INFECTED BLOOD INQUIRY

OXFORD HAEMOPHILIA CENTRE

Contents

INTRODUCTION

1. This Note is intended to provide an overview of the Oxford Haemophilia Centre ("the Centre") and its activities, based on the documents received by the Inquiry. It covers, broadly, the timeframe from the late 1960s to the early 1990s. The oral presentation on 30.09.20 will draw on these documents (as well as referring to evidence of people who were treated at the Centre). The Inquiry hopes to receive written and/or oral evidence from relevant clinicians relating to the Centre's policies and practices; it is possible, therefore, that there may be a further hearing day or days looking at the Centre's policies and practices.

2. The Centre was established in 1967 at the Churchill Hospital, Oxford. As well as being a treatment centre, it had a research laboratory and a blood plasma fractionation laboratory on site (the Plasma Fractionation Laboratory, "PFL"). It was established as one of seven supra-regional Reference Centres and became the largest haemophilia centre in the country. Its multi-disciplinary team treated both adults and children. A large proportion of patients came from outside the area for treatment.[1]

3. The Centre built on earlier work conducted at the Blood Coagulation Research Unit at the Churchill Hospital under the leadership of Dr RG Macfarlane. The new Centre's first Director was Dr Rosemary Biggs, who served until 1977. On her retirement, Dr Charles Rizza took over as Director, and held the post until his retirement in 1993.

4. Other key personnel at the Centre from its inception to the early 1990s were:

    a. Dr Ethel Bidwell, research scientist and Head of the PFL.

    b. Rosemary Spooner, researcher, who collected and analysed the annual data returns from all the Haemophilia Centres.

[1] Over 50% in 1976 (OXUH0001052_001). The Centre also provided a supra-regional service for factor VIII assays and other investigations (OXUH0003765_027, OXUH0003765_026).

c. Dr James Matthews, Associate Specialist.

d. Mrs Mary Fletcher, Clinical Nurse Specialist.

e. Dr JK Smith, Chief Project Scientist, PFL.[2]

5. Dr Joan Trowell, who worked at the Radcliffe Infirmary/the John Radcliffe Hospital in Oxford seeing patients with acute and chronic liver disease, would, at the request of Dr Rizza and Dr Matthews, attend the Centre to see patients who had received blood products and had developed abnormalities of liver function.[3] She was also a member of the Hepatitis Working Party set up by the Haemophilia Centre Directors Organisation ("UKHCDO") and involved in some of the research studies undertaken at the Centre.

Key documents

6. Key documents include the following:

a. Dr Rizza's statement made as an expert witness in the HIV Litigation in 1990[4] (his "Litigation Report"). This provides a detailed account, although its focus is general rather than specific to Oxford, and it was, of course, prepared at the request of the defendants in the litigation.

b. The transcript of a Witness Seminar held at the Wellcome Institute for the History of Medicine, London on 10.02.98. This includes input from Dr Bidwell, Dr Rizza, Dr Matthews and Professor Robert Duthie, Orthopaedic Surgeon at the Nuffield Orthopaedic Centre, Oxford.[5]

c. The transcript of Professor Giangrande's evidence to the Lindsay Tribunal (although it should be noted that he did not become a consultant at Oxford until

[2] Dr Smith's witness statement is WITN3433001.

[3] Dr Trowell's statement is WITN3740003.

[4] HCDO0000003_001. Dr Rizza was one of a number of clinicians instructed as "experts" by the defendants – see, e.g., OXUH0000002_018.

[5] RLIT0000022.

1991 and the thrust of his evidence was, unsurprisingly, concerned with matters from the early 1990s onwards).[6]

d. Other relevant documents are listed in the footnotes to this note.

[6] LIND0000330.

USE OF BLOOD PRODUCTS

7. The PFL was a smaller operation than the Blood Products Laboratory ('BPL') at the Lister Institute in Elstree. However, it did supply blood products to the Oxford Haemophilia Centre, other Haemophilia Centres and hospitals.[7] In particular, the PFL came to specialise in the manufacture and supply of factor IX.[8]

8. An article by Dr Rizza in June 1970 identified the *"therapeutic materials at present available for the treatment of haemophiliacs"*: whole blood; fresh frozen human plasma; cryoprecipitate prepared from human plasma; freeze dried human AHG; freeze animal AHG.[9] The same article described the role of the (then) 36 designated haemophilia centres, commenting that *"Full use must be made of these centres if the patient is to be treated to his best advantage and prevented from becoming an ill-educated cripple and a burden to himself, to his family and to society"*.

9. Due in part to its co-location with the PFL, the Centre made the switch from cryoprecipitate to factor concentrates relatively early. In a 1977 article, Dr Biggs wrote that:

> "*It will be seen that at Centres other than Oxford the amount of cryoprecipitate used has increased steadily over the years ... This increase has been due to the efforts made by Regional Transfusion Centres. In 1974 cryoprecipitate still accounted for nearly 80% of all material used (at Centres other than Oxford). By contrast, at the Oxford*

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[7] Including the Royal Free – see letter dated 28.01.72 from Dr Biggs to Dr Dormandy detailing an increase in supply of factor IX at OXUH0000923_002.

In OXUH0001060_002, Dr Rizza wrote on 25.06.75 that the PFL did supply concentrate to other Centres and to hospitals but declined to supply factor IX concentrate to St Albans City Hospital due to possible contraindication for use in patients with liver disease.

[8] See e.g. OXUH0000949 03.12.70 – letter from Dr Bidwell to Dr Meynall at the Queen Elizabeth Hospital, Birmingham regarding supply of factor IX; OXUH0001060_001 03.06.75 - letter from P. M. M. Roberts, St Albans City Hospital to Dr Rizza, requesting a supply of Factor IX concentrate; OXUH0001057_001 22.12.76 - letter from N. M. Naik, West Kent General Hospital to Dr Biggs, requesting freeze-dried factor IX concentrate for therapy in Christmas disease.

[9] HSOC0022512 - 'The Management of Haemophilia" by C. R. Rizza, reprinted from The Practitioner, Symposium on Disorders of the Blood, June 1970, Vol. 204, pages 763-772.

Centre cryoprecipitate has never constituted more than 43% of material used and since 1971 the proportion of cryoprecipitate has fallen steadily… In Oxford, plasma previously used to make cryoprecipitate is now fractionated to make NHS concentrate. The amount of NHS concentrate used in Oxford reflects close proximity and the good co-operation between the Oxford Regional Transfusion Service and the Plasma Fractionation Laboratory which has enabled plasma to be fractionated to make all valuable components rather than used for cryoprecipitate and red cells alone."[10]

10. During the period 1969 to 1974, the use of cryoprecipitate at the Centre dropped from 21.99% to 3.86% of total factor VIII material used, while the use of NHS concentrate rose from 45.93% to 60.89% of the total. Commercial factor VIII was introduced in 1973, when it made up 17.74% of product used, rising to 35.25% the following year. [11]

11. The Centre did not use any commercial factor IX at all during this period[12], presumably because it was able to meet its requirements from the PFL. Dr Biggs noted in relation to its UK-wide use: "*Commercial factor IX is sold in the United Kingdom but since there are adequate amounts of NHS factor IX available little of the commercial material is used.*" [13]

12. By 1976, 42.61% of the material used at the Centre was NHS concentrate (Factor VIII), just 1.54% was cryoprecipitate and the rest commercial concentrate, produced by Hyland and Immuno.[14]

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[10] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 (PRSE0004645).

[11] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 at 493-4 (PRSE0004645).

[12] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 at 495 (PRSE0004645).

[13] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 at 497 (PRSE0004645).

[14] OXUH0003775_005, OXUH0003775_080.

Shortages and budget constraints

13. During the 1970s, the Centre experienced shortages and budgetary pressures.[15] On 23.05.74, Dr Biggs wrote to Dr Maycock at the BPL, *"The present supply position of factor VIII is rapidly becoming intolerable. I am not at all sure how the Oxford Region will greet a bill for £100,00 odd for factor VIII in 1974, only £30,000 being allowed for by the Ministry. I am unable to see how we can manage with less… We are getting more and more patients and the operation list… stands at 24".* [16] Dr Rizza wrote on 15.10.76 of his concern about budget cuts, noting that "*our bill for Factor VIII is already very large and increasing yearly*".[17]

14. In 1977, correspondence with Dr R. H. Cowdell at the Oxfordshire Area Health Authority demonstrated the tensions caused by the costs of haemophilia treatment.[18] Dr Cowdell wrote to Dr Rizza,

> "*No blame lies with you that treatment of haemophilia is expensive but your colleagues cannot avoid expressing some resentment when their legitimate and often very small needs are refused for lack of funds while your expenditure is so enormous...*"

15. Dr Rizza responded that:

> *"…since April 1977 there has been a greatly increased supply of plasma from the Blood Transfusion Centre to the Plasma Fractionation Laboratory and we are now beginning to receive nearly twice as much locally made National Health Service factor VIII compared to last year. As a consequence of this we are now, as from this month, able*

[15] OXUH0000673, 18.07.72 – need to buy in commercial product due to chronic shortage; OXUH0000664, 17.10.73 and OXUH0000663 19.10.73 – seeking budgetary increase from DHSS; OXUH0000646, 14.05.74 – insufficient space, staff and supply of factor VIII.

[16] DHSC0100005_098. Dr Maycock's reply of 30.05.74 stated, *"The unpleasant fact is that there is no cash for NHS and this is borne in upon me almost daily…"* (OXUH0000649).

[17] OXUH0001052_001.

[18] OXUH0003761_050, OXUH0003761_053, OXUH0003761_052.

to transfer several of our patients from commercial factor VIII to National Health Service factor VIII and this should lead to a reduction in our expenditure on factor VIII."[19]

Prophylaxis and home treatment

16. These shortages and constraints appear to have affected the Centre's ability to develop a home treatment and / or prophylactic treatment programme for its patients.

    a. At the Haemophilia Centre Directors' meeting on 27.10.72,[20] it was noted that *"the supply position in some areas was so poor that Directors could not allow any material to be kept in patients' homes as this policy would deplete stocks"*.

    b. At the same meeting, Dr Biggs explained she had trouble devising a prophylactic treatment protocol and that the only place this could realistically be trialled was at Treloar College (this was agreed to). The trial was to be conducted using imported concentrates. Dr Biggs felt that *"any material which could be made in England was too urgently needed for treatment of serious bleeding for it to be allocated to a clinical trial of prophylactic therapy"*.

    c. At the Witness Seminar at the Wellcome Institute in 1998, Dr Matthews recalled that "*Home treatment was not used for some time as the materials were in short supply and those which were available were not really suitable for using at home*."[21]

    d. In his correspondence with Dr Cowdell in 1977, Dr Rizza wrote *"We are at present, not using factor VIII at ideal dosage levels because this would entail prophylaxis and we do not feel with the present shortage of money and factor VIII that this would be right*".[22]

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[19] OXUH0003761_052.

[20] OXUH0003728.

[21] RLIT0000022 p.34.

[22] OXUH0003761_052.

17. While Dr Katherine Dormandy at the Royal Free established an early home treatment programme using cryoprecipitate, in Oxford home treatment appears to have only become available with sufficient supplies of factor VIII concentrate.

    a. At the same meeting of Haemophilia Centre Directors on 27.10.72[23] Dr Matthews *"outlined the policy at Oxford using freeze dried concentrate and Dr Dormandy that at the Royal Free Hospital using cryoprecipitate".*

    b. This is reflected in Dr Matthews' and Dr Rizza's comments at the Wellcome Seminar comparing their approach using "*freeze-dried pooled plasma concentrate in preference*" to Dr Dormandy's approach. [24]

    c. In her 1977 article, which examined data from 1969 to 1974, Dr Biggs reported that "*Cryoprecipitate is much less satisfactory for home therapy than are the freeze dried preparations. Thus an increase in the number of patients on home therapy is likely substantially to increase the demand for freeze dried preparations to replace cryoprecipitate. When considering the introduction of patients to home therapy it is usual to give priority to the most severely affected patients who need most frequent treatment...*" [25]

18. A home treatment programme commenced at the Centre in 1971 with just 7 patients. By 1975, there were 54 patients receiving home therapy, representing about 25% of the haemophilia A patients. [26] This is probably the same home treatment trial referred to in

[23] OXUH0003728.

[24] RLIT0000022 p.35.

[25] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 (PRSE0004645).

[26] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 (PRSE0004645).

1975 which was supplied with factor VIII material prepared by Dr Bidwell at the PFL.[27] By 1976, 24.80% of factor VIII material used by the Centre was used for home treatment.[28]

Relationship with pharmaceutical companies

19. During the 1970s and 1980s, there appears to have been a cordial relationship between the Centre and pharmaceutical companies supplying blood products.[29] [30]

20. On 13.05.77 Dr Rizza wrote to another hospital to recommend commercial factor products; his order of preference was (1) Hemofil, made by Travenol; (2) Factorate, made by Armour Pharmaceutical; and (3) Kryobulin, made by Immuno.[31] He referred also to Prophylate (made by Abbot) and Koate (made by Speywood) and observed that *"We have used all 5 preparations and we find them all equally effective clinically ... We tend to use Hemofil.*"

21. By 1982, pharmaceutical companies including Armour, Cutter, Travenol and Alpha Therapeutics were developing heat-treated factor products to address the risk of hepatitis. Companies were in competition to recruit patients of Haemophilia Centres for their own drug trials. Dr Rizza, through the UKHCDO, with Professor Bloom and Dr Craske, advocated for collaboration between Haemophilia Centres and pooling data in order to maximise the effectiveness of trials – see further below.[32]

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[27] OXUH0000917_002.

[28] OXUH0003775_005.

[29] OXUH0001129_001, 13.06.75 – letter from Bayer UK Limited thanking Dr Rizza and Dr Biggs for "*The information that you gave me will enable me now to make a realistic approach to the assessment of the market, and I feel sure that I can make some realistic proposals for the supply of factor 8*."

[30] In 1981 Dr Rizza approached Armour Pharmaceutical Company Limited asking them to sponsor the salary of a Health Visitor to undertake work relating to hepatitis research (although this was not provided within the timescale he sought) (OXUH0001624_004, OXUH0001624_003).

[31] OXUH0003761_036.

[32] Circular Memorandum dated 29.03.84, CBLA0001831, described further below. Further correspondence between Dr Rizza and other Centre Directors about these product trials is at OXUH0001891_003, OXUH0001890_002, OXUH0000678_002, OXUH0001890_001 and OXUH0000678_001.

Self-sufficiency

22. Dr Biggs appears to have been an advocate for self-sufficiency:

a. On 22.08.67[33] she wrote to the Ministry of Health that "*concentrates from human plasma of factors VIII and IX"* were *"in very short supply in England and… also scarce everywhere else in the world".* She emphasised that *"their use makes the difference between life and death in many cases".* She noted that the current demand required product from about 50,000 donors per year, but demand was anticipated to increase once the efficacy of factor concentrates became better known. She anticipated that a large quantity of commercial material would shortly become available from the United States and warned that *"we shall be obliged to buy it at a very high costs for our patients unless the English shortage can be remedied."* The letter went on to explain that England had the expertise and personnel and *"could easily"* obtain sufficient blood plasma but lacked *"the organisation, apparatus and buildings in which to work."* It would be "*less costly*" to expedite the manufacture of factor concentrates domestically and she suggested it was time to assess demand and *"work out an emergency plan to try to meet the need."*

b. At the Haemophilia Centre Directors' meeting on 27.10.72[34] she emphasised the urgency of increasing *"British Supply"* in order to increase home treatment and explained that it was unlikely to be more expensive than commercial product.

c. On 20.03.73 the Expert Group on the Treatment of Haemophilia and Allied Conditions[35] met at the Department of Health and Social Security ("DHSS"). Dr Biggs and Dr Rizza attended, and Dr Biggs presented a paper. The minutes[36] refer

[33] DHSC0100025_062.

[34] OXUH0003728.

[35] This group was set up to "*to consider the supply of the therapeutic materials in relation to the treatment of haemophilia and allied disorders*" (BPLL0008096_002, CBLA0000135). Dr Maycock, Director of the BPL, was a key member who had also lobbied for self-sufficiency (BPLL0008090). The meeting on 20.03.73 was the inaugural meeting (CBLA0000143, PRSE0004706). The group was reconstituted in April 1976 (DHSC0100007_010) and met on 04.05.76 (DHSC0100007_034, HCDO0000003_039).

[36] PRSE0004706.

to *"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"* and one of the recommendations made was *"the U.K. should aim to become self-sufficient as soon as possible by increasing home production of freeze-dried AHG concentrate"*.

d. In a paper co-written for the Medical Research Council she assessed the quantity of factor VIII concentrates required to supply the demand of the haemophiliac population (equating to 547,540 to 750,000 blood donations per year). [37] She noted, *"Even if the estimated cost of fractionation were doubled it would be far less than the commercial price which includes payment to donors."* [38]

e. On 23.05.74, she wrote to Dr Sheila Waiter at the DHSS in the strongest terms of the risk of *"arthritis and deformity"* that would be avoidably caused to her patients due to lack of factor VIII treatment. She argued that commercial factor VIII should be funded as an interim measure until sufficiently supplies could be produced in the NHS: *"I am not in favour of any preferential use of Commercial Factor VIII and feel that the NHS could well provide its own in absolutely adequate amounts, if only a little money and effort could go into the fractionation laboratories"*. [39]

f. The Lancet published a letter from Dr Biggs on 29.06.74 referring to evidence that 90% of haemophiliac patients in the UK were receiving less (and in some cases much less) than the optimum treatment for their complaint. She noted that *"The blood donated in the United Kingdom is freely given by responsible citizens; the best use of this valuable resource clearly lies in the best use of all parts of the blood.*

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[37] PRSE0002350 - Biggs, R., Rizza, C.R.C., et al., "*Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia Based on Studies Made during 1969 – 1972"*, on behalf of the Medical Research Council's Blood Transfusion Research Committee Working Party on the Cryoprecipitate Method of Preparing AHF Concentrates at p.20. The paper is undated but refers to another study in 1974.

[38] PRSE0002350 - Biggs, R., Rizza, C.R.C., et al., "*Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia Based on Studies Made during 1969 – 1972"*, on behalf of the Medical Research Council's Blood Transfusion Research Committee Working Party on the Cryoprecipitate Method of Preparing AHF Concentrates at p.13.

[39] CBLA0000206. Dr Waiter replied on 11.06.74, *"You mention 'a little money and effort'. It will certainly require a significant sum of money to collect and process the mount of plasma needed…"* (HCDO0000392_029).

With regard to the provision of factor VIII by the N.H.S., we can say with certainty that we have the skill, experience and capacity in this country to provide factor VIII of very high quality in the amounts required". She acknowledged the expense of setting up an infrastructure capable of such production, but argued that in the long term this would be cheaper than paying for the *"inevitable consequences of undertreatment."* [40]

g. On 13.02.75 she wrote a letter[41] emphasising the great need for plasma at the Centre which "*is the largest centre of its kind in the world*", and warned that without a drive to increase supply, use of expensive commercial concentrates would go up.

h. In a 1977 article, she argued that "*A fourfold increase in NHS freeze dried factor VIII would be needed to supply enough factor VIII for the basic needs of haemophilic patients if the average use per patient were to stay the same and if 25% of patients were on home therapy…. We have the scientific and technical knowledge to make all of the factor VIII that is needed within the United Kingdom using blood that is collected in the United Kingdom. The sooner this objective of self reliance is reached the less costly will the treatment for haemophilia A patients become. There are reasons other than cost which should encourage every effort to have the supply of factor VIII made from United Kingdom blood. For one thing our haemophilic patients should not be dependent on commercial blood donors recruited in other countries. Also* ***blood from these donors may be more likely to transmit infection than the blood of voluntary donors***" [42] (emphasis added).

23. On 30.11.76 Dr Rizza wrote to Dr Stuart at the Queen Elizabeth Hospital, "*I am sure it will be sometime, probably years, before the output of N.H.S. Concentrates meets the*

[40] PRSE0002515. A copy of this letter was enclosed in the letter to Dr Waiter referred to in the footnote above.

[41] OXUH0001046.

[42] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 at 502 (PRSE0004645).

requirements of the Haemophilia Centres of the United Kingdom and until that time I think it will be necessary to continue buying the commercial Factor VIII'.[43]

24. On 12.11.80 Dr Rizza, together with Professor Bloom and on behalf of UKHCDO, wrote to Patrick Jenkin, the Secretary of State for Social Services, highlighting the shortfall in NHS concentrate and the need to buy large amounts of commercial factor VIII.[44]

Heat-treated factor products

25. In what appears to be the note (produced by Dr Lane) of a meeting held at the BPL on 15.12.82, which was organised and attended by Dr Rizza, it was said that *"the random approach"* being adopted by commercial manufacturers to haemophilia directors in the UK to study hepatitis safe Factor VIII *"has many severe disadvantages for the NHS and gives little or no payback to the UK in return for the opportunistic and non-contractual use of the special potential of the UK Haemophilia Service as a collective entity"*. Proposals were made to coordinate controlled clinical trials. [45] Similar observations were made at the next Haemophilia Centre Directors' meeting on 19.01.83. [46]

26. In a letter dated 11.01.82[47] (but which may have been misdated and sent on 11.01.198**3**[48]), circulated by Dr Rizza and Professor Bloom to all Haemophilia Centre Directors, they stated, *"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…"* The letter went on to note

[43] OXUH0001040_001.

[44] HCDO0000003_001 p.48 and HCDO0000394_049. The response of Sir George Young, Joint Parliamentary Under Secretary of State, on 18.12.82 is at DHSC0001188.

[45] CBLA0003258.

[46] HCDO0000558.

[47] HCDO0000252_042.

[48] Penrose Inquiry Final Report p.958 fn.176.

that "*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.*" They recommended that these studies be carried out using patients who had not previously been exposed to large pool concentrates patients in order to assess infectivity. It was said that the use of *"hepatitis-safe"* products on a named patient basis *"would be undesirable and might seriously hinder controlled studies in the future".*

27. On 01.03.83 Dr Rizza wrote to Dr Watt at the Scottish National Blood Transfusion Service ('SNBTS') regarding trialling SNBTS heat-treated product.[49] He stated:

> *"I was glad to hear of the progress you are making…especially since 3 drug companies have been in touch with me in the past 3 weeks pushing strongly to formalise studies of their different preparations in mildly affected haemophiliacs. I think it will be necessary to use infrequently or previously untransfused haemophiliacs, von Willebrand's patients and carriers of haemophilia to ascertain to what extent hepatitis risk has been reduced. I see no ethical problem with this. The difficulty with this kind of study has been and always will be I think the small number of previously untransfused patients who come for treatment. At this Centre we have managed to collect about 30 suitable patients over a 2 year period but the patients were not recruited all at once but came in for treatment in the usual random manner and I think that this should be remembered. In other words, although we may have a group of 500 mildly affected patients on our books, only a few of those per year require factor replacement for surgical procedures. I do not think it would be ethically justified to give the material without a good clinical indication."*[50]

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[49] PRSE0000609.

[50] Dr Watt's reply of 09.03.83 (HSOC0002719) set out his agreement with the "ethical points" raised by Dr Rizza and added *"I had been concerned that it might prove necessary for us to carry out animal experiments in Chimpanzees to satisfy the licensing authority but have been assured that, provided we do not make claims of freedom from infection, this will not be necessary. They would be prepared to accept a claim that the material had been treated in a manner which could be expected to reduce the risk of viral transmission. Apart from the fact that I believe it to be irresponsible to use Chimpanzees as laboratory animals for any purpose it is difficult to understand how two or three controlled*

28. In March 1983 Dr Rizza, Dr Craske and Professor Bloom circulated a protocol for trials of 'hepatitis reduced' factor VIII, which had been drawn up by the Hepatitis Working Party under Dr Craske to address the concern about uncoordinated trials of new heat-treated products.[51] The protocol set out a process whereby participating Centres using new heat-treated products, whether NHS or commercial, were to monitor patients for hepatitis and submit the data to Oxford. The protocol stated that the object of the study would be explained to patients and their consent (or their parents' consent) obtained.

29. The following year Dr Rizza, Dr Craske and Professor Bloom circulated a further memorandum dated 29.03.84[52] updating the Haemophilia Centres on clinical trials being undertaken by providers of heat-treated commercial factor VIII. It said:

> "*there are at present 8 different products in preparation or available for trial. Clinical trials have only been completed on one product, the "Hemofil HT" factor VIII, which is prepared using a 'dry heat' method. The results indicated that there was still a 63% attack rate of non-A, non-B hepatitis on first exposure to this product in patients who have not received factor VIII concentrate previously. These trials are difficult to evaluate as for ethical reasons no control group was used*."

30. Centres were advised to:

> "1. *Draw up a list of patients in your Centre who might be suitable for such a trial on the basis of previous blood product exposure, and who are likely to require treatment with factor VIII in the near future.*
> *2. Notify Miss R.J.D. Spooner at the Oxford Haemophilia Centre of the number of such patients available.*

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administrations can do much beyond encourage hope. The ultimate proof of freedom from the danger of infection transmission will come only when very large numbers of patients have received treatment."

[51] HCDO0000003_105 – draft letter to Directors, re: Trials of 'Hepatitis Reduced' Factor VIII, HCDO0000270_044 – the protocol.

[52] CBLA0001831.

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

31. The commercial heated products were from Armour, Cutter, Travenol, Alpha Therapeutics and German firm Behringwerke; they were made from imported US plasma and therefore noted to carry a "*putative risk of transmission of AIDS*". Heat-treated NHS factor VIII from the PFC in Edinburgh was expected to be available shortly and from the BPL later in the year.

32. In his Litigation Report, Dr Rizza claimed that *"The availability of various heat treated commercial preparations caused some concern to Directors. The companies were promoting their products at such a pace that it was difficult to evaluate their safety. They were mostly unlicensed and were being used on a 'named patient' basis. Proof of safety required studies lasting one to two years in previously untransfused patients. Such patients are very rare so that to study even one heat treated product requires a good deal of time, effort and collaboration with other Centres to get the appropriate numbers of patients. With so many products becoming available there was a danger that they would be used indiscriminately and without proper evaluation."*[53] Available results discussed at the meeting of the Hepatitis Working Party (which included Dr Rizza) on 15.09.84[54] suggested that Travenol's heat-treated Hemofil had showed a 63% incidence of elevated transaminases[55] in patients and that the trial of Armour's product had been suspended after an occurrence of hepatitis.

[53] HCDO0000003_001 p.67.

[54] HCDO0000561.

[55] The minutes refer to *"elevated transience"* but this is assumed to be a mis-transcription.

33. On 23.11.84 Dr Rizza wrote to Dr Lane (BPL).[56] He wanted to know: how soon would NHS heat-treated product be available; which categories of patient would be eligible to receive it; and how they would be followed up. He speculated that it might only be available for children and mildly affected patients (i.e. groups who had not been heavily treated in the past) or possibly "*HLTV-III negative patients?*"

34. On 10.12.84 a highly significant meeting was held at Elstree to discuss the risk of AIDS with the Reference Centre Directors, representatives from the blood services, the DHSS and others.[57] Dr Rizza attended from the Centre. It was agreed that haemophiliacs should receive heat-treated factor concentrates and that **all** patients should be transferred to this form of treatment, as soon as possible. That included patients who were HLTV-III antibody positive, if sufficient heat-treated material was *"freely available",* whereas patients who tested HLTV-III antibody negative *"must"* be given heat-treated product. Following this meeting an "AIDS Advisory Document" was produced by the UKHCDO on 14.12.84.[58]

35. However, budgetary constraints continued to pose a problem in relation to the Centre.

    a. Three days after the 10.12.84 meeting, Dr Rizza wrote to the District Treasurer of the Oxfordshire Health Authority, "*We should like to pursue this course of action* [i.e. heat-treated product for all patients] *and have already placed our first order for a batch of heated material for use at this Centre. The heated material at present available, costs 12-14p/unit compared with 8p/unit for non- heated factor VIII. We… calculate that our bill for factor VIII may rise from between £0.39 - £0.50 million per annum to between £0.72 - £0.84 million per annum*".[59]

[56] OXUH0000429_002.

[57] HCDO0000394_117.

[58] HCDO0000270_007.

[59] OXUH0003761_020.

b. The Treasurer replied on 20.12.84 that there was "*no budget provision*" for heat-treated factor VIII and instructed Dr Rizza not to buy any more until the funding issue had been clarified.[60]

c. A memorandum of the same date from the Churchill Hospital to the Treasurer[61] warned of "*the enormous and wide ranging difficulties your embargo will place on the Haemophilia service*" and asked for permission to overspend. It noted that the Centre only held 4-6 weeks' supply of heat-treated factor VIII. An inability to obtain heat-treated Factor VIII commercially would mean that: they would be exposed to "*supplies of dubious quality*" offloaded onto the UK market as other countries switched to heated products; staff and patient morale would drop; pressure from patients, the press and the public would mount; and "*we could be faced with greater costs through litigation if a preventable untoward incident occurs*". It was anticipated that heat-treated NHS factor VIII would be available from April 1985.

d. Dr Rizza appears to have prevailed; by 28.03.85 a new expenses code had been set up to track the impact of AIDS on haemophilia budget.[62]

36. On 30.01.85, Dr Rizza wrote to an (unknown) patient "*As we discussed when you changed to heated factor VIII, it is very important that we see you and take a blood sample at monthly intervals, in order to assess the effect of the new factor VIII*".[63]

37. As outlined under the heading 'Research' below, the Centre participated in a study of the NHS heat-treated factor VIII 8Y. On 24.04.85 Dr JK Smith at the PFL wrote to Dr Rizza that he was sending supplies of high purity, heat-treated factor VIII concentrate 8Y for use in Stage 2 of a clinical trial monitoring transmission of HLTV-III and NANBH.[64]

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[60] OXUH0003761_019.

[61] OXUH0003761_018.

[62] OXUH0003761_008.

[63] OXUH0000422_003.

[64] OXUH0002310_008.

38. On 22.06.85 a letter written by Dr Rizza, together with Professor Bloom and Dr Forbes, was published in the British Medical Journal[65] expressing concern that a significant number of Haemophilia Centres were still using non-heat-treated NHS factor VIII and factor IX. They considered that due to the increasing prevalence of HLTV-III in the population, cryoprecipitate and other non-heat-treated products could no longer be assumed to be safe. They also recommended the introduction of anti-HLTV-III testing for blood donors.

39. In his Litigation Report, Dr Rizza commented that the continued use of unheated NHS products at this time was due to a concern that heat-treated commercial products came from a US donor population more heavily infected by HIV. He further stated:

> "*With regard to NHS Factor VIII the material available in January 1985 was mainly non heat treated and Directors had to decide whether to give heated commercial Factor VIII to patients who normally received NHS Factor VIII or whether to continue using non heat treated NHS Factor VIII. This latter option was discussed in the recommendations of December 1984 and* ***some Directors, myself included opted to use unheated NHS Factor VIII during January 1985 arguing that unheated NHS material might be safer than heat treated American material give****n the size of the AIDS problem in USA and the uncertainties about the effectiveness of heat treatment in destroying HIV*"[66] (emphasis added.)

40. 8Y (prepared from untested donors) was used at the Centre from June 1985 onwards. On 30.07.86 Dr Rizza wrote to Dr Smithies at the DHSS:

> "*More than thirty patients are receiving it routinely. To date no patient has sero-converted to being HIV positive. Furthermore, there has to date been no evidence of*

[65] PRSE0001917.

[66] HCDO0000003_001 p.105 & p.139.

transmission of Non A Non B hepatitis using this material in patients not previously transfused or only infrequently transfused."[67]

41. In 1986 heat-treated product made using plasma from donors tested for HLTV-III antibodies began to be available. In the 30.07.86 letter,[68] Dr Rizza wrote that he would prefer to continue to use NHS heat-treated factor VIII (8Y) from untested donors until tested NHS 8Y was available (anticipated in September 1986), rather than switch to tested commercial products:

"I would be most reluctant to make this change in therapy as I feel that untested but strongly heated 8Y is probably safer than the anti-HIV tested but less strongly heated commercial material from the point of view of transmitting HIV infection and hepatitis."

Other products used

42. On 16.08.76, Dr Matthews wrote that AHG concentrate from pig and beef blood was still kept in stock and used (rarely) when human AHG was not available to treat a life threatening bleed or for patients with antibodies to human AHG.[69] (The use of animal-derived concentrates had been pioneered at Oxford by Dr Bidwell in the 1950s.)

43. In the mid-1970s, the Centre also still used Stypven, a clotting treatment made from Russell viper venom for topical use on superficial bleeding, buying up the entirety of the remaining stock when the product was discontinued in December 1975.[70]

[67] OXUH0003771_003.

[68] OXUH0003771_003.

[69] OXUH0001050.

[70] OXUH0001041, OXUH0001142_001, OXUH0001142_002.

KNOWLEDGE OF, AND RESPONSE TO, RISK

Serum hepatitis, transfusion hepatitis and Hepatitis B

44. Hepatitis as a consequence of transfusion was well known to the Centre.

45. In 1967 the Centre wrote to the GPs of patients receiving treatment at the Centre asking if "*any patients have suffered from serum jaundice following treatment with blood, plasma or plasma concentrates*".[71]

46. In 1972, Dr Biggs suggested that serum hepatitis had not been found to be lower with cryoprecipitate than larger pool concentrates: "*The use of relatively small numbers of donors to prepare each dose, a theoretical advantage in the use of cryoprecipitate, has not been proved to be beneficial in reducing the risk of serum hepatitis.*"[72] (However, this should be viewed as a reflection on her experiences up to that date, when NHS concentrates were made from relatively small pools and before commercial concentrates were licensed for wholesale use in the UK. This comment therefore relates to perceived similar risk levels arising from cryoprecipitate and early NHS concentrate.)

47. At the meeting of the Expert Group on the Treatment of Haemophilia and Allied Conditions which Dr Biggs and Dr Rizza attended at the DHSS on 20.03.73 (referred to above), it was noted that a possible disadvantage of factor concentrates by comparison with cryoprecipitates was 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".* However, it was noted that the incidence of hepatitis in severely affected haemophiliacs was *"not very much higher"* for those who were treated with freeze-dried factor concentrates and *"It was*

[71] OXUH0001714_001.

[72] In: *Can Hemophilic Patients be adequately maintained with cryoprecipitates? Or is it desirable or even necessary to manufacture and administer highly concentrated AHF products?* Vox Sang: 1972: BAYP0000022_050.

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". [73]

48. Following an analysis of data returns over six years, Dr Biggs published on jaundice as a post-transfusion complication in 1974, observing that *"Transfusion hepatitis is a disease caused by several viruses which may occur in donor plasma. There is every reason to suppose that these viruses may be present in the various protein fractions used to treat haemophilia and Christmas disease ... The theoretical danger of exposure to infection increases with the number of donations contributing to the doses of material used."*[74] A comparison with other Centres showed that *"the incidence of jaundice is lower at the other Centres than at Oxford. Patients at Oxford receive more concentrate and thus more donation-exposures than patients elsewhere".* She also provided a provisional report to the Haemophilia Centre Directors recording (amongst other matters) the incidence of jaundice.[75] Further, Dr Biggs and Dr Rizza were co-authors of a report assessing the use of cryoprecipitate and freeze-dried concentrate which noted that about 1 in 800 blood donors were HBV antigen positive.[76] The authors reported what they described as *"theoretically a greater chance"* of a patient contracting hepatitis if treated with a free-dried preparation than if plasma or cryoprecipitate were used, but considered that *"the frequency of hepatitis in severely affected patients did not seem to increase very greatly with increased use of freeze-dried concentrate".*

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[73] PRSE0004706.

[74] HCDO0000581 - Biggs R. (1974) *"Jaundice and antibodies directed against factors VIII and IX in patients treated for haemophilia or Christmas disease in the United Kingdom"*, *British Journal of Haematology* Vol. 26, pp. 313–329.

[75] CBLA0000242. Undated but prepared in and probably presented to the Haemophilia Centre Directors meeting on 18.09.75 (HCDO0001019).

[76] PRSE0002350 - Biggs, R., Rizza, C.R.C., et al., "*Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia Based on Studies Made during 1969 – 1972"*, on behalf of the Medical Research Council's Blood Transfusion Research Committee Working Party on the Cryoprecipitate Method of Preparing AHF Concentrates.

49. On 01.11.74 at a meeting of the Haemophilia Centre Directors,[77] Dr Biggs presented the results for 1973 in the directors' study of jaundice. Dr Rizza reported 11 episodes of hepatitis in Oxford patients since January 1974. Nine of these had received commercial concentrates but all also had NHS concentrate and it was not easy to identify the material which caused the jaundice, nor to determine incubation periods. Dr Biggs said it was not yet proved that commercial factor VIII was much more dangerous for causing hepatitis. She hoped the material would not get an unnecessarily bad name and stated that it was clinically invaluable while the NHS supply was so limited.

50. From the early to mid-1970s, concerns about batches of factor VIII potentially transmitting HBV were frequently documented.[78] The Centre participated in studies following up specific concerns regarding Hemofil.[79] There is also a chain of correspondence referring to HAV.[80] A list of causes of deaths of patients of the Centre compiled in 1975 included one death from "*post-transfusion hepatitis*".[81]

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[77] HCDO0001017.

[78] OXUH0000915_003, 24.07.74 - two batches had tested positive for HB Ag and "*Both batches have been used completely and exclusively in the Haemophilia Centre*"; OXUH0001569_035, 30.08.74 - Dr MacCullum at the local Virology Laboratory at the Radcliffe Infirmary wrote to Dr Rizza concerning *"Hepatitis in patients with Haemophilia"* referring to antibody and antigen test results for a number of patients; OXUH0003763_022, 20.09.74 - the MRC informed Dr Biggs that a particular batch of Factor VIII had tested positive for HBV antigen but provided that *"If, nevertheless, you are prepared to use this material on your own responsibility, please sign and return the attached letter..."*; OXUH0001569_009, 21.10.74 – an internal memo regarding a batch found by Professor Zuckerman to be infected with HB Ag; OXUH0001569_005, 31.10.74 – two further batches found positive for HB Ag; OXUH0001574_002 & OXUH0001574_001 – correspondence regarding testing a list of patients exposed to a particular batch of Hemofil for HB Ab/Ag In September 1975, with Dr Rizza stating that *"We will certainly continue to take samples from our patients whenever the opportunity arises and send them to you"*.

[79] BART0000887 and HCDO0000392_057.

[80] On 14.06.74, the DHSS Medicines Division notified the Centre of a batch of Hemofil produced by Travenol Laboratories Ltd that was implicated in 6 cases of jaundice which *"appears to have been due to infection by hepatitis A (short incubation)"* (OXUH0001606_006); 13 patients at the Centre had received doses from that batch *"but, as far as we are aware, having spoken to all of their GPs, only one patient has developed hepatitis"* (OXUH0001606_005). The hold on the batch was subsequently lifted (OXUH0001606_003).

[81] OXUH0001085_004.

51. However, in his Litigation Report Dr Rizza asserted that, *"During the early to middle 1970's I think it is fair to say that hepatitis was probably not perceived as a long term problem in haemophiliacs"*.[82] He suggested that it was during the late 1970s that studies showed persistently abnormal liver function test results in haemophiliacs who were clinically well.

52. There is one document which suggests supply constraints may have affected the Centre's actions when it came to the risk of hepatitis infection. A letter on 19.11.74[83] noted there were as yet no hepatitis antigen tests available for Batch 8IP 556 but "*Dr Rizza has agreed to accept this batch for use in the haemophilia centre in the absence of any other material*".

53. Dr Rizza was involved in designing an early prospective hepatitis study in conjunction with Treloar College in 1975,[84] which 25 patients at the Centre participated in. [85]

54. In 1977, Dr Biggs noted that commercially obtained blood had been shown to be 10 times more likely to transmit hepatitis than blood collected from unpaid donors.[86] The Haemophilia Centre Directors' data returns from 1969 to 1974 showed that of 62 patients who had died, five had "jaundice" listed as the cause of death, four of whom had received no material other than cryoprecipitate.[87]

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[82] HCDO0000003_001 p.57.

[83] OXUH0000915_005.

[84] OXUH0001589_001, OXUH0001587_002.

[85] HCDO0001019, p.9.

[86] PRSE0004645 - R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 citing (Maycock, 1972).

[87] PRSE0004645, p.490.

55. In his Litigation Report, Dr Rizza cited studies in 1977 and 1978 which found that haemophiliacs treated with factor VIII concentrate were more likely to have abnormal liver function tests than those treated with cryoprecipitate.[88] (However, he took the view that for severely affected haemophiliacs the need for frequent treatment would undermine the statistical relative safety of cryoprecipitate.) He explained that the introduction of HBV antibody testing in the early 1970s helped to reduce the risk of transmitting HBV in blood products but did little to reduce the incidence of NANBH, discussed further below.

HIV and AIDS

56. It is not currently known when Dr Rizza or his colleagues first knew of the possibility of an association between blood/blood products and AIDS. The issue of AIDS was first raised in a meeting of Haemophilia Reference Centre Directors (attended by Dr Rizza) on 06.09.82: "*Prof Bloom asked Dr Craske if he had any information about the acquired immune-deficiency syndrome following reports in the United States and the possible relationship with this syndrome of blood products and hepatitis. Dr Craske said that he would find out more about this and agreed to try to have some information available the haemophilia centre directors at the Manchester meeting.*"[89]

57. A letter from Dr Rizza to Dr Craske of the Public Health Laboratory Service dated 08.10.82[90] noted,

> "*Shortly after you 'phoned me last week I received a telephone call from a physician in the States asking what our experience in this country was. He has just been to a meeting where the 3 cases of haemophilia with AIDS already publicised were discussed along with another one or two possible cases presented at the meeting. Apparently the whole problem has caused quite a stir in the haemophilia world in the States so much so that one very senior physician has withdrawn his factor VIII concentrates from the accident room and insists on vetting the patients himself before any dose is given. I feel the whole*

[88] HCDO0000003_001 p.50.

[89] HCDO0000410.

[90] OXUH0001617_001.

thing should be looked at urgently if only to clear the air and dispel some of the apprehension that has been stirred up".

58. In his Litigation Report, Dr Rizza noted that an editorial on 13.01.83 in the New England Journal of Medicine raised the question of whether haemophilia treatment should be changed in light of the risks of hepatitis and AIDS. Looking back at that point in time, he commented,[91]

> *"to have changed to using cryoprecipitate on such a large scale would almost certainly have reduced the quality of treatment of bleeding episodes. It would not have been possible to continue with the home therapy programme as cryoprecipitate is not suitable for home treatment. The perception was that with haemorrhage being the commonest cause of death it would be unreasonable to put the patient at greater risk of haemorrhage in view of the limited information on AIDS and its long term prognosis."*

59. Later in his Litigation Report, Dr Rizza acknowledged that it may have been possible for smaller Haemophilia Centres to switch back to using cryoprecipitate:[92]

> *"In 1983 a large Centre such as that at Oxford was using approximately 7 M units of Factor VIII to treat its haemophilia patients. To provide this as cryoprecipitate would have meant handling approximately 100,000 bags of cryoprecipitate a year, or more than 250 bags per day. This would have been extremely difficult to do. Smaller Centres of course might have managed. Whether or not the Blood Transfusion Centres in UK could have provided 70 M units of Factor VIII in the form of cryoprecipitate is a moot point. Production of raw plasma would have had to increase two to three fold. Also a switch completely to cryoprecipitate would have resulted in the Blood Transfusion Centres not sending plasma to BLP for fractionation so that development and large scale production of safe NHS concentrates would have been delayed if not stopped completely. Finally and not least few patients given the lack of knowledge of AIDS and*

[91] HCDO0000003_001 p.78.

[92] HCDO0000003_001 p.119-120.

its implications were prepared to modify their treatment and life routine to such an extent."

60. On 19.01.83, Dr Rizza attended a meeting of the UKHCDO Hepatitis Working Party[93], at which Dr Craske gave an update on the situation in the United States, including the fact that ten cases of AIDS had occurred in haemophilia A patients in the USA and that the CDC AIDS Task Force was working on the hypothesis that an infective agent was involved; further support for the hypothesis had come from the report of three cases associated with whole blood or platelet transfusions. It was agreed that both retrospective and prospective studies should be conducted in the UK haemophiliac population.

61. Dr Rizza was also present at a key meeting with Immuno at a London airport hotel on 24.1.83, at which there was a discussion about AIDS.[94] It was reported that up to 10.12.82 some 800 people had been reported as suffering from AIDS and there was a 45% mortality. Ten haemophiliacs in the US had been affected and five had died (the youngest aged 7). The incubation period for the syndrome appeared to be six months to two years.

62. On 11.05.83, Dr Rizza wrote to the Regional Medical Officer at the Oxford Regional Health Authority:[95]

"*There is no doubt that the recent publicity concerning AIDS has created a good deal of apprehension in haemophiliacs, their medical attendants and the DHSS. I think it is important that we act quickly to set up screening tests to detect the patients who might be at risk of developing the full blown condition.*

Apart from their value in helping us to manage our patients better, I think it is particularly important to set up tests in Oxford for the following reason. The Oxford Haemophilia Centre is the largest in the country and in addition to using American

[93] HCDO0000558.

[94] PRSE0002647.

[95] OXUH0002245_007.

factor VIII concentrates which are said to carry a risk of transmitting AIDS, we also use large amounts of NHS factor VIII. Our system of treatment is such that many patients have received only NHS factor VIII and others only U.S. concentrates. It should therefore be possible to find out if patients on NHS concentrates are immuno suppressed to the same degree as those on U.S. concentrates. The results will have important implications for plasma fractionation policy in this country.

The matter is one of great urgency and I hope that it will be possible to set up the necessary screening test within the next few weeks."

63. Dr Rizza convened a special meeting at St Thomas' Hospital for representatives from the Haemophilia Reference Centres to discuss the clinical implications of AIDS on 13.05.83.[96] At the meeting, it was decided that although it would be *"circumspect"* to use NHS concentrate to treat children and mildly affected haemophiliacs, there was "*insufficient evidence to warrant restriction of the use of imported concentrates in other patients in view of the immense benefits of therapy*".

64. This advice was circulated to all Haemophilia Centre Directors by letter of 24.06.83 on Oxford Haemophilia Centre headed paper and signed by Dr Rizza and Professor Bloom.[97] The letter noted one possible case of AIDS in the UK haemophiliac patient population, but that this "*cannot be considered as a definite case*". The letter did not include all of the information that had been disseminated at the meeting on 24.01.83. A letter from Professor Bloom to Dr Boulton, copied to Dr Rizza, dated 23.05.83 stated that *"I do not think that anyone is complacent about the situation but I think that we all agree that it would be counter-productive to ban the importation of blood products at this moment. We are however taking steps to recommend that imported products from the USA at least meet with the new FDA regulations".*[98]

[96] OXUH0002246_010, BPLL0001351_024.

[97] OXUH0000004_005.

[98] HSOC0001272.

65. In his Litigation Report, Dr Rizza defended the decision in May 1983 to continue using imported factor VIII, other than for less severe cases and children. He said:

> "*The decision of May 1983 must be viewed against the background of treatment policies in UK at that time and the perceived risks of AIDS developing in haemophiliacs compared with risks associated with modifying treatment… Approximately half of the treated patients, mostly severely affected, were on home treatment with concentrates. In spite of wide availability of potent Factor VIII concentrate since 1972 and widespread use of home therapy haemophiliacs were still becoming crippled and death from haemorrhage was not uncommon… In practical terms the problem of handling large numbers of doses of cryoprecipitate rapidly and safely would have been very great….*"[99]

66. On 06.07.83 Dr Craske wrote to Dr Rizza noting that he and Professor Bloom had been asked to give evidence to the Committee on the Safety of Medicines on 13.07.83 regarding *"the implications for factor VIII therapy and the possible association of AIDS with factor VIII treatment"*.[100] Dr Rizza was asked to let Dr Craske know of any matters he thought should be included in the presentation. It is not known whether, and if so how, he responded to this invitation. The letter concluded with a reference to *"some political problems regarding cases of AIDS in other countries in Europe"* and to the recent report of a case of AIDS in a haemophiliac in Vienna.

67. In a letter dated 29.07.83,[101] Dr Rizza summarised the developing situation in the UK as follows:

> "*As far as the haemophiliacs in the U.K. are concerned, all 110 haemophilia centres have been sent guidelines for diagnosing AIDS, information on tests to be carried out, and samples to be kept. To date there is only one <u>possible</u> AIDS case in a total of 4,500 haemophiliacs in the U.K. This patient is being closely observed and all the batches of*

[99] HCDO0000003_001 p.129.

[100] OXUH0001612.

[101] OXUH0002246_007.

factor VIII transfused into him during the past 3 years are being followed up to see which other patients have received those batches and to try to find the donor sources of the batches."

68. By July 1983, the Centre was sending serum samples for testing of T subset ratios at the Royal Free to check whether patients showed signs of compromised immunity. A letter dated 18.07.83 from Dr Lee at the Royal Free to Dr Rizza[102] shows they were keen to discover: (1) whether patients treated with NHS concentrate were less affected than those treated with commercial concentrate; and (2) whether recipients of factor IX were less affected than recipients of factor VIII.

69. This interest was developed into a joint study, the Oxford Immunity Study. Dr Lee commented in a letter of 03.10.83, "*I hope you are not all worn out telephoning patients your end! If we manage to obtain this data it should make a valuable contribution and perhaps even silence the Daily Mail.*"[103] The first batches of results showed nothing concerning[104] but Dr Lee wrote to Dr Rizza on 16.11.83, "*I do have a nasty feeling that NHS concentrate is going to turn out safer!*"[105]

70. On 19.09.83 the Haemophilia Reference Centre Directors including Dr Rizza met at St Thomas' Hospital and received a presentation on the AIDS situation from Dr Craske.[106] It was agreed that the patients who had received the same batches of NHS or commercial factor VIII as the first identified case (a patient who died in Bristol) should be followed up.

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[102] OXUH0002971_006.

[103] OXUH0002972.

[104] OXUH0002974_002, OXUH0002974_001, OXUH0002977_002, OXUH0002977_001.

[105] OXUH0002971_001.

[106] HCDO0000413; Dr Craske's report is at CBLA0001758.

71. In his Litigation Report, Dr Rizza stated that by December 1983 there was strong epidemiological evidence that AIDS was caused by a transmissible agent, probably a virus. Haemophilia experts were recommending that severely affected haemophiliacs should continue to use factor VIII concentrate as the risks of haemorrhage outweighed the risks of AIDS. However, for mildly affected patients, cryoprecipitate or DDAVP was recommended if practicable, and for children cryoprecipitate if practicable. [107]

72. An HLTV-III antibody test was developed in 1984, although there was initially a degree of uncertainty about the relationship between being antibody positive and developing AIDS. It appears that some early HLTV-III tests at the Centre may have given false positive results.[108] On 16.07.85 Dr Craske wrote to Dr Rizza that "*the results which appeared to show a positive converting to a negative, in serial samples from several patients, were undoubtedly due to a false positive reaction in the first test*".[109] He praised the reliability and sensitivity of ELISA, radioimmunoassay and immunofluorescence tests for HLTV-III antibodies by then available.

73. On 23.11.84 in a letter to Dr Lane,[110] Dr Rizza queried how plasma samples from HLTV-III positive patients should be handled in the laboratory. By 23.01.85, he was distributing the Centre's interim rules for handling HTLVIII positive samples and sharing the "*Interim Guidelines for Acquired Immune Deficiency Syndrome (AIDS)*".[111]

74. At the meeting at Elstree on 10.12.84, [112] virologist Dr Tedder advised that patients who tested positive for HLTV-III antibodies had been infected with the virus, were likely to be

[107] HCDO0000003_001 p.89.

[108] Dr Rizza's Litigation Report, HCDO0000003_001 p.139.

[109] OXUH0000404_002.

[110] OXUH0000429_002.

[111] OXUH0000416_002.

[112] HCDO0000394_117.

infectious, and may go on to develop AIDS but would not necessarily do so. The risk of transmission from patients to family members was also noted. Dr Kernoff commented that "*some 70% of haemophiliacs are now +ve*".

75. The Centre collected data on HLTV-III testing from the other Haemophilia Centres. Dr Rizza and Rosemary Spooner analysed this data.

    a. On 27.09.85 they produced an 'Interim Report on Survey of HTLVIII Antibody in Haemophiliacs in UK'.[113] Some centres had declined to send data for reasons of confidentiality but 81 (74%) centres had participated. Approximately 88% of haemophilia A patients treated in 1984 had been tested for HTLV-III antibody, and 44% tested positive. Of those with severe haemophilia A, 59% were positive, and 68% of those in the age group 10-14 years were positive. When it came to haemophilia B patients, 81% had been tested of whom 6% were positive.

    b. An updated report was produced by Dr Rizza and Rosemary Spooner on 03.10.86 entitled 'Provisional Report on 1986 survey of anti-HIV in haemophiliacs in U.K.'.[114] 42 haemophilia A patients, 7 haemophilia B patients and no von Willebrand's patients had sero-converted since the first survey. Some different centres had provided data, meaning that the overall results were not directly comparable to the previous year. Of haemophilia A patients who had been tested, 40% were seropositive, including 58% of severely affected haemophilia A patients. In the case of haemophilia B patients 7% of the total number of patients tested were anti-HIV positive. Of 327 patients with von Willebrand's disease tested 2.75% were antibody positive compared with 5% in 1985.

    c. The 'Report on 1987 survey of anti-HIV in haemophiliacs in the U.K.' was produced on 29.01.88.[115] By that time, 32% of haemophilia A patients tested were anti-HIV positive and 54% of severely affected (i.e. most intensively treated) were positive. By contrast 4.7% of haemophilia B patients tested and 8% of those

[113] PRSE0000476; see also HCDO0000518, a report of the same date but with slightly different data.

[114] PRSE0003912.

[115] OXUH0001219_007.

severely affected tested positive. 3% of those tested who had von Willebrand's disease tested positive. 5.3% of partners of positive patients tested positive. No partners of negative patients tested positive. It was recorded that 4 patients seroconverted in 1986 and 1 in 1987 (although the latter was to be further investigated). A handwritten note on the report records, "*to date 81 AIDS 53 dead*."

d. A draft article or report dated 21.10.88 co-written by Dr Rizza, 'Seropositivity for HIV and Incidence of AIDS and AIDS related complex in the UK Haemophiliacs: Report on Behalf of the Directors of Haemophilia Centre in the UK'[116] summarised the data findings:

> *"Out of 3545 haemophiliacs in the UK who had received blood products in the period 1980-87 and who had been tested for HIV antibody, 1179 (39%) patients with haemophilia A and 27 (5%) patients with haemophilia B were seropositive. No seroconversions are known to have taken place after November 1986. The rate of progression to AIDS was strongly dependent on age."*

76. A meeting of the Oxford Region Health Authority AIDS Clinical Working Group, attended by Dr Rizza, was held on 27.01.88.[117] During the meeting, it was discussed whether the Oxford Blood Transfusion Service could test for HIV stored non-blood donor samples which had been referred for other tests such as tissue typing. They concluded that testing without confirmation that informed consent had been obtained would be contrary to national and the developing regional policy and legal advice. However, it was agreed that anonymous testing of *"for example, a week's bloods from each laboratory in the Region once they were finished with"* would be permissible in principle in order to ascertain prevalence across the region.

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[116] OXUH0002251_014. An article based on further analysis of the same data set was later published: *'Incidence of AIDS and excess of mortality associated with HIV in haemophiliacs in the United Kingdom: report on behalf of the directors centres in the United Kingdom'* by SC Derby, CR Rizza, RJ Spooner, IM Stratton, B Thakrar, *British Medical Journal*, (1989) 298, 1064-1068 (OXUH0000165_002).

[117] OXUH0002260_076.

77. In 1989, two inquests were held for HIV positive patients of the Centre who died in the Oxford area. In the first, HIV was held not to be contributory and the Coroner wrote to Dr Rizza, *"The relatives certainly seemed most appreciative of the care given to him at your centre".*[118] In the second, the Coroner directed Dr Rizza to provide a statement, noting that death as a result of a transfusion was not a natural cause of death so had to be investigated.[119] In his statement Dr Rizza explained that the patient had seroconverted as a result of factor VIII from the Centre between November 1979 and August 1984 and subsequently died of non-Hodgkin's lymphoma secondary to HIV.[120] The Coroner had invited Dr Rizza to include in his statement an assurance that blood products no longer carried an HIV risk (*"I do not wish to put words into your mouth but if it is the case I would certainly have no objection to your saying that although contamination was a problem in the past advances in knowledge and testing procedures have eliminated it"*), but he did not do so.

78. In January 1992 Dr Rizza wrote to Dr Mayne (Director, Belfast Haemophilia Centre) concerning *"the need for inquests in haemophiliacs who die from AIDS or who are HIV positive but die from some other condition"*[121]; he referred to having had several conversations by telephone with the Coroner for Oxfordshire as well as the correspondence referred to above.

NANBH / Hepatitis C

79. Transmission of NANBH to haemophiliacs was, according to Dr Rizza's Litigation Report, first reported in 1975 in the UK.[122] Dr Biggs' 1975 report *"The incidence of Jaundice and Antibodies in Patients in the United Kingdom – A Six Year Survey"* noted the probable existence of *"unidentified long incubation type viruses. In a recent review Prince (1975)*

[118] OXUH0001262_003.

[119] OXUH0001262_007.

[120] OXUH0001262_004.

[121] OXUH0001262_001. See also the Coroner's letter of 17.04.89 to Dr Rizza at OXUH0001262_007.

[122] HCDO0000003_001 p.57.

suggests that a high proportion (80% of hepatitis cases) may be due to long incubation type viruses other than type B. The evidence is that on average only 20% of hepatitis cases show positive serological evidence of type B infection and so presumably 80% are not type B"[123].

80. "Non-B hepatitis" was referred to in correspondence in 1976, when Dr Craske wrote to Dr Rizza requesting that he check if any patients had contracted it, after two patients had been infected after transfusion of Kryobulin Batch No O9N12975.[124] In an exchange of correspondence between the Centre and Dr Aronstam (Lord Mayor Treloar College) in February 1980, the suggestion was made that *"invasive investigations in this group of patients more often than not show some liver changes suggestive of chronic liver disease".*[125]

81. Dr Rizza collaborated with Dr Craske in researching NANBH. A report by Dr Craske dated 23.09.82 on a "*prospective study of the incidence of acute and chronic hepatitis in haemophiliacs as a result of first exposure to Factor VIII concentrate or Cryoprecipitate*" observed that *"the risk of chronic hepatitis following an acute attack of non-A, non-B hepatitis after a transfusion of factor VIII concentrate is between 20 and 40%".* 9 out of 9 patients treated with factor VIII or IX concentrate for the first time at the Centre contracted non-A, non-B hepatitis.[126] This study was also discussed at the Haemophilia Centre Directors' meeting on 06.09.82[127] and reported in the British Medical Journal.[128]

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[123] CBLA0000242.

[124] OXUH0000761_004, letter from Dr Craske to Dr Rizza dated 03.08.76.

[125] TREL0000241_037.

[126] HCDO0000135_015.

[127] HCDO0000410.

[128] CBLA0001772 - *"Non-A non-B hepatitis after transfusion of factor VIII in infrequently treated patients"* by M. L. Fletcher, J M Trowell, J Craske, K Pavier, C R Rizza, *British Medical Journal*, vol 287, 10.12.83.

82. On 26.11.83, Dr Craske wrote to Dr Rizza[129]:

> "*I have been considering the problem of the small donor pool factor VIII which you are at present using on patients coming to operation at Oxford…. Previous experience with hepatitis B suggests that some patients transfused with this material may contract a symptomless infection of non-A, non-B hepatitis which we are unable to detect owing to the fact that no significant elevation of transaminase levels occur in the patient. It would seem prudent, therefore, that we should collect serial sera at least up to twenty-six weeks after transfusion with a view to attempting to devise an immunoassay for the long incubation hepatitis transmitted by this batch.*"

83. As noted above, Centre Directors had been encouraged by Dr Rizza to coordinate to ensure that suitable patients were allocated to trials in relation to "hepatitis-reduced" products. The Centre continued to study the incidence of NANBH in previously untransfused patients using factor concentrate for the first time. During 1984, some patients studied were given heat-treated SNBTS factor VIII.[130] From June 1985, the Centre used heat-treated NHS factor VIII 8Y. In 1987 the draft study protocol for a more formal multi-centre study, 'An Evaluation of the Incidence of NON-A NON-B Hepatitis and Transmission of Other Viruses After a First Exposure to BPL Factor VIII Concentrate' [131] stated:

> *"Some 15-25% of multi-transfused haemophiliacs have liver biopsy evidence of chronic active hepatitis or cirrhosis, and recent studies suggest that liver disease is an increasingly common cause of death. A major cause or liver disease is thought to be the transmission of the agent(s) responsible for non-A, non-B hepatitis (NANBH) by therapeutic clotting factor concentrates.* ***In patients receiving conventional unheated concentrates for the first time, acute post-infusion NANBH is a virtual certainty, implying invariable contamination of these products****. Because* ***there are no reliable serological tests for NANBH****, attempts to*

[129] OXUH0001615.

[130] OXUH0000679_002, OXUH0000679_001, CBLA0001823, OXUH0000677_002, OXUH0000677_001, OXUH0000676_001 (Dr Rizza to Dr Cash: *"I should like to have a look at some of your heat treated factor VIII and give it to some of our severely affected haemophiliacs to see what is half-life is and to make sure there are no undue side effects"*).

[131] HCDO0000003_061.

eliminate this contamination have largely focussed on the possibility of sterilizing concentrates by chemical or physical means.

Although heating in the freeze-dried state at 60°C is probably effective against human immunodeficiency virus (HIV), clinical studies in 'first exposure' recipients have shown that the ***incidence of NANBH still remains close to 100%****. Heating in solution appears to be more effective in neutralizing NANBH but there is a penalty in decreased yield of factor VIII. The Blood Products Laboratory (BPL) has recently developed fractionation methods which allow factor VIII to be heated to 800C for 72 hours with minimal loss of factor VIII activity. This material is issued under the code name 8Y"* (emphasis added.)

84. During 1988-1989 an antibody test for NANBH, by then known as HCV, was developed. [132] On 24.07.89, J. K. Smith, Chief Project Scientist at the PFL, wrote to Dr Rizza: [133]

"*There is now candidate test for "HCV" developed by Chiron and marketed by Ortho. If you have already supplied samples for this test to Dr. Mortimer at PHLS, I would be grateful to know the result, and a summary of the products used by the patient since entering our study.*

If you have not yet forwarded samples to PHLS, I would be pleased to make arrangements for the testing of any remaining samples (>6 months from first injection with our concentrate) or a current sample from the patient if he has used only our concentrate since.

Our information to date is that at least 32 patients on 8Y only for up to four years are all negative for anti-HCV, but some questions of specificity remain to be checked and we do not have full information on the treatment history of all 32. It is unlikely that the HCV test can completely replace the ISTH protocol for trials of NANBH transmission, but it is essential to establish the correlation between them."

[132] HCDO0000003_001 p.54.

[133] OXUH0000725_005.

85. On 17.07.91 Dr Rizza wrote to Dr Cash at SNBTS [134]:

> "*I have just looked through the results of our HCV testing in our patients with haemophilia A, haemophilia B and von Willebrand's disease and without analysing the figures in any great detail it looks as if* ***63% of 379 patients with haemophilia A, 57% of 61 patients with haemophilia B and 20% of 39 patients with von Willebrand's disease are anti HCV positive****. I should stress that those are Oxford Haemophilia Centre data, not UK data*" (emphasis added.)

86. In his Litigation Report, Dr Rizza asserted that *"the prevalence in blood donors of the virus causing non A non B hepatitis is 1 in 150".* [135] He further noted that HCV was the most frequent cause of post-transfusion hepatitis, accounting for 60%-90% of post-transfusion hepatitis in most countries. He said that he understood it to be a mild condition which often passed unrecognised, but which progressed to a chronic form in 40%-50% of infections, and to cirrhosis in 50% of those with chronic disease. [136]

[134] OXUH0001861_002.

[135] HCDO0000003_001 p.51.

[136] HCDO0000003_001 p.55.

TREATMENT OF PATIENTS

87. Consideration of the evidence given to the Inquiry by people who were infected and affected gives a picture of their treatment experiences at the Centre. Common themes are:

    a. a lack of communication about the risks of treatment;

    b. to the contrary, factor concentrates when newly introduced were presented as safe and seen as a 'wonder drug';

    c. a high degree of trust placed in the medical professionals;

    d. examples of patients not being told of or asked for consent to testing;

    e. delays in being told the results of tests diagnostic or indicative of viral infections;

    f. concern that they had been used as 'guinea pigs' in clinical trials;

    g. a lax or perfunctory approach to communicating diagnoses;

    h. a lack of adequate information or advice following diagnosis.

    There are also some positive comments about the quality of care and treatment received.

HIV and AIDS

88. As the risk of AIDS became public knowledge in 1983, this, according to Dr Rizza (see his letter of 11.05.83 referred to above), caused apprehension for patients at the Centre. Dr Rizza noted in a letter dated 06.09.83, *"many of the patients that I have spoken to already are most anxious to participate in research which might throw some light on AIDS"*.[137] (Later, in 1987, he wrote in reply to a request for serum samples from a researcher at Oxford University: *"I foresee no difficulty in obtaining relevant blood samples from our patients who are on the whole a most co-operative group of people"*.[138]).

[137] OXUH0002245_003.

[138] OXUH0002184_001.

89. A letter to the Centre from Lord Mayor Treloar College in July 1983 referred to the examination of a patient for *"the stigmata of AIDS"* and the carrying out of *"AIDS related tests"*.[139]

90. The evidence of patients regarding lack of communication and clarity around testing is consistent with some of the contemporaneous documentation:

    a. On 23.11.84 Dr Rizza wrote to Dr Lane at BPL regarding testing for HLTV-III antibody *"What policy should we adopt with regard to telling patients?"*[140]

    b. At the Elstree meeting on 10.12.84, "*A long discussion took place on whether persons found to be +ve were to be informed. Several differing views were expressed. It was agreed that each clinician would decide for each case depending on the facts of the case but in general to provide information if asked for*".[141]

    c. At the same meeting, the need to counsel patients to avoid risk of transmission to families was noted. (It is difficult to see how this was reconciled with Professor Bloom's advice that "*information on the test results, should not be given automatically but if asked for*".)

    d. In his Litigation Report, Dr Rizza referred to difficulties in advising patients at a time when the doctors themselves were unsure of the significance or prognosis of a positive HLTV-III antibody test. He stated:

> "*All these difficulties with testing made it extremely difficult to know what to tell patients. It was generally recommended that a positive result should be confirmed by repeat testing before informing the patient and offering counselling to him and his sexual partner. This meant that there was often delay in informing patients of their antibody status. Concern about the slowness in introducing testing of all blood donations by the Blood Transfusion Centres was expressed by Professor A. L. Bloom, Dr. C. D. Forbes and Dr. C. R. Rizza in a*

[139] TREL0000172_056.

[140] OXUH0000429_002.

[141] HCDO0000394_117.

letter to the Lancet on 22nd June, 1985. Testing of all blood donors for anti HTLV3 in UK came into effect in October 1985."[142] [143]

91. On 19.03.87 Dr Rizza declined to enter any of the Centre's patients into a trial using AZT to treat AIDS. In a letter to the Wellcome Research Laboratories[144] he noted that he had 3 or 4 patients who might meet the inclusion criteria for the trial, *"They are at present all very well and at work and although they have had candida in the past they do not have candida at present. Given the known side-effects of AZT I am reluctant at the moment to enter those 4 patients into the study. These particular patients are being closely watched and should their condition deteriorate at all I think it might be justified to consider putting them in."*

92. During the meeting of the Oxford Region Health Authority AIDS Clinical Working Group on 27.01.88,[145] it was noted that under the regional policy for prescribing of zidovudine (Retrovir), this should be done by a nominated GP "*to ensure that prescribing of Retrovir was treated with caution… to encourage discussion and collaboration among clinicians on the treatment of individual patients and to ensure that the criteria for prescribing were met*".

93. In 1988 Dr Rizza decided the Centre should participate in an MRC trial of zidovudine in asymptomatic HIV infection.[146] At that time, there was a live debate over the optimum time for HIV-positive patients to commence this treatment.[147]

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[142] OXUH0002184_001.

[143] HCDO0000003_001 p.129.

[144] OXUH0001250_001.

[145] OXUH0002260_076.

[146] OXUH0001243_005.

[147] See the minutes of the Oxford Regional Health Authority AIDS Clinical Working Group meeting on 21.06.88 - OXUH0002260_062.

94. On 09.06.89 Dr Rizza provided the following summary to the DHSS: [148]

> "*We have, at present, 135 HIV antibody positive haemophiliacs. A total of 14 of those have developed AIDS of whom 7 have died. Of the remaining 7 AIDS cases 6 are receiving treatment with AZT and have been receiving the drug for 15, 8, 7, 6, 6 and 4 months. One of the 7 patients who died received AZT for three months before death. Of the patients taking AZT 3 have had to stop treatment temporarily because of anaemia requiring blood transfusion or because of severe nausea. At this Centre we have used AZT only in patients diagnosed as suffering from AIDS, we have not used AZT in other patients but are participating in the MRC CONCORDE I STUDY. To date, only 3 of the 60 patients approached have agreed to enter this Study.*"

Hepatitis C

95. The date when the Centre commenced testing patients for HCV is unclear from the documents. There is also a lack of clarity as to what patients were or were not told about the significance of a positive test. According to Professor Giangrande's evidence to the Lindsay Tribunal, the task of testing for HCV began in October 1990 and was largely completed by the end of 1993. [149]

96. On 18.06.91 Dr Rizza wrote to Dr Selkon at the John Radcliffe Hospital asking when HCV antibody testing would resume and noting that patients had been asking for this; the reason for the hiatus is not explained. [150]

[148] OXUH0001299_005.

[149] LIND0000330.

[150] OXUH0001865.

97. On 25.06.91 Dr Rizza wrote to Dr Tedder at University College and Middlesex School of Medicine, agreeing to a proposed study into the risks of HCV infection to spouses of haemophiliacs. He stated:

> *"I am very anxious to find out to what extent there has been sexual transmission of HCV to the spouses of HCV positive haemophiliacs. As you know, one of the early serological methods revealed a rate of transmission approaching 20% in our group. Given the uncertainties of method I have found it extremely difficult to know what to say to the couples. They are aware of the tests that are becoming available and many wish to know what a positive result means."*[151]

98. He expressed similar sentiments in a letter dated 11.07.91 to Dr Hallam at the John Radcliffe Hospital:

> "*… many of our patients and their partners are aware that HCV testing is now available. They are asking about it and several questions have been raised as a consequence. In particular, what does it mean if a person is anti HCV positive? Is their antibody protective? Are patients that are anti HCV positive more likely to go on and develop chronic liver disease? and finally, and the most important, are anti HCV positive patients infectious and likely to transmit it to their sexual partners? To date, I have told our patients that the test methods for anti HCV are being evaluated and that I was not prepared to give a definite answer on the results.*"[152]

99. A meeting was held at the John Radcliffe Hospital on 17.07.91 to discuss HCV testing and the significance and management of positive results.[153] The Oxford Regional Transfusion Centre produced, in July 1991, "Recommendations and Information for Donors/Patients Found Hepatitis C (HCV) Antibody Positive".[154]

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[151] OXUH0001863_002, OXUH0001863_001

[152] OXUH0001864.

[153] OXUH0001862_002.

[154] OXUH0001862_003.

100. On 17.07.91 Dr Rizza wrote to Dr Cash at SNBTS that at the Centre: "*63% of 379 patients with haemophilia A, 57% of 61 patients with haemophilia B and 20% of 39 patients with von Willebrand's disease are anti HCV positive.*"[155]

101. In August 1991, it was reported to Dr Rizza that two wives of haemophiliac patients at the Centre had tested positive for HCV antibodies.[156] His reply (*"I found the results most interesting"*) revea1ed that one of the partners had recently been found to be HIV positive.[157]

102. On 11.12.92 Dr Rizza wrote, *"We are not at present using interferon in any of our haemophiliacs although we are looking at a protocol for its use in haemophiliacs with chronic liver disease".*[158]

Record-keeping

103. In a letter dated 39.5.76, Dr Rizza expressed concern that a patient's file had been destroyed, asking *"Could you please ensure that no further files on haemophilia or Christmas disease patients are destroyed without my approval?"*.[159]

[155] OXUH0001861_002.

[156] OXUH0001860_002. The letter is dated 23.08.90, but it seems likely from the reference in the letter to a seroconversion taking place "in October 1990 or thereabouts" and from the date of the reply (see the next footnote) that the date should be 23.08.91.

[157] OXUH0001860_001.

[158] OXUH0001570_001.

[159] OXUH0001158, letter of 30.05.75.

104. In August 1985 there is a suggestion in correspondence that the Centre might require extra staff to undertake a counselling role.[160] In October 1985, according to the Litigation Report, the DHSS gave each Reference Centre £15,000 to set up counselling services, topped up by a further recurring sum of £45,000 from December 1985.[161] The nature of the counselling available is unclear from the documents.

105. This funding appears to have continued for a period - in 1989/1990, £45,000 was allocated from the Oxfordshire Health Authority for the provision of counselling services for haemophiliacs with AIDS.[162] Psychology input seems to have been provided at some stage by local mental health services at the Warneford Hospital.[163]

106. On 05.03.91, Dr J Catalan, Senior Lecturer in Liaison psychiatry, wrote to Dr Rizza, *"You mentioned on March 1st in the chat we had after our talk that a variety of psychological and social support systems have been developed at the Centre, presumably outside, over the last couple of years".*[164] He asked Dr Rizza for a list of the kind of activities that had taken place, suggesting he would include on the list *"things like the visits that patients have paid to the laboratory to look at their own blood being used in research, and any initiative that you have developed concerning pregnancy, artificial insemination etc".* Reference was made in the letter to data on the psychological state of men with haemophilia and HIV infection. It may be that this is a reference to a study funded by the Wellcome Trust: at a meeting of the Oxford Region Health Authority AIDS Clinical Working Group on 27.01.88 Dr Catalan reported that a grant had been awarded *"for a 5*

[160] OXUH0000399_002, letter of 15.08.85 from the Oxford Regional Health Authority.

[161] HCDO0000003_001 p.130.

[162] OXUH0001391_001.

[163] OXUH0001387, although the letter is concerned with psychological services for HIV/AIDS generally.

[164] OXUH0001362_001.

year study of the psychological state, a range of related issues and neuropsychiatric state of all HIV positive patients in the Oxford Haemophilia Centre compared with a sample of negative haemophiliacs. Virological and immunological testing would also form part of the study".[165]

Stigma / access to services

107. In 1990, the Dental Department of the Oxfordshire Health Authority decided to discontinue operating on patients with HBV and HIV on safety grounds from 01.10.90.[166]

108. In 1991, the Centre wrote to reassure the Buckinghamshire Ambulance Service that HIV positive patients could be transported like anyone else, following a concern that they posed a risk of infection to ambulance service staff.[167]

[165] OXUH0002260_076. The report of the study, dated 01.02.91, is at OXUH0001328_011.

[166] OXUH0001293_006.

[167] OXUH0001374.

RESEARCH

109. Oxford was a hub for haemophilia research and data analysis. Some of the key pieces of research undertaken are summarised below.

Annual returns data

110. The Centre received and analysed data returns from the other Haemophilia Centres on an annual basis from the late 1960s.[168] The annual returns were used by the UKHCDO and its working parties to study a variety of issues, including the quantity of blood products required by the patient population and the risk of adverse side effects including inhibitor development, jaundice and viral infections.

111. The process was described by Dr Rizza in 1982 as follows:

> "*The work which is done here for the U.K. Haemophilia Centre Directors is of a very general nature and includes the patient's name, date of birth, Centre at which he is registered, whether or not he has antibodies to Factor XIII, whether or not he is on home treatment and also the amount of factor XIII or IX used. All of this kind of information is collected once a year from Centres round the U.K. and analysed and then included in an annual report sent out to the Centres*".[169]

112. The type of information collected changed over time. A memorandum from Dr Rizza dated 22.09.86[170] details the approach taken at that time:

> *"Forms Al-A7 deal with the total amount of the different therapeutic materials used to treat the different categories of patient during the previous year. These 7 forms do not contain the names of patients. Form A8 collects information on patients who have died*

[168] In 1978 the returns were analysed using "*the Oxford Regional Health Authority's computer*", singular - OXUH0000212_002. Prior to that the data had been handled manually.

[169] OXUH0001534_002.

[170] HCDO0000248_010.

in a particular year and asks for name of patient, diagnosis, date of birth, date of death and cause of death. Forms Bl, B2 and B3 are used throughout the year for notification of new cases with congenital coagulation defects, new cases of factor VIII and IX antibody and cases of acquired haemophilia A, B or acquired von Willebrand's disease… Form Cl and C2 are concerned with survey of hepatitis and request the patient's name, date of birth, and clinical and laboratory details of the patient's hepatitis… Form vW(ii) is for notification throughout the year of von Willebrand's disease… Form AIDS/3 is marked confidential and is used for surveillance of AIDS-related illness."

113. The memorandum noted that data relating to AIDS was not entered onto the computer but kept in a locked cupboard to ensure confidentiality; it was also sent to Dr Craske in Manchester.

Factor IX concentrate

114. A trial of use of Factor IX concentrate commenced in 1976. Dr Bidwell commented in a letter of 13.05.76 that "*the importance of the trials resides in the fact that the materials are already being used for purposes covered by the proposed trials, without adequate data of safety and effectiveness since supplies of the products are available in the hospitals that receive them for the treatment of patients with Christmas disease*".[171]

Hepatitis prevalence

115. During 1969-1974, Dr Biggs oversaw a study into jaundice and factor VIII antibodies, using data supplied from the Haemophilia Centres in their annual returns.[172] These were seen by Haemophilia Centre Directors to be the two most serious potential adverse side-effects of transfusion.[173] She noted the evidence suggested an increase in jaundice

[171] OXUH0000963_001 & OXUH0000980_001.

[172] CBLA0000242.

[173] DHSC0002173_048, p.1, HCDO0000003_024.

possibly related to the use of commercial concentrates made from large donor pools – "*every effort should be made to increase the supply of intermediate potency concentrates made from United Kingdom blood*".[174] As noted above, she subsequently published an article in 1977 arguing for self- sufficiency[175], drawing on analysis from this study.

116. In 1978-1981, the Centre participated in a DHSS-funded prospective Hepatitis Surveillance Programme.[176] This was coupled with follow-up of chronic sequelae of factor VIII associated hepatitis, on long-term patients at the Centre, including full blood count and liver function tests.[177]

117. A more formal follow up multi-centre study, titled "*A Prospective study of the incidence of acute and chronic hepatitis in haemophiliacs after treatment with freeze dried factor VIII or IX concentrate for the first time*", was commenced in or around 1982.[178]

118. The grant proposal for the follow up study[179] stated that results from the initial survey indicated that NHS product manufactured at Oxford (pool size around 500 donors) had significantly lower risk of hepatitis infection than that prepared at BPL at Elstree (around 3,500 donors). A report by Dr Craske dated 23.09.82[180] regarding the proposed study stated,

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[174] CBLA0000242, p.7.

[175] R. Biggs, 'Haemophilia Treatment in the United Kingdom from 1969 to 1974', *British Journal of Haematology* 1977, 35, 487 (PRSE0004645).

[176] CBLA0000831, OXUH0000504_002, OXUH0001633_005.

[177] HCDO0000270_089, HCDO0000135_021, PRSE0000044. See also, as an example of individual follow-up, OXUH0000228_002.

[178] OXUH0001613_002, OXUH0001630_003, HCDO0000135_015.

[179] OXUH0001613_002.

[180] HCDO0000135_015.

"*It is proposed to extend these observations by undertaking similar studies in other Haemophilia Centres to compare the incidence of acute hepatitis after first exposure to factor VIII and IX concentrate of different brands and to obtain accurate information about the risk of chronic sequelae. There are also several commercial products under development where attempts have been made to inactivate viruses present in the concentrate using heat, UV light and β-propio-lactone or other method. The only way of determining whether any of these methods is effective in inactivating hepatitis viruses in these products is by chimpanzee inoculation or a prospective study in haemophiliacs who have had no previous exposure to concentrate.* ***Chimpanzees are in short supply, so in the absence of laboratory tests for non-A, non-B, hepatitis trials in patients likely to be susceptible to non-A, non-B, hepatitis present the only possible way of evaluating this risk***." (emphasis added.)

119. It is unclear whether the Central Oxford Research Ethics Committee saw Dr Craske's report referring to using humans instead of chimpanzees. By letter dated 12.01.83,[181] the study received firm approval from the Committee Chair:

"*It seems to me that the follow-up proposed really falls into the category of continued clinical care of the patient, as patients stand to benefit from this very careful follow-up. I, therefore, feel that there are no research ethics implications with this study and feel that I can give you approval to continue with the study without bringing the matter to the attention of the Central Oxford Research Ethics Committee*."

HBV vaccine

120. In 1982, there was an immunogenicity study of a vaccine for HBV produced by US company Merck, Sharp & Dohme, for which Dr Rizza sought Ethics Committee approval.[182] There was some delay in obtaining ethics approval for trialling the vaccine in children but this was ultimately granted.[183] On 03.09.84, Dr Craske wrote to Dr Rizza,

[181] OXUH0001630_002.

[182] OXUH0001743.

[183] OXUH0001740, OXUH0001737, OXUH0001736, OXUH0001734.

regarding the 'Hepatitis B Vaccine Trial', explaining that a patient's wife had been immunised and 6 months later not produced an antibody response.[184] Dr Craske's report on the study dated 11.09.84 concluded that the vaccine produced an adequate immune response in patients under 40 years old.[185]

HIV and AIDS

121. The Centre conducted an Oxford Immunity Survey from 1984 to 1986 looking at the association between blood products and AIDS, and in particular whether reduced immunity was linked to the particular type of factor product. Patients signed a consent form which explained that they would have their blood drawn every 3 months over 2 years for this purpose, would be asked a number of questions and be examined by a doctor and would have a set of skin tests.[186] There also appears to have been a template form requesting consent from parents.[187] Ongoing results gathered from this study were followed through into the study of HIV antibodies in 1985 - 1987[188] (after anti-HLTV-III testing was made available in August 1984) and the surveillance of AIDS related illness in 1985 – 1986.[189]

122. In a letter dated 13.02.87 concerning collaboration on a research study for which Ethics Committee approval was being sought, Dr Rizza asked for coding to be introduced to protect confidentiality: "*Many patients are very sensitive about the confidentiality issue and they might not be happy about the prospect of their names being known to people other than those involved in their management.*"[190]

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[184] OXUH0001614.

[185] CBLA0001884_006.

[186] OXUH0002508.

[187] OXUH0002339_001/ OXUH0002339_002.

[188] DHSC0006354_079.

[189] BART0002337.

[190] OXUH0002188_001.

123. As noted above, Dr Rizza and the Centre were involved in a number of studies regarding heat-treated factor products.

124. Patients from the Centre were entered into a trial of NHS heat-treated concentrates 8Y and 9A during 1985-1988, which looked at the possible virus transmission by these concentrates in previously untreated patients.[191]

125. On 29.09.86 Dr Kernoff wrote to Dr Rizza regarding the draft protocol for this study: *"more effort should be made to foster a sense of "belonging" among study participants"*. He referred to a need to sort out *"legal and ethical issues"*. He also wrote that *"since we are dealing with two lethal diseases, patients safety and protection must be our top priority"*.[192]

126. The study involved following up previously untransfused patients treated for the first time with 8Y, with data from multiple centres submitted to Oxford.[193] On 23.10.87, Dr Rizza sought approval for the study from the Central Oxford Research Ethics Committee on the basis that 8Y was known to be safer than commercial preparations: "*It is our routine treatment for children and others who have received few transfusions in the past*".[194]

[191] OXUH0000562_005; PRSE0000044; CBLA0002348.

[192] OXUH0003853. A final version of the protocol is at HCDO0000003_061.

[193] OXUH0003754_035, OXUH0000593.

[194] OXUH0003754_012.

127. However, the study was not without ethical problems. In one case, a participating patient from another centre was not given the hepatitis B vaccine "*as it may interfere with the results and will be a further guide to infectivity of the product*".[195]

128. The initial protocol for the study stated that information was only sought on patients who gave informed consent.[196] This was subsequently confirmed in the published article on the study, which stated that all patients gave informed consent.[197]

129. None of the patients in the study developed high AST or ALT levels during the follow up period.[198] Therefore, it was concluded that NANB did not develop in any of the patients exposed to 8Y and 9A concentrates. However, it was acknowledged that the findings of the study required careful assessment because the ICTH recommendation that patients entering such trials had normal liver function and no prior exposure to blood products was not met.[199] Accordingly, a second trial of 8Y and 9A 'rigorously in line with ICTH criteria' was commenced, to allow for a more precise quantification of any residual risk.

130. The Centre then coordinated and participated in a follow up study into NHS factor 8Y from 1988-1991.[200] One of the stated criteria for admission to the study was that informed consent had to be obtained.[201] However, it is noteworthy that the summary procedure for first infusion and entry into the trial detailed explaining the trial to the patient and obtaining informed consent as the final step to be taken by clinicians.[202] In effect this would mean that patients were infused with 8Y and the relevant samples taken, before their consent was obtained for participation in the trial.

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[195] OXUH0002107_021.

[196] CBLA0002035, p.5.

[197] PRSE0000044, p.815.

[198] PRSE0000044, p. 815.

[199] PRSE0000044, pp. 815-6.

[200] PRSE0000192, p.1.

[201] HCDO0000003_061, p. 3.

[202] HCDO0000003_061, p.11.

131. Although tests for HCV antibody were not available when the study commenced, as soon as these tests became available all participant centres were asked to test for anti-HCV as an additional test. It was found that the risk of transmitting HCV with 8Y was between 0 and 11%, which supported the findings of the earlier 8Y study. All patients in the original study who were tested and had received no other type of concentrate had also remained negative for anti-HIV and anti-HCV.[203] It was concluded that heat-treating concentrate at 80 for 72 hours in the final vial, prevented transmission of HCV.[204]

[203] PRSE0000192, p.3.

[204] PRSE0000192, p.3.

OTHER ORGANISATIONS

UKHCDO

132. The first meeting of the UK Haemophilia Centre Directors was held in Oxford in 1968 at the invitation of Dr Biggs (described by Dr Rizza at the Wellcome Seminar[205]). The practice of annual data collection arose from that meeting.

133. Dr Rizza was a central figure in UKHCDO. He was the Secretary/Secretary General of UKHCDO from 1977 to 1987 and in that role was instrumental in organising the establishment of new working parties in 1977.[206] He chaired the organisation from 1987 to 1990.[207] He was part of the Hepatitis Working Party and chaired the working party studying assay of factor VIII activities from 1978 to 1984 and the AIDS subcommittee from 1987 to 1990.

134. Dr Rizza was also a member of the Expert Group on the Treatment of Haemophilia and Allied Conditions, which advised the Department for Health and Social Security, the Scottish Home and Health Department, and the Welsh Office.[208]

Haemophilia Society

135. Dr Rizza had a long-standing relationship with the Haemophilia Society:

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[205] RLIT0000022 p.64.

[206] A letter from Dr Maycock to Dr Rizza on 28.02.77 recommended working parties, in order of priority, on: the incidence of haemophilia; the incidence of factor VIII antibodies; cause and prevention of the development of factor VIII antibodies and their treatment; home treatment of haemophilia and staffing of haemophilia centres; and *"incidence of hepatitis in haemophilia"*, which Dr Maycock *"put ... last"*, observing that *"I think it possible that hepatitis may have attracted undeserved attention"*: CBLA0000579.

[207] HCDO0000003_001 p.7.

[208] Reconvened on 01.04.76 (DHSC0100007_035); further meeting on 04.05.76 (HCDO0000394_048).

a. He was at one stage a member of the Council of the Haemophilia Society.

b. He was present when Professor Bloom addressed the Council and a large meeting of the Haemophilia Society in London on 08.10.83 on the subject of AIDS. [209]

c. He was a member of the Society's Medical Advisory Panel from the 1970s to the early 1990s. [210]

136. On 29.01.90 Dr Rizza responded to Mr Watters, of the Haemophilia Society, that it would be difficult to provide information to him concerning prevalence of severe liver damage in haemophiliacs *"for a variety of reasons not least because of the on-going litigation"* and said that he would *"discuss the matter with the Regional Centre Directors and also our Lawyers and I shall be in touch with you again"*.[211]

Treloar's

137. The relationship between Oxford and Treloar's will be considered during the Inquiry's hearing on Treloar's in spring 2021.

[209] DHSC0001297 p.7.

[210] See, e.g., HSOC0010954, meeting of the Medical Advisory Panel on 27.04.90, at which Dr Rizza observed that he *"felt that safety was of first importance and purity second. He therefore would continue to prescribe 8Y until it was proved that another product was safer"*. There was a discussion about HIV treatments and the *"Problems over Hepatitis C were raised. A number of people are known to be Hepatitis C positive from blood tested from stored samples. This brought up the old ethical dilemma of how to inform people of a test result that they have not asked for"*. The role played by the Medical Advisory Panel will be considered further during the Inquiry's hearing on evidence relating to the Haemophilia Society in early 2021.

[211] HSOC0024278.

138. The Oxford Haemophilia Centre under (in particular) Dr Rizza occupied, like the Cardiff Haemophilia Centre under Professor Bloom, a central role in relation to decision-making, treatment and research. As set out above, it is possible that the Inquiry will receive written and/or oral evidence relating to the Centre's policies and practices: for this reason this Note provides an overview of documentary material rather than a comprehensive assessment of what was, or was not, done by the Centre and by those in positions of responsibility there.

139. Key issues and/or questions which the Chair may need to consider in relation to the Centre, once he has all the available evidence, include[212] the following:

a. What was the Centre's, and in particular Dr Rizza's (as its Director), state of knowledge, as a matter of fact, about the risks of infection associated with blood products and how did that knowledge develop over time?

b. Did the Centre, and in particular Dr Rizza as its Director, underestimate the potential seriousness of Non A Non B Hepatitis and if so why?

c. When did the Centre, and in particular Dr Rizza as its Director, first appreciate the risk of developing AIDS in consequence of the use of factor products?

d. What steps did the Centre, and Dr Rizza as its Director, take in response to that risk? Were they sufficient? Should more have been done and if so what?

e. What influence did Dr Rizza have on the actions and decisions of the UKHCDO? Should the UKHCDO have provided different and/or earlier advice to centre directors and if so what?

f. What information and advice was provided by clinicians at the Centre to patients about:

    i. the risks, benefits and disadvantages of treatment with factor concentrates;

[212] This is not intended to be exhaustive.

ii. the availability, suitability and safety of alternatives;

iii. the risks of, and seriousness of, hepatitis;

iv. the risks of, and seriousness of, HIV/AIDS?

g. What were the arrangements for testing for HIV and for HCV and were patients told that they were being tested?

h. How and when were patients informed of the test results? Was appropriate and adequate information provided to them about their diagnosis?

i. How was the care and treatment of those diagnosed with HIV and/or HCV managed at the Centre?

j. Did the Centre provide to the patients who participated in one or more of the multiple research studies undertaken there sufficient information to enable them to give express and informed consent?

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