Annex A: Chronology of events

Date	Event
Early 1970s	Use of factor concentrates becomes more widespread.
November 1971	Screening for hepatitis B becomes available.
Early 1973	It becomes apparent that the production of factor VIII in the UK is insufficient to meet the stated needs of clinicians.
March 1973	DHSS Expert Group on the Treatment of Haemophilia recommends that the NHS should be self-sufficient in blood products as soon as possible.
03 August 1974	NANBH strain of hepatitis first predicted by Prince et al.
December 1974	The Minister of State earmarks central funds of £0.5m (half of which was to be recurring). This was to be used to increase the output of plasma from RTCs to 275,000 blood donations annually for the preparation of factor VIII and 100,00 donations for cryoprecipitate.
Beginning 1975	Expert Group on the Treatment of Haemophilia estimated that 275,000 donations of blood would be required to achieve self-sufficiency in factor VIII.
March 1975	Department gave Regions provisional targets of increased production of plasma and invited estimates of the additional expenditure that would be incurred.
May 1975	WHO resolution states that each country should be able to supply sufficient quantities of its own blood and blood products to meet clinical needs.
August 1975	Mannucci et al. report 45% of patients with NANBH had raised ALT levels; Craske et al. links an outbreak of hepatitis (some NANBH) after intravenous injections of commercial factor VIII concentrate.
April 1976	Department issues a press release re-affirming the aim of the UK to become self-sufficient in the supply of blood products by mid-1977.
June 1977	Factor VIII production target set in beginning of 1975 attained; however demand had increased.

Date	Event
December 1977	Working Group on trends in the demand for blood products confirms estimate of 1000 iu per 1000 population pa and recommends complete transfer from the use of cryoprecipitate to fractionated freeze dried concentrate.
July 1979	Medicines Inspectorate inspection report published on plasma fractionation facilities at BPL recommending a set of actions that should take place immediately, and others that should be implemented in the long term.
Early 1980	Blood products begin to be heat-treated; however, yield is very low and not shown subsequently to inactivate NANBH.
August 1980	Short-term upgrading of facilities at BPL agreed at cost of £1.3m. Expected to double production capacity from 15m iu pa to 30m iu pa.
October 1980	Craske claims that NANBH is mild and often asymptomatic, but might cause chronic liver disease not associated with overt disease.
November 1980	£21m allocated to the building of a new fractionation facility on existing site at Elstree.
1 April 1981	Regions started to received BPL products relative to amount of plasma supplied i.e. pro rata distribution.
Mid 1981	Advisory committee to NBTS estimated that demand for factor VIII would increase to 100m iu pa by mid-1980s; regional targets for plasma set.
1982/1983	Studies published that indicate that NANBH is more serious than previously thought.
1983	Studies, such as that by Fletcher et al. confirm that commercial and BPL concentrates contain equal risk of transmitting hepatitis.
1983	Rizza and Spooner paper showing cerebral haemorrhage most common cause of death for patients with haemophilia; only 2% of patients die as a result of chronic hepatitis infection.
1983	US patients with haemophilia contracted AIDS strengthening concerns over the safety of imported commercial blood products.
March 1983	FDA introduces new regulations for the collection of plasma excluding donors from high-risk groups. The use of pre-March stocks was not banned owing to concerns that this would lead to a crisis in supply.
May 1983	Construction started at BPL.

Date	Event
18 May 1983	Haemophilia Society appeal not to ban imported blood products and urge patients not to stop treatment in response to concerns over potential risks.
May 1984	Trial issues of HT1 factor VIII.
10 Dec 1984	HCD's meeting at BPL. Heated product preferred for all new patients, subject to availability; otherwise preferentially for treatment of HIV-antibody negative patients. BPL confirmed all factor VIII would be heated by April 1985. Heating would carry a 15-20% yield penalty.
1985	Studies revealed almost 100% transmission of NANBH following treatment with unsterilised large donor pool clotting factor concentrate. Hay et al. reported that progressive liver disease in patients with haemophilia was an understated problem.
February 1985	First issues of heated (HT2) factor VIII.
February 1985	Trial issues of heated (HT3) factor VIII.
July 1985	Trials of a new, high purity product, 8Y, conducted in selected patients.
September 1985	BPL starts general issue of its new 8Y heat-treated factor VIII.
02 Oct 1985	Heat-treated factor IX issued from BPL on this date.
Mid-1986	Re-development project costs escalate to around £52m; however project remains fully funded owing to Government's commitment to self-sufficiency.
September 1988	UK was still not self-sufficient in blood products owing to errors in estimating both the amount of plasma stockpiled and the net yield for factor VIII production at BPL, and could only be expected to become self-sufficient in a couple of years.
1989	NANBH virus isolated by Choo et al.
April 1989	System of cross-charging in place to encourage RTCs to produce maximal amounts of plasma.
1991	Second-generation HCV screening assays become widely used in the screening of donor blood in the UK.
1993	Domestically sourced blood products account for 75% of the UK factor VIII market. There were concerns, however, at this time, that absolute self-sufficiency was not without its own risks.

HT1 = 60°C for 72 hours; HT2 = 70°C for 24 hours; HT3 = 80°C for 72 hours

HOUSE OF COMMONS
LONDON SW1A 0AA

The Rt. Hon John Moore MP,
Secretary of State for Health
And Social Security,
Elephant and Castle,
London SE1 6BY.

17 November 1987

Dear John.

I am glad to see that you have made an ex-gratia payment for haemophiliacs who, as a result of transfusion, find themselves HIV Positive.

What concerns me however is how this situation has been allowed to occur. I note that in Hansard 393 on 22 January 1975, I said "I believe it is vitally important that the National Health Service should become self-sufficient as soon as practicable in the production of Factor VIII, including AHG concentrates".

On 22 April in a written answer I was even more explicit "I hope that the National Health Service can become self-sufficient in the production of all forms of Factor VIII within two or three years". The same answer was very much reiterated on 8 July (column 108).

I would be grateful if you could let me know what happened to the extra money that was allocated to the regional transfusion centres, and why they did not become self-sufficient. I think I should in fairness warn you that I have it in mind to refer the issue to the Ombudsman on grounds of maladministration unless I receive a satisfactory explanation.

Yours sincerely

David

DAVID OWEN

HOUSE OF COMMONS
LONDON SW1A 0AA

Mr G L Ross
J Keith Park & Co
Claughton House
39 Barrow Street
St Helens
Merseyside WA10 1RX

11 October 1988

Dear Mr Ross

Thank you for your letter. I cannot I fear clarify what I said since I have not been able to go back to the DHSS records of the time since they have apparently been disposed of. I can therefore not be of much help.

Yours sincerely

David Owen

THE PARLIAMENTARY
OMBUDSMAN

OFFICE OF THE PARLIAMENTARY COMMISSIONER FOR ADMINISTRATION
MILLBANK TOWER, MILLBANK, LONDON SW1P 4QP.
SWITCHBOARD 020 7217 3000, FAX 020 7217 4000, DIRECT LINE 020 7217 4211

From the Commissioner
Sir Michael Buckley

Our Ref: 124/02/COM

The Rt Hon the Lord Owen CH
House of Lords
London
SW1A OPW

4 September 2002

Dear Lord Owen,

Thank you for your letter of 14 August.

I am sorry that you are dissatisfied with the way in which my office has handled correspondence from you and Lord Morris, and in particular with the fact that we did not reply to your letter of 22 March until 1 July. The delay was largely due to the need to search for relevant information on the matters you had raised, which relate, as you know, to events that occurred many years ago. As Miss Corrigan explained in her letter of 1 July, our file relating to the complaint made by your former constituent, Mr [redacted] had been destroyed in accordance with our normal policy, and we had to ask your office to provide copies of the previous correspondence. Nevertheless, I am sorry that we did not keep you informed of what was happening; and I must add my apologies to those already offered by Miss Corrigan for the delay.

I hope you will forgive me if I begin with the technicalities. I realise only too well that they can look like bureaucratic pettifogging. But the plain fact is that I have to work within the constraints of the Parliamentary Commissioner Act 1967. If those constraints are too restrictive, that is a matter for Parliament to see to. So long as they are there, I must obey them. My predecessor, Sir Anthony Barrowclough, decided not to investigate Mr [redacted]'s complaint when you referred it to him in 1988. That complaint can be revived, if I may so put it, only by a serving Member of the House of Commons; and if I were to investigate it I could report only to such a Member. Without a specific complaint from a member of the public, properly referred by a Member of the House of Commons, I have no legal power to take any action.

Putting the technicalities aside, what we have is the fact that the NHS did not become self-sufficient in Factor VIII as you had decided in 1975 that it should. There are many possible reasons for that, such as the unexpectedly large and rapid increase in demand for blood products, and changing expenditure priorities. The relevant decisions would have been discretionary decisions; and I have no authority to question such decisions unless they are

taken with maladministration. No evidence of maladministration has so far been offered; and the chance of an investigation by me discovering such evidence when the files have been destroyed and many of the officials concerned will have retired or died is as near zero as makes no difference. The chance of establishing a causal link with Mr [redacted] misfortunes is even more slender. Finally, even if it could be shown that there was such a link, the injustice which Mr [redacted] sustained, according to the earlier correspondence, was that he contracted HIV. I do not for one moment underestimate the gravity of that; but it appears to have been remedied, so far as circumstances permit, by the establishment of the payments scheme to which you referred in your letter of 22 March. There is simply no basis for investigating his complaint.

I am sending a copy of this letter to Lord Morris.

Yours sincerely.

Richard Buckley

3AS

EXPERT GROUP ON THE TREATMENT OF HAEMOPHILIA

Note of the meeting held at DHSS on 20th March 1973

PRESENT:

Dr J J A Reid - Chairman
Dr Rosemary Biggs
Professor E K Blackburn
Professor A S Douglas
Dr W d'A Maycock
Dr C Rizza
Mr G John, Supply, DHSS
Dr I S Macdonald, SHHD
Dr D P Thomas, B2, DHSS
Mr W A Walters, HS22, DHSS
Mr I G Gardiner, B4, DHSS, Secretary
Dr Sheila Walter, B4, DHSS, Secretary

Several significant advances in the treatment of haemophilia have taken place in recent years. Various therapeutic materials are now available. The most recently developed is human freeze-dried anti-haemophilic globulin concentrate which is expensive and may be in limited supply. Nevertheless, it appears to be the therapeutic agent of choice in the majority of cases, and would be used widely if available in larger quantities.

A short time before this meeting took place, product licences were granted to two firms which import freeze-dried AHG concentrate from overseas, making it available to hospitals and haemophilia centres. The Department decided to assemble a group of experts to advise generally on the likely trends in treatment of haemophilia and, more specifically, to make proposals on which realistic planning for the future can be based.

The terms of reference of this group are as follows:

> "To advise the Department on trends in methods of treatment of haemophilia and allied conditions: and to consider possible future requirements for the treatment of the condition and the consequences for the supply of therapeutic agents".

Following introductory remarks by the Chairman, the group considered papers which had been prepared by Dr Biggs and Dr Maycock. A general discussion followed and the main points are summarised in this note. At the conclusion of the meeting, several recommendations were made to the Department. These are also enumerated.

1. THE SIZE OF THE PROBLEM

The number of individuals suffering from haemophilia in the U.K. is not known. It was agreed that the number registered with haemophilia centres (1,754) is an under-estimate. Based on

the generally accepted ratio of 5/100,000 in the U.K., a figure of 3,000 can be used as a reasonable estimate for forward planning. There was originally a central register of haemophiliacs but this was discontinued; there might be advantages in resuming national registration but there are no plans to do this at present.

2. PRESENT TREATMENT

Haemophilia is caused by the lack from the blood of an essential coagulation factor: factor VIII. Various therapeutic agents contain factor VIII, and each has advantages and disadvantages in its use. These were discussed by Dr Biggs in her paper. It is agreed by clinicians that the preferred treatment of episodes of bleeding before and during surgical procedures is with the more purified products, namely cryoprecipitate and AHG Concentrat

3. COMPARISON OF THERAPEUTIC MATERIALS

Cryoprecipitate is currently the most commonly used therapeutic agent. In 1972, figures from a summary of questionnaires sent to Directors of haemophilia centres indicate that cryoprecipitate from 250,000 donations of blood (in England and Wales) was issued while human AHG concentrate from 30,000 donations of blood (England, Wales and N. Ireland) was issued. There are disadvantages to using cryoprecipitate compared with AHG Concentr

(a) Cryoprecipitate is presented frozen and must be kept in deep-freeze until immediately before use.

(b) The process of making up the material is tedious and could be abused by non-experts.

(c) The yield of factor VIII is variable from batch to batch of cryoprecipitate. This was clearly demonstrated in table III of Dr Bigg's paper. It is possible to bring the post-infusion level of plasma factor VIII to a particular desired level but in practice this will be difficult with variable potency of the therapeutic agent.

Freeze-dried concentrate is presented in bottles, each containing about 400 units of factor VIII activity. The bottles should be kept at 4-10°C and have a very significantly longer life than cryoprecipitate kept under ideal conditions. The material at present available is of variable solubility but that of good solubility is very convenient to use, easy to make up and the dose can be determined accurately. Adverse reactions following infusions of freeze-dried AHG concentrate are rare.

A possible disadvantage arises from the fact that AHG concentrate is prepared from a larger pool of donations, and in theory therefore, the risk of hepatitis is greater. About 1 in 800 of the donors who present to the transfusion service is a carrier of hepatitis B antigen.

possible disadvantage of these was no possible about it

62

The present policy of rejecting donations which give a positive test for hepatitis B antigen will reduce the incidence of virus in the blood used to make plasma pools. In practice, studies in several centres have shown that the incidence of hepatitis among severely affected patients who have been treated with the freeze-dried preparation is not very much higher than that at centres not using freeze-dried concentrate and this suggests that the development of hepatitis in these multitransfused patients may be dose-related. It was agreed that the theoretically increased risk of acquiring hepatitis(which does not seem to be borne out in practice) should not be a deterrent to using the freeze-dried preparation and in any case this complication will decrease with universal screening of donors for hepatitis antigen.

A survey quoted by Dr Biggs indicates that the incidence of anti-factor VIII anti-bodies in about 6% of patients does not seem to be related to the type of therapeutic material used.

At a meeting of the Haemophilia Centre Directors in 1972 there was a consensus of opinion in favour of freeze-dried concentrate, and this was confirmed in a survey, undertaken by Dr Haycock, of the opinions of clinicians. The limiting factors are the capacity for production (and the cost) of this preparation.

4. FUTURE REQUIREMENTS OF THERAPEUTIC AGENTS

During 1972 considerably more cryoprecipitate than freeze-dried concentrate was issued in terms of donations of blood.

It was generally agreed that 400,000 donations would be required to treat UK sufferers from haemophilia of all degrees of severity, and more if strenuous efforts were made to clear surgical waiting lists and if home treatment or eventually prophylactic treatment became accepted ways of dealing with the problems of haemophiliacs. Life-saving surgery has been undertaken for some time using the therapeutic agents which are available, but clinicians must now look to the possible improvement in the quality of life of boys and men who suffer from haemophilia.

Since more freeze-dried AHG concentrate has become available from two foreign sources the prospects of improved management of day-to-day bleeding episodes using this therapeutic agent has become realistic. If the anticipated annual uptake of 20 million units of the freeze-dried AHG concentrate is to be met from foreign commercial sources the cost will be of the order of £2 million p.a (assuming the cost to be 10p per unit).

At present, UK production is considerably less than the required amount of the freeze-dried preparation. It was agreed that there was an immediate need to discuss the advisability of central purchase and distribution of the two commercially produced preparations. There is also a pressing need to seek ways of increasing UK production with the intention of reducing and as soon as possible ending purchase from foreign sources.

Freeze-dried AHG concentrate is made at the Blood Products Laboratory, Elstree; at the Plasma Fractionation Laboratory, Oxford

and at the Blood Products Laboratory, Edinburgh. It is essential the production and distribution of the therapeutic agents concerned should be considered as a U.K. exercise.

In any consideration of increased UK production of freeze-dried AHG concentrate, the immediate problems are those of the organisation and cost of increasing donations of either whole blood or plasma (by plasmapheresis) and the difficulties, including cost, of increasing the capacity of the laboratories at present engaged in production.

Close co-operation between England (including Wales and N.Ireland and Scotland will be required in order to co-ordinate and optimise blood collection and transport, the fractionation processes, distribution of the therapeutic agents, and utilisation of other blood fraction by-products.

RECOMMENDATIONS BY THE EXPERT GROUP

1. DHSS should give early consideration to central purchase of freeze-dried AHG concentrate from the firms who have recently been granted product licences.

2. Distribution to other haemophilia centres and hospitals should be through the Regional centres, 3 of which are in Oxford, Manchester and Sheffield in England, 1 in Scotland (Edinburgh or Glasgow) and 1 in London (to be decided). The establishment of such a distribution scheme would be a pre-requisite of Recommendation 1 in order to ensure the most effective use of available material.

3. At the same time the U.K. should aim to become self-sufficient as soon as possible by increasing home production of freeze-dried AHG concentrate.

4. The Regional Transfusion Directors should be consulted about the consequences of Recommendation 3 in terms of increased demands upon the Blood Transfusion Services throughout the U.K. Discussions should take place between DHSS and the directors about problems of decreasing production of cryoprecipitate, increasing production of fresh-frozen plasma for fractionation and the possibly increased collection of plasma by plasmapheresis.

5. There should be further meetings of this expert group, at times to be arranged. Several subjects need to be discussed further, including home treatment, and, in due course, prophylactic treatment.

6. The expert group membership might be expanded to include representatives of each of the Regional haemophilia centres, a representative of the Regional Transfusion Directors, and possibly a SAHO. It was also suggested that the National Medical Director of the Scottish National Blood Transfusion Association and Mr Watt of the Edinburgh BPL should be invited to join the group.

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Aberdeen, Md. 21010

PUBLIC HEALTH SERVICE-CDC-Atlanta
EPI-74-78-2 July 24, 1975

FOR ADMINISTRATIVE USE
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NOT FOR PUBLICATION

TO : Director, Center for Disease Control

FROM : Viral Diseases Division, Bureau of Epidemiology

SUBJECT: Hepatitis - Lansing, Kansas

SUMMARY

Over a 2-week period in February-March 1974, 11 clinical and 8 subclinical hepatitis cases were detected among inmates at the Kansas State Penitentiary. The majority were HB_sAg-positive. Investigation revealed that 18 of these 19 cases were in plasma donors at the prison plasmapheresis center; however, risk of hepatitis could not be definitely associated with the plasmapheresis operation, since intravenous drug abuse--including the sharing of equipment--was commonly practiced by plasma donors.

INTRODUCTION

On February 28, 1974, Paul H. Rouse, M.D., Medical Director, Kansas State Penitentiary, telephoned John A. Brman, M.D., Deputy Director, Viral Diseases Division, Bureau of Epidemiology, CDC, to discuss a cluster of hepatitis cases. Dr. Rouse reported that in the 9-day period February 20-28, 7 cases were seen in his infirmary; all were jaundiced, and 4 of 6 tested were positive for hepatitis B surface antigen (HB_sAg) by radioimmunoassay (RIA).

All 7 ill persons had participated in a plasmapheresis program which opened at the penitentiary in July 1972; in contrast, only one-third of the total prison inmate population were participants. Because of the possible association with plasmapheresis, the program was discontinued on February 28 pending further investigation. However, since cases were continuing to be reported daily and because there was an urgent need to define the source and type of hepatitis, Donald E. Wilcox, M.D., Kansas State Epidemiologist, requested assistance from CDC in the evaluation and control of the outbreak. On March 3, John A. Walker, M.D., EIS Officer, Viral Diseases Division, Bureau of Epidemiology, and Jeffrey P. Koplan, M.D., EIS Officer, Bureau of Smallpox Eradication, journeyed to Lansing to meet with prison health authorities and begin an investigation.

BACKGROUND

Kansas State Penitentiary (KSP) is a maximum security correctional institution with approximately 574 inmates. It is located in Lansing, Kansas, 25 miles northwest of metropolitan Kansas City. The prison has a capacity for 1,900 inmates but has decreased its census as violators with less serious crimes or those who are felt to be more amenable to rehabilitative programs have been sent to other institutions. Approximately 60% of the prison population is white and 40% black.

Copy of Original letter

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PUBLIC HEALTH SERVICE-CDC-Atlanta
EPI-74-78-2 July 24,1975

TO : Director, Center for Disease Control

FROM : Viral Diseases Division, Bureau of Epidemiology

SUBJECT: Hepatitis - Lansing, Kansas

SUMMARY

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(The above are excerpts from an official letter sent to the CDC-Atlanta).

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305 • (415) 497-6785

STANFORD UNIVERSITY SCHOOL OF MEDICINE
J. Garrott Allen, M.D.
Professor of Surgery

CBLA

HA(OTC)

January 6, 1975

Dr. W. D'A. Maycock
Blood Products Laboratory
Lister Institute
Elstree, Harts, England

Dear Doctor Maycock:

It has been many years since I last corresponded with you. At this point, I would like to ask a question that deals primarily wit Factors VIII and IX.

It is my understanding from Dr. Judith Pool that the only plac where these two components are prepared in Great Britain is at Oxfo Am I correct in assuming that your laboratory does not produce them No doubt you also know what the practices in Glasgow are at the Wes of Scotland Blood Centre, as I last knew it, then run by Dr. John Wallace. Do they produce Factors VIII or IX? I would appreciate a information you can provide about the Lister Institute and the one Glasgow regarding the preparation of these components.

Dr. Pool spent the past year at Oxford and tells me that at le one of the sources for commercial Factor VIII and IX is the Hyland Laboratories in the Los Angeles area. Dr. Biggs mentioned in her l in LANCET, last June 29th, that there were two other commercial sou but Judy Pool did not know which they were or whether they were fro the United States. As you know, Cutter's product Konyne, for Factc deficiency, has proved extraordinarily hazardous, a 50 to 90 percen rate of icteric hepatitis developing from it. About half of these prove fatal. Cutter's source of blood is 100 percent from Skid-Row derelicts (Transfusion: May/June, 1974).

The other imponderable which has troubled most of us is the ir effectiveness in screening for the HB antigen (Transfusion:July/Aug 1973). This failure, of course, dates back to at least 1971, and gests that half, if not more, of the cases of posttransfusion hepa are caused by an agent other than Hepatitis A or B. Whatever this agent(s) may be, it still seems to be more frequently encountered the lower socio-economic groups of paid and prison donors. It is mal among volunteer donors. It seems that the most certain method have for reducing the number of carrier donors at the present time still to determine whether or not the donor has been paid in money in reduction of his prison sentence.

A blood bank for these groups in the United States is a monet tropic establishment. The commercial blood banks attract these ki of donors. Until we understand this problem better, I would hope Great Britain would give some thought to what the purchase of Fact VIII and IX from the United States tends to do to our attempts to a volunteer program. Commercial blood banking perpetuates the high risk rates for hepatitis we encounter with their products, and it

HA (UK).1

tempts these same commercial firms to sell the residual products of these high risk donors (red cells, platelets, leukocytes, etc.) to non-immunized patients who tend to be more succeptible to post-transfusion hepatitis than is so far the non-virgin hemophiliac.

I would appreciate knowing the situation as it is in the U.K. Would you write to me about it?

Best wishes.

Sincerely yours,

J. Garrott Allen, M.D.

JGA:as

(K)

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Reference .....

Mr Harley

BLOOD PRODUCTS LABORATORY: POSSIBLE TAKE-OVER BY INDUSTRY

I think it best if I confine my comments on the possible take-over of BPL by Beechams to purely technical and medical comments, although I do have major worries also about many other aspects of the proposals, as, I think, you yourself have.

1. The principal medical worry is presented by Beecham's intention to import plasma for fractionation. Unless it were Beecham's intention to process such plasma in an entirely separate plant or with complete duplication of all facilities in a single plant, it would be impossible to prevent contamination of the UK material with imported hepatitis viruses.

I must emphasise that 90% of all post-transfusion (and blood-product infusion) hepatitis in the USA and elsewhere is caused by non-A, non-B hepatitis viruses which (unlike Hepatitis B) cannot, at present, be detected by testing donor blood. This form of hepatitis can be rapidly fatal (particularly when acquired by patients with pre-existing liver disease) or can lead to progressive liver damage. It can also result in a chronic carrier state, thus increasing the "pool" of these viruses in the community.

In my view, the Department has a moral obligation to ensure that any collaboration with industry does not increase the health hazards, not only to recipients of blood products, but to the community as a whole.

2. If the DHSS did not agree to Beechams fractionating imported plasma other than in a separate plant etc, Beechams would probably feel constrained to obtain the necessary extra volume of plasma by buying it in the UK. That is, it is likely that the company would establish plasmapheresis centres in this country for paid donors and thereby seriously undermine the voluntary donor principle in the UK.

3. I have just visited PFC Liberton with colleagues from HS2. Although we have no formal information about its capacity to expand production, it was conveyed to us informally that Liberton had a substantial capacity for expansion, notwithstanding staffing difficulties etc. If Liberton were to take on $\frac{1}{4}$ - $\frac{1}{3}$ of the England and Wales fractionation requirements in addition to meeting Scottish needs, UK vulnerability in the event of Beechams pulling out would be reduced and the price of Beechams (or imported) products might be kept down. My impression from that meeting was that the Scots are very willing to consider UK fractionation as a whole and that, having provided the DHSS (through the SHHD) with detailed schedules of their products and performance since commissioning of the plant, anticipate expanding production by an agreed amount for the benefit of England and Wales. Perhaps, therefore, we should be very cautious before asking Beechams to provide totally for the requirements of England and Wales when we may not need it to do so.

4. I have just seen the tables on cost-benefit analysis prepared by FB. I think the paragraph 4 note to table 1 may underestimate the requirement

99

of FFP for "self-sufficiency" for England and Wales. Dr Lane has said that he would need 500,000 litres FFP to meet anticipated demands for products. Each litre of FFP is made up of 5.6 "donations" of plasma (0.18 litres plasma per whole blood donation). Therefore there is a requirement for (500,000 x 5.6) FFP donations = 2.8 million FFP donations. Previously Dr Lane has given the FFP requirement as nearer 400,000 litres of FFP which is equivalent to 2.2 million donations. In the FB table, the anticipated need for FFP has been taken to be only 1.6 million donations.

I cannot comment on the figures arrived at for the equivalent 80/81 commercial value for FVIII and PPF because I'm not sure what prices have been used. However the minimum qunatities under consideration by FB should have been

FVIII : 90 m iu

{ PPF : 6,900 kg
and other albumin fractions }.

Perhaps Mr Brechin could confirm that these were indeed the sort of figures on which the calculations were based and if not, what figures were used. I should add that the projected requirements for FVIII, which were based on advice given to the Department earlier this year, may have to be revised in the face of very recent evidence which indicates that UK clinicians are coming under pressure from various quarters to step-up the dosage regime for the home treatment of haemophilia.

Diana Walford

DIANA WALFORD
MED SM4
Room 919 HAN H
Ext 3487

15 September 1980

cc

Dr Oliver
Mr Wormald
Mr Godfrey
Mr Hart
Dr Wintersgill
Mrs Firth
Mr Brechin
Mr Sharpe
Dr Davie
Miss Helson
Mr Connor

DRAFT

This has been the third and final year of the retrospective hepatitis survey financed by the D.H.S.S. This report will deal with some preliminary results of the 3 year survey, and propose further subjects for further study by the Hepatitis Working Party (W.P.)

HEPATITIS SURVEILLANCE

Table 1 shows the preliminary results of hepatitis reports where there was enough information to categorise these incidents as being related to factor VIII or IX therapy. Cases not considered to be associated with replacement therapy have been excluded. A total of 283 episodes of hepatitis were reported by the Haemophilia Centre Directors, including 253 patients; 26 patients had 2 attacks of hepatitis and 4 patients 3 attacks. Of the total of 283, 197 were non-B hepatitis and therefore probably non-A, non-B, and 86 incidents were hepatitis B. Table 1 classifies each incident according to the brand of product implicated in each incident. The differing proportions of incidents related to each brand does not reflect the relative incidence of hepatitis due to each product. Hemofil and Kryobulin were used in the U.K. 2 to 3 years before the other commercial products, and the relative amounts of other products have varied since due to market forces. Further evidence concerning the relationship of different types of hepatitis to different brands of concentrate is given later in this report.

From the patient's point of view most episodes of acute hepatitis were mild. Hepatitis B still occurs related to all types of product, but the incidence has continued to decline. This must be attributed to the improved methods of donor screening for HB_sAg and quality control of the products.

COMPLICATIONS

The question of the significance of chronic hepatitis observed by several groups of workers in liver biopsies of patients with chronically elevated transaminases is still unanswered. Current investigations are attempting to relate the results in different groups of patients to their transfusion history, and there is strong evidence that different types of non-A, non-B hepatitis are related to different products (see later). Most patients in this group are still entirely symptomless. The natural history of there disease in non-haemophiliacs is still not known, though there is some evidence to suggest that some patients with liver biopsy appearances of chronic active hepatitis have a better prognosis than patients with similar histology on liver biopsy whose liver disease is considered to be of non-viral origin. There have been no further deaths directly or indirectly attributed to liver disease in the past year.

FACTORS AFFECTING THE INCIDENCE OF HEPATITIS

a) Incidence of hepatitis due to commercial versus NHS associated hepatitis

Table (2) compares the figures for B and non-B hepatitis in patients receiving only one product in any year for the years 1977-9 and was presented in last years report. It shows that there is a 4-20 times higher incidence of overt non-A, non-B hepatitis associated with U.S. Commercial concentrate compared with NHS. There is no demonstrable effect with hepatitis B probably due to the effect of screening plasma donations for HB_sAg. We have, as yet, no data for symptomless hepatitis, but a prospective study of patients treated with factor VIII or IX is planned at several Centres.

b) History of transfusion with concentrate

Table 3 analyses 137 cases of non-A, non-B hepatitis by transfusion history. The chief finding is that 70-80% of cases of non-A, non-B hepatitis were associated with the first dose of concentrate that the patient received. Four out of 91(4.4%) cases occurred where US Commercial concentrate was the implicated brand, in which the patient gave a history of 1-3 years treatment with these products. In contrast, 6 out of 46 (13.7%) cases occurred associated with NHS concentrate or Kryobulin (both intermediate factor VIII concentrate) occurred where the patients had previously been treated with NHS factor VIII or Kryobulin.

Table 4 gives an example of the current pattern of non-A, non-B hepatitis. Most of the patients treated with any batch of concentrate will be immune to non-A, non-B hepatitis, since batches of concentrate of any brand are contaminated with one (or more) serotypes of these agents. Recently a batch of Kryobulin was investigated when 3 cases were reported to be associated with transfusion of this batch. The only criteria one can use when assessing possible immunity to reinfection is a history of previous exposure to a similar product. Table 4 shows that 13/57 (22.8%) patients treated were probably not immune to non-A, non-B hepatitis and of these, 4 developed hepatitis, giving an attack rate of possible susceptibles of 30.8%, excluding symptomless cases.

c) Screening of donors for hepatitis B

Hepatitis B is still present at a low level but donor screening appears to have eliminated any difference between Commercial and NHS concentrate in this respect - see table 2.

d) Occurrence of different serotypes of virus in different products

Apart from different sources of donor, there are 2 different types of factor VIII concentrate available in the U.K.

1) High purity factor VIII made by variants of the glycine/PEG method of fractionation (U.S. Commercial factor VIII concentrate) and

2) Intermediate factor VIII (NHS factor VIII and Kryobulin).

Table 5 shows the differences between 2 products, Hemofil (a commercial U.S. Concentrate) and Kryobulin (an intermediate factor VIII) with respect to the chance that a patient will contract non-A, non-B hepatitis with the first batch of material that he receives or a second or subsequent batch. With Hemofil in 1974-5 there was a 20 times greater chance of contracting overt non-A, non-B hepatitis with the first batch than with the second or subsequent batch. In contrast, there was an equal chance when treated with the first or subsequent batch of Kryobulin of contracting overt non-A, non-B hepatitis.

One of 2 explanations is likely for this. The first is that the attack rate of Hemofil associated hepatitis was much higher than that associated with Kryobulin. The attack rate of Hemofil associated non-A, non-B hepatitis in 1974-5 was (12.9%) and that of Kryobulin was (10.1%) - Unpublished data - Hepatitis Working Party.

These differences therefore cannot be explained by differences in attack rates above. The second possible explanation is that Hemofil is contaminated with one serotype of non-A, non-B hepatitis and that Kryobulin contains 2 or more serotypes.

That the second explanation is the more likely and is confirmed when the data relating to multiple attacks of non-A, non-B hepatitis are examined (table 6). Six patients developed 2 attacks of non-A, non-B hepatitis where the first was associated with U.S. Commercial concentrate (all similar to Hemofil) and the second with Kryobulin or NHS material. However no multiple cases were observed where U.S. Commercial concentrate was implicated in both attacks. In contrast, 4 patients had 2 attacks of non-A, non-B hepatitis associated with intermediate products. In 2 instances the first and second were associated with NHS factor VIII and in the second 2 the first was associated with Kryobulin in both patients, and the second attack with Kryobulin in one and FEIBA in the second. The right hand column in table six gives the ratio of hepatitis associated with different products in the proportion in which they occurred in this series.

One hypothesis to explain the results of the survey is that high purity U.S. Commercial factor VIII is contaminated with one virus, and the intermediate factor VIII being a 'cruder' product contains 2 non-A, non-B viruses. Therefore it is likely that one agent is removed in the fractionation process for high purity concentrate. There is as yet no evidence to suggest whether the U.S. Commercial associated agent is the same as one of these in the intermediate concentrates.

REINFECTION

Some recent evidence suggests that reinfection with non-A, non-B viruses may occur in haemophiliacs when transfused with a large quantity of factor VIII where a large dose of virus is present. This has been shown to occur with hepatitis B prior to the introduction of screening of plasma donations for HB$_s$Ag. It is possible that the cases associated with second or subsequent batches of Hemofil (see page 1) represent instances of this, though there may be other explanations.

FUTURE OF HEPATITIS SURVEILLANCE

The Working Party has considered the results of surveys collected so far and we wish to make the following recommendations:-

1) That the survey should continue by the pursuance of the surveillance scheme to follow changes in incidence of hepatitis related to changes in types of treatment and of blood products.

2) There is little information about the incidence of subclinical hepatitis. Some work on commercial contrate has been carried out at the Royal Free Hospital. However, there is a need for a prospective study comparing different products, and an application for a project grant has been made to the Medical Research Council to support a multicentre study in patients coming to operation. A feasibility study has so far shown that 4 out of 4 of patients studied who had had no previous transfusic of concentrate developed non-A, non-B hepatitis.

Table 1

FACTOR VIII/IX ASSOCIATED HEPATITIS 1974-9

CASES ASSOCIATED WITH DIFFERENT BRANDS 6 years

Type of Hepatitis	Brand Hemofil	Kryobulin	Factorate	Koate	Profilate	NHS Elstree	NHS Oxford	Cryoprecipitate	NHS IX
B	32	7	11	1	3	23	4	2	3
Non-B	87	25	22	10	6	21	10	9	7
Total	119	32	33	11	9	44	14	11	10

A Total of 283 episodes were reported involving 253 patients.
26 patients had two attacks of Hepatitis and 4 patients had three attacks.

Total 283 Non-B 197; Hepatitis B 86.

Table 2

FACTOR VIII ASSOCIATED HEPATITIS : COMMERCIAL AND NHS BRANDS
ATTACK RATES IN PATIENTS RECEIVING ONE PRODUCT

Year	Brand	Cases of Hepatitis						
		Non-B (Overt)	B (Overt)	B Symptomless	Total Overt Hepatitis	Total Transfused	Ratio Commercial/NHS Non-B	Ratio Commercial/NHS B
1977	Commercial	3 (2.67)	2 (1.78)	0	5 (4.46)	112	4.76	0.79
	NHS	1 (0.56)	4 (2.23)	0	5 (2.79)	179		
1978	Commercial	14 (7.7)	1 (0.5)	0	15 (8.3)	180	19.7	0.79
	NHS	1 (0.39)	2 (0.63)	0	3 (0.96)	313		
1979	Commercial	10 (6.32)	1 (0.63)	0	11 (6.96)	158	21.73	(Not significant)
	NHS	1 (0.29)	0	0	1 0.29)	342		

Table 3

FACTOR VIII AND IX ASSOCIATED NON-A, NON-B, HEPATITIS 1974-80

ASSOCIATION WITH PREVIOUS TRANSFUSION HISTORY

Total Cases Non-A, Non-B, Hepatitis 137

Previous Transfusion History	Freeze Dried Concentrate	Yes	No	Total
Current Attack of Hepatitis		31	106	
1. Associated with U.S. Commercial Concentrate		18(20%)	73(80%)	91
2. Associated with NHS or Immuno Concentrate		13(28%)	33(72%)	46

TRANSFUSION HISTORY - EFFECT OF TRANSFUSION OF DIFFERENT BRANDS OF CONCENTRATE

Brand Implicated	No. Cases Transfused U.S. Commercial	No. Cases Transfused NHS or Immuno	Total Previous Concentrate	Total No. Previous Concentrate
U.S. Commercial	4	15	18	91
NHS or Immuno	6	8	13	46

Hepati[illegible]s | N[illegible]epa[illegible]tis

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[illegible] of attack rate of first batch transfused to that of second or subsequent batches } = $\frac{20.7}{1}$

2. Kryobulin

151 Patient Exposures from 12 Batches → 6* | 76 Patient Exposures → 4

Therefore 12.58 Patient Exposures/Batch → 0.5/Batch | 6.33 " " /Batch → 0.33/Batch

Or 25.16 " " → 1.0 | 19.18 " " → 1.0

Or Ratio of attack rate of first batch transfused to second or subsequent batches = $\frac{19.18}{28.16} = \frac{0.76}{1}$

(* If 2 Cases possibly related to Hemofil included 18.8 patient exposures → 1.0 case of hepatitis on first transfusion).

Table 3

FACTOR VIII AND IX ASSOCIATED NON-A, NON-B, HEPATITIS 1974-80

ASSOCIATION WITH PREVIOUS TRANSFUSION HISTORY

Total Cases Non-A, Non-B, Hepatitis 137

Previous Transfusion History — Freeze Dried Concentrate

Current Attack of Hepatitis	Yes 31	No 106	Total
1. Associated with U.S. Commercial Concentrate	18(20%)	73(80%)	91
2. Associated with NHS or Immuno Concentrate	13(28%)	33(72%)	46

TRANSFUSION HISTORY - EFFECT OF TRANSFUSION OF DIFFERENT BRANDS OF CONCENTRATE

Brand Implicated	No. Cases Transfused U.S. Commercial	No. Cases Transfused NHS or Immuno	Total Previous Concentrate	Total No. Previous Concentrate
U.S. Commercial	4	15	18	91
NHS or Immuno	6	8	13	46

Table 6

MULTIPLE ATTACKS OF NON-A, NON-B HEPATITIS IN HAEMOPHILIACS

Brand Implicated First Attack	Second Attack	No. Patients	No. of Cases Associated each Brand Expessed as Ratio Second to First Attack
U.S. Commercial	Kryobulin (Immuno)	3	18/91
U.S. Commercial	NHS or Cryo	3	29/91
U.S. Commercial	U.S. Commercial	0	45.5/45.5
Kryobulin	FEIBA (IX) or Kryobulin	2	9/9
NHS VIII	NHS VIII	2	14.5/14.5
Kryobulin	NHS	0	18/29

HEALTH AUTHORITY

MOPHILIA CENTRE

Churchill Hospital.
Headington.
Oxford OX3 7LJ.

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29 APR 1982

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ophilia Centre Directors' Meetings

s f the Twelfth Meeting, held in
81, which have been revised in accord-
eived to my memorandum of 24th February.
te that the Thirteenth Meeting will
ield.
13th-14th September, 1982. Further
ting will be circulated nearer the

on.

C.R. Rizza
Consultant Physician

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Centre, as their Assistant Co-ordinator (Services). Her appointment would be for two years and would be funded by fou pharmaceutical companies. Sister Turk would work very closel with the Society's branches and also hoped to liaise with the Haemophilia Centres.

8. Factor VIII Quality Control Study

Dr. Savidge reported that it had not been possible for him to attend the first meeting of Dr. Poller's group which was held after his appointment as a member of the group. He hoped that it would be possible for him to attend future meetings. It was agreed that Dr. Savidge should continue to represent the Haemophilia Centre Directors on Dr. Poller's group and that Dr. Savidge would report back to the Haemophil Centre Directors at their next meeting.

9. Reports from Working Party Chairmen

a) Hepatitis

Dr. Craske presented the report which he had pre-circulated to all Haemophilia Centre Directors. The report summarised the findings of the three-year retrospective study which had just been completed. A full written report was in preparation for publication. Following the completion of the study, Dr. Craske had several recommendations to make to the Haemophilia Centre Directors.

i. He recommended that the surveillance should continue as n

ii. Subclinical hepatitis: A multicentre prospective study of hepatitis in first time treated/seldom treated patients was planned. It was hoped that the study would be supported by a grant from the Medical Research Council. This group of patients seem to be running a higher risk of contracting Non-

Non-B hepatitis whatever type of material was used for their treatment.

iii. Dr. Craske felt that it was important for the Working Party to continue to collect data on the batch numbers of materials received by patients who developed hepatitis. He thought that it might be necessary in the future to again ask for details of all patients who had received treatment with a particular "suspect" batch of concentrate.

iv. Post-Mortem Specimens: Dr. Craske said that he would be most interested to receive samples of liver from patients who came to autopsy, especially where there was evidence of chronic liver disease.

v. Chronic Hepatitis: Dr. Craske hoped the Directors would continue to report cases of chronic hepatitis to the Working Party on the appropriate form.

vi. Merck, Sharpe and Dohme had approached Dr. Craske to ask if the U.K. Haemophilia Centre Directors would be interested in an immunogenicity study of hepatitis B vaccine. He was looking into the possibilities of a trial of the vaccine and would contact the Directors again at a later date.

vii. Hepatitis-Free Factor IX concentrates: There had been claims from commercial firms that a factor IX concentrate was now available which was free of hepatitis. Dr. Craske thought that this may well be true but there were problems in proving the safety of each batch of concentrate made as only a limited number of laboratory animals were available for testing the materials.

Some discussion followed Dr. Craske's report and several questions were raised. Some Directors were unhappy about the

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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.

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 necessery 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,

A.L. Bloom C.R. Rizza

BLA/1/4 2207

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DEPARTMENT OF HEALTH AND SOCIAL SECURITY
FRIARS HOUSE
157-168 BLACKFRIARS ROAD
LONDON SE1 8EU
Telex 883669
Telephone 01-703 6380 Ext 4423

Your reference
Our reference

M Prescott Esq
H M Treasury
Gt George Street
LONDON SW1

31 July 1981

Dear Michael,

BLOOD PRODUCTS LABORATORY - REDEVELOPMENT

1. DHSS Ministers have decided that the Blood Products Laboratory (BPL) should be redeveloped within the NHS, and have instructed officials to begin planning and design work for the redevelopment. This letter seeks Treasury Stage I approval in principle for the project so that we can begin incurring expenditure on planning the redevelopment of the Laboratory. The capital cost is unlikely to be less than £17m at Survey 81 prices, and, when completed, is expected to increase the Laboratory's revenue costs from £2.2m to £5m per annum (staff costs represent some 50 per cent of total running costs).

Background

2. The National Blood Transfusion Service in England and Wales comprises 14 Regional Transfusion Centres run by RHAs, and 3 central blood laboratories (the Blood Products Laboratory, the Plasma Fractionation Laboratory and the Blood Group Reference Laboratory) run by a Joint Management Committee (DHSS and NW Thames Scotland has its own blood transfusion service and Protein Fractionation Centre.

3. BPL is essentially a pharmaceutical factory, employing some 125 staff. It receives plasma from Regional Transfusion Centres and fractionates it into various products - notably Factors VIII and IX for the treatment of haemophiliacs, protein solutions for the treatment of burns etc, and normal and specific immunoglobulins for the treatment of certain diseases. Some of BPL's products are not available commercially. The plasma is supplied without charge; at present BPL does not charge RHAs for its products, but this arrangement is to be reviewed. There is, meanwhile Vote provision (DZ4) for BPL to recover its costs for products and services made available outside the NHS. The cost of maintaining BPL is borne on NHS Vote X1-1, Subheads D3-D4.

4. A Laboratory was first established at Elstree in 1952, mainly to salvage plasma from time-expired blood. A new manufacturing unit was commissioned in the 1960s, since when fractionation technology has changed considerably, and the demand for blood products has increased far beyond what could reasonably have been predicted. As a result, the present Laboratory cannot meet the demands for products nor can it comply with modern pharmaceutical manufacturing standards (see paragraph 5 below) Although BPL's production has increased steadily over the years and is currently worth about £11m a year to the NHS, health authorities are obliged to supplement supplies from BPL with expensive and, because of the hepatitis risk, less safe imported commercial blood products at a cost of up to £10m annually.

E.H.

5. As you can see, EPL was not purpose built for manufacturing on the present scale. Although it originally conformed with the criteria for medical manufacturing thought appropriate at that time, it now falls considerably short of the standards of good pharmaceutical manufacturing practice applied by the Medicines Inspectorate under the Medicines Act 1968 - standards which successiv Ministers have agreed should be observed by NHS manufacturing facilities as wel as being required of commercial firms. In 1979 the Laboratory was inspected by the Medicines Inspectorate. The gist of the Inspector's report was that conditions of manufacture at EPL were unsafe and potentially hazardous to patients. The report concluded, "If /EPL/ were a commercial operation we would have no hesitation in recommending that manufacture should cease until the facility was upgraded to a minimum acceptable level". The Inspectors recommend the complete replacement of the Laboratory, with suitable short-term measures t improve things while rebuilding took place. They pointed out that the Laborato would have to be redeveloped, since much of its structure would not be useable beyond five years. Ministers agreed that in the interests of patients, closure of the Laboratory could not be contemplated, and they approved a short-term upgrading programme to remedy some of the deficiencies highlighted by the Medicines Inspectorate, and to enable EPL to increase the output of its two major products (Factor VIII and albumin), while consideration was given to the question of redeveloping the Laboratory. The cost of upgrading (almost £2m) is expected to be more than covered by the value of increased production before the present Laboratory is closed.

Redevelopment

Discussions with Industry

6. Last year, the Department investigated the possibility of a British pharmaceutical company rebuilding the facilities and manufacturing blood products on an agency basis for the NHS. Ministers concluded, however, that there was no place for a commercial company in the management of a service whic depended upon volunteer donors, and decided that the Laboratory should be redeveloped within the NHS. This was confirmed by Sir George Young in an Adjournment Debate on 15 December, although no commitment was given about the timing of redevelopment.

Planning/design work

7. Some of the preliminary planning work has already begun, and Ministers have agreed to the establishment of a small Policy Steering Group to act on behalf of the Joint Management Committee in planning the redevelopment. The specialised nature of the facility makes it difficult at this stage to estimate with any precision the cost involved. (A cost cannot satisfactorily be based on that of the Scottish plant which is on a much smaller scale and uses a different technology that would not be appropriate for the scale of production required in England and Wales). It would however be unwise to assume that the cost (including fees and equipment) of even minimal rebuilding (say, key areas only) will be less than £17m at Survey 81 prices spread over the period 1982/83 to 1986/87. It could well amount to substantially more. Costed design options should be available later this year, and I will write again when these are rea further work to produce a firm budget cost based on the chosen option and a well-developed design (Stage II) will take 6 months more.

8. A major factor in the cost is the target capacity required of the new Laboratory. For example, demand for Factor VIII is expected to rise from 55 million international units in 1980 to 100 million units by 1985 because of changes in the clinical use of the product and other factors such as the ageing of the haemophiliac population. I should perhaps explain that we tend to concentrate on Factor VIII demand when estimating the level of production [illegible] to enable the NHS to become self-sufficient in blood products because

E.K.

the production technology is such that if we achieve self-sufficiency in this Factor we will also achieve self-sufficiency in other products.

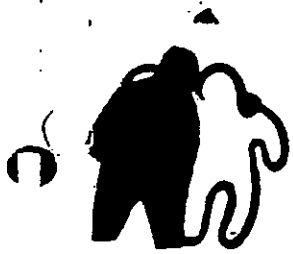
9. The 28th World Health Assembly on "Utilisation and Supply of Human Blood and Blood Products" urged World Health Organisation Member States to become self-sufficient in blood and blood products. The principle of self-sufficien has been fully endorsed by the Government, though Ministers have stated that i must inevitably be a long-term aim. To achieve it, however, would require health authorities to increase six-fold their supply of raw material to BPL, and we are currently studying a range of options in terms of target capacity o which we will be consulting the NHS. We may also be able to make some very limited use of the Scottish plant's capacity. It would seem, nevertheless, tha the economy of scale in the production process is such that it is unlikely tha we should make directly proportionate savings in the cost of redeveloping BPL if we were to aim at producing only a proportion of the products required by t NHS.

10. We are preparing an initial economic appraisal of the options available to us but a cost benefit analysis prepared at the end of last year, on the basis that redevelopment of the Laboratory to achieve self-sufficiency would cost £25m suggested that the outlay would be paid back (in terms of the replacement of imported commercial products) after six years' operation. We are working on better costings for the plasma supply side of the redevelopment equation as a matter of urgency, and we will refine our cost benefit analysis as more information becomes available. Given that the Laboratory has to be redeveloped the main question before us is the optimum target capacity, balancing costs of developing the Laboratory itself and of increasing the supply of plasma against savings to be made by reducing our dependence on imported blood produc

11. I would be grateful for early approval to proceed with planning on the basi outlined above. Because of the specialised nature of this development, I would be happy to arrange a meeting with those directly concerned if you feel it woul be of assistance.

Yours sincerely

D R HARRIS



THE
HAEMOPHILIA
SOCIETY

P.O. Box 9
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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.

[redacted]

4 May 1983

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PHLS

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61 Colindale Avenue
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Telex 8953942 (DEFEND G)
Telephone 01-200 6868

Our ref NSG/MHC Your ref

Dr. Ian Field
Dept. of Health & Social Security
Alexander Fleming House
Elephant & Castle
London SE1 6BY

9th May, 1983

Dear Ian,

Action on AIDS

Last week whilst you were away in Geneva a case of the Acquired Immune Deficiency Syndrome in a haemophiliac in Cardiff who had received USA factor VIII concentrate was reported. The case fits the recognised criteria for the diagnosis of AIDS. In the Lancet of 30th April three cases in haemophiliacs in Spain are reported; I have confirmed that they received USA factor VIII concentrate. In the same issue of the Lancet the tally of 11 reported cases in haemophiliacs in the USA is recorded and a paper describes a case in a multiply-transfused child in the USA.

I have reviewed the literature and come to the conclusion that all blood products made from blood donated in the USA after 1978 should be withdrawn from use until the risk of AIDS transmission by these products has been clarified. Appended is a paper in which I set out my reasons for making this proposal. Perhaps the subject could be discussed at an early meeting with haematologists, virologists and others concerned so that a decision may be made as soon as possible.

In conclusion may I say that I am most surprised that the USA manufacturers of the implicated blood products have not informed their customers of this new hazard. I assume no official warning has been received in the United Kingdom?

Kindest regards,

Yours sincerely,

Norman

N.S. Galbraith

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OXFORDSHIRE AREA HEALTH AUTHORITY (TEACHING)

OXFORD HAEMOPHILIA CENTRE

Tel: Oxford (0865) 64141
Ext. 575

Churchill Hospital
Headington
Oxford OX3 7L

24th June, 1983.

Dear

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

DA1: 44

/cont'd

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A2

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,

A.L. Bloom
Chairman, Haemophilia Centre Directors Organization

C.R. Rizza
Secretary, Haemophilia Centre Directors Organization

CONTESTANTS WANTED: SUPERMAN Contest Mon., June 7—Dillon's—Win over $275. Call (714) 692-1967 / You can sign up Monday night!

NORTH COUNTY GAY ASSOCIATION MEETS Weds., 7:30pm, at Aunt Joan's Deli, 105 N. Rancho Santa Fe Rd., San Marcos. For info call (714) 942 0730

...ou at ... couple ... maybe ... meals in evening) per week. Please age low 20's. CREATIVE, MAYBE INTO JOINT VENTURE IN PLANT SALES VIA SWAP MEETS & to shops. Salary + Send phone, short note about yourself & plans to Box 115, 4835 Voltaire, S.D. 92107. Picture optional

from gay men entered the plasma pool for haemophilia treatment

Books

for the Study of Human Resources, njunction with One, both in Los ngeles, are coming down the home-erch with their massive four-volume prehensive *Bibliography of Homosex-*, coedited by W. Dorr Legg and yne Dynes. It will contain 30,000 en- from Europe and America, re- ng such previous shorter bibliog-nies as that by Vern L. Bullough 76), William Parker (1971, 1977), berg & Bell (1972) and Ian Young). A project that would strain the ources of even a university, it has n grossly underfunded and needs tions to ISHR, 2256 Venice Blvd., 203, Los Angeles, CA 90006.

The worst reception of the season has accorded *The Nazi Extermination of sexuals* by Frank Rector (Stein & y), a work "unaccompanied by scho-y or reportorial skills," according to lew York *Times*. Looks like we'll to wait for Richard Plant's defini-book on the subject, due next year n Holt, Rinehart and Winston.

demise of Catalyst Press, described Young in these pages a few issues , has left him with unsold inventory, ng them poems by Judith Crewe), by Tom Meyer ($3.95), by Gavin d ($2), essays on dance by Graham son ($6.95), a memoir of erotic ad- es abroad by E.A. Lacey ($5) and titles. For complete list write Cata-, 315 Blantyre Ave., Scarborough, ., Canada, M1N 2S6.

andsome hardcover edition of *Ami mile*, a *chanson de geste* written nd 1200, has been translated from French by Samuel Danon and l N. Rosenberg. A powerful tale of ric love between two knights, a e version of the tale was translated William Morris (1896) and abridged in d Carpenter's *Iolaus: An Anthology riendship* (1902) from which the ex- in Byrne Fone's *Hidden Heritage* is This edition, in prose also, offers lysis of sources and helpful notes. $10 plus $1 from French Literature ications, Box 707, York, South na 29745.

The Gay Caucus of the American ksellers Association met at this year's a convention in late May. The was formerly coordinated by Paul es of the Lambda Book Club, whose mely death of cancer in early May is mourned by many of us. Informa-bout the Caucus is now available Michael Denneny, St. Martin's

AD

Cutter

TO: Those Copied

DATE: 1/6/83

FROM: John Hink

COPIES TO:

SUBJECT: AIDS Meeting Jan. 4th at CDC Atlanta

Copies To:

*Dr. K. Fischer	J. Cherry	*M. Mozen
S. Ojala/C. Moore	*C. Turner	J. Lundblad/D. Schroeder
*E. Potere	*T. Monroe(Clayton)	*M. Sternberg
R. Hein	E. Cutter	*R. Schwartz/R. Rousell
*R. Barden	J. Ryan, et al	J. Hjorth
		*W. Schaeffler

* meeting handouts attached

The meeting was well attended (80 to 100 people) by representatives of Gay Rights, CDC, FDA, Blood Banking Community, our Industry and the news media. Alpha had 8 attendees, Hyland and Armour 2 each. Rodell of Hyland and Martin of Alpha represented PMA. Cundall of Armour and Reilly represented ABRA.

Most of the morning was devoted to presentation of information and data by individual experts. (See attached agenda.) There is little question that these individuals knew their subject but as the day wore on, it was evident that experts in other fields paid little attention to these overviews. For instance it became obvious that few people understood, or cared about the differences between blood and plasma collection regulations or procedures and just how all this relates to manufacture of AHF. Consequently while one individual would be proposing some action with regard to AHF donors processed by plasmapheresis, he would refer to blood donors and an argument with a blood banker would arise. (This is just an obvious example. There appeared to be a considerable communication difficulty between experts within restricted but diverse fields and between experts and the non-scientific types on a number of other issues.)

I believe, but am not certain, that the objective of this CDC sponsored Workshop was to arrive at a meaningful recommendation for action(s) which would reduce the rapidly increasing number of AIDS disease cases being identified in the U.S. In particular it appeared they directed attention to the 8 or 10 hemophiliacs with confirmed or suspected AIDS assumed to have been caused by infusion of blood products and what should be done quickly to prevent a further increase in these numbers.

However, difficulties in communication and political power struggles made progress toward these objectives difficult. The anti-discrimination position of the gays, self-serving comments of blood bankers and lack of data to provide legitimacy to many proposals resulted in an overall stalemate. I felt a great deal of empathy for the meeting chairperson who I felt did a good job under the circumstances.

The subject of prison plasma came up twice during the meeting. While describing actions taken by the plasma collection group, Donahue mentioned a minor quantity of plasma used in the manufacture of AHF comes from prisons. Later in the day the Gay Rights countered what they considered a discriminatory proposal with "what about blood from prisons" but the question was stonewalled by the PMA representatives as immaterial to that discussion.

The two ever recurring proposals for actions to prevent AIDS in hemophiliacs seemed to be:

1. Conduct an educational campaign on the subject to all homosexual populations and allow them to voluntarily exclude themselves as blood and plasma donors. (Gay Rights definitely in favor of first part, greatly opposed to later.)

2. Conduct anti-HB_c testing of all blood and plasma donations - reject all "positive" from use in transfusable products. (Question of cost and implementation bothered many but not CDC, several objected on scientific grounds.)

A few of my raw notes to provide a better feel for the meeting follow: (Steve Ojala has a good taped reproduction of the whole meeting for those who wish further detail.)

Kellner - do we really have a problem related to blood and blood products

Evatt - increase of AHF cont. umpteen % since 1966 - at same time increase of AIDS in hemophiliacs . No indication that cases occurred prior to '82; association with blood not established yet.

Aledort - Do we have an agent here? Are we transmitting? Can it not be the situation that multiple infusions themselves of the product itself may cause patient to be a host for disease. 10 years ago we didn't have cirrohsis of liver in hemophiliacs - now have 9%, a dramatic increase.

Curran - if infectivity of donor increases then logic says infectivity of product would increase.

Perkins - 5 other patients received units from implicated Irwin donor, all followed for 6-13 mo. no symptoms.

Curran - CDC-T cell ration, lymphadenopathy evidence for AIDS speculative however, pneumocystis cases in hemophilics not. This is solid evidence of a new disease for hemophiliacs.

Armstrong - CDC - convinced disease is transmitted as an agent thru sexual acts and blood and blood products - we have to find the agent. He does not believe efforts to develop surrogate testing well placed.

Aledort - can we follow anti-HB_s as marker - maybe use ALT? anti-HB_c also came into discussion.

Donahue - believes HB_s serves as a good marker. AHF will shortly be improved in the sense the marker will be reduced. Cryo ppt has logistical problems. Pooling will ameliorate logistical problems. Industry will take action to assure donations from homosexuals not used in coagulation products. "HS-AHF" will be licensed within one year.

Ratnoff - does not believe that elimination of agent from mega donation pools will occur in next year or thereafter. Prefer to use cryo ppt. until genetic engineering product available.

McCaulley - Alpha working on heat pasteurized AHF, is excluding homosexual donors from donor panel.

Dr. Eblo - San Francisco population 7-8,000,000-homosexual population 100,000 - good working numbers.

Armstrong - do not screen donors on basis of sexual preference. Use voluntary exclusion by "risk group". Do we have a test that is indicative and not too expensive.

Gay Rights representative - has personal concern about blood needs.

Voeller - counterproductive to openly exclude "gay" voluntarily or otherwise; will have homosexuals donate just to "prove" they are not.

Kellner - suggest pilot operation S.F.-Irwin; L.A.-ARC; N.Y. Blood Center work for 6 mo. or so - each develop program.

Fetzer - proposes to run lymphadenopathy, anti-HB_c at his shop.

Unknown - to determine anti-HB_c on all donations would cost at least $100,000,000 per year.

Gerity - anti-HB_c is not licensed and will not be this year, besides doesn't think it a good marker.

Aledort - how do we know we accomplish anything by running test and excluding donors; if everybody runs test, where are our controls.

.....and so it went.

MY RECOMMENDATION FOR CUTTER

1. Institute a "High Risk Donor" educational-voluntary exclusion program at all Cutter source plasma collection facilities.

2. Continue to exclude all plasma collected from centers dealing predominately with homosexual populations (i.e., anti-HB_s plasma collection facilities) from use in coagulation products.

3. Take no extraordinary actions (other than #1 above at our two prison centers which supply about 3000 liters/mo, (there are no data to support the emotional arguments that prison plasma collected from adequately screened prisoners is "bad". To exclude such plasma from manufacture of our coagulation product would only be a sop or gratuity to the Gay Rights and would presage further pressure to exclude plasma collected from the Mexican border and the paid donor.)

4. Continue to attend further meetings of this type, accumulate and evaluate all information and data developing on AIDS and make independent investigations on the cost, implementation and potential effectiveness of using new (to Cutter) assay procedures.

R. Barden for
J. Hunt

JHH:gma
*Attachments:

Sources of Plasma (Human) for Fractionation "CONFIDENTIAL - MDL 986"
Cutter Laboratories, Inc., August 6, 1974

Raw Material Supplied - Type I-C. Firm owned and operated by others, not Cutter, plasma collected by plasmapheresis, most with Cutter equipment, according to their own procedures which have been approved by Cutter.

Facility	KIH Establishment License No.	Facility Location Code
Banco de Sangre Biologico Mexicano, S.A. Colima No. 126 Mexico D.F.		
Banco de Sangre Biologico Mexicano,S.A. Via Lactea No. 4 Mexico, D.F.	-	MM
Banco de Sangre Biologico Mexicano,S.A. Circuito Margaritas 156 San Bartolo Xaxalpan Edo. de Mexico	-	MX
Industrias Biologicas Mexicanas,S.A. Av. Lopez Mateos 335 Netzahualcoyotl, Estado de Mexico	-	MI
Plasma Mexicano,S.A. Alianda 104 Toluca, Mexico	-	MT
Binary Associates		
Binary Plasma 1840 South Wahsatch Colorado Springs, Colorado 80906	-	BC
Geneva Plasma Center 994 Geneva Avenue San Francisco, California 94112	-	BG
Tennessee Street Plasma Center 337 Tennessee Street Vallejo, California 94590	-	BV
Biotechnics Research, Incorporated		
Stockton Donor Center 246 E. Church Street Stockton, California 95203	-	BT
Sacramento Donor Center 1517 E Street Sacramento, California 95814	-	BC
Blood Plasma Services, Inc. P. O. Box 750 Clarksdale, Mississippi 38614		
Blood Fractions of Tulsa, Inc. 401 South Detroit Avenue Tulsa, Oklahoma 74120	-	X
Blood Plasma Services, Inc. 305 West Main Street Chickasha City, Oklahoma 73102	-	B

SUPERSEDED

JKB 007727

MSP000124

MDA005768

Sources of Plasma (Human) for Fractionation
Cutter Laboratories, Inc., August 6, 1974

Raw Material Supplied - Type 2-3. Cutter owned, plasma collected by plasmapheresis with all Cutter equipment, according to Cutter's procedures.

Facility	FDA Establishment License No.	Facility Location Code
Arizona State Prison P. O. Box 349 Florence, Arizona 85232	-	F
Greenville Plasma Center 618 Washington Avenue Greenville, Mississippi 38701	-	GN
Hattiesburg Plasma Center 610 Main Street Hattiesburg, Mississippi 39401	-	HT
Jackson Plasma Center 123 East Griffith Jackson, Mississippi 39202	-	JK
Louisiana State Plasma Louisiana State Penitentiary Angola, Louisiana 70712	-	AL
Meridian Plasma Center 2104 8th Street Meridian, Mississippi 39301	-	MN
Mobile Plasma Center 550 Church Street Mobile, Alabama 36602	-	MZ
San Diego-Fifth Center 1025 F Street San Diego, California 92101	-	D

Cutter-owned and affiliated plasma centers are located in the following cities:

Auburn, AL
Birmingham, AL
Mobile, AL
Montgomery, AL
Tuscaloosa, AL
Florence, AZ
Phoenix, AZ
Scottsdale, AZ
Tempe, AZ
Berkeley, CA
Long Beach, CA
Oakland, CA
Sacramento, CA
San Diego, CA
Stockton, CA
Colorado Springs, CO
Denver, CO
Pueblo, CO
Daytona Beach, FL
Fort Lauderdale, FL
Port Meyer, FL
Gainesville, FL
Jacksonville, FL
Orlando, FL
Augusta, GA
Macon, GA
Davenport, IA
Des Moines, IA
Fort Wayne, IN
Indianapolis, IN
Muncie, IN
Louisville, KY
Kansas City, KS
Baton Rouge, LA
Lafayette, LA
Ann Arbor, MI
Detroit, MI
Flint, MI
Kalamazoo, MI
Lansing, MI
Ypsilanti, MI
Minneapolis, MN
Kansas City, MO
Springfield, MO
Greenville, MS
Jackson, MS
Meridian, MS
Billings, MT
Lincoln, NE
Albuquerque, NM
Indian Springs, NV
Las Vegas, NV
Stewart, NV
Cincinnati, OH
Columbus, OH
Oklahoma City, OK
Tulsa, OK
Eugene, OR
Easton, PA
Pittsburgh, PA
Scranton, PA
Columbia, SC
Rapid City, SD
Nashville, TN
Austin, TX
Brownsville, TX
Corpus Christi, TX
Dallas, TX
Del Rio, TX
Eagle Pass, TX
El Paso, TX
Houston, TX
Laredo, TX
Lubbock, TX
McAllen, TX
San Antonio, TX
Ogden, UT
Salt Lake City, UT
Norfolk, VA
Roanoke, VA
Seattle, WA
Milwaukee, WI

A18

(21)

The Revd Alan J Tanner MA
Chairman
The Haemophilia Society
PO Box 9
16 Trinity Street
LONDON
SE1 1DE

When we met on 8 September, I promised to write to you confirming some of the information I gave you of our meeting. I am sorry I have not done so sooner.

I would first of all like to reassure members of the Haemophilia Society of the Government's commitment to self-sufficiency in blood products. The Central Blood Laboratories Authority has embarked on a £21 million redevelopment programme. The target date for completion is the end of 1985, by which time the Authority aim to have a new laboratory of a size capable of meeting the demands of England and Wales for blood products.

The manufacture of any product is of course dependent upon an adequate supply of raw material - in this case blood plasma from Regional Transfusion Centres. Regional Health Authorities have agreed in principle to the need for national self-sufficiency in blood products, and are examining ways to gradually build-up plasma supplies for the Blood Products Laboratories to the necessary volume.

Meanwhile, until self-sufficiency in Factor VIII is achieved we shall be dependent upon additional material to make up the short-fall in the home-produced supply and this is imported primarily from the USA. The question whether these imports should cease has been widely publicised and is a cause of great concern to haemophiliacs, but against the possible risks of infection from AIDS must be balanced the obvious risks from not having enough Factor VIII. In March this year the US Food and Drug Administration initiated new Regulations for the collection of plasma, designed to exclude donors from high-risk groups. Although future supplies of Factor VIII both for export and for use in America will be manufactured from plasma collected in accordance with these Regulations, there is still a quantity of stock, some already in the UK and more in America awaiting shipment here, which has been made from "pre-March" plasma. The FDA has recently decided not to ban the use of similar stocks intended for the USA market because to do so would cause a crisis of supply. The same considerations apply here.

103

You suggested that genetically engineered Factor VIII, because it would not carry the risks associated with human plasma, may be the ultimate answer, but this is very far from being a reality at the moment. Although it is being intensively researched, there is still a long way to go before it can even be estimated when such material might become available.

Perhaps I could also mention Government-funded research efforts into AIDS generally. May I reassure you that we are most concerned to fill the gaps in our knowledge of this disease as only then shall we be able to make inroads into prevention and treatment. As I mentioned when we met, the Medical Research Council has established a Working Party to review scientific knowledge and research on AIDS in this country and abroad and to advise the Council accordingly. It will encourage contact and co-operation between research workers in this field and will also advise on grant applications for research on AIDS. The Council has in fact already awarded one such grant, under which a particular aspect of the depression of the immune system in homosexual males with AIDS and related disorders will be investigated. Other applications are under consideration.

I hope you will agree that the establishment by the Council of this group of eminent professionals provides the best hope of ensuring that centrally-funded research is soundly based scientifically and does not duplicate work being done elsewhere. We have of course much to learn from the experience of the United States in this field and any attempt to develop research in the Uk must take full account of research being undertaken there. I understand that the Working Party will have this very much in mind, the Medical Research Council being in close touch with activities sponsored by the US National Institutes of Health.

A further, but somewhat different, aspect of centrally funded investigation into AIDS is the work being carried out by the Communicable Disease Surveillance Centre of the PHLS at Colindale. They have established a surveillance system to detect AIDS in the UK and to monitor trends in its incidence. This involves detailed notification of all individual cases of AIDS which will provide an invaluable data base for those undertaking research. The PHLS is represented on the MRC Working Party.

THE LORD GLENARTHUR

AIDS
3245

Dr Abrams

MEETING OF THE HAEMOPHILIA REFERENCE CENTRE DIRECTORS - 10 DECEMBER 1984

1. Background

So far three patients with haemophilia are known to have contracted AIDS, two of these have died. About twenty four other cases are known to have persistent generalised lymphadenopathy (PGL). Some eight hundred haemophiliac patients have now been tested for HTLV III antibody. The incidence of antibody to HTLV III in haemophiliac patients overall is of the order of thirty five per cent. However seventy five per cent of patients with severe haemophilia have the antibody. Of four thousand haemophiliac patients some two thousand can be considered to be severe the remainder being moderate and mild cases.

2. As you know I was invited to the above meeting held at CBLA headquarters and arranged to discuss the implications of AIDS for haemophilia patients. We can expect a letter from the Directors to the Department with a statement of their policy decisions. A letter will also be sent to all Haemophilia Centre Directors advising of the decisions taken by the Reference Centre Directors. The following main issues were discussed:

a. Testing haemophiliac patients for HTLV III antibody

Directors would like to test all haemophiliac patients in order to establish their antibody status. [redacted](PHLS) thought that provided they were not overwhelmed by all specimens at once they could test most of these patients. They would need additional resources to do this.

Inconsistencies in the results of the tests reveal that a study of the haemophiliac population would provide the invaluable material to increase our knowledge of the disease. [redacted] at PHLS has developed the same test as [redacted] using the Gallo isolate obtained with his permission through [redacted]. I believe a study of haemophiliac patients could be regarded as a research project now and [redacted] could provide facilities for doing these tests. However I was told that little support has been given to the relevant section of the Virus Reference Laboratory while working on a shoe string. It may be appropriate to ask PHLS to treat testing as a priority.

b. Dealing with haemophiliac patients

It was agreed that all haemophiliac patients should be counselled to use barrier methods of contraception in order to protect their heterosexual contact. Patients who asked for their HTLV III antibody test results should be informed of them otherwise it is up to individual Directors to decide whether or not they wish to tell the patients their results.

(c) Use of heat treated Factor VIII

After prolonged discussion it was agreed that children should be treated with cryoprecipitate or if necessary with heat treated Factor VIII. New haemophiliac patients should be treated with heat treated Factor VIII. It was agreed that it was not proven that heat treatment inactivated HTLV III and that was essential for studies to be made of sero negative patients given heat treated material in order to monitor the efficacy of the heat treatment. Moreover the virologists considered that there was no evidence that haemophiliacs already HTLV III antibody positive would suffer if they received further doses of antigen (this view is based entirely on theoretical consideration). Nevertheless Directors felt that they should use commercial heat treated Factor VIII in preference to commercial non heat treated Factor VIII. Most agreed that untreated BPL Factor VIII could continue to be used until heat treated Factor VIII was available from Elstree. There will be some Directors who are not willing to do this, notably [redacted] of Newcastle who has declared that all patients will have 'safe' heat treated Factor VIII and has already had sanctioned by his District the extra money required to buy the heat treated product. He will therefore be prescribing commercial heat treated Factor VIII on a named patient basis until the Committee on Safety of Medicines have agreed to variations of license.

There was a little concern that a variation in license of all the commercial heat treated Factor VIII might result in a shortage of heat treated Factor VIII and the variations would prevent the usage of non-heat treated Factor VIII if necessary.

[redacted] is able to produce a certain amount of heat treated Factor VIII which he can release for children and new patients. He cannot greatly increase production until the two new ovens arrive. (Scotland have been able to produce the heat treated product because they are using a [redacted] method of heat inactivation, that is two hours at 68 degrees centigrade. The commercial companies and BPL are using 24 hours at 68 degrees centigrade).

(d) Handling of HTLV III antibody postive plasma samples

From information, mainly I understand gathered from their MLSO's who presumably have had copies of drafts from ACDP members Directors were aware of the likely recommendation in the ACDP Interim Guidelines. They were much concerned at the implications for patient care once samples from haemophiliacs are known to be HTLV III antibody positive. It will mean that all coagulation testing will have to be carried out in containment level 3 laboratories. It seemed that in Scotland this would be impossible at the present time.

Directors consider that they should have been drawn into the discussion about the Guidelines and the Chairman intends to write to [redacted]

I attach a copy of the Newcastle policy developed folowing the death of a haemophiliac who had contracted AIDS. Directors agreed that they would recommend that patients relatives should not donate blood for the time being.

Alison Smithies

12 December 1984

Dr Alison Smithies
MED SEB
Room 1025a Hannibal House
Ext 3487

copies

[redacted]

1989 - July

Ortho HCV 1.0 free of charge evaluation product for UK Blood Transfusion Centres

1989 - November

Ortho HCV 1.0 ELISA commercially launched in Europe, routinely available for screening/evaluations to detect Hepatitis C Virus (HCV).

1990 - January

Belgium - blood donor screening for HCV initiated, primarily as trial period, which was subsequently mandated.

1990 - March

France - 1st March, all Blood Donor Centres initiate HCV antibody screening, following publication of a decree making HCV testing mandatory for blood donors.

Holland - All blood donors screened for Hepatitis C Virus antibodies.

Spain - Pais Vasco (Blood Centre) tested donors for HCV.

1990 - April

Finland - Mandatory screening of blood donors for HCV.

Germany - 50% of Blood Donor Centres initiated HCV screening.

1990 - September

Initial evaluations of HCV product at 3 Blood Transfusion Centres (Newcastle, North London, Glasgow) in the UK; utilising Ortho Diagnostics and Abbott Laboratories products.

1990 - October

Spain - All regions performed HCV screening on blood donors.

1991 - February

Ortho HCV 2.0 ELISA commercially launched in Europe. Organon Teknika launched a (UBI) Hepatitis C Virus screening product.

1991 - March

Scandinavian countries (Denmark/Sweden/Norway) initiate mandatory HCV screening on all blood donors.

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PAGE

C4

1991 - March

Repeat trials on Ortho/Abbott and Organon products at UK Blood Transfusion Centres.

1991 - April

Germany - all Blood Donor Centres now perform HCV screening on every donation.

1991 - September

HCV screening initiated on blood donations in the UK. Mandatory screening at all donations from 1st October 1991.

1992 February

Murex Diagnostics launch HCV screening test in UK.

1993 - January

Ortho HCV 3.0 ELISA launched in Europe.

A21

UNDERTAKING TO BE GIVEN BY AN INDIVIDUAL NOT UNDER A DISABILITY IN ACCORDANCE WITH CLAUSES 12, 15, 17, 18, OR 20 OF THE DEED OF THE MACFARLANE (SPECIAL PAYMENTS) (NO.2) TRUST

THIS DEED of undertaking is made the xxxxxxxxx day of xxxxxxx 1991 by xxxxxxxxxxxxxxxxxxxx of xxxxxxxxxxxxxx.

In expectation of receiving from the Macfarlane (Special Payments) (No.2) Trust the sum of £xxxxx I undertake with the Secretary of State for Health that I will not at any time hereafter bring any proceedings against the Department of Health, the Welsh office, the Licensing Authority under the Medicines act 1968, the Committee on Safety of Medicines, any district or regional health authority or any other Government body involving any allegations concerning the spread of the human immuno-deficiency virus or hepatitis viruses through Factor VIII or Factor IX whether cryoprecipitate or concentrate) administered before 13th December 1990.

Signed and delivered by)
)
xxxxxxxxxxx)
)
as a Deed in the presence)

Name and address of witness:

.....

.....

.....

.....

A 22

CONCRETE
films

November 12, 2003

Stephen Grimes QC
Deans Court Chamber
24 St John Street
Manchester
M3 4DF
England

Subject: Peter Longstaff & U.S. prison blood

Dear Mr. Grimes:

For more than three decades, the Arkansas prison system profited from selling blood plasma from inmates infected with viral hepatitis and AIDS. Thousands of unwitting victims around the world who transfused products made from this blood died as a result. Mr. Peter Longstaff, whose case is to be heard before the High Court, is one of many British victims of U.S. prison plasma.

As a journalist and documentary filmmaker, I have conducted a six-year investigation into this subject. That investigation uncovered a great deal of information relevant to the Longstaff case, demonstrating that:

- U.S. federal regulations were violated, allowing drug users, prostitutes, and sick inmates to routinely donate in the prison plasma programs.
- Blood companies claimed prison plasma was safe even though they knew it was harmful.
- Despite 20 years of blood industry studies showing that prisoners were a high-risk population for diseases, drug companies continued taking blood from inmates because it was cheap.
- Factor concentrate products made from prison plasma were exported throughout Europe and the United Kingdom, and British officials were warned of its risks.

I have conducted in-depth interviews with former officials from the Centers for Disease Control and the Food and Drug Administration, state prison officials, former employees, high-ranking politicians and inmate donors, all of which paint a horrifying portrait of an industry with few safeguards.

Hemophiliacs were considered "canaries in the coal mine" for blood-borne diseases. But while patients like Peter Longstaff were kept in the dark about the use of prison plasma in their

Concrete Films • PO Box 24701 Little Rock, AR 72221 • 501.310.4843 • email KellyDuda@aol.com

medicines, the pharmaceutical industry was aware of the health threats associated with this dangerous source early on, long before AIDS. In fact, the first plasma centers were in prisons.

In the early 1960s, Cutter Labs opened its first collection facilities in Oklahoma, Alabama and Arkansas prisons and the "biologics" industry was born. So, too, were the problems.

The prisons were plagued with viral hepatitis outbreaks because of sloppy practices and the use of unsterile equipment. Hundreds of infections and an undetermined number of inmate deaths occurred as a result. More prison operations sprang up in the late 1960s and 1970s as medical journals began reporting cases of viral hepatitis in users of blood coagulation products.

Yet, the bloodletting was allowed to continue, even as the Nuremberg Code was cited and federal investigators labeled prisoners a "high-risk group of plasma donors" for spreading hepatitis and other diseases.

In 1970, a federal court declared the entire Arkansas prison system unconstitutional. Underweight and malnourished prisoners worked as slave labor. Torture devices such as "the strap" and the "Tucker telephone" -- a hand-cranked telephone that sent electrical shocks to an inmate's testicles -- were routinely used. Medical care was nonexistent. Inmate trusties held guns on other prisoners, held keys to the barracks and ran the plasma program.

Despite this, Cutter Biologics continued to purchase plasma from this and other prison systems.

The prison system remained unconstitutional in May 1980, when for three days, Peter Longstaff infused several vials of Koate, the brand name of Cutter's factor concentrate, to stop a bleeding episode. He had no idea when he took his medicine from Lot number NC 8196 that it was made with the plasma of 297 inmates from Arkansas and an undetermined number of convicts from Avon Park, Florida.

John Andervont, a former inspector and retired director of Blood Center Licensing for the FDA, remembered catching inmates performing phlebotomies at the Arkansas prison. Bill Douglas, a former Arkansas inmate infected with hepatitis C, who sold plasma regularly at the time Longstaff infused Cutter Lot NC 8196, stated: "They didn't care. If you could crawl to get there you were able to give blood."

In July 1982, operators were forced to pay a $250,000 settlement after products made from tainted plasma were shipped to Europe. Two international recalls of contaminated plasma in the U.S, Canada, Spain, Italy, Switzerland and Japan were unsuccessful. The following year, the FDA shut down the operation and revoked its license when it was discovered that an inmate clerk had allowed diseased prisoners to donate. But after a six-month suspension, the center was up and running again with the full approval of federal regulators and the Clinton state leadership.

In addition to Cutter (Bayer), Baxter Healthcare, a division of Hyland Laboratories, and Alpha Therapeutics purchased and used prison plasma in their manufacturing of factor concentrate.

Given the above information, and the fact that even before AIDS, the hepatitis rate among prisoners was estimated to be 30 to 60 percent higher than that of the outside population, it becomes clear that Peter Longstaff and others like him should not have been advised to take medication made from sources like this.

Should the United Kingdom choose to hold a full and open public inquiry into contaminated blood products including imported plasma, I would welcome the opportunity to present more information/evidence about the prison plasma trade. People around the world need to know what happened.

Sincerely,

Kelly M. Duda

Concrete Films – PO Box 24202, Little Rock, AR 72221 – 501.351.4844 – Email: KellyDuda@anl.com

A23

March 22, 2001

Mr. Tony Blair, British Prime Minister
10 Downing Street
London, England

Dear Mr. Blair:

My name is Linda Tant Miller and I live in the state of Washington in the United States. The purpose of this letter is to provide you some of the information to which I am privy regarding the collection of HIV and hepatitis-tainted human blood plasma from the Cummins Unit of the Arkansas Department of Correction, (ADC) and its distribution throughout the world.

My brother, Bud Tant was a prisoner in the Cummins Unit from 1984 until his death from hepatitis C on March 14, 1999. Neither my brother nor his family was aware of the fact that he had this virus until approximately 1996, but according to John Byus, the current Medical Administrator of the ADC, Bud had the virus at the time he was first incarcerated there. During part of the time that my brother was donating plasma, Mr. Byus, a Registered Nurse worked in the Cummins Unit Infirmary, so he is in a position to know this fact. Bud was, nonetheless permitted to donate plasma at every collection session from 1984 until the program was terminated in 1992.

I first learned of the sickness in Canada as a result of the Cummins Unit plasma just prior to my brother's death, but I didn't have time to address the subject in depth until after he died. As I watched my brother die a death more gruesome and agonizing than I'd ever dreamed in my worst nightmares, I realized that millions of people all over the world would suffer his same horrendous fate and their families would stand helplessly by, suffering the same grief and agony we were enduring. I realized that most of them would never know the source of their infection, but **I knew**, and I vowed to my brother that I would see the atrocity exposed and those responsible for it brought to justice. I have devoted my life to this cause since that date.

Several years ago Sgt. McAlpine of the RCMP, indicated to me that they had little hope of bringing to justice the ADC administrators responsible for the knowing and deliberate harvesting and sale of tainted plasma, because by the time they got to Arkansas the paper trail was gone, so I promised him that I would find eye-witnesses and participants who would be willing to testify to what happened. I have since that time located many current and former inmates, former Cummins Unit Plasma Program staff members and a former ADC Compliance Officer who are anxious to testify to the facts of this crime.

Here are just a few of the facts I have uncovered:

- Known homosexual prison prostitutes, even those in the final stages of AIDS were routinely permitted to donate plasma.
- Men who were bloated and jaundiced from the final stage of hepatitis were routinely permitted to donate plasma.
- Even when available, tests for HIV and hepatitis were seldom utilized, and when they were, results were often falsified.
- Needles re-sharpened with sand paper and collection tubing were re-used from inmate to inmate, thereby cross-infecting virtually the entire donor base.
- The collected plasma was stored in a freezer that was often out of order. Plasma rendered unfit by thawing was re-frozen and shipped out in regular shipments.
- Plasma that was rejected by the plasma brokers as unfit was returned to the Cummins Unit for destruction. Out of each returned case of plasma, one or two units were destroyed and the rest was re-frozen and re-shipped.
- During periods of time when the US Food and Drug Administration had shut down the Cummins Unit program due to their unsafe practices, the ADC administrators continued to collect and sell plasma, using names collected from the local telephone book and selling it through a community plasma center.

All of these charges and more can and will someday be proven in a court of law.

As I'm sure you are aware, many thousands of innocent British citizens have been sickened and killed due to the deliberate crimes committed by the MEDICAL PERSONNEL who administered the Cummins Unit Plasma Center. I hope therefore that you will join your voice to those of us who are working to see justice served in this matter. I urgently implore you to use the power of your office to spur the FBI and the US Department of Justice to implement a full-scale investigation of the people and institution that made the tainted plasma available to the pharmaceutical companies. Had it not been for the greed and corruption of the plasma collectors the people and governments of the world would not now be facing the tragedies and financial burdens with which we're now forced to struggle

I know all too well the effect my brother's suffering and death has had on my family. We will never be the same. I no longer work at a paying job because seeing justice done in this matter is far more important to me than my own personal comfort and finances. My parents have developed health problems due to the stress and grief of our tragedy that will soon see both of them in their graves. My sister and I have debilitating flashbacks to the time of our brother's dying which haunt us day and night, turning our lives into nonstop nightmares of pain and grief. Multiply our suffering by BILLIONS, since the secondary infections from the Cummins Plasma Program will continue to the end of time unless science discovers cures or vaccines against the plague the Arkansas Department of Corrections and its employees have unleashed upon the world. Sir, the people who are guilty of this atrocity are the worse criminals in history and I hope you will be as incensed and determined to see justice done as I am.

I also pray you will heed the pleas of my good and wise friend Carol Grayson and take the steps necessary to see to it that no other British subjects will be infected with deadly diseases during medical treatment and to assure that fair and equitable compensation is made to ALL the victims of this atrocity.

For more information on the Cummins Unit Plasma Program please visit my web site at http://www.geocities.com/bloodcows. In addition, a friend of mine is producing a documentary film about the Cummins Unit Plasma Program that contains yet more testimony and information. It will air in a few months and I will notify you of the date and time as soon as they are known.

I will appreciate a response to this letter, apprising me of your thoughts and intentions regarding this atrocity and the plight of the victims.

Thank you for your time and attention to this urgent matter of justice.

Sincerely,

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