of antigen formation.

11. Clinical trials are planned in other areas including USA, Japan and Central Europe.

12. Within three months, the patent will be released and information on the additives will be released. By this time five batches of concentrate will be available.

13. The possibility of reducing the risk of AIDS was not known at this stage. In any case, it is not known if AIDS is caused by a virus or an attacker inimical to T cells.

Professor Bloom then summarised as follows:

(a) Clarification should be sought from DHSS as to whether the treatment of the final product could be covered by a Product Licence variation or if a Clinical Trial Exemption Certificate was necessary. It was agreed that the best procedure would be to seek a Product Licence, if necessary via Clinical Trials in preference to use on a named patient basis.

(b) Haemostatic activity in terms of in vivo recovery and half life and absence of toxicity should be ascertained in adult haemophiliacs.

(c) The material should then be assessed in the treatment of adult haemophiliacs susceptible to non A, non B hepatitis by a properly conducted trial in susceptible patients in appropriate need of treatment. It was agreed that it should be possible to identify sufficient U.K. patients for such trials.

(d) The material could then be used on newly diagnosed children.

(e) Trials could be arranged by the Committee of the Haemophilia Directors, and it would be best to use five separate batches with two patients receiving each batch.

Professor Bloom then closed the meeting with thanks to the participants and Immuno, then Mr. Berry thanked the Chairman.

APPENDIX 60

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Professor A.L. Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XN.

20th June 1983
NB/BMC

Dear Arthur,

I have some up to date information concerning virus inactivated concentrates which may be helpful to you at the forthcoming Stockholm meetings.

Since our meeting at Heathrow Airport we have made steady progress with the methods briefly outlined there, but as you can well imagine the testing procedures are bound to be prolonged, especially as additives are used in both methods. We are, therefore, continuing to pursue these ideas, but have designated them generation two inactivated products.

We are also working on a scheme known as first generation inactivation where lyophilised material is heat treated. Here progress is more rapid as the checking procedures are greatly reduced and we hope to have this sort of material available in the very near future.

Looking forward to seeing you in Stockholm.

Yours sincerely,

GRO-C

Norman Berry

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Prof A L Bloom
Dept of Haematology
University Hospital of Wales
Heath Park
Cardiff CF4 1XW

16 March 1983

Dear Prof Bloom

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Following the recent upsurge in interest and media publicity regarding this problem I have obtained from our parent company in the USA (Alpha Therapeutic Corporation of Los Angeles) more details of the precautionary steps that have been introduced to minimise the risk of this disease being transmitted via our pool of donors to the haemophilia population. They are as follows:-

1 Effective December 27 1982 all donors are screened to exclude those potential donors who are from or who have been in Haiti; have ever used illicit drugs intravenously; and male donors who have had sexual contact with a man. The plasmapheresis centre manager must accompany each shipment of plasma with a declaration to the effect that the exclusions above have been carried out.

2 Each potential donor is now issued with a leaflet on arrival at the centre giving the basic background information on AIDS and its possible transmission through plasma donations. The importance of them not donating if they belong to one of the exclusion groups is emphasised.

I also attach a transcript of a press release issued by the Corporation in January 1983.

I hope this adequately demonstrates the company's rapid response to the concern expressed by the medical community and that we appear to be 'leading the way' as far as major plasma fractionaters are concerned to make our final products as safe as possible. If you have any other points you would like to raise on this issue please contact me asap.

Yours sincerely

GRO-C

I D Marshall

Enc.

ALPHA THERAPEUTIC ACTS TO PROTECT HAEMOPHILIACS FROM AIDS EPIDEMIC

LOS ANGELES, CALIFORNIA 7 January 1983 ..... in one of the first public health actions intended to protect hemophilia patients and other blood product users from AIDS - the deadly new epidemic that technically is called acquired immune deficiency syndrome - Alpha Therapeutic Corporation, a leading producer, has taken steps to exclude from its donor pool persons who may be at high risk of transmitting the disease to others.

Alpha Therapeutic Corporation of Los Angeles which is one of the world's principal suppliers of antihemophilic factor and other plasma products, has told its several hundred plasma suppliers that, as of 20 December 1982, they must "exclude donors" who may be part of three potentially high-risk groups: persons who have been in Haiti: drug abusers and male homosexuals. There is a "higher incidence of AIDS" in these groups than in the community at large, the company says.

The new Alpha policy was initiated in response to a request from the National Hemophilia Foundation (NHF), which recommended late last year that individuals belonging to these high-risk groups be excluded from donor pools. The Foundation issued its request after a half-dozen AIDS cases were discovered among hemophilia patients. None of these hemophiliac AIDS victims is homosexual.

The evidence suggests, although it does not absolutely prove, that a virus or other disease agent was transmitted to them in the Factor VIII concentrate, derived from pooled human plasma which they rely on for life - and for sustaining a relatively normal lifestyle.

Surveys now being conducted by NHF are producing other disquieting findings:

* AIDS has jumped from the seventh to the second most common cause of death in hemophiliacs within a year.
* The case rate appears to be rising.

cont/.....

The Alpha move to bar the putative AIDS agent from Factor VIII donor pools was hailed by NHF medical advisor Louis Aledort, MD, a haematologist at the Mt Sinai School of Medicine in New York City. He said that he anticipated that other plasma and blood products suppliers quickly will follow Alpha's lead.

The new Alpha policy was announced by their medical director, Clyde McAuley, MD, at the US Centres for Disease Control (CDC) on 4 January 1983, at the second meeting of an ad hoc Workgroup to Identify Opportunities for Prevention of AIDS.

"I have a responsibility to hemophiliacs to produce a product that is not at increased risk of AIDS" Dr McAuley said. "We are excluding male homosexuals, Haitians, and drug users because frankly we don't have anything else to offer at this time".

These restrictions are not unique. Blood banks rountinely exclude as donors recent travelers from Africa, who may be carrying malaria and persons who have suffered from hepatitis.

In the future, Dr McAuley and other plasma industry and government experts predict, other ways will be found to safeguard Factor VIII. At present, for example, Factor VIII concentrate - the most economical and convenient form of the clotting factor - is not heat-treated, because heat reduces its potency. In light of the apparent risk that it may carry an infectious agent for AIDS, however, drug companies are working with the US Food and Drug Administration (FDA) to develop and test effective heat-treated Factor VIII concentrate products.

Other safeguards were proposed at the CDC meeting, including tests - which now are being evaluated - which would detect donor blood and plasma that is at high risk of transmitting AIDS.

cont/.....

Hemophiliacs are not the only potential beneficiaries of these actions. In recent months, three cases of AIDS appear to have occurred in persons who are not hemophiliacs, as the result of receiving blood transfusions - and blood bankers are fearful that there soon may be many more.

Pending firm identification of the AIDS causative agent, and the introduction of definitive measures to stop its transmission - which could take years - the introduction of measures to exclude high risk donors thus may be an important line of defence for the community at large.

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O: Joe Kimoto - GREEN CROSS CORP., Osaka, Japan APPENDIX 62

M: David J. Gury - ALPHA THERAPEUTIC CORPORATION, Los Angeles, California, U.S.A.

c: Executive Committee
AIDS Task Force

E: AIDS REPORT - For Discussion with the Japanese Ministry of Health June 6, 1983.

HISTORY OF AIDS IN THE UNITED STATES

Not since Hepatitis in the 1960's was associated with blood and blood products has there been an issue as significant and complex within the blood products industry as AIDS. AIDS (Acquired Immune Deficiency Syndrome) has touched virtually every aspect of collection, processing and use of blood and blood products. The following is a brief chronology of AIDS in the United States:

1 : First cases of AIDS were reported to the Centers for Disease Control; establishmen of agnosis not yet determined.

1980 to 1981: Many cases of opportunistic infections reported to the Centers for Disease Control, largely Pneumocystis Carini Pneumonia and Kaposi's Sarcoma among pr ously healthy, largely male homosexual individuals.

July 1982: Several hemophiliacs diagnosed with opportunistic infections and immune deficiencies similar to those previously reported in male homosexuals. A review of AIDS and the potential transmission in blood and blood products was made by a joint meeting in Washington of Office of Biologics people and representatives of blood banking and blood and plasma industries. No action specifically taken at that point.

December 10, 1982: Meeting held with similar participants to July meeting to discuss case of infant in San Francisco who received a unit of platelets from a donor subsequently diagnosed with AIDS. Platelet unit received by infant along with 17 other blood products. Implications at this time strongly indicated possible transmission through blood and blood products. Further meeting of concerned parties set for January 4, 1983 at the request of Dr. Brandt, Assistant Secretary of Health. At this time, the National Hemophilia Foundation recommended screening out donors from the high risk groups by both plasmapheresis operations and blood banks as a means of controlling the spread of AIDS to hemophiliacs.

January 4, 1983: Meeting held at the Centers for Disease Control in Atlanta to review history of AIDS and make recommendations concerning the donor selection, blood and blood products collection, handling and processing and the precautions for health care workers caring for AIDS patients. No specific official recommendations were made by the groups, however, the CDC made recommendations concerning the selection of blood donors excluding donors from high risk groups (but not directly asking donors if they were in high risk groups) and the application of Hepatitis-like practices in the care and treatment of AIDS patients.

March 4, 1983: The Centers for Disease Control in their Weekly Morbidity and Mortality Report, made recommendations concerning the selection of blood donors and the use of blood products.

March 24, 1983: Office of Biologics issued recommended procedures for blood banks and plasma centers to be followed in screening potential blood and plasma donors.

May 12, 1983: Review by a panel of experts of blood transfusion-related cases of AIDS dicates few, in any, transfusion-associated cases.

May 24, 1983: Dr. Brandt, Assistant Secretary for the Department of Health, Education and Welfare, and Chief Public Health Officer in the United States announces that AIDS is an important health problem but limited to specific population segments: homosexual or bisexual males with multiple partners, I.V. drug abusers recent Haitian entrants and persons with hemophilia. He indicates that various agencies of HEW are and will be funding substantial research efforts in the area of AIDS, making AIDS the number one of research by public organizations. He also announced the licensing of a heat-treated AHF thought to reduce the risk of transmitting virus of which AIDS may be one.

CURRENT STATUS OF AIDS

Since the cause of AIDS is not currently known, AIDS is defined with a clinical diagnosis. The clinical diagnosis ultimately must include the presence of opportunistic infection in patients with no explanation for an immune defect. While many AIDS patients have T helper-suppressor ratios that are reversed, this is not true in all AIDS patients. There is yet, at present, only a clinical diagnosis for AIDS.

AIDS continues to be confined to several special population groups. These groups are as follows:

1. A limited sub-population of the homosexual community which is defined as the sexually active homosexual with multiple partners in multiple sexual practices. The exposure rate or infection rate is approximately 1 in 150 exposures.

2. I.V. drug abusers, principally in New York City, developed AIDS about the same time as homosexuals and continues to be confined principally to New York City.

3. Haitians have a rate of approximately 1 in 1000 exposures with the disease.

4. Hemophiliacs. Approximately 1 in 1000 or 12 known hemophiliacs in the United States have AIDS with some question whether it is truly the same disease as seen in other high risk groups.

5. Blood transfusion recipients. Approximately 11 adults have questionable transmission of AIDS through blood products. In no case has there been a clear cut adult transmission from one donor with AIDS to one recipient who gets AIDS. Tragically, no AIDS patient has regained lost immunity.

While the cause of AIDS in the United States is still unknown, a substantial amount of work in research is being undertaken to determine the possible etiology of the disease. There is a strong suggestion that a new infectious agent is the possible cause of the disease. The most important research is focused on finding the agent. Blood, blood cells, tissue, plasma, etc. have been taken from AIDS patients and developed in both conventional tissue culture and in cloned tissues but have yet to show an agent. Material from AIDS patients has been injected into a large number of primates and monkey groups with no clinical manifestations of the disease as yet. Work on different types of retro viruses, human T-cell Leukemia virus, and parvo viruses (especially

feline virus known previously to change its host group from cats to dogs in the late 1970's) are being looked at.

finding the agent is the key to the identity of high risk individuals and high risk products. Finding the agent, however, as is known from Hepatitis, will not necessarily resolve the problem.

At present, individuals with AIDS are not known to have reversed their status, that is, the immune deficiency has not changed. The present mortality rate is in excess of 40%, however, it approaches 100% of AIDS patients diagnosed two or more years ago. AIDS patients have an average of six opportunistic infections before death. Death generally comes from Pneumocystis Carini Pneumonia or from Cytomegalovirus. One of the earliest infections apparent in AIDS patients is Kaposi's Sarcoma which often is the first indicator of the existence of AIDS in previously healthy individuals.

Widespread media coverage of AIDS and the emotional issues involved with the various sub-populations included in the high risk groups have made AIDS a very public issue in the United States. This has led to widespread concern in the blood banking community by donors and recipients. Currently, blood donations are down 5% to 10% in the United States. Additional concern from outside the United States has been expressed by users of blood products originating in the United States. Several European countries have either closed imports of U.S. products or put restrictions on the points of origin within the United States for such products. The level of concern for this issue outside the United States appears to rise as the information becomes more generally available outside the U.S.

One of the most significant impacts of AIDS on Alpha currently is the reduction in use of AHF concentrate in the hemophilia population. This has led to a substantial reduction in Alpha's sales in the United States of AHF and increased competition among AHF producers for the market. We estimate the reduction at approximately 24% for 1983. In addition, the reduction in plasma procurement principally in procuring blood bank plasma as a result of the early postiion Alpha took concerning screening of donors at a time when blood banks were not required by Federal regulations to screen donors, cost a substantial amount of blood bank plasma to be removed from our procurement opportunity. Blood bank plasma is one of the lowest cost plasmas and the need to replace it with source plasma has required substantial procurement penalties in higher plasma costs in 1983.

WHAT HAS ALPHA DONE FOR AIDS

Up to December 10, 1982, Alpha's principal position with AIDS was to monitor information and be ready to take a position when information so indicated. After the December 10, 1982 review of the first transfusion suspected case, Alpha initiated an AIDS program as follows:

1. Plasma procurement for AHF preparation was discontinued from those areas indicated as being at high risk which included San Francisco, New York, Los Angeles and Miami.

2. Alpha initiated, effective December 21, 1982, in all Alpha Donor Centers, a program to educate donors on the high risk of AIDS and those groups that were particulary at high risk. In addition, each potential donor at each time of donating is asked specific questions whether they were of the high risk groups that is, male homosexual, I.V. drug abuser, Haitian or other individual with contact with one of the high risk groups.

3. For plasma obtained from blood banks, Alpha's specifications were changed requ that plasma collected after January 1, 1983, be from donors screened in the sa manner as those at Alpha's Plasma Centers. (At first this was applied to all plasma. Later in January, it was reduced to apply only to plasma to be used in the manufacturing of AHF since other products are subject to heat treatment

   The result of this requirement was a severe reduction in plasma procurement fr blood banks as blood banks, at this point in time, refused to follow Alpha's lead and would not follow the screening requirements until forced to by regulations from the Office of Biologics on March 24, 1983.

4. An Alpha Task Force was established to collect data, communicate information within Alpha and make recommendations and policy as related to AIDS. This group was established in late December as a result of the very rapid increase in information and the resulting potential for misinformation or lack of proper communication on this highly sensitive issue.

5. The priority of Heat-treated AHF, which if AIDS is similar to Hepatitis would offer some potential for reducing the risk of transmission, was moved to an escalated number one position within Alpha.

6. Educational programs to hemophiliacs, treaters and the general public was developed in the provision of questions and answers concerning AIDS and the treatment of hemophilia. Attendance at hemophilia meetings on a regional level with blood banks and in dealing with the media at a donor center and national level, provided Alpha with substantial public educational public education opportunities in this field. Dr. Drees and Dr. McAuley made public announcements concerning Alpha's leading role in establishing donor criteria related to AIDS.

THINGS ALPHA CONTINUES TO DO CONCERNING AIDS

1. Continue to monitor closely action relative to AIDS on the scientific level withi the blood banking community and among hemophilia users and treaters and internati We will continue to look out for the best corporate interest, to mold public policy where appropriate and to take advantage where possible of our positioning in the market place.

2. Push at maximum speed for the production of Heat-treated AHF.

3. Label AHF with a warning for AIDS to reduce potential liability of Alpha.

4. Investigate potential research projects with government funding that may be of advantage to Alpha.

Mr. K.W. Fitch,
Chairman and Managing Director,
Armour Pharmaceutical Company Ltd.,
St. Leonards House,
St. Leonard's Road,
Eastbourne,
Sussex BN21 3YG

23rd May, 1983

Dear Mr. Fitch,

Thank you very much for your letter of 19th May and for the reassurance about Armour factor VIII concentrates. At the same time some of the Haemophilia Centre Directors are concerned that fractionators in the U.S.A. and elsewhere who use American source plasma may have stocks of concentrate prepared from plasma collected before March 24th, the date of the FDA revised recommendations. We are worried that if such material would be difficult to sell in the U.S.A. it may be preferentialy exported and I would be most grateful if Armour could reassure me that such a policy would not be taken with regard to your own products.

With all best wishes,

Yours sincerely,

A.L. Bloom

Armour Pharmaceutical Company Limited
St. Leonards House, St. Leonards Road, Eastbourne, Sussex BN21 3YG
Telephone: Eastbourne (0323) 21422 Telex: 87141

May 19, 1983
Ref: KWF/mb

TO ALL HAEMOPHILIA CENTRE DIRECTORS

Dear Doctor,

Re: ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

The Armour Pharmaceutical Company is acutely aware of the current concern of the Medical world regarding Acquired Immune Deficiency Syndrome (AIDS) and its possible implication to Haemophilia care and treatment.

Despite the fact that there is little evidence to associate plasma component therapy with the transmission of AIDS, Armour, through its affiliate organisation, Plasma Alliance, has had programmes in operation for several months, which have been designed to help prevent the utilisation of plasma obtained from members of high risk groups associated with AIDS in the production of clotting factor concentrates.

General Background

The Centres for Disease Control (CDC), an agency of the U.S. Department of Health and Human Services, has been actively engaged in investigating the incidence and epidemiology of a relatively recently encountered health problem; namely, Acquired Immune Deficiency Syndrome (AIDS). This condition, occurring in increasing frequency since first reported in 1979, involves the depression of an individual's cellular immune system, thereby enabling opportunistic organisms and/or other agents to successfully attack the victim. As defined by that Agency, AIDS is a disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause of diminished resistance to that disease. Disease states encountered include Kaposi's sarcoma (KS), Pneumocystis carinii pneumonia (PCP), and a variety of other opportunistic infections.

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Not considered to be within the scope of the CDC definition for AIDS are patients receiving immunosuppressive therapy, patients with widely spread cancer of lymphoid or histiocytic tissue, patients under 28 days or over 60 years of age, and patients with congenital or acquired hypogammaglobulinaemia.

Data reported by CDC in May, 1983, indicate that since the initial cases were reported, approximately 1500 cases of AIDS have occurred. Of even more alarming nature is the increased rate of incidence of reporting; an accession rate of 100 patients per month appears to be current. Approximately 40% of the reported AIDS patients have died; the mortality rate is significantly higher among those patients who contracted AIDS earlier than more recent cases, indicating that mortality increases as a function of length of the disease state.

APPARENT TARGET POPULATIONS

Analysis of morbidity data by the CDC shows that several groups appear to have a higher incidence of AIDS than does the general population. Over 90% of cases reported to the CDC have occurred among homosexual or bisexual males with multiple sexual contacts, users of non-prescribed self-injected drugs, and immigrants from or visitors to Haiti. AIDS has also been reported to occur in children of drug abusers and other individuals having close contact, e.g., sexual intercourse, with AIDS victims.

The great majority of AIDS cases appears to be in the New York City, Miami, San Francisco and Los Angeles metropolitan areas, although the syndrome has been reported in at least 30 states throughout the United States as well as in several European locations.

Of additional concern to Ammour Pharmaceutical Company and to others in the health care field is the indication, from data generated by the CDC, that AIDS is being seen in recipients of blood, blood components, and blood derivatives. In a summary presentation made in May, 1983, the CDC stated that 14 haemophiliacs have apparently contracted AIDS, and that an as yet unidentified number of non-haemophilic recipients of blood and blood components also have developed the syndrome. The CDC is investigating the possible relationship between AIDS and the use of blood and blood derivatives, and is attempting to determine whether transmission of AIDS via transfusion is indeed occurring.

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EPIDEMIOLOGY AND LABORATORY TESTING APPROACHES

As pointed out earlier, the majority of those contracting AIDS are in three groups of the population - homosexual or bisexual males, drug abusers, and immigrants from or visitors to Haiti. These groups, according to the CDC, also have a very high incidence of Hepatitis B infection. This leads to the possibility that social relationships and interchanges between these groups result in the transmission of an unknown causative agent analagous to the manner in which Hepatitis B is transmitted.

The high incidence of Hepatitis B infection in each of these groups suggests that testing for laboratory markers of this virus might be of value in screening potential AIDS victims. Testing of AIDS patients for antibody to Hepatitis B core antigen (anti-HBc) shows that over 85% of them are positive for this marker. However, extrapolation of these findings to a general screening programme in order to identify potential AIDS victims or carriers may not be practical. Information developed by various organisations shows that approximately 15% of the population also tests positive for anti-HBc, indicating that this would not be a specific test for AIDS.

Since AIDS results in a disruption of the cellular immune system, it is not surprising that patients demonstrate unusual findings in some aspects or components of this system. Over 85% of AIDS patients demonstrate significantly reduced ratios (±1.0) of T-helper (T_H) to T-suppressor (T_S) cells, but this finding is of limited value in predicting the likelihood of someone without signs or symptoms of AIDS being a potential victim or carrier. Recent information developed at the University of New Mexico shows that a large number of acute infections resemble AIDS by decreasing the number of T_H cells, thereby causing an inversion of the T_H/T_S ratio. The CDC agrees that such alterations are not specific for AIDS.

Thus, until the causative agent responsible for transmission of AIDS is identified and isolated, it is highly unlikely that a suitable laboratory tool will be available for implementation of any general testing programmes. The absence of any specific and sensitive test to identify potential AIDS victims and carriers has resulted in activities and programmes to be described in subsequent portions of this summary statement.

PLASMA COLLECTION AND UTILISATION BY ARMOUR PHARMACEUTICAL COMPANY U.S.A.

Armour Pharmaceutical Company U.S.A., through its subsidiary, Plasma Alliance, operates 16 centres located in the Midwest and Southeast portions of the United States. None of these centres are located in the AIDS high incidence areas of the country (New York City, Miami, San Francisco, Los Angeles) mentioned earlier, nor is plasma used in the manufacture of clotting factor products obtained

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from facilities located in these areas. Furthermore, no plasma is obtained from collection facilities located outside of the United States. Nevertheless, the AIDS issue cannot be treated solely on the basis of geography, since incidence of the syndrome is scattered over a wide area.

Taking the first of several steps designed to avoid collecting plasma from members of groups shown to be at high risk for contracting AIDS, informational posters were displayed at our centres in December, 1982. These posters advised potential donors about AIDS and its possible impact on the treatment of haemophilia, and requested donors in any of these groups to defer themselves from plasma donation.

In February, 1983, a more aggressive programme was initiated, following discussions with organisations such as the U.S. Food and Drug Administration Office of Biologics, the National Haemophilia Foundation, the Centres For Disease Control, and other commercial manufacturers of clotting factor concentrates. This programme included direct communication with each donor in the form of written and oral information and questions, designed to defer from the donor population individuals at risk for contracting AIDS. Each donor is presented a fact sheet describing the high risk groups thus far identified with AIDS, the seriousness of the syndrome, and the possible link to the treatment of haemophilia. Furthermore, all donors are questioned by trained processors as to their being members of high risk groups and as to the presence of any signs (night sweats, diarrhoea, chills, etc.) that might be indicative of AIDS. Donors are required to affirm in writing that they are not members of any of the several high risk groups involved, without having to reveal any facet of their personal and private lives. Periodic physical examinations performed by plasma centre attending physicians also include evaluations for possible signs and symptoms of AIDS.

We will continue to move forward, in co-operation with other responsible segments of the health care team, both governmental and non-governmental, to implement additional plasma collection activities and programmes deemed to be effective and appropriate.

SUMMARY AND ADDITIONAL ACTIONS

The plasma collection actions described earlier in this statement are designed to prevent the use of plasma obtained from individuals in one or more of several high risk groups in the production of clotting factor concentrates. They are predicated on the possibility that AIDS may be transmitted through blood and certain blood derivatives, although it must be re-emphasised that no

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agent responsible for transmission has yet been identified. However, one must consider that an infectious organism may be involved, and that the appearance of AIDS is prevalent in groups with high incidence of Hepatitis.

Armour Pharmaceutical Company U.S.A. has provided information to the U.S. Food and Drug Administration Office of Biologics, regarding a revised manufacturing process that includes heat treatment. The process is designed to reduce the Hepatitis risk associated with the use of clotting factor concentrates, and approval of the process change is anticipated within the near future. The effectiveness of such procedures in preventing the possible transmission of AIDS cannot be directly determined at this time, since appropriate challenge studies cannot yet be designed. However, it should be pointed out that the occurrence of AIDS has not been noted with administration of products such as Normal Serum Albumin, which also undergo heat treatment during their manufacture.

The Revlon Health Care Group, of which Armour Pharmaceutical Company is a member, is firmly committed to providing safe and effective products to the medical community, and will continue to devote considerable time and attention to the problems associated with AIDS and haemophilia treatment, and to efforts undertaken to resolve them. We believe that, given the level of today's knowledge regarding AIDS and its transmission, the programmes in place at our plasma collection centres provide an effective way to reduce the potential for use of plasma obtained from high risk groups. Activities involving increasing the safety of clotting factor concentrates relative to their Hepatitis risk may also prove to be of benefit in the AIDS situation as well.

Yours faithfully,

GRO-C

K.W. Fitch,
Chairman and Managing Director

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June 8, 1983
Ref: KWF/mb

Professor A.L. Bloom,
Department of Haematology,
University Hospital of Wales,
Heath Park, Cardiff
WALES, CF4 4XN.

Dear Professor Bloom:

Thank you for your kind letter dated May 23, 1983, in response to my statement as set out in a letter dated May 19. I am aware that my Secretary has briefly acknowledged your correspondence in my absence, but having just returned from the United States, I can now respond to your queries.

First of all, I have to tell you that the Armour Pharmaceutical Company U.S.A. in anticipating the FDA ruling established the FDA protocols in compliance one month before the actual FDA recommendations were issued.

For your further advice and assurance, you should know that we supplied Plasma prior to February 24, on a business-as-usual basis, but that most of this stock was supplied to customers in the U.S.A., since 70% of our Plasma business is in the U.S.A. At no time have we preferentially exported Plasma stocks ex the U.S.A. pre-February 24 or March 24.

I do hope that these comments answer your queries and provides the assurance which you so rightly seek. If I can be of any further assistance, please do not hesitate to let me know.

With best wishes.

Yours sincerely,

GRO-C

K.W. Fitch,
Chairman and Managing Director

APPENDIX 64

TRAVENOL

Travenol Laboratories Ltd.,
Caxton Way, Thetford,
Norfolk, IP24 3SE, England
Telephone: Thetford (0842) 4581
Telegrams: Travenol - Thetford
Telex: 81319

MDRABAR/JM

May 9, 1983

Professor A.L. Bloom,
Director,
Cardiff Haemophilia Centre,
University Hospital of Wales,
Heath Park,
Cardiff CF4 4XN.

Dear Professor Bloom,

I want to advise you of important developments and actions being taken by Hyland Therapeutics and Travenol Laboratories in connection with the risks of Acquired Immune Deficiency Syndrome (AIDS). While the causative agent of this disease remains to be identified, some evidence suggests it is caused by a virus that can be transmitted by blood and certain blood products. Based on epidemiologic experience with AIDS, certain groups of potential plasma donors have been identified as representing a higher risk of transmitting the disease. Hyland Therapeutics instituted donor screening procedures designed to eliminate the high risk donor groups from its donor population well before the March 24, 1983 directive on screening procedures issued by the National Centre for Drugs and Biologics in the United States.

In spite of these precautions, Hyland Therapeutics recently became aware that one of its plasma donors, though not finally diagnosed, has been identified as a possible victim of AIDS. The donor in question is a member of the high risk groups, although on several occasions prior to donating, he denied being a member of such group. While healthy at the time of donation, he subsequently developed some of the clinical findings associated with AIDS, including an inverted T4/T8 ratio and generalised lymphadenopathy. His final diagnosis is still in question.

This donors plasma was included in pools that were fractionated into several therapeutic products for the haemophiliac, including Anti Haemophilic Factor VIII, Factor IX complex, and Anti Inhibitor Coagulant Complex. No therapeutic products fractionated from plasma pools that contained this donors plasma have been shipped to any customer in Europe.

In the United States, Hyland has recalled the only coagulation product fractionated from plasma containing that donor's plasma that had been distributed to customers. The recall involves one

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lot of Anti Inhibitors Coagulant Complex and is being taken at Hyland Therapeutics initiative, and not at the request of the National Centre of Drugs and Biologics. As a precaution, all lots of Factor VIII and Factor IX Complex that were manufactured from this donors plasma have been placed in quarantine pending future resolution of this donor's medical condition. None of these quarantined products have been distributed to customers in either the United States or Europe.

In addition to screening procedures to eliminate high risk donor groups, and placing in quarantine all products made from plasma pools affected by this donor, Hyland is taking a third major action it believes could contibute to the safety of the Haemophiliac. Hyland will, as expeditiously as possible, convert both its European and U.S. facilities to manufacture only heat treated Factor VIII product.

This new heat treated product, (Hemofil T) which Hyland Therapeutics has recently introduced, has equal potency and effectiveness as normal Hemofil (Anti Hemophiliac Factor (Human)), but has been subjected, during manufacture, to an additional heat treating step designed to reduce active viral content. This new product is being offered at only a small price premium over the regular non-heated product.

Since the causative agent for AIDS has not been identified, and since the effects of the heat treating process on all viruses have not been determined, Hyland Therapeutics cannot, at present, give assurance that the heat treated product eliminates the risk of transmission of AIDS. However, Hyland Therapeutics believes that administration of the heat treated product, designed to reduce active viral content, may increase patient and centre personnel safety.

Hyland Therapeutics will also as expeditiously as possible, file for US and European regulatory approval of heat treated Proplex, Factor IX Complex (Human) and Autoplex Anti Inhibitor Coagulant Complex and convert its facilities so as to manufacture only heat treated versions of these products.

Travenol Laboratories believes that the above steps represent the most responsible action that can be taken at this time to assure a continued safe supply of coagulation factor concentrate to the Haemophiliac population.

I would welcome your comments and suggestions.

Yours sincerely,

GRO-C

A.W. Barrell
Managing Director

CONFIDENTIAL

MRC Working Party on AIDS

AIDS and Haemophilia : Research in U.K.

It is not possible to give an exhaustive review of AIDS research in haemophilia in UK because it is probable that some is being undertaken under the aegis of various grant awarding bodies or other agencies and is not known to the reviewer. In addition no attempt has been made to list projects already completed and published e.g. surveys of immune function in haemophiliacs undertaken at Cardiff, Glasgow, Edinburgh and elsewhere.

Information set out in this document refers to reports received confidentially from the following sources.

Haemophilia Centre Directors Organisaation (U.K.)
Medical Research Council
Scottish Home and Health Department (through grant applications)
Haemophilia Society.

Haemophilia Centre Directors Organisation (HCDO)
The HCDO has kept detailed statistics on haemophilia patients in the U.K. since the early 1970's. This includes data on various clinical syndromes, treatment materials used (e.g. blood products), development of complications, death statistics and causes of death where known etc. The available evidence supports the conclusion that the vast majority of patients with haemophilia in the U.K. are included in this annual survey. The data are collected, collated, stored (on computer) and analysed at Oxford by Dr. C.R. Rizza and his colleagues under the general direction of the HCDO. This system is unparalleled in any other large country in the world and has been an invaluable source of data, published and unpublished, to physicians and to Health Departments. With the emergence of HIV infection in haemophiliacs the system has been enlarged to encompass this aspect and the following additional surveys are under way. The main virological advisor to HCDO has been Dr. J. Craske of the PHLS Laboratories at Manchester.

(a) A survey of HIV antibody test results in haemophiliacs treated with blood or blood products since 1980. Data for 1985 have been published and data for 1986 has been tabulated. Where there has been apparent seroconversion of individual patients during these two periods detailed treatment records are being analysed to determine if there are any genuine seroconversions attributable to heat-treated factor concentrate. These data have also established the pattern of HIV exposure in adults and children with haemophilia in the U.K. This has formed a basis for advice by Health Departments and DES to schools etc. and as a base-line for assessing rate of development of AIDS or aids-related syndromes.

(b) From the initial appearance of HIV antibody in patients treated only with (unheated) U.K. concentrate treatment data from recipients of individual batches has been analysed retrospectively and a longitudinal survey of seroconverted and non-seroconverted recipients is being undertaken. This survey has established criteria by which transmission of HIV by a batch of concentrate can be judged.

(c) A notification system for AIDS, ARC and other AIDS-related features has been established and data are collated by Dr. Craske. This will give information on the progression from HIV seroconversion to AIDS which already appears to be slower than that in other risk groups.

(d) A survey of family and sexual contacts of haemophiliacs is being undertaken. Returns so far indicate no casual spread within households of seropositive haemophiliacs. Following the initial results of the study on sexual contacts the second stage will be a case controlled study of seropositive contacts by an experienced investigator using a comprehensive questionnaire. This part of the survey is ready to be commenced.

Detailed virological studies on these cohorts will also be considered.

Medical Research Council

(1) 1984. Dr. J. Craske PHLS Withington Hospital Manchester.

An epidemiological study of the relationship of AIDS in patients with disorders of blood coagulation to its possible acquisition through treatment with blood products. £27K over 2 years.

(2) 1985. Dr. C.A. Ludlam Haematology Edinburgh Royal Infirmary.

Clinical and immunological study of haemophiliacs treated exclusively with NHS factor VIII/IX concentrates. £47.4K over 3 years.

Scottish Home & Health

(1) Dr. C.A. Ludlam and J.F. Reutheren, Royal Infirmary Edinburgh.

Further studies of immune function and HIV infection in haemophiliacs treated exclusively with NHS factor VIII/IX concentrates. This study is aimed partly to continue existing studies and to undertake HIV viral culture experiments in order to correlate immune changes with the presence of virus or viral antigens.

Haemophilia Society

1985.

(1) Dr. Philip Mortimer & Dr. Richard Tedder, Middlesex Hospital. PHLS

£26K for support of HIV antibody testing in patients with haemophilia. This project includes:-

(a) identifying and following up seronegative treatment recipients
(b) family studies
(c) viral isolation studies.

1985.

(2) Dr. C.D. Forbes, Dept. of Medicine, Glasgow Royal Infirmary.

£2K. Equipment to support a long term study to determine the incidence of HIV antibody in patients with haemophilia, their family contacts and long term effects of transfusion with heat treated plasma products.

1986

(3) Dr. C.B. Dobson & Dr. L.A. Parapia , Psychosocial Research Unit University of Bradford and Haemophilia Centre Bradford Royal Infirmary.

£10.5K 3 years. Identifying psychosocial factors in HIV positive haemophiliacs and their families that relate to ability to cope and their need for counselling support. Psychological variables are being monitored over the period.

1986

(4) Dr. P. Jones, Haemophilia Centre Royal Victoria Infirmary Newcastle.

£24K (approx) over 2 years. To determine the effects of diagnosis of HIV positivity in haemophiliacs on psychosocial behaviour and development and family living and on the effectiveness of current teaching and counselling as modification of life-style and sexual practices will be assessed.

1986

(5) Dr. C.D. Forbes and Mrs Wilkie,Department of Medicine, Glasgow Royal Infirmary.

£8K for a study to identify major needs created by the uncertainty of AIDS in haemophilic patients, siblings and partners of sero-positive patients. (Further details not known).

Projects under Consideration 1987

(1) Professor F.E. Preston, Haematology, Dr. M.J. Sagar, Neurology, Royal Hallamshire Hospital, Sheffield.

Prognostic markers of higher cerebral function in HIV infection in haemophiliacs. This will involve detecting early signs of dementia, memory defects, mental ability by sequential testing with controls. Detection of early predictions with view to assessing therapeutic intervention. Approx. £20K 2 years requested.

(2) Dr. I.W. Delamore and Dr. G.R. Taylor, Haematology Manchester Royal Infirmary.

To develop a DNA amplification method for producing a hybridisation probe to detect HIV and to compare this with conventional viral detection methods in haemophiliacs. £12K over 3 years requested for reagents.

(3) Dr. S.J. Machin, Haematology Middlesex Hospital.

To develop a method for serial lymphocyte subset analysis in haemophiliacs. £5k over 1 year requested.

This account summarises information on research in the AIDS in haemophilia in the U.K. as known to the reviewer. Although the epidimological surveys are well in hand there seems to be a short-fall of virological investigations e.g. designed to show if haemophiliacs have been usually infected with live virus or perhaps exposed mainly to non-viable or killed virus in factor concentrates. This type of information could be correlated with sexual transmission of the virus using newer cultural or serological (antigen) techniques and no doubt investigations along the lines are underway or being planned. One difficulty in organising and stimulating these sorts of studies is that haemophilia is an uncommon disorder and concentrations of patients do not necessarily correlate with the presence at centres of an expert retro-virologist. An important exception is the recent application from Oxford (McMichael and Townshend) on cytotoxic T lymphocytes in haemophilic patients which has been submitted to the MRC.

March 16 1987

A.L. BLOOM

DHSS

DEPARTMENT OF HEALTH AND SOCIAL SECURITY

To:
Regional Health Authorities) for action
Family Practitioner Committees)

Area Health Authorities)
Boards of Governors) for information

February 1976

HEALTH SERVICES DEVELOPMENT
ARRANGEMENTS FOR THE CARE OF PERSONS SUFFERING FROM HAEMOPHILIA AND RELATED CONDITIONS

Summary

This circular encloses a memorandum which sets out revised arrangements for the care of persons suffering from haemophilia and related conditions; lays down revised criteria for the designation of haemophilia centres; and asks Regional Health Authorities to review, in the light of these criteria, centres at which treatment is at present available to patients.

1. On 5 March 1968 a memorandum was circulated to hospital authorities, under cover of HM(68)8, listing centres which had been designated for the diagnosis, treatment and registration of persons suffering from haemophilia and related conditions and describing the functions of these centres. Following a review, which was carried out in consultation with the Directors of the present Haemophilia Centres, some alterations to the existing arrangements have been worked out and agreed and these are incorporated in the revised memorandum attached as Appendix 2.

Criteria for Designation as Haemophilia Centres

2. To qualify for designation, Haemophilia Centres must be able to provide clinical treatment to patients at short notice at any time of the day or night and be capable of undertaking assays of specific coagulation factors as part of their diagnostic and therapeutic procedures. With the introduction of new therapeutic agents the prospects of haemophiliacs reaching active adulthood have considerably improved and Haemophilia Centres should therefore be able to provide a wider advisory service than hitherto to haemophiliacs and their families particularly in the fields of preventive medicine and dentistry, education, employment, genetic counselling and social medicine.

Associate Centres

3. Centres which were designated in 1968 but which do not fully meet the new criteria may nevertheless, to avoid inconvenience to patients already registered with them who live or work nearby, continue to be recognised for the purpose of giving emergency treatment. These centres will be known as Associate Centres. Each will be linked with a convenient designated Haemophilia Centre so that together they will be in a position to offer patients a full therapeutic, diagnostic and advisory service.

Reference Centres

4. The introduction of new therapeutic agents, accompanied by the growth in experience of the treatment of haemophiliacs, has led to changes in the role of the three centres which were designated in 1968 as Special Treatment Centres. Although it is no longer necessary to refer the majority of patients to them for surgery these Centres, and a few others, have during recent years developed an advisory role towards individual Haemophilia Centres, and it has been decided that this role could usefully be officially recognised and further developed by designating them as Reference Centres and describing in some detail their functions.

Other facilities in the United Kingdom

5. As it is important that patients and Directors of Haemophilia Centres should be aware where treatment for haemophilia is available in the United Kingdom, haemophilia centres in Wales and Northern Ireland and regional haemophilia centres in Scotland have, with the agreement of the Welsh Office, the Department of Health and Social Services, Northern Ireland and the Scottish Home and Health Department respectively, also been included in the list of centres in England (attached as Appendix 1). The organisation of haemophilia centres in Scotland differs from that in the rest of the United Kingdom in that each centre provides the whole range of services for its area.

Action

6. Regional Health Authorities are asked to review, in consultation with the appropriate Reference Centre, the list of centres in England at which treatment is available to patients in the light of paragraphs 2 and 3 above and to inform the Department by 30 April 1976 which Centres are to be designated as Haemophilia Centres and which are to be known as Associate Centres.

7. Family Practitioner Committees are asked to send a copy of the attached FPN and Appendix 1 for information to all general medical and dental practitioners on their lists and to the Local Medical and Dental Committees. Enough copies are being sent separately.

8. The Department (HS2B) will continue to supply the Special Medical Card (Haemorrhagic States) and the booklet "Notes on the care of patients with hereditary haemorrhagic disorders".

From:

HS2B Division
Hannibal House
Elephant and Castle
London SE1 6TE

01-703 6380 Ext 411

H1/H7/14

Further copies of this document may be obtained from DHSS Store, Scholefield Mill, Brunswick Street, Nelson, Lancashire BB9 0HU Tel: (0282)62411/2

FAMILY PRACTITIONER NOTICE

FPN 105
(HC(76)4)

NATIONAL HEALTH SERVICE

GENERAL MEDICAL AND DENTAL SERVICES

ORGANISATION OF HAEMOPHILIA CENTRES

Summary

1. This Notice advises general medical and general dental practitioners of the revised arrangements for the care of persons suffering from haemophilia and related conditions; the Appendix lists the centres at which treatment is available in the United Kingdom.

Background

2. The arrangements under which centres are designated for the diagnosis, treatment and registration of persons suffering from haemophilia and related conditions have been in existence since 1968. Following a review which was carried out in consultation with the Directors of the present Haemophilia Centres some alterations have been agreed; the new arrangements are described in the succeeding paragraphs.

Haemophilia Centres

3. The functions of these Centres are to provide:-

(i) a laboratory service able

(a) to carry out the tests, including the identification and assay of specific coagulation factors and anti-coagulants necessary for an exact diagnosis to be made

(b) to monitor coagulation factors and anti-coagulants during treatment

(c) in collaboration with the appropriate Reference Centre (see paragraph 7 below) to investigate relatives of patients with haemophilia or related conditions.

(ii) a clinical service for the treatment of patients at short notice at any time of the day or night

(iii) an advisory service to patients (and, in the case of child patients, to their parents) on matters of concern to them such as preventive medicine and dentistry, education, employment, genetic counselling and social medicine. Advice should also be given to general practitioners about the emergency treatment of haemophilic patients on their list and the procedure for securing these patients' admission to hospital when required including what the patient should do to obtain ambulance transport in an emergency.

4. A record of all patients to whom haemophilia cards are issued should be maintained at each Haemophilia Centre including at least the following information:-

Name, address and telephone number of patient
Date of birth
Disgnosis
Mother's maiden name
Maternal Grandmother's maiden name
Name, address and telephone number of general practitioner
Name of consultant in charge of the case

Associate Haemophilia Centres

5. Centres which were designated in 1968 but which do not fully meet the new criteria laid down for designated Haemophilia Centres (see paragraph 3 above) may wish to continue to provide emergency treatment to haemophiliacs living or working nearby and registered with them. These centres will be known as Associate Haemophilia Centres. Each will be linked with a convenient designated Haemophilia Centre so that together they will be in a position to offer a full therapeutic, diagnostic and advisory service to haemophiliacs and their families.

Reference Centres

6. In 1968 the centres at Oxford, Manchester and Sheffield were designated as Special Treatment Centres where special skills were available to patients requiring major surgery. At that time management during and after surgery was the most difficult aspect of the treatment of haemophilia. This is no longer the case because the management of patients undergoing surgery has become easier as a range of therapeutic materials have become more widely available. Today the emphasis in the treatment of haemophilic patients is on the early day-to-day care on demand and this treatment must be provided at all centres.

7. However, although it is no longer necessary to designate centres for the specific purpose of carrying out surgical treatment there are administrative and other advantages to be gained in designating some centres to be Reference Centres, to which Haemophilia Centres can look for guidance and support. The centres currently so designated and the areas which they broadly cover are:-

St Thomas' Hospital The Royal Free Hospital	London, the South East and East Anglia
The Churchill Hospital Oxford	Oxford, Wessex, the South West, the Midlands and Northern Ireland
The Royal Infirmary Manchester The Royal Infirmary with the Children's Hospital, Sheffield	The North West, North Wales, Trent and Yorkshire
The Royal Victoria Infirmary Newcastle	The North of England
University Hospital of Wales Cardiff	South Wales

8. The functions of these Reference Centres are:-

(i) to provide a 24-hour telephone advisory service to Haemophilia Centres and Associate Haemophilia Centres and to support them particularly during holiday periods

(ii) to provide a specialist consultant service for surgery and for orthopaedic, dental, paediatric and social care for those Haemophilia Centres and Associate Haemophilia Centres wishing to use such a service

(iii) to advise on and organise when called upon home therapy and prophylactic therapy for haemophilia patients

(iv) to provide a reference laboratory service for Haemophilia Centres and Associate Haemophilia Centres including the diagnosis of atypical cases, the assay of antibodies and the supply of assay standards and reagents

(v) to provide education facilities for doctors, technicians, nurses and others as required in order to promote optimum care of patients and a comprehensive laboratory diagnostic service

(vi) to ensure close co-operation between the Haemophilia Centres, Associate Haemophilia Centres and the Regional Centres of the Blood Transfusion Service

(vii) to co-ordinate, as necessary, the allocation of available therapeutic materials to Haemophilia Centres and Associate Haemophilia Centres

(viii) to co-ordinate statistics collected by Haemophilia Centres and Associate Haemophilia Centres

(ix) to co-ordinate meetings and research programmes.

APPENDIX 2

MEMORANDUM ON THE FUNCTIONS OF HAEMOPHILIA CENTRES

1. In the memorandum attached to HM(68)8 a description was given of the functions of a number of centres, known as Haemophilia Diagnostic and Registration Centres, which were designated for the diagnosis, treatment and registration of persons suffering from haemophilia and related conditions. It has been decided to make some changes in the existing arrangements and these are described in this memorandum.

HAEMOPHILIA CENTRES

2. The functions of these Centres are to provide:

(i) a laboratory service able

(a) to carry out the tests, including the identification and assay of specific coagulation factors and anti-coagulants necessary for an exact diagnosis to be made

(b) to monitor coagulation factors and anti-coagulants during treatment

(c) in collaboration with the appropriate Reference Centre (see paragraph 6 below) to investigate relatives of patients with haemophilia or related conditions

(ii) a clinical service for the treatment of patients at short notice at any time of the day or night

(iii) an advisory service to patients (and, in the case of child patients, to their parents) on matters of concern to them such as preventive medicine and dentistry, education, employment, genetic counselling and social medicine. Advice should also be given to general practitioners about the emergency treatment of haemophilic patients on their list and the procedure for securing these patients' admission to hospital when required including what the patient should do to obtain ambulance transport in an emergency.

3. A record of all patients to whom haemophilia cards are issued should be maintained at each Haemophilia Centre including at least the following information:

Name, address and telephone number of patient
Date of birth
Diagnosis
Mother's maiden name
Maternal Grandmother's maiden name
Name, address and telephone number of general practitioner
Name of consultant in charge of the case

ASSOCIATE CENTRES

4. Centres which were designated in 1968 but which do not fully meet the new criteria laid down for designated Haemophilia Centres (see paragraph 2 above) may wish to continue to provide emergency treatment to haemophiliacs living or working nearby and registered with them. These centres will be known as Associate Centres. Each will be linked with a convenient designated Haemophilia Centre so that together they will be in a position to offer a full therapeutic, diagnostic and advisory service to haemophiliacs and their families.

REFERENCE CENTRES

5. In 1968 the centres at Oxford, Manchester and Sheffield were designated as Special Treatment Centres where special skills were available to patients requiring major surgery. At that time management during and after surgery was the most difficult aspect of the treatment of haemophilia. This is no longer the case because the management of patients undergoing surgery has become easier as a range of therapeutic materials have become more widely available. Today the emphasis in the treatment of haemophilic patients is on the early day-to-day care on demand and this treatment must be provided at all centres.

9. Regional Health Authorities have been asked to review the list of centres in England at which treatment is at present available to patients, as shown in the attached Appendix, and to inform the Department which centres are to be designated as Haemophilia Centres and which are to be known as Associate Haemophilia Centres. As it is important that patients and others should be aware where treatment for haemophilia is available in the United Kingdom, haemophilia centres in Wales and Northern Ireland and regional haemophilia centres in Scotland have also been included in the list. The organisation of haemophilia centres in Scotland differs from that in the rest of the United Kingdom in that each centre provides the whole range of services for its area.

10. The Department (HS2B) will continue to supply the Special Medical Card (Haemorrhagic States) and the booklet "Notes on the care of patients with hereditary haemorrhagic disorders".

January 1976

From HC(76)4.

6. However although it is no longer necessary to designate centres for the specific purpose of carrying out surgical treatment there are administrative and other advantages to be gained in designating some centres to be Reference Centres to which Haemophilia Centres can look for guidance and support. The centres currently so designated and the areas which they broadly cover are:

St Thomas' Hospital The Royal Free Hospital	London, the South East and East Anglia
The Churchill Hospital Oxford	Oxford, Wessex, the South West, the Midlands and Northern Ireland
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The Royal Victoria Infirmary Newcastle	The North of England
University Hospital of Wales Cardiff	South Wales

7. The functions of these Reference Centres are:

(i) to provide a 24-hour telephone advisory service to Haemophilia Centres and Associate Centres and to support them particularly during holiday periods

(ii) to provide a specialist consultant service for surgery and for orthopaedic, dental, paediatric and social care for those Haemophilia Centres and Associate Centres wishing to use such a service

(iii) to advise on and organise when called upon home therapy and prophylactic therapy for haemophilia patients

(iv) to provide a reference laboratory service for Haemophilia Centres and Associate Centres including the diagnosis of atypical cases, the assay of antibodies and the supply of assay standards and reagents

(v) to provide education facilities for doctors, technicians, nurses and others as required in order to promote optimum care of patients and a comprehensive laboratory diagnostic service

(vi) to ensure close co-operation between the Haemophilia Centres, Associate Centres and the Regional Centres of the Blood Transfusion Service

(vii) to co-ordinate, as necessary, the allocation of available therapeutic materials to Haemophilia Centres and Associate Centres

(viii) to co-ordinate statistics collected by Haemophilia Centres and Associate Centres

(ix) to co-ordinate meetings and research programmes

APPENDIX 1

CENTRES AT WHICH TREATMENT IS AVAILABLE TO PATIENTS SUFFERING FROM HAEMOPHILIA AND RELATED CONDITIONS

ENGLAND

Alton	Dr. J. Fowler (Con. Physic) Dr A. Aronstam, (Con. Haemat.) Treloar Haemophilia Centre Lord Mayor Treloar Hospital Alton Hampshire	0420-82811
Birmingham	Dr. J.R. Mann (Temp. Dir) Department of Haematology The Children's Hospital Ladywood Middleway Birmingham B16 8ET	021-454-4851
	Dr J Stuart Department of Haematology Queen Elizabeth Hospital Edgbaston Birmingham B15 2TH	021-472 1311
Bournemouth	Dr D Stern Department of Pathology Royal Victoria Hospital Shelley Road Boscombe Bournemouth BH1 4JG	0202-35201 (9 am - 5 pm weekdays Ext 323. At other times please ask for doctor on call for Haemophilia Control)
Bradford	Dr R L Turner Haematology Department The Royal Infirmary Bradford BD9 6RJ	0274-42200 Ext 289
Bristol	Dr G L Scott Department of Haematology Bristol Royal Infirmary Bristol BS2 8HW	0272-22041 (9 am - 5 pm weekdays Ext 2614. At other times please ask for Sister-in-Charge of the Accident and Emergency Department)
Cambridge	Dr D G Chalmers Department of Haematology Addenbrooke's Hospital Hills Road Cambridge CB2 2QQ	0223-45151 Ext 7125 (At night and at weekends please ask for the Duty Haematologist)
Carlisle	Dr A Inglis Department of Pathology Cumberland Infirmary Carlisle CA2 7HY	0228-23444 (Hospital switchboard will contact relevant member of team on duty)
Coventry	Dr N K Shinton Department of Haematology Coventry and Warwickshire Hospital Stoney Stanton Road Coventry CV1 4FH	0203-24055

...ngton	Dr A E S Mustafa Memorial Hospital Darlington	0325-60100 (Hospital switchboard will contact relevant member of team on duty)
Derby	Dr D A Winfield Royal Infirmary Derby	0332-47141
Exeter	Dr J O P Edgcumbe Department of Pathology Royal Devon and Exeter Hospital Exeter EX1 1PQ	0392-77833 Ext 2093
Hereford	Dr J.J. Kramer, Hereford County Hospital, Hereford.	
Hull	Dr C G L Raper Department of Pathology Kingston General Hospital Beverley Road Hull HU3 1UR	0482-28631
Leeds	Dr L M Swinburne St James' Hospital Leeds LS9 7TF	0532-33144
Liverpool	Professor A J Bellingham Liverpool Royal Infirmary Pembroke Place Liverpool L3 5PU	051-709 5511
London	Professor J W Stewart Bland-Sutton Institute of Pathology The Middlesex Hospital Mortimer Street London W1N 8AA	01-636 8333 (At night and at weekends please ask for the Duty Pathologist).
	Dr R S Mibashan Haematology Department Royal Postgraduate Medical School Hammersmith Hospital Du Cane Road London W12 0HS	01-743 2030 Ext 510 (At night and at weekends please ask for the Haematology Registrar on duty).
	Professor P L Mollison Department of Haematology St Mary's Hospital Praed Street Paddington London W2 1NY	01-262 1280 Ext 37
	Professor J G Humble Haematology Department Westminster Hospital Dean Ryle Street London SW1P 2AP	01-828 9811
	Professor R M Hardisty Department of Haematology The Hospital for Sick Children Great Ormond Street London WC1N 3JH	01-405 9200 Ext 331 (At night and at weekends please ask for the Resident Assistant Physician).

Dr G C Jenkins Department of Haematology The London Hospital Whitechapel Road London E1 1BB	01-247 5454
Dr Katharine M Dormandy The Haemophilia Centre The Royal Free Hospital Pond Street London NW3 2QG	01-794 0500 (After 5.30 pm and at weekends please ask for the doctor on call for the Haemophilia Centre).
Professor T A J Prankerd Haematology Department University College Hospital Gower Street London WC1E 6AU	01-387 9300
Dr P Barkhan Department of Haematology Guy's Hospital London SE1 9RT	01-407 7600 (At night and at weekends please ask for the Resident Pathologist)
Professor J. M. White, Haematology Department King's College Hospital Denmark Hill London SE5 8AF	01-274 6222
Dr C A Holman Haematology Department Lewisham Hospital High Street Lewisham London SE13 6LH	01-690 4311
Professor G I C Ingram Department of Haematology St Thomas' Hospital London SE1 7EH	01-928 9292 Ext 2268 (At night and at weekends please ask for the doctor on duty for Haemophilia)
Professor P T Flute Haematology Department St George's Hospital Blackshaw Road Tooting London SW17 0QT	01-672 1255
Manchester Dr I W Delamore Department of Clinical Haematology The Royal Infirmary Manchester M13 9WL	061-273 3300
Dr D I K Evans Department of Haematology Royal Manchester Children's Hospital Pendlebury Nr Manchester M27 1HA	061-794 4696

Margate	Dr H Sterndale Isle of Thanet District Hospital (Margate Wing) St Peter's Road Margate Kent CT9 4AN	0843-20222
Middlesbrough	Dr R E Potts Middlesbrough General Hospital Ayresome Green Lane Middlesbrough Teesside TS1 5JE	0642-83133 (Hospital switchboard will contact relevant member of team on duty)
Newcastle	Dr P Jones Royal Victoria Infirmary Newcastle upon Tyne NE1 4LP	0632-25131 Ext 773 (At night and at weekends please ask for Ward 8 (children) or Ward 13 (adults))
Nottingham	Dr T E Blecher Dr E A French Haematology Department The General Hospital Nottingham NG1 6HA	0602-46161 Ext 603 or 385 (At night and at weekends please ask for the doctor on call for Haematology)
Oxford	Dr Rosemary Biggs Dr C Rizza Oxford Haemophilia Centre Churchill Hospital Oxford OX3 7LJ	0865-64841 Ext 575 (After 5.00 pm and at weekends please ask for the doctor on call for the Haemophilia Centre)
Portsmouth	Dr J R O'Brien Central Laboratory St Mary's General Hospital (East Wing) Milton Road Portsmouth PO3 6AG	0705-22331
Sheffield	Professor E K Blackburn Dr J S Lilleyman* Dr F E Preston Dr H T Swan Departments of Haematology The Royal Infirmary Sheffield S6 3DA and Sheffield Children's Hospital Sheffield S10 2TH	0742-20977 (At night and at weekends please ask for the doctor on call for the Haemophilia Centre)
Shrewsbury	Dr M. O'Shea Copthall Hospital, Shrewsbury.	
Stafford	Dr C. Giles, North Staffordshire Royal Infirmary, Stafford.	
Southampton	Dr Morag Chisholm Royal South Hants Hospital Fanshawe Street Southampton SO9 4PE	0703-26211
Sunderland	Dr A MacKenzie The Royal Infirmary Durham Road Sunderland Co Durham SR2 7JE	0632-56256 (Hospital switchboard will contact relevant member of team on duty)
Whitehaven	Dr P J Whitehead West Cumberland Hospital Hensingham Whitehaven Cumberland CA28 8JG	0946-3181 (Hospital switchboard will contact relevant member of team on duty)

* Dr J S Lilleyman

Wolverhampton

Dr W.S.A. Allen
Royal Hospital,
Wolverhampton

Worcester

Dr R.W. Payne
Royal Infirmary,
Worcester.

WALES

Cardiff	Dr A L Bloom Department of Haematology University Hospital of Wales Heath Park Cardiff CF4 1XW	0222-755944 (After 5 pm and at weekends please ask for the House Physician to the Haematology Department)

NORTHERN IRELAND

Belfast	Professor M G Nelson Department of Haematology Royal Victoria Hospital Grosvenor Road Belfast BT12 6BA	0232-40503

SCOTLAND

Regional Haemophilia Centres

Aberdeen	Dr Audrey A Dawson Haematology Unit University Medical Buildings Foresterhill Aberdeen AB9 2ZB	0224-23423 Ext 2623
Dundee	Dr G R Tudhope Wards 5/6 Ninewells Hospital Dundee DD1 9SY	0382-60111 Ext 2574
Edinburgh	Professor R H Girdwood University Department of Therapeutics The Royal Infirmary Edinburgh EH3 9YW	031-229 2477 Ext 2523
	Dr S H Davies Department of Haematology The Royal Infirmary Edinburgh EH3 9YW	031-229 2477 Ext 2099
Glasgow	Dr C J M Prentice Department of Medicine Royal Infirmary Glasgow G4 0SF	041-552 3535 (If not available ask for the Receiving Physician)
	Dr G.A. McDonald, Department of Haematology, Royal Infirmary, Glasgow, G4 OSF.	
Inverness	Dr. I.A. Cook, Regional Blood Transfusion Centre, Raigmore Hospital, Inverness IV2 3UJ.	0463-34151