1981

JANUARY

The first document in this section is a copy of a letter appearing in The Times on 2nd January 1981 relating to the inability of the NBTS to provide adequate supplies of blood products in the United Kingdom. Brian Meakin's letter states that the precision has largely been self imposed by bureaucracy. I would say he was speaking out of turn. John Watt had probably "bent his ear" during the course of a meeting at the University of Bath.

The next document, a memorandum from Mr. Leavens dated 5th January 1981 relates to some of the specific matters raised by the Medicines Inspectorate. **[DO We have the "Three Documents" originated by Mr. Flint and Mr. Ayling?].**

The next document is a memorandum dated 9th January from Mr. Pettet headed "pro-rata of distribution of products". This goes into the detail of pro-rata. Originally, the concept was to apply to Factors VIII and IX, but was never implemented for Factor IX as self-sufficiency in this product was attainable.

The next documents, sent under the cover of Mr. Godfrey's letter of 19th January 1981 are internal DHSS memoranda following the visits made by the Medicines Inspectors in 1980. These form part of an on-going series of Reports from the Inspectorate. The inspections were all "informal", because the BPL was a Crown body. At that time, there was no formal quality control department. Dr. Maycock himself was required to sign the Release Certificates for the product. This specific task should have been dealt with by a Control Department. Although Dr. Maycock's department did analytical testing, there was no formal quality control in the true sense of the word.

The next document is a memorandum from Dr. Smith dated 19th January 1981 which relates back to Mr. Pettet's memorandum of 9th January. At around this time, Dr. Smith took over as production manager of coagulation at Elstree. Again, this memorandum concerns the intricacies of pro rata distribution of products.

The next document is a letter dated 26th January 1981 from Mr. Lee, Principal Assistant Treasurer for North West Thames RHA, to Mr. Bailey concerning RIA

tests. By now, the RIA system was on board, but it could have been brought in a lot earlier if there had been less haggling about money.

The next few documents relate to the BPL/PFL Oxford budget. The position on both the revenue and capital accounts as at 31st December 1980 was that they were under spent. Expenditure was difficult to determine at that time, because with all the changes taking place we were unable to anticipate the levels of production.

The next document is a set of notes prepared by Dr. Cash for the Scottish Home and Health Department. The paper considers trends which may affect the planning of the availability of Factors VIII and IX concentrates within the Scottish Health Service. On page 4, under the heading "PFC Factor VIII Yields", he sets out the figures in terms of iu of Factor VIII produced by PFC which will reach the bed-side, per litre of fresh-frozen plasma processed, for the period 1975 to 1980. On page 9, under the heading "Viral Hepatitis Transmission" he says that:-

> "Several Reports have implied that the risks of transmitting agents likely to cause hepatitis is higher for Factor IX than VIII concentrates. The evidence is not firm but may relate to differences in pool size (the former usually being larger)".

Appendix 1(c) sets out in iu, issues of intermediate Factor VIII to Regional Centres. At that time, Scotland was ahead of England, but it had a newer centre.

FEBRUARY

The opening documents, which refer to the BPL Capital Programme 1980-83 are followed by a letter dated 2nd February 1981 from Mr. Collins at North West Thames RHA. This letter concerns the approval for "Marp 01" to proceed. A Project Team had met a week previously (I doubt very much whether I have a copy of the Minutes), and authority to proceed to tender was given on the assurances of readiness by the Project Team. However, final adjustments to design and cost were required before they could go to tender. Therefore, a start on site was not envisaged until the summer.

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On 3rd February 1981, the Minutes of the eighth meeting of the Scientific and Technical Committee for the Central Blood Laboratories, were circulated. The meeting had taken place on 3rd December 1980. **[Do we have STC80/6-Technology Working Party?]**. At the top of page 3, Dr. Walford reports on the proposed marketing of the BPL RIA test, from 1st March 1981. It is reported that "my request for funds to start production of the test was being considered by the Department". The Department were making heavy weather of it. The procedures were delaying the implementation of the BPL test. Yet it was in everyone's interests to improve the quality of plasma. The re-development of the BPL was the topic of discussion at the bottom of page 5 onwards. So far as the short-term upgrading programme was concerned, it was anticipated that work would be completed by the autumn of 1982. Over the page, it is noted that so far as long-term re-development of the Laboratory was concerned, I thought that in its present condition it could probably only function until 1984/5. In fact I was not far out: in 1985/6 our old building ran into problems affecting albumin production. On the rest of that page, the question of a quality control programme at the BPL is considered. I was anxious to get this programme up and running. **[DO WE HAVE STC 80/7 - STAFF APPOINTMENTS IN QC AT BPL?]**.

The next document is a long paper I prepared headed "Blood Products Laboratory: summary of performance since September 1979". This paper, dated 4th February 1981 coincided with the first round of discussions with the Medicines Division. I start off in the summary on page 2 by explaining that:-

> "The interim programme must be seen as an intensely uncomfortable period for the Laboratory in which the strains are applied in all directions. The Medicines Division are correct in viewing the interim programme as an extended period of high risk to products and a situation only removed by re-development of the Laboratory. The sense of urgency is evident".

The main drift of the summary is in relation to deficiencies encompassing buildings and staff. The first section touches upon MARP 01. The section entitled "Production" goes into great detail as to the structure of buildings and the layout of particular areas. The Report also goes into great detail on equipment and the cleaning services employed at the Laboratory. From page 19 onwards, I comment on the shortcomings of the Technical Services Section as highlighted by the Inspectorate's Reports. I note in the first paragraph:-

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"The Director and Manager of Technical Services are very aware of the shortcomings of this area of BPL. As this Report seeks to show, it has been the Cinderella of BPL although there is keen competition for this position".

At the top of the next page I talk of the "vacuum" in which I had worked since taking up my appointment as Director. I go on to comment about the long term management requirements for the BPL and I advocate the formation of an executive management body. The documents which follow on immediately after this section are a series of memoranda relating to Factor VIII production for the period January to December 1980, bacteriological performance in 1980, 1980 production summary, and various tables setting out data on sterility, pyrogen and toxicity tests etc together with a crop of documentation relating to cleaning and laundry services. This is followed by the next section, entitled "Staffing" which commences on page 21. Again, this is complemented by a series of documents containing job descriptions, training programmes and a table showing the proposed management structure encompassing adequate standards of quality control. Leon Vallet was appointed to the position of Deputy Director (Research and Development) at the BPL and PFL Oxford. He had no pharmaceutical experience. He deputised for me in my absence. The next section, commencing on page 23 is entitled "Environmental Surveillance and Control". The final section of the Report headed "Documentation" commences on page 26.

Dr. Gerrard Vaughan, Minister for Health, wrote to Dr. Peter Dunnill on 4th February 1981 concerning the re-development of the BPL and long-term management arrangements for the BPL. His letter in fact says very little. **[DO WE HAVE DR DUNNILL'S LETTER OF 26 JANUARY 1981?].**

On 5th February 1981 Dr. Dunnill sent me a copy of a report from the Protein Fractionation Technology Working Party set up under the Scientific and Technical Committee. **[WHERE IS THE REPORT?].**

The next document is the minutes for the JMC meeting held on 6th February 1981. Dr. Walford reports on page 2 that the BPL was to market its RIA test to Regional Transfusion Centres from 1st March 1981 at a cost of 20 pence per test. Paragraphs 21 to 25 deal with the long-term development of the BPL. In particular, the setting up of a JMC Policy Steering Group under the Chairmanship of Mr. Smart. So far as long-term management of the Central Blood Laboratories was concerned, Mr. Smart's Policy Steering Group prompted recognition for the

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need for a management group to take on the statutory functions of the laboratories.

On 12th February 1981 Mr. Godfrey, DHSS, circulated a discussion paper for the next meeting of the Advisory Committee on the NBTS. The paper examines the question of whether Factor VIII supplies should be held by Regional Transfusion Centres. The paper says:-

> "present annual consumption of Factor VIII in England and Wales is about 55 million iu, but demand is expected to reach 90 million iu by the mid 1980's. As a result of the short-term up-grading programme, the BPL will increase production from 15 million to 30 million iu by the end of 1982, but this will not eliminate the need for commercial purposes".

Purchases

The last sentence of the discussion paper is also worth noting:-

> "the Advisory Committee recognises that purchasing and distribution policy must remain a matter for local decision, but strongly commends this arrangement to RHA's for consideration".

The next document is a note prepared for my benefit by David Wesley, dated 12th February 1981 containing his comments on the Protein Fractionation Technology Working Party Report **[WHERE IS THE REPORT?].** He sets out a number of comments relating to the production of coagulation Factors at Liberton. In particular, he queries whether the method of continual operation during a 24 hour period is capable of producing a high purity product in reasonable yield. These manuscript notes are followed by Dr. Bidwell's comments on the same Report. Leon Vallet adds his comments on the Report is his manuscript note dated 13th February 1981. Dr. Smith's comments are contained in his note dated 16th February 1981. **[DR LANE WILL LOOK AT THE ORIGINAL, TO SEE IF IT IS CLEARER].**

The note on the file made by Mr. Harley at the DHSS on 20th February 1981 is very important as it sets out some of North West Thames RHA's responsibilities in connection with the re-development of the BPL. One of the points he had discussed with Mr. Armour was the question of the RHA's representation on the Policy Steering Group; officers of the RHA who were members of the Steering Group would be helping to make policies which the RHA would have to execute.

The second meeting of the Advisory Committee on the National Blood Transfusion Service took place on 23rd February 1981. The first matter under discussion was increasing the supply of plasma. We have already seen a letter circulated on 4th February 1981, together with a summary of current and possible future supplies of plasma to the BPL. It is clear that, on the basis of 600 iu per thousand population the consensus was not to go along with the view that 100 million iu per annum were needed. The figures were based on less than 1 iu per capita amounting to some 60 million iu per annum. Dr. Harris goes on to explain that planning work on the re-development of the BPL was to begin and it seemed possible that North West Thames RHA were to take on the project management. He adds that it was thought that the new laboratory might be completed in five years' time. Under the discussion on Factor VIII, it is worth noting that the Northern Ireland BTS intended to send plasma (both time-expired and fresh-frozen) to the PFC, Edinburgh. In the next paragraph, I point out that the United Kingdom is self-sufficient in Factor IX and therefore there is no need to operate a pro rata system for this product. The role of plasmapheresis as a means of increasing plasma supply, is discussed on page 4. **[DO WE HAVE AC (81) 4?]**. The target for Factor VIII production mentioned here, is 90/110 million iu. Consideration of a plasma volume to meet a target requirement of 135 million iu of Factor VIII is also considered. It was agreed that a Working Party should be set up under the Chairmanship of Dr. Gunson, Dr. Tovey and Dr. Walford amongst its members. It general, the Working Party was to consider and advise on supplied of plasma for self-sufficiency in blood products in England and Wales.

The long-term management of the Central Blood Laboratories is considered on page 5. It seems that Ministers had decided against commercial management of the BPL and were considering other long-term solutions. The present role of North West Thames RHA was described by the Chairman as to carry out the day to day management functions, with general oversight by the JMC.

The next document is an article appearing in Medical Laboratory Sciences by Angela Dike entitled "Post-Transfusion Hepatitis B Transmitted by HBsAg Negative Blood Containing Anti-HBc". The thrust of the article is that hepatitis B surface antigen testing has reduced, but not abolished the incidence of post transfusion hepatitis B. It says that cases have been reported of post transfusion hepatitis B where the donors were HBsAg negative by RIA. The article concludes that it would not at present seem worthwhile screening all blood donors for core antibody: at the Oxford Regional Blood Transfusion Centre all donations had been tested for HBsAg by RIA since February 1979. Of approximately 110,000

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donations negative by this test, only one donor had shown to be a transmitter of hepatitis B infection.

On 13th February 1981 I circulated a memorandum concerning the availability of DHSS funds for research and development for appropriate and supported projects. One of the research project proposals submitted, was for the "development of methods for the production of coagulation Factor concentrates with reduced risk of hepatitis transmission", dated 27th February 1981. This represented the beginning of the stirings for a viral inactivation programme. Again, reference is made to the dramatically reduced incidence of hepatitis B in recipients of Factors VIII and IX concentrates, since the introduction of improvements in detection methods for the hepatitis B surface antigen. As a result, the importance of NANB hepatitis had been highlighted. The proposal says that:-

> "although there is some evidence that the risk of transmitting NANB hepatitis is greater for imported blood products (Craske 1980), the incidence of NANB hepatitis following infusion of NHS concentrates is still a cause for concern".

The next document, dated 27th February 1981 contains the Chairman's comments (Dr. Dunnill) on the Protein Fractionation Technology Working Party Report, 1981. This paper is a summary of the report to follow and to which we have already referred above, although not seen. This was a partisan comment from Dr. Dunnill: he was really pushing for Edinburgh, in fact more so than he wished to divulge. In paragraph 1 he reflects on the uncertainty about the contribution to be made by the Edinburgh Centre: "in the Chairman's view, maximum use must be made of the Scottish facility and the lack of concerted action on this is regrettable". In the next paragraph, he suggests that a site other than Elstree may be preferable. Automation had been brought into the plant in Edinburgh, but the laboratory was plagued by man power problems and a refusal to work shifts. Reference in the third paragraph to "coherent management", is an unrealistic proposition: the real problems lay in terms and conditions imposed by the union, and the structure within the NHS. In the next paragraph, he advocates that the new facility should be built within 3 years.

The paper which follows that summary, is the full report of the Working Party.
The report speaks of the need to fractionate 450,000 litres of plasma a year to meet the projected demand of 90 million iu for Factor VIII per annum. Plasma supply is the subject matter of appendix 7, on page 24. Reference is made to the

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development of the single pack plasma: the first regional trial of 6000 single plasma packs is taking place.

The next document is headed "Pro-rata Supply of Blood Products" (AC (81) 3). This was an attachment to the agenda for the second meeting of the Advisory Committee on the NBTS which took place on 23rd February. This was essentially a status report, setting out the information for the new Committee. The paper puts forward for the consideration of the Committee, the possible arrangements for the distribution of the products. The paper distinguishes between the present system of distributing Factor VIII in accordance with regional requirements (based mainly on the number of haemophiliacs treated within a given region) and the proposed basis of pro-rata whereby the BPL will calculate how many iu's of Factor VIII are due to each RHA, according to quantity and quality of plasma supplied. To take into account deductions for quality control, failed batches and unsuitable plasma, the initial target was to return to RTC's 80 per cent of the notional gross yield. Appendix 1 shows how the regions' allegations under pro-rata might compare to current allocations. This document was probably originated in Mr. Pettet's department at Elstree.

The next document is AC (81) 5, which relates back to agenda item number 7 for the meeting on 23rd February 1981.

Lastly, document AC (81) 6 is a note on the long-term management arrangements for the Central Blood Laboratories.

MARCH

The first document is the Minutes of the 9th Meeting of the Scientific and Technical Committee for the Central Blood Laboratories, held on 4 March 1981. The meeting was attended by Mr. Ayling of the Medicines Inspectorate. Consideration is given on page 3 to the availability of central funding to research projects at the BPL. Amongst the projects that I mention in paragraph 12, is the development of coagulation Factor concentrates with reduced risk of hepatitis transmission. Mention is made at the top of page 4 of the visits to the BPL on 26th November and 9th December 1980, by the Medicines Inspectorate. Mr. Ayling said that these visits had been intended as informal inspections, to look at progress being made with the short-term re development programme and to offer

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advice where necessary. In paragraph 22, the question of Scotland's contribution to UK fractionation is still under discussion.

The meeting note is followed by two further copies of Dr. Dunnill's paper which was tabled at that meeting and which I have commented upon above.

The next document is a useful paper on hepatitis NANB which sets out the time at which the various tests were introduced in the Transfusion Service. The paper was published in Medical Laboratory Sciences and was written by J. Barbara and M. Briggs. The paper studies the incidence of post-transfusion hepatitis of the NANB variety, in the region served by the North London Blood Transfusion Centre. The paper reports than in an American survey 90 per cent of post-transfusion hepatitis cases, were of the NANB type. It also said that there seems to be a higher incidence of post-transfusion hepatitis generally in the USA than in the UK. The paper describes the screening methods used in North London:-

> "From 1974 all donors were tested by reverse passive haemagglutination (RPHA) and "new" donors were additionally tested by a radioimmunoassay (RIA). In 1977 we changed from a standard RPHA (hepatest) to a modified form of the test)".

The graph on the next page charts the introduction of the various tests. The graph shows how hepatitis B has fallen substantially. The report concludes that :-

> "the clinical importance of chronic aspects of NANB hepatitis is not yet clear, and much chronic NANB hepatitis resolves itself within 2 years. Probably post-transfusion hepatitis B is more important than the NANB variety, since not only does it appear to be a more severe infection but, if transmitted to a patient in hospital, it may be the source of more obvious infections among staff".

The next document is a paper I prepared for publication in Medical Laboratory Sciences relating to the development of the RIA kit for the detection of HBsAg. This article is a marker of our interest and involvement at that time. It noted the introduction of a reliable and economic test. In the second paragraph, I mention the possibility that positive donations may have been incorporated into pools for fractionation: a single plasma donation may be negative using the

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haemagglutination test and would probably be missed by RIA when pooled with 25 other donations. In the next paragraph, I comment that:-

> "reference to pooling for fractionation is mainly in connection with Factor VIII, but Factor IX and immunoglobulin preparations.... also present the risk of transmission of hepatitis since these products are not well suited to pasteurisation. Thus, where pools of plasma prepared for fractionation are likely to contain more than 5000 donations (1000 killogrammes) from the normal blood donor programme the need for sensitive surveillance of hepatitis markers is obvious".

The BPL decided to prepare its own RIA test for general distribution throughout the NBTS, to alleviate the need for the high cost of conversion to commercial RIA throughout the NBTS. The article concludes by saying that the BPL/RIA test is now available for use.

The next letter on the file is from Corning Medical and Scientific dated 4th March 1981. Corning are a medical health equipment distribution agency. The letter is not important, but acts as a marker for the fact that there was no hepatitis NANB test available.

The next document is a draft report which followed a further inspection of the BPL on 5th and 6th March 1981, by Mr. Ayling and Mr. Flint. The report is annotated with my comments on the discussions that took place with the inspectors. The inspection covered general conditions of processing areas and standards of house keeping. It concludes that:-

> "the processing areas themselves are intrinsically below acceptable levels in many areas".

And in the final paragraph is states that:-

> "it must be re-affirmed that BPL does not conform with accepted standards of GMP (Good Manufacturing Practice) and at best will not do so for some time, depending upon appointment of senior staff and up-gradings and rebuilding".

The next document in this section appears to be the final version of the report

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by Mr. Ayling, dated March 1981. There are two further recommendations in this version of the report:-

> "if it is Departmental policy that this site must continue then it must be accepted that in depth inspections by the Medicines Inspectorate to apply normal GMP requirements are counterproductive at present".

It continues:-

> "if an agreed programme of up-grading, rebuilding and staff appointments are instituted then a compromise level of inspections can be agreed".

On 9th March 1981 I wrote to Dr. Harris concerning the management of the Central Laboratories. I was advocating central control and management of the Transfusion service and the establishment of a Special Health Authority. I conclude that:-

> "if this government continues to support self-sufficiency in blood and blood products for the UK, then presumably it will not nullify the major financial investment by disregarding the co-existent requirement for competent management".

The next document in this section is the Minutes for the eleventh meeting of the UK Haemophilia Centre Directors held on 13th September 1980, which was circulated to the Directors on 18th March 1981. On page 4, Dr. Rizza presented a report on the 1979 annual returns from the Haemophilia Centres. The total amount of Factor VIII used annually had now reached 50 million iu. Half the material used was commercial Factor VIII concentrates. On page 5 there is big discussion as to what the Department of Health were doing at the time. Some people were advocating the use of commercial firms to make NHS material. Dr. Walford said that the Department was actively discussing this question. Professor Bloom refers to the "very severe short-fall in National Health concentrate which was a worrying situation". Targets for Factor VIII production were the subject of discussion on page 6. Dr. Aronstam said:-

> "a few years ago 50 million units was set as the target but even this amount of material was not available from NHS sources therefore what was the point in setting a new target if the original target had not been achieved".

On page 9, Dr. Craske presented a short report on the work of the Hepatitis Working Party. He reported that hepatitis B vaccine was still unlicensed for use in the United Kingdom but was under trial in the United States. On the next page, Dr. Craske comments on the relative merits of NHS product over commercial product:-

> "the NHS product was certainly better than the commercial products because of the screening of the blood donors and the regular donor panels which we used in the UK. The screening procedures used for donors of plasma used for commercial Factor VIII is radioimmunoassay but because of the unstable population and the poor social background, it is more likely that there will be a higher incidence of carriers of the hepatitis virus than in the UK volunteer blood donors".

The next document in this section is the Minutes of the eleventh meeting of the JMC held on 20th March 1981. Various matters were discussed, including the appointment of key personnel and also the long-term development of the Central Laboratories. Mr. Armour reported that North West Thames RHA could accept the task of project management for the BPL, provided that agreement could be reached on arrangements for accountability and control. The ASTMS' views on long-term management is set out in JMCCL (81) 13, which follows the Minutes. They agreed with my view that BPL/PFL should be constituted as a Special Health Authority with an executive committee or board responsible directly to the DHSS.

The next document is a manuscript note prepared by Mr. Leaven dated 10th March 1981 which relates to the Medicines Inspectorate's visit to the BPL on 5th and 6th March 1981.

The letters which follow relate back to a letter I wrote concerning lost production at the BPL.

The last two letters in this file appear to be those to which Dr. Rizza and others were responding, in relation to making up the delivery of lost Factor VIII production.

APRIL

A Meeting was held at Elstree on 3rd April 1981 to consider the "quality control of incoming plasma". The Minute was taken by Mr. Pettet. The Medicines Inspectorate Reports had highlighted the need to revise present testing practices of raw materials.

The next document is the packaging leaflet for Factor IX concentrate, dated May 1979. The leaflet is by way of information for users of the product. On the back of the leaflet, under paragraph 2 of the "Warning", the screening of the plasma from which the preparation is derived, is described with the proviso that:-

> "Nevertheless the most sensitive tests cannot eliminate the possibility that the fraction may be infective. Therefore, the risk of transmitting hepatitis cannot be disregarded".

This is followed by a copy of the package leaflet for Intermediate Purity Factor VIII concentrate dated March 1978, together with proposed revisions marked in manuscript and dated April 1981. The leaflet contains a warning as to the risk of transmitting hepatitis, in the same wording as that for the Factor IX leaflet.

The next document is a memorandum from Mr. Pettet dated 9th April 1981 which comments on a DHSS document on pro-rata distribution. The letter appears at the end of this section. The memorandum was written at the inception of the pro-rata distribution policy and followed the first month's issue of pro-rata.

I wrote to Mr. Ayling on 16th April 1981 setting out my corrections to the draft report following the Medicines Inspectorate's visit on 5th-6th March 1981. **[WHERE ARE THE ENCLOSURES?].**

Dr. Smith prepared a draft for Dr. Gunson's Working Party on Plasma Supply. His Paper is dated 27th April 1981. The Paper considers the relative merits of frozen cryoprecipitate, small pool freeze-dried cryoprecipitates, large pool freeze-dried cryoprecipitates and intermediate purity concentrates. The conclusion he reaches is that:-

> "Small-pool frozen or freeze-dried cryoprecipitate has unique advantages for patients needing only infrequent treatment..... However, a close examination of yields....supports the conclusion that the major component

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in our national strategy for Factor VIII production should be intermediate purity concentrate".

Dr. Smith sent me a memorandum on 29th April 1981 headed "Small-Pool Freeze-Dried Cryoprecipitate and Other Small-Pool Products". This is not particularly important, as it was merely a theoretical consideration which never progressed any further. However, at the top of page 2, Dr. Smith mentions that plasmapheresis is a "major source of plasma for Factor 8".

The last few pages in this section appear to be the letter referred to above, from the DHSS in respect of pro-rata distribution of blood products. The DHSS was agreeing the terms and conditions of pro-rata distribution. There was also a table showing how the new allocation would operate.

MAY

On 14th May 1981, Dr. Walford circulated a summary of the main points discussed at a meeting of representatives of Haemophilia Centres/Blood Transfusion Service Directors which took place on 23rd April 1981. The object of the Meeting had been to consider the foreseeable requirements of blood products containing coagulation factors used in the treatment of haemophilia, in the light of the Ministers' aim of national self-sufficiency in blood products. In terms of the quantity of Factor VIII, the use in 1979 totalled 52 million I.U. per annum. It was felt that by the mid-1980's some 80-100 million I.U. Factor VIII would be required. It was guessed that 150 million I.U. for the end of the decade would be an upper limit:-

"It was agreed that the projected figure for Factor VIII usage for the mid-1980's was 100 million I.U.".

So far as Factor IX was concerned, no significant increases in usage were envisaged for the mid-1980's. On page 3 of the note, consideration is given to other types of material required: these have been dealt with in Dr. Smith's Paper, as above.

On the next page, it is staged that about 80 per cent of the Factor VIII requirement would need to be in the form of intermediate purity concentrate. A

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maximum of 10 per cent of the total Factor VIII requirement would be needed as high purity concentrate.

The letters emanating from the DHSS dated 18th May 1981 highlight the fact that formal inspections of the Regional Transfusion Centres were only just starting.

JUNE

The memorandum from Dr. Bidwell to Mr. Evans dated 3rd June 1981 relates to a specific batch which was associated with a donor found to have jaundice. The memorandum is evidence of the action taken in such circumstances.

[QUERY RELEVANCE OF DOCUMENTATION PRODUCED AS A RESULT OF THE INSPECTIONS BY THE MEDICINES INSPECTORATE]

Mr. Pettet's memorandum of 8th June 1981 relates to the detailed problems of pro-rata. The question he addresses is whether the recovery of Factor VIII concentrate from a "rotten" pool should affect the distribution to the Blood Transfusion Centre in question. However, irrecoverable losses were taken into account on the basis that distribution was a return of only 80 per cent. In other words distribution was on a net, rather than a gross basis. This point is, in fact, covered in my memorandum to Dr. Pettet of 9th June 1981.

On around 8th June 1981 the DHSS circulated a Paper prepared by Mr. Harley on the manufacturing activities of the Central Blood Laboratories. The Paper was to be a subject of discussion at the meeting of the Scientific and Technical Committee on 10th June 1981. Mr. Harley's note contemplates whether it was relevant for the Central Laboratories to be manufacturing the RIA test. The essence of the argument was whether the Laboratories could be said to be performing their proper functions as befitting a public organisation. This is followed by my own note dated 8th June 1981. **[QUERY THE RELEVANCE OF THESE DOCUMENTS].**

The next document in this section is the Minutes of the 10th Meeting of the Scientific and Technical Committee held on 10th June 1981. Reference is made on page 2 of the Minutes to the proposed trials of shiftworking at PFC Liberton. These trials were planned to take place in October 1981. Their relevance to the BPL was stated to be in the context of assessing a target capacity figure for the

re-developed BPL. The re-organisation of PFL, Oxford is the subject of discussion at the bottom of page 3. I was aiming for a division of functions as between PFL and BPL. I was thinking ahead at the time and envisaging PFL directing its resources at new products and process development. I was well aware that funds of the extent made available to the BPL would not be available to the PFL.

Dr. Harvey's document headed "Albumen Recovery using Affinity Chromatography" is an annex to the Meeting notes above, but is not relevant here.

On 11th June 1981 the DHSS circulated Papers AC(81)11 and AC(81)13 for discussion at the third Meeting of the Advisory Committee on 22nd June 1981. The Paper AC(81)13 is considered below. The other Paper was the Preliminary Report dated June 1981 produced by the Working Party to advise on Plasma Supplies for Self-sufficiency in Blood Products. In paragraph 1 to the summary of the Report, it says that:-

> "It has been determined that 100,000,000 I.U. Factor VIII concentrates is a reasonable estimate for clinical requirements in England and Wales by the mid-1980's".

The Report concludes that:-

> "Intermediate Factor VIII concentrate is the product of choice for the treatment of the majority of patients suffering from Haemophilia A together with a requirement for a small proportion of high purity concentrates and frozen/freeze-dried cryoprecipitates".

To meet these requirements, an estimated 500,000 kilograms of plasma were required. Under the heading "Requirement for Factor 8" at paragraph 2.1 on page 1, the present combined capacity of BPL and PFL is 15,000,000 I.U. Factor VIII per annum. It was anticipated that after the interim expansion period, to be completed during 1982, production could be increased to a maximum of 30,000,000 I.U. per annum. It was said that forecasting requirements beyond the mid-1980's could not be accurate, but it was considered that by the 1990's the need for Factor VIII could reach 150,000,000 I.U. per annum. For a total requirement based on 100,000,000 I.U. Factor VIII per annum, it was considered that of this 80,000,000 I.U. would be comprised of intermediate purity concentrate.

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Consideration is given to the various means of obtaining plasma by means of plasmapheresis. The conclusion at the top of page 6 is that:-

> "The option of plasmapheresis has advantages over the procurement of plasma entirely from whole blood donations in that the wastage of red cells is avoided and donor panel size can be reduced because of the increased frequency of attendance of plasmapheresis donors".

The table attached to appendix 1 sets out the relative advantages and disadvantages of the various Factor VIII preparations. It is worth noting the disadvantages to frozen cryoprecipitate available in Regional Transfusion Centres: it is said to cause "reaction", to be of variable potency leading to over-use, requires frozen storage, difficult reconstitution and poor quality control.

On 12th June 1981 the DHSS circulated the remaining papers to the JMC Meeting to be held on 19th June. **[DO WE HAVE THE FOLLOWING DOCUMENTS: JMC CL (81)21; JMC CL (81)23; JMC CL (81)24].**

On 12th June 1981 I wrote to Dr. Entwistle at the John Radcliffe Hospital, Oxford concerning the anomaly that Oxford and Wessex were the only regions not appearing on the pro-rata league table for Factor VIII supply. PFL, Oxford obtained all its plasma from Oxford Regional Transfusion Centre. However, if there were any problems with the plasma, the Haemophilia Centre would have received no Factor VIII. At some point in the future, Oxford was brought into line with the rest of the country. **[QUERY: WAS DISTRIBUTION AT 80 PER CENT OR 90 PER CENT OF THEORETICAL PRODUCTION LEVELS?].**

The next document appears to be the final version of the Minutes for the Meeting of Representatives of Haemophilia Centres/Blood Transfusion Service Directors held on 23rd April 1981. I commented on the draft of these Minutes towards the start of the section for May 1981. The only additional comment I would make, is that the Haemophilia Centre Directors drew back at the proposal that supplies of Factor VIII be held in and distributed from Regional Transfusion Centres. Dr. Kernoff in particular opposed this idea: he wanted to keep his own budget.

The next document is a Progress Report prepared by Mr. Collins, Project Co-Ordinator from North West Thames RHA. It was hoped that work on MARP 01 would commence in July 1981 with a contract period lasting up to the end of

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1982. Things were at last beginning to happen. **[WHAT IS THE HEPATITIS LABORATORY?].**

On 16th June 1981 I wrote to Dr. Gunson with my comments on the Preliminary Report by the Working Party to advise on Plasma Supplies for Self-sufficiency in Blood Products. I anticipated reaching the situation where not enough plasma was available because of a lack of money available for plasma collection. I suggested the possibility of buying plasma collected by plasmapheresis in the United States. I added that:-

> "The risks of using US plasma are inherent in the plasma and in the final product to the same extent. However, it would be argued that control over fractionation in the UK would provide a better measure of assurance than by leaving fractionation to US laboratories".

I continued:-

> "The Authorities will eventually have to decide whether the additional safety and control and benefits to the NBTS that accrue from plasma collection within the NBTS are worth the additional cost. Certainly, there are no ultimate savings since we either buy plasma or we buy finished products".

Although the purchase of plasma is not unrealistic, it was thought to be politically unrealistic.

The DHSS circulated a draft of the Inspection Report by Mr. Haythornthwaite of the visit to BPL, Elstree on 13th May 1981. The final version of this Report is included in the July 1981 section, below.

The next document is the Minutes of the third meeting of the Advisory Committee on the National Blood Transfusion Service held on 22nd June 1981. Reference on page 2 to the supply of blood products to Northern Ireland arose out of my suggestion that plasma from Ireland be sent to Liberton to use up some of the spare capacity. The plasma was of poor quality: it was sent in three litre bags in an unfrozen form. It is interesting to note at the bottom of page 2 the comment that if the BPL were in a position to produce the required quantity of Factor VIII "it might become necessary to insist on clinicians using the BPL product except were it was absolutely essential to use a particular commercial substitute".

This was contrary to the belief that clinicians should have freedom of choice as to the use of product for any particular patient. On the next page, Dr. Harris makes the illuminating comment that:-

> "Although self-sufficiency was a desirable goal, it would be necessary to balance the cost of collecting plasma against the value of products, especially at that level after which the plasma might be needed to meet the demand for Factor VIII only".

The Committee rejected the possibility of buying in plasma from abroad as a means of enabling the BPL to utilise its capacity to the full. Dr. Walford pointed out that:-

> "Apart from increasing the risk of hepatitis, if foreign plasma were purchased, it would need to be fractionated separately from UK plasma, and this would have serious cost implications for the re-development of BPL".

So far as the increased risk of hepatitis was concerned, this comment was not justified in the light of Dr. Craske's Reports. **[IS THIS CORRECT?: DR CRASKE'S REPORT WAS IN 1983].**

On 23rd June 1981 Dr. Entwistle responded to my letter of 12th June relating to Oxford practices as to distribution of Factor VIII. In his letter, Dr. Entwistle agrees that it would be proper for the Oxford Centre to come in line with the others and that it was right that they should contribute to the Lord Mayor Treloar school.

The next document in this section is Mr. Ayling's Report on the inspection of PFL, Oxford on 23rd-24th June 1981. The PFL came out of the inspection quite well because it was a small, compact laboratory (employing 23 people and never more than 28 people) and generally staffed to a high level of competence. It was easier to recruit staff than it was for Elstree and there was a certain elan associated with working next to the Oxford Haemophilia Centre. Time was available to develop documents and procedures for Factor IX production. The laboratory made Factors VIII and IX but not much else. It was always perceived as a development unit, whereas Elstree's role was very much as a straightforward production unit. Facilities at Oxford for production at Oxford were grand, yet the laboratory only produced 2,000,000 I.U. Factor VIII at that time, in

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comparison with 14,000,000 I.U. at Elstree. Yet the facilities at Oxford justified higher levels of production. I was able to use a lot of talented staff from Oxford, at Elstree; for example, Dr. Snape started up the Quality Control section at Elstree.

The first page of the Report provides a useful background to the personnel at Oxford and the products manufactured. It is also worth noting the general background paragraphs under the heading "Quality Assurance". Dr. Rizza, the clinician responsible for the Haemophilia Centre, advised that potential screening for NANB Hepatitis and Hepatitis A by excluding plasma drawn from patients with raised liver enzyme activity was thought unnecessary and impractical. Under the next heading, "The Role of the PFL, Oxford", it is stated that:-

> "PFL, Oxford itself exercises no direct control over the plasma supplied, which is its main raw material. Reliance is placed on the dialogue which occurs between BPL, Elstree and the Transfusion Directors".

So far as hepatitis testing is concerned, (HBsAg), the BPL RIA test is used to test the final product. In addition, sub pools are also tested from the supernatant. By way of conclusion on the final page, although staffed by people of a higher academic standard, the Laboratory had not been brought up to modern standards and it was necessary to bring it up to standards of good manufacturing practice.

An agenda was circulated to Members of the Working Party on Post-Transfusion Hepatitis, for a meeting to be held on 25th June 1981 at the instigation of the Medical Research Council ("MRC"). Included in the items on the agenda, was the removal of viruses from blood products. I was present at that meeting. On page 2 of the Minutes, Professor Zuckerman presented a report on the identification of agents carrying NANB Hepatitis. There was evidence of two types of NANB Hepatitis associated with the transfusion of blood and blood products. He said that one type, with a short incubation period (7-70 days) was usually associated with the transfusion of Factor VIII manufactured in the USA. The second type associated with blood products, especially Factor IX, had a longer incubation period. **[PAGES 5 ONWARDS ARE MISSING FROM THE FILE: <u>IMPORTANT</u> - WE NEED PARAGRAPH 4.3 "REMOVAL OF VIRUSES FROM BLOOD PRODUCTS"].**

On the same day, in the afternoon, the second meeting of the Blood Transfusion Research Committee took place. Again, I was present at that meeting. The

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formal disbandonment of the Cryoprecipitate Working Party was noted. At the bottom of page 2, Dr. Gunson outlined the role of the Hepatitis Working Party. Dr. Gunson noted that:-

> "Large pool blood products were especially likely to cause liver damage in haemophiliacs".

It was agreed that there was at present:-

> "No need to screen potential blood donors for NANB Hepatitis but the production of a vaccine would be awaited with interest.....".

This was ironic, as the NANB virus had not yet been identified!

On 30th June 1981 Dr. Craske sent me a paper entitled "Reducing the risk of Hepatitis B associated with antihemophilic factor and Factor IX complex". In the first paragraph of the abstract, the presence of anti-HBs in antihemophiliac factor ("AHF") was 100 per cent in 1979. This was a reflection of the pool size. I did not feel that the presence of anti-HBs assisted in the prediction of the occurrence of NANB Hepatitis, which, as far as I could tell, contaminated each and every batch. In the introduction, it is stated that:-

> "AHF and Factor IX are manufactured from large pools of human plasma with the possibility of contamination by Hepatitis B Virus (HBV) despite the testing of all pooled plasma units for Hepatitis B surface antigen (HBsAg)".

The next document is a review paper, mulling over the possibilities of getting rid of virus from the product. The paper emanated from the R & D Department, in consultation with Mike Harley. Heat treatment is mentioned in paragraph 4 on page 3, in relation to albumen products which could be pasteurised. It was said to have a good record in the elimination of hepatitis virus infectivity from these products. The presence of a stabiliser was a pre-requisite. It is commented at the end of the paragraph that:-

> "If similar stabilisers can be established for coagulation factor products, then heat inactivation would become the treatment of choice".

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JULY

The question of ASTMS representation at meetings of the JMC is once again the subject of correspondence in a DHSS letter dated 2nd July 1981. No decision had yet been reached as to the long-term arrangements for the management of the Laboratories. Mr. Harris did, however, go so far as to say that he would personally keep the operation for joint consultative machinery under review.

Dr. Bidwell's memorandum dated 6th July 1981 concerns two new incidences of patients showing abnormal liver function tests following treatment with PFL Factor VIII. A policy decision had in fact been taken by that time and we were already looking at ways of inactivating the virus.

Mr. Godfrey at the DHSS circulated the Minutes of the Meeting of the Scientific and Technical Committee held on 10th June 1981. I have commented on the Minutes in the June section above.

The DHSS letter dated 7th July 1981 marks the establishment of the Policy Steering Group which was to act on behalf of the JMC in the re-development of the BPL. This was my formal invitation to become a Member of the Group.

Dr. Smith's memorandum dated 27th July 1981 represents a coming together of thoughts on virus inactivation on therapeutic concentrates, with NANB Hepatitis specifically in mind. Dr. Smith was contemplating spiking products with infective virus, inactivation or removal of virus by simple manipulations and testing for possible infectivity in chimpanzees. Work on heat treatment for Factor VIII had already been carried out by ~~Behring Werke~~ Behringwerke. However, there was no reputable evidence that their product was non-infective. With regard to Factor IX, mention was made of the Meeting which was to take place in September [1981] in Scotland, which heralded the start of joint participation on heat treatment projects for Factor IX.

Dr. Tovey sent a paper to Dr. Harris at the DHSS headed "The Provision of Blood Fractions to the NHS". This was yet another shot at conveying thoughts on future management of the Laboratories. The proposal here was for a properly constituted limited company wholly owned by a Trust which could be registered as a charity. The benefits of such an arrangement would have been the adoption of a commercial approach, whilst retaining the Laboratories within the public service.

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AUGUST

The first document in this section is a final Report for the Medical Research Council ("MRC") reporting on data as to the incidence of NANB Hepatitis in the United Kingdom. The Report is not confined to the incidence of hepatitis following treatment with blood or blood products. Amongst the cases in the study, 3 per cent of the cases of NANB Hepatitis died between 3 to 5 weeks after onset of illness. This is contrasted to the number of deaths attributable to hepatitis A, which is 0.5 per cent. The Report concluded that further study of the relationship of NANB Hepatitis to blood and blood-product related disease and to chronic hepatitis, was required.

Mr. Ayling sent me the draft Report on PFL, Oxford on 4th August 1981 in relation to the inspection carried out on 23rd and 24th June 1981. I have already considered this Report in detail in the June 1981 section above.

The next document is a letter entitled "Post-transfusion Hepatitis" appearing in the British Medical Journal on 8th August 1981. **[DO WE HAVE THE ARTICLE ON POST-TRANSFUSION HEPATITIS IN THE BMJ ON 04.07.81?].** The article was advocating the use of small-pool products such as dried cryoprecipitate whenever possible, until such time as a reliable test for the markers of NANB Hepatitis became available. This suggestion, however, was right out of the mainstream: cryoprecipitate for distribution was made in uninspected, unlicensed facilities. The merits of cryoprecipitate are again extolled by the same writers in the letter over the page entitled "Factor VIII Cryoprecipitate and Hepatitis Risk". The fact that donor exposure resulting from concentrate prepared from large donor pools increased, must have effected the risk of hepatitis.

The Policy Steering Group for the re-development of the BPL met for the first time on 24th August 1981. One of the documents circulated prior to the Meeting was a DHSS note on financial provision for re-development (PSG 81/3). The estimated cost of re-development of £17,000,000 was based on 1978 prices. In 1978 I had estimated expenditure to comprise the following:- £10,000,000 on building; £5,000,000 on plant and £5,000,000 allocated between revenue consequential and small equipment. The Department had picked out those figures and two years later were saying that the cost was unlikely to be less than £17,000,000. **[DO WE HAVE PSG 81/2?].**

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It is reported on page 2 of the Minutes of the first Meeting of the Policy Sterring Group that the potential for the PFC, Liberton to fractionate a proportion of English plasma, had not yet been decided. The 24-hour a day processing system, mentioned in paragraph 7, we in fact decided against. It was recognised on page 3 that spare capacity to process plasma must be built into the BPL. As well as an increase in the level of plasma supplied by the RHA's, I was hoping for a 20 per cent improvement in yield from fresh frozen plasma over the next two years. It was the general feeling of the Group that the Laboratories should be planned so as to meet the target for self-sufficiency, whilst at the same time paying regard to the Regions' estimates of likely plasma supply. The role of PFC, Liberton is again the topic of discussion at the bottom of page 6. This marks a shift in thinking: Dr. Walford suggested that it may prove uneconomical to send plasma to Liberton to fractionate.

At the first Meeting of the Policy Steering Group, Mr. Bench from the DHSS undertook to describe the options for project management open to the Group. The next document on the file is his Paper, dated August 1981. The Paper sets out the ways and means of running a building contract.

SEPTEMBER

On 8th September 1981 the Medical Research Council circulated the Minutes of the second Meeting of the Working Party on Post-transfusion Hepatitis. **[DO WE HAVE THESE?]**.

Next we come to the Minutes of the ninth Meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party held on September 11th 1981. At the Meeting, Dr. Craske presented some data arising from his four year study of Factor VIII and IX associated hepatitis. Three infectious agents were involved: Hepatitis A and two types of Hepatitis NANB. Hepatitis B was still occurring, but at a reduced level. He notes that there had so far been no evidence of any change in the risk of contracting NANB Hepatitis after first exposure to Factor VIII or IX concentrate. US commercial Factor VIII was noted to have a four-twenty incidence of symptomatic NANB Hepatitis in patients treated with one product in any treatment year compared with NHS concentrate. NHS NANB Hepatitis was asymptomatic. On the second page of the Minutes, it was felt that although the identification of infected batches of concentrate was a useful source material for future research, infected batches could not be identified in sufficient time to

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prevent widespread distribution and use. The question of recalling those batches was therefore not practical. Reference is made in paragraph 5 to the availability of a Hepatitis B vaccine, to be licensed early in 1982.

The next document is a note dated 21st September 1981 of my discussions with Dr. Harvey and Dr. Smith a week previously. Our discussions centred around hepatitis antigens in plasma and final products and the establishment of protocols for research and development. In paragraph 1 it is noted that various commercial manufacturers were producing both Factors VIII and IX claiming that "in-process modifications" had substantially reduced the risk of transmission of hepatitis. **[WHAT ARE THESE "MODIFICATIONS"?].** The note continues:-

> "The basis for these claims may lack scientific integrity but the ethical pressure brought on clinicians to use such products is clearly established".

Nine approaches for reducing hepatitis antigen are set out on page 1. The second of these is heat inactivation. These methods were all considered within the general scheme of trying to obtain central funding for research and development. Dr. Harvey and Dr. Smith were to proceed with a submission in the area of hepatitis transmission in time for the Scientific and Technical Committee meeting on 6 October 1981. The Paper which follows, entitled "Procedures for Reducing Hepatitis Risk in Plasma Products" has been considered in the June 1981 section above.

A Meeting of representatives of Haemophilia Directors, Blood Transfusion Service Directors and DHSS took place on 15 September 1981. The Meeting was chaired by Dr. Tovey, Consultant Advisor. The concept of retaining the clinicians' right to choose their products is brought out once again on page 2. The current purchasing systems varied as between the Centres. The system of purchase of Factor VIII through Regional Transfusion Centres could only operate effectively, however, if the Haemophilia Centre Directors kept the Regional Transfusion Directors informed of commercial purchases by means of monthly reports. These reports never in fact came about. At the bottom of page 2, the Directors reconsidered their original estimated requirements for freeze-dried cryoprecipitate and for high-purity concentrate. It was stressed that if more intermediate purity concentrate were made available, the need for frozen cryoprecipitate would drop.

Dr. Smith's manuscript note to me dated 23rd September 1981 recalls the fact that during 1981 the combined fractionation capacity of BPL and PFL ran at 150,000

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kilograms per annum and that during the same year the laboratories were together producing about 20,000,000 I.U. finished product at current rates. So, production was increasing, notwithstanding the direction by the Medicines Inspectorate to the contrary.

The fourth Meeting of the Advisory Committee on the National Blood Transfusion Service took place on 28 September 1981. Dr. Tovey ducked the issue of keeping Regional Transfusion Directors informed of commercial purchasers made by Haemophilia Centre Directors. There was clearly no way the Haemophilia Centres would give up their budgets. Also, no procedure was implemented to ensure that Regional Transfusion Directors were kept informed of commercial purchases. On the question of plasma supply, as a result of the latest meeting of the Haemophilia Centre Directors (above), it had been decided that target plasma supply required to achieve self-sufficiency could be reduced to 435,000 kilograms from 500,000 kilograms [DO WE HAVE "TABLE 1"?]. The quantity of plasma to be made available in fact changed once AIDS came on the scene. On page 3, it is clear that Mr. Harley was still envisaging at that time the PFC Liberton jointly meeting the UK's need for blood products, with the re-developed BPL. "Further discussions" would be needed between the Health Departments. Another matter for discussion was the future role of the Working Group. It's important role was recognised in terms of increasing plasma supplies. However, it should be noted that the Group was merely an advisory body, with no executive powers. This is ironic, when one examines the issues relevant at the time and what was going on in the background.

On 1st October 1981 the DHSS wrote to me regarding the project management of the redevelopment of BPL.

Following on the meeting of the Policy Steering Group for the redevelopment of BPL, an action list was prepared by Mr. Godfrey of the DHSS and this is the next item in this section dated 2nd October 1981. As I have mentioned previously, David Smart was the Chairman of the Policy Steering Group, and it was on his initiative that we tried once and for all to lay the ghost of PFC Liberton by proposing a trial to see whether the claims made for PFC Liberton by Mr. Watt and, to some extent others, were in practice borne out so far as they related to PFC's capacity. There is reference to this in the action list with the DHSS responsible for pressing for definitive data on capacity and, as a prelude to any further review, both BPL and PFC were to provide product specifications for what was manufactured by each. It will also be seen from the action list that a

feasibility study with regard to the redevelopment was, and this of course required agreement to a certain amount of expenditure. This was to be approved by the Joint Management Committee.

On or about the 5th October, I wrote to various parties identified by the DHSS inviting them to tender for proposals for a feasibility study for the redevelopment of BPL **[the various letters have in fact been removed from the file for the time being since they are all in standard form]**. Following the responses received and further discussions, we eventually decided to instruct Matthew Hall & Co. Ltd. to carry out the feasibility study following approval by the Joint Management Committee and this is touched on in more detail below.

In advance of the 12th meeting of the U.K. Haemophilia Directors on the 9th October 1981, I received a copy of the annual returns put together by Charles Rizza and Rosemary Spooner and these comprise the next documents in the file. Table 1 is interesting. It shows the complete eclipse of cryoprecipitate (8m. iu used during 1980) by commercial concentrate (35m. iu) and the level of NHS concentrate produced by BPL and PFL hovering around our then maximum capacity at 14.5m. iu **[our realistic capacity at the time was somewhere in the region of 15m. iu]**.

The next item in the section is also a paper prepared for the forthcoming meeting of the Haemophilia Centre Directors. This paper entitled "Haemophilia Centre Directors, Hepatitis Working Party Report for the year 1980/81" was prepared by Dr. Craske. The position regarding hepatitis was, at this time, becoming clearer. It will be seen in the second paragraph under the heading "Hepatitis Surveillance" that hepatitis non-A non-B was being referred to and from this time onwards, with hepatitis B declining in importance, knowledge of non-A non-B increased. As I have mentioned elsewhere, there was still, at this time and for a few years to come, that the belief that in some way commercial concentrate was more infective than NHS concentrate and this arose from the fact that the commercial concentrate appeared to give patients a different, apparently more acute, hepatitis NANB than the NHS concentrate. In fact, as it later emerged, there was very little real difference between the subacute and chronic manifestations of the "U.S." or "U.K." types of NANB (if indeed they were truly different). In effect, what had happened was that with the improvement in screening for hepatitis B and, as we see later in the paper the subsequent emergence of vaccine against hepatitis B, hepatitis NANB was being diagnosed by "exclusion" of hepatitis B. This is apparent from the way Dr. Craske deals with

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the reporting of episodes of hepatitis in the second paragraph of his note. He says "of the total of 283 [episodes of hepatitis reported by the Haemophilia Centre Directors] 197 were non-B hepatitis and therefore probably non-A non-B, and 86 episodes were hepatitis B."

One sees, therefore, NANB "taking over" from hepatitis B at about this time. At the bottom of the first page under the heading "Incidence of hepatitis due to commercial versus NHS associated hepatitis, Dr. Craske suggests that the figures demonstrate that there was a 4-20 times higher incidence of overt non-A non-B hepatitis associated with U.S. commercial concentrate compared with NHS but, as I have indicated above, this did not really convey the true picture in that both types of concentrate were equally infective when it came to hepatitis NANB and each equally capable of an infection leading to chronic aggressive hepatitis.

I should also mention in relation to sub-paragraph (B) on the second page of the paper that whilst Dr. Craske states that most of the patients treated with any batch of concentrate will be immune to non-A non-B hepatitis since batches of concentrate of any brand are contaminated with one (or more) serotype of these agents, in fact this has been shown by recent research to be incorrect. It would seem that the NANB virus (or viruses) do not behave in an orthodox fashion, and that an individual may have both antibodies present in the blood stream (indicating immunity) whilst, at the same time, still having active virus in the body.

Note that in paragraph (C) Dr. Craske states:-

> "Hepatitis B is still present at a low level but donor screening appears to have eliminated any difference between commercial and NHS concentrate in this respect."

On paragraph 3 of the paper under the heading "Future of Hepatitis Surveillance", it will be seen in paragraph (2) that Dr. Craske records that a feasibility study (into the incidence of sub-clinical hepatitis) had shown that 4 out of 4 patients studied who had no previous transfusion of concentrate developed non-A non-B hepatitis [following treatment].

Finally on page 4 of the note, it will be seen, under the heading "Recent Hepatitis Research" (paragraph 1), that the hepatitis B vaccine has emerged and that discussions were proceeding with a view to carrying out a limited trial of

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the vaccine in the U.K. Subsequently this trial was just effectively getting off the ground when HIV appeared and the vaccine came under suspicion in that it was prepared from the blood of people who had suffered with hepatitis B. There was a fear that since the same class of person being used to obtain the vaccine might be considered to be at risk of infection through HIV with the possibility that the vaccine prepared from their blood to deal with hepatitis B might be infected with HIV. Subsequently it was proved that the anxiety in this regard was unfounded, but of course when HIV emerged, it did so against the background of a great deal of uncertainty as to what it was and how it was transmitted, and it was perhaps understandable that a good deal of misinformation was generated and incorrect conclusions drawn during the early days.

As to the tables which appear immediately behind the paper, I would only reiterate that until a proper awareness of the extent of sub-clinical NANB emerged, no real reliance can be placed on figures such as those in the documents produced by Dr. Craske which purport to show the "hit rate" for infection with hepatitis NANB. In reality, firm conclusions could only be drawn from special trials involving PUPS (i.e. new and not previously treated patients).

The next document in this section **[should this be moved]** comprises the minutes of the meeting of the Policy Steering Group for the redevelopment of BPL held on the 30th September which were forwarded to me by the DHSS on the 13th October. I would comment in relation to paragraph 3 under the heading of "Financial Provision for Redevelopment" that the redevelopment cost there as amounting to approximately £17m. proved ultimately to be quite wrong. However, even at the time, the figure of £17m. was derived from my original 1978 costings for redeveloping the existing buildings. The figure I came up with in 1978 was £20m. but of this, £5m. constituted, as to 50 per cent, various revenue expenditures, whilst the other 50 per cent covered the purchase of various small pieces of equipment. What the DHSS did was to deduct from the figure of £20m. the amount referable to revenue expenditure and use the remaining sum (£17.5m.) as an approximate costing for building an entirely new plant on a green field site some three years after my original figures were produced. Small wonder final cost (some £50m.) was in excess of the original figure approved by the Treasury.

It turned out that Matthew Hall somehow got to hear of the £17m. estimate that had been approved in principle by the Treasury. When their initial proposals were formulated as part of the feasibility study they were instructed to carry out, it was not particularly surprising (being a little cynical) that their own estimate

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came out in the region of £21.5m. The fact that the cost eventually ended up at some £50m. was not solely attributable to the underestimate on the part of the DHSS inherent in using my old figures for a different type of redevelopment. When it was eventually built, the BPL was larger than at first planned and was totally air filtered. In addition there were a number of improvements, additions and enlargements over the original plan. In reality, I suspect that if one had done a proper job of revising the £17m. figure produced in 1978 so as to adjust it for inflation and the change in nature of the project, the true cost as at about September 1981 would have been in the region of some £30m. It must be remembered that this was a period when inflation was rife.

I would also comment that the reference in paragraph 7 under the heading "Increasing the Supply of Plasma to BPL" to yields of international units of Factor VIII from plasma, should be looked at in the proper historical context. I think in retrospect my figures were a little optimistic at the time but of course what they did not foresee was the move to a higher purity product with consequential reduction in yield and the need for more plasma as a consequence.

The next item in this section is a letter of the 14th October 1981 from Mr. Watt to the Scottish Home and Health Department (the "SHHD"). As I have mentioned above, David Smart's view was that the mirage of PFC Liberton supplementing or replacing BPL as a fractionation facility had floated ahead of BPL for plans redevelopment for some years and really had to be tested once and for all so as to eliminate it from the various considerations which could conceivably delay a decision on BPL's redevelopment. The letter itself was intended to be a contribution to the data which the DHSS were gathering regarding the products produced at PFC Liberton and BPL. PFC did not eventually produce all the relevant data because, I suspect, some of it was not particularly flattering. In particular under the heading "Factor VIII Concentrate", Mr. Watt states that the characteristics of the product being issued from PFC was in the state of change. In my experience it nearly always was since they were continually tinkering with the production process.

With regard to what is said in the second page of the letter under the heading "Stable Plasma Protein Solution", I should perhaps clear up one point which arises from John Watt's misdescription of the English albumin product. He deliberately obscures the true nature of the albumin products produced in England and in Scotland. He refers to "English SPPS" but in fact we never used SPPS as a description of our albumin but instead called it PPF (having a purity of greater

than 92 per cent). Pharmacologically this is a much purer product that SPPS. In fact it was so pure (our actual purity rate was plus 95 per cent) that we subsequently changed the name to "albumin in saline solution". We suspected that the Scottish "albumin" which it was in fact not a product that they regularly produced, was almost certainly what would be called USP (that is to say plus 85 per cent pure). USP is the U.S. standard for this level of purity and we had some reason to believe that the Scottish product occasionally struggled to achieve even this fairly low standard. By describing the Scottish product as SPPS suggesting that the English product was the same, Mr. Watt was really obscuring the reality which was that the English product was a far superior one.

I mention this not because of its particular relevance to HIV, but simply as an illustration of the general misinformation which was spread around to promote the cause of PFC at various times. This carried through into the product specifications themselves which appear immediately behind the letter. So far as Factor VIII concentrate was concerned, we were suspicious about the number of international units said to be contained in files produced by PFC. They always assayed rather too high. Additionally, as I have already mentioned above, the percentage range of purity in relation to "SPPS" was, in our view, somewhat suspect and on occasion we believed that the albumin which was produced by PFC (and there was not much) was actually less than 85 per cent pure.

Following a letter from Matthew Hall regarding the feasibility study for redevelopment of BPL, there are to be found our product specifications produced by Dr. Snape. I am not sure that the data is complete since, for example, there are no details on our albumin product.

The next document in this section is a letter from Mr. Godfrey to members of the Joint Management Committee dated 15th October which enclosed the final version of the Medicines Inspectorate report. This is followed by the agenda for the Policy Steering Group for the redevelopment of BPL meeting to be held on the 19th October, and then the list of action points arising from that meeting. **[Where are the minutes of the meeting?]** The action list records the decision to commission Matthew Hall to prepare a feasibility study and also the arrangements to witness the trial production run at PFC Liberton. The reference to "other possible sites" and to ABPI is to the Association of British Pharmaceutical Industries and the possibility that there might be some vacant pharmaceutical manufacturing premises which it would be possible to utilise instead of

redeveloping BPL. In the event after investigation it was found that there were no old factories which we could use.

There follows some correspondence between myself and Matthew Hall dated 20th October on the subject of the feasibility study. I should mention in connection with the list of facilities on page 2 (paragraph 6) that we did not eventually obtain approval for the staff facilities, the restaurant or the library. Additionally some of the information on page 3 of the letter was rendered incorrect by the passage of time. For example in relation to the production figures, we assumed a pool size of 1,000 kilograms whereas we now use 3,000 kilogramme pools. These figures were really the first "cut" at estimating and planning for the (then) assumed capacity of the new plant.

The next document in the file is headed "Blood Products Laboratory MARP 01". The pages which follow relate to the 1.3m. building programme which had by this stage been designated MARP 01.

The first item in this section is a letter from Mr. Godfrey at the DHSS enclosing the minutes of the Policy Steering Group for the redevelopment of BPL meeting that took place on the 19th October, and the full product specification for both BPL and PFC. The meeting on the 19th October touched on the possibility of converting an existing factory (although eventually none was found to be suitable) and in addition, dealt with the appointment of a Project Manager and the commissioning of a feasibility study. The choice of Product Manager and the company to carry out the feasibility study was made (see below). There was also discussion about the proposed trial at PFC Liberton, and it will be noted that PFC had not been receptive to idea that we send observers. Unfortunately such was the atmosphere between PFC and BPL by this stage that there was a degree of distrust on both sides and so far as I can recall, the objection to observers was not so much to the principle that there should be observers but to the fact that I would be one of them.

The next document in the file comprises the notes of a meeting held on the 21st October to consider the report by the consulting architect on the replacement of the existing autoclaves. A few months earlier there had been a crisis when the North West Thames Regional Health Authority personnel inspected BPL's autoclaves and decided that they were in a bad state and would have to be replaced. The problem was that the cost of this exercise would be in addition

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to the £1.3m. already earmarked for MARP 01. In the event, the work was carried out.

On 22nd October 1981, Diana Walford wrote to me enclosing a copy of the letter from John Watt to the SHHD which I refer to above, and invited me to provide her with details of the BPL product range.

The next document in the file comprises the agenda for the Joint Management Committee meeting for the Central Blood Laboratories which was to be held on the 23rd October. **[Where are the minutes of the meeting? Where also is the Medicines Inspectors' report on PFL Oxford designated JMC CL(81)32?]**

On the 23rd October 1981, I wrote to Matthew Hall to confirm that they had been selected to prepare and submit a feasibility study. I also wrote to Gordon Collins at North West Thames Regional Health Authority to advise him that the Joint Management Committee had approved his acting as Project Manager for the redevelopment.

The balance of the documentation in this section comprises an invitation for Mr. Godfrey to myself to give some details of the action taken to remedy deficiencies identified by the Medicines Inspectorate.

NOVEMBER

The product specifications which Mr. Godfrey sent with his letter of the 2nd November were, I believe, the final form of this documentation which was used for comparative purposes in conjunction with the data obtained from the trial at PFC Liberton which took place later and is described below.

The next note in the file is from Leon Vallet to myself dated the 5th November and this deals with what I have mentioned above with regard to the apparently deliberate misdescription of the U.K. albumin product as Stable Plasma Protein Solution by Mr. Watt in his letter to the SHHD. As Mr. Vallet points out, the misuse of the nomenclature is somewhat surprising given that John Watt had for many years been on the blood products panel of the Pharmacopoeia Europa.

The next letter dated the 9th November 1981 from South London Transfusion Centre to myself is illustrative of the sort of letter we occasionally received from

Transfusion Centres in relation to the testing of plasma (in this case for hepatitis B). This would have been the result of our testing the plasma after receipt and using the RIA test **[query]** finding, that there was a strong positive result which should, in practice, have been picked up by the Transfusion Centres **[albeit less sensitive]** Hepatest. The occasional error still happens, even today.

Next in this section will be found the minutes of the Finance Sub-Committee of the Joint Management Committee meeting held on the 11th November. This is a review of our budget figures against the limits which had been imposed by the Preliminary Estimates Standing Committee. The only point to mention is in respect of the MARP 01 programme on page 2 which is down as costing £692,000. This figure was in fact formulated prior to the Minister's decision to permit expenditure of £1.3m.

There follow a few letters written on the 12th, 13th and 16th November relating to a meeting at Matthew Hall's offices to discuss their feasibility report, and then a letter of the 16th November 1981 from Dr. Gunson to Regional Transfusion Directors which advises them of the way in which he proposes to discharge the role of Consultant Adviser to the DHSS (which was a role he had taken over from [Sir William Maycock]). As will be seen from his letter, there was an element of downgrading of the role of the Consultant Advisor, but in discharging his duties, Dr. Gunson encouraged his colleagues to keep in touch with him and in particular asked to be sent agendas and minutes from Working Party meetings.

The next document in the file is an internal memorandum dated 16th November from Brian Combridge to myself which deals with another case where the Transfusion Centre had missed a fairly positive hepatitis B infection in a plasma pool which we had picked up by RIA testing on receipt.

There follows my letter to Mr. Godfrey of the 16th November enclosing my response to the final report on the inspection of PFL at Oxford. **[Where is the actual report?]** In fact the response was largely drafted by Dr. Ethel Bidwell who was retiring at about this time, and amended (this is the second version in the file bearing my manuscript notes show) by me before it was sent. None of the comments are particularly relevant in connection with HIV. They are mainly points of detail. There is in addition a set of notes prepared by Dr. Snape incorporating comments from Drs. Smith and Ellis.

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In their letter of the 17th November 1981 to Mr. Godfrey of the DHSS, Matthew Hall provided their initial advice on the cost of the redevelopment and it will be seen that the figure they came up with (suitably hedged around with caveats), was in the order of £22m. which, as I mentioned above, was not very far outside the general range of figures that the Treasury had been predisposed to accept.

There follow the agenda for and minutes of the meeting of the Scientific and Technical Committee which took place on the 24th November. Of particular relevance is the short address Dr. Jim Smith gave on the subject of inactivation of hepatitis in BPL products which is summarised in annex A. Our thoughts were beginning to turn to this subject as the link between hepatitis NANB and chronic aggressive hepatitis increased and with it the desirability of inactivating the hepatitis virus if we could. As will be apparent from annex A, which is the summary of the points covered by him in the short address, we were not only thinking of the possibility of heat treatment at that time. It was thought that the fractionation process itself might be modified, for example through the filtration/precipitation stages, to screen out viruses and, in addition, that we might use B-propiolactone as an additive to kill the virus. There is reference to "heating in the presence of re-agents preserving the biological activities of plasma proteins" and this refers to pasteurisation (wet heat) treatment.

[Discuss with Dr. Smith what evidence there is aside from this minute of his thinking/research/discussions on this subject at the time].

The second important event recorded in the minutes was the shift working experiment which had just been carried out at PFC Liberton. This was the experiment to determine whether a continuous operation system could be run at PFC Liberton so as to increase its capacity. If the experiment had been a success, then it might have led to a decision to reduce the scope of the redevelopment of BPL and to split the plasma fractionation for England and Wales between Scotland and England. At that stage the report on the exercise had not been received, but I was concerned from what little I had heard as to whether or not it was truly a representative exercise. First, the plasma used for the exercise was time expired plasma which we had supplied sometime previously, and I was not convinced that the circumstances in which the experiments had been carried out truly reflected the pressures which the Laboratory would be working under in ordinary circumstances. I had also picked up that there might be some disparity between the information and data provided by the senior staff at the PFC to our

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observers and that which had been supplied by the "PFC" staff actually carrying out the work.

The only other point to specifically mention as far as the minutes are concerned was that the timescale envisaged at that stage for the redevelopment of BPL (see paragraph 9(ii)) was three years. In retrospect this was ambitious in the extreme.

[There appears to have been considerable discussion of the research and development work to be carried out at BPL (see paragraph 12) and a paper STC(81)16 prepared by you was discussed. Do we have a copy of this paper? It appears to have described all the proposed research projects then in mind - did these extend to include work on virus inactivation?]

There follows another note from Leon Vallet dated 25th November 1981 on the subject of the "English SPPS" which was the description of our albumin product used by Mr. Watt. Of some interest is the enclosure with that note which are minutes of a meeting at BPL on the 1st November 1968. It will be noted that the PFC at Edinburgh which was then being planned, was to have the capacity to fractionate 1,500 litres of plasma per week. In the event, later claims by Mr. Watt were to the effect that capacity was 6,000 litres per week in contrast to what was intended in the building specification.

The last document in this section comprises a summary of the work of the Medical Research Council Blood Transfusion Research Committee which appears to have met only twice in the two years prior to the report but does touch on the Working Party it had set up on the subject of post transfusion hepatitis and in turn the work of Dr. Craske in relation to hepatitis in haemophilia. I had joined the Committee with effect from 1st April 1981. The Chairman was Dr. Gunson.

DECEMBER

The first letter in this section is one from Dr. Gunson to Dr. Diana Walford at the DHSS following up the visit he had made to the PFC and suggesting that whilst it was probably uneconomic to upgrade the Centre, there might be some re-examination of the possibility of sending plasma from Northern Regional Transfusion Centres to the PFC. I am not sure what, if anything, came of this.

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There follows a letter from myself to Dr. Walford containing information concerning the labelling of our products which was again part of the BPL/PFC comparison exercise which in turn was part of the investigation into the wisdom, or otherwise, of enhancing PFC's role in relation to the fractionation of English plasma. Some of the points I made by way of observation on Mr. Watt's product specifications are those which will have been seen earlier in the internal notes on which I have commented.

There follows an internal memorandum from Dr. Smith setting out some thoughts on potential ways of improving the yield of Factor VIII. I am not sure for what purpose this memorandum was produced, but it illustrates our continuing concern with yield.

The next memorandum from Norman Pettet to Dr. Smith deals with points of detail on the pro rata system which by then had been running for some 10 months and which required over this period and for the next year or so some fine tuning to get it right.

The next item in this section comprises a file note of the meeting which took place at the offices of Matthew Hall on the 16th December 1981 to discuss various aspects of the feasibility study which they had prepared. **[Where is this document?]** As will be seen from paragraph (f), Matthew Hall had heard of the original £17-18m. costing. Their feasibility study suggested costs in the region of £21.6m.

There follows an action list arising from the fourth meeting of the Policy Steering Group for the redevelopment of BPL, and it will be noted under the heading "PFC Liberton" that Mr. Harley of the DHSS was to obtain from the SHHD a firm "offer" of the amount of plasma from England which PFC could fractionate and an indication as to how much this might cost.

This is followed by the agenda and the minutes for the Joint Management Committee meeting of the 18th December 1981. Paragraph 6, 7 and 8 deal with the experiment that had been carried out at PFC Liberton. Mr. Hibbert **[who is he?]** reported that PFC was capable in improvement although adjustments would have to be made to its layout if the (then) system of production were changed to facilitate continuous production on a shift work basis. He commented that, as constituted, PFC appeared less cost efficient than BPL, but also that PFC hoped it would eventually service the Northern English Regions. Mr. Hibbert said that

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he did not expect the findings of the exercise to prove conclusively that continuous working would overcome the shortcomings of the existing system, but the experiment had shown that equipment could function on such a basis. I expressed reservations regarding the experiment and, in particular, the fact that there appeared to be inconsistencies in the information provided **[can you amplify as to what these were]** and that the study had concentrated on one stage only of the production process. It was all very well fractionating plasma on a continuous basis but the equipment up and down stream of that which was capable of continuous operation **[can you specify what this was]** had to be similarly able to accommodate continuous production and this was not the case at PFC at the time. In short, the experiment at PFC Liberton was inconclusive and therefore quite a lot turned (as paragraph 7 shows) on what commitment the Scottish Home and Health Department could make with regard to the amount of plasma from England, PFC Liberton could fractionate and of course cost would be a relevant consideration as well. Meanwhile as the minute showed, discussion of the redevelopment at BPL was continuing with the feasibility study being further reviewed.

There follows a letter from Matthew Hall to myself dated the 18th December following up the feasibility study meeting between Matthew Hall and representatives of the Policy Steering Group. Again the price of the redevelopment (although not a greenfield site redevelopment) is said to be some £22m.

[Where is Mr. Wesley's report on the PFC "experiment"? - do we have all the reports on the PFC "experiment"?]

UNDATED 1981

The first item in this section is paper STC(81)15 which is a revised version of my response to the Medicines Inspectors' report of 5th/6th March 1981. This really deals with points of detail arising out of the Inspectors' report and, as such, has limited relevance, save that it will be seen there was reference (paragraph 2(b)) to MARP 01 having commenced various aspects of which dealt with points raised by the Inspectors.

There follows a DHSS produced summary of the new laboratory scheme produced by the DHSS - "Project Management Arrangements" which is a paper designated

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PSG81/20. This sets out some proposals with regard to a project team and, once again, is of limited relevance, save that it shows the tentative steps which were being taken to redevelopment of BPL pending a final decision on the project as a whole which, amongst other things, was awaiting the SHHD's proposals with regard to PFC Liberton's contribution (if any) to the problem.

Also in this section is a preliminary draft of proposals for a prospective study of post-transfusion hepatitis in the U.K. which, I recollect, was produced as part of the discussion between Dr. McClelland and the MRC with regard to funding research in this area. I do not believe that the research in the proposal was ultimately funded. The study itself would have been to look at the incidence of sub-clinical hepatitis **[hepatitis non-A non-B]** following transfusion of blood or of single donor blood products and, as such, would have limited importance so far as Factor VIII was concerned but, nevertheless, might have produced some interesting information on the subject.

The next document in this section entitled "Working Party on Plasma Supply-Factor VIII: Presentation of Plasma to Fractionation Centres" was a paper prepared, I believe, by Dr. Tovey and relates to the proposals to replace the 5 litre plasma pack with a single donor pack. This was of course one of the innovations along with "pro rata" which assisted us in increasing the plasma supply.

The next document in this section entitled "Summary of Discussion Document" is, I suspect, a document prepared by Dr. Gunson. It examines the need to increase plasma production to meet the increasing capacity of BPL predicted for mid-1981/82. I am not sure of the context in which this document was produced, but I suspect it may have been for a Regional Transfusion Directors meeting at some point.

The next document in this file is a handwritten memorandum prepared by Dr. Harvey who, at the time, was head of Research and Development at BPL. The memorandum sets out his views on the report of the Fractionation Technology Working Party. There are a number of detailed comments on the note but one in particular relates to the need for research and development facilities which Dr. Harvey obviously thought had not received sufficient attention in the report.

This is followed by a handwritten note (two pages) in my handwriting which contains comments on the same report **[do we have this report?]** and this deals

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with my continuing concerns about the inaccuracy of their description of their albumin product. This is followed by a two page note on headed notepaper which again contains comments on the position with regard to Liberton. These do not appear particularly relevant.

1982

JANUARY

On the 5th January 1982, I sent David Smart a copy of David Wesley's report on the PFC Liberton experiment. It seemed to me that the report supported my concerns about PFC Liberton's ability to assist England and Wales in the production Factor VIII. I was anxious, as the third paragraph of my letter makes clear, that PFC Liberton should be asked the correct question. It was not sufficient to ask how much Factor VIII and albumin they could produce, since the answer would, on the basis of past performance, result, as I indicated, in poorly supported claims or a request for more time. What was needed was a concrete and underwritten promise. The point I particularly noted from David Wesley's report on the Liberton experiment was paragraph 4 in his conclusions, i.e. that during the feasibility exercise, Factor VIII production had been limited to the normal quantity required and there was no evidence, according to David Wesley, that the continuous production process would actually lead to an increase in the volume of Factor VIII produced. In a number of ways the trial was unrepresentative of what would happen in practice. However, the main point was that the product produced on a continuous basis during the experiment was SPPS albumin (not Factor VIII) and by concentrating on the production of just this one product without also attempting to produce similar quantities of the other products which were part and parcel of the fractionation process, the experiment was distorted and did not give a representative picture of PFC's ability (or otherwise) to contribute to the fractionation of English and Welsh plasma. I think the best that could be said of the experiment was that it was inconclusive.

It will also be noticed from the report, which appears immediately behind my letter to David Smart, that there were serious problems when it came to quarantine storage which would very quickly be overwhelmed by the volume of product being produced on a continuous basis. Similar reservations were expressed about the inspection packing and dispatch aspects of the process and ethanol reclamation. I also had some concerns that the plasma being fractionated

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was time expired rather than fresh frozen plasma with the consequence that once again this did not replicate the circumstances which would obtain if proper continuous production were under way. Of course by using time expired as opposed to fresh frozen plasma, this material could not be used to produce Factor VIII in any event.

David Wesley's report is useful in that it contains a description of the continuous fractionation process which PFC Liberton employed and which it called "CSVM". As will be seen from the report, it was necessary to reach a special agreement with the Trade Unions to work on a shift basis, and I recall that not only did this take a long time to achieve, but there was some considerable doubt as to whether, had continuous production been brought in, the Trade Unions would have been prepared to work on a shift basis or at least one which made economic sense. On the 5th January, I also sent a copy of the report to Mr. Godfrey at the DHSS.

On the 8th January, I wrote to Dr. Harris in his capacity as Chairman of the Joint Management Committee and, as will be seen from my letter, I advised him that the combined output of BPL and PFC of Factor VIII for 1981 was 22m. iu (up from approximately 15m. iu the year before). Given the problems which we had faced in 1981, particularly the interim building programmes and the need to comply with the Medicines Inspectorate requirements, I felt that the performance had been extremely good [and there was really no spare capacity which was unutilized at that time.]

The next letter dated the 11th January 1982 from the SHHD to the DHSS is particularly important, since this is the letter which effectively layed the PFC ghost once and for all.

Although couched in language which would suggest that PFC could make a substantial contribution towards processing English plasma, this positive statement was submerged beneath a series of very serious caveats which collectively qualified the positive aspects of the letter to such an extent that subsequently no further consideration was given to PFC Liberton being utilised to assist in fractionating English and Welsh plasma. The letter bears reading in full but the essential caveats were:-

(a) the need to negotiate terms with the relevant Trade Unions through the Whitley Council machinery to operate on a shift work

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basis (something which would almost certainly have had quite substantial cost implications);

(b) the need to invest some £6-£7m. to expand ancillary facilities to cope with the workload, e.g. in relation to the provision of space for freeze drying, packaging, labelling, storage, etc. This estimate itself could scarcely be relied upon since Mr. McPherson, the author of the letter, made it clear that it was not possible to give any detailed breakdown of this "estimate";

(c) it was suggested that the work (for which no estimate was available) could be completed in 2½ years, but again the general uncertainty which pervades the letter, gives the impression that this could not necessarily be relied upon;

(d) particularly significant, however, is a statement in the letter that the Revenue implications of fractionating plasma at Liberton to produce, inter alia, Factor VIII had not been costed. In short, no clear idea of the cost of using PFC Liberton could be given.

In summary, it was clear that without substantial changes in working practices, an investment of some £6/7m. (but with no guarantee this was an accurate estimate), a delay of some 2½ years (again with no guarantee that this was an accurate estimate) would PFC Liberton be in a position to fractionate sufficient amounts of English plasma, but at a cost which no one could estimate. The conclusion is that PFC Liberton did not have then, and indeed did not have at any time prior to the experiment, any real capacity to fractionate material amounts of English and Welsh plasma assuming, which was not frequently the case, that there were supplies of plasma in England and Wales which exceeded BPL and PFL's capacity to fractionate it.

The next item on the file is a request from Dr. Smith to myself for consent to increase the pool-size for Factors VIII and IX. As his note makes clear this increase in pool-size to the equivalent of 7,500 donations per pool was intended to make optimum use of our freeze drying plant and the manufacturing process generally. Consent was given to increase the pool and PFL and BPL labels and quality control documentation suitably altered. As I had mentioned previously in my statement John Craske had confirmed some time ago that above a certain level (which we were already operating above) the risk of infectivity was not affected

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by increases in pool-size and therefore this did not feature as a consideration in determining whether we should increase pool-sizes. Indeed, as previously indicated as far as hepatitis NANB was concerned, (which by this time was the only form of hepatitis with which we were really concerned) pool-size had no real affect.

On the 13th January 1982 Dr. Harris, the Deputy Chief Medical Officer, wrote to me in response to my news about the increase in production during 1981 and echoed my enthusiasm for making sure this news got to the ears of Ministers.

On the 19th January 1982 Dr. Gerrard Vaughan, the Minister, wrote to ASTMS following up questions which the union had raised regarding the disposal by BPL of surplus [plasma] [material] which was not required for the manufacture of the products which BPL produced. [Was this in fact excess plasma which BPL could not fractionate because of capacity problems at the time, or simply material which was the by-product or end product of the process which produced, for example, Factor VIII and which could have been utilised to produce other products which were less in demand but in respect of which there was a limited requirement?] Dr. Vaughan's letter makes clear that whilst there was a possibility that BPL could dispose of surplus material for profit any decision to do so would only be taken after very careful consideration and then only in the context of the planning of the laboratories re-development. [Can you explain what the union's concerns were as this is not immediately apparent from Dr. Vaughan's letter?]

The next document in this section is Memorandum from Mr. Pettet to Dr. Smith with a copy to myself dated 21st January dealing with yet another aspect of the pro-rata system, this time in relation to Wessex Regional Transfusion Centre. [Query relevance]. This is followed by a further memorandum from Dr. Smith to myself on the same subject dated 24th January and memorandum of the 29th January from Mr. Pettet to Dr. Smith again on the proposed allocation to Wessex. **[Again query relevance?]**

The last letter in this section dated 29th January records the proposed visit of Mr. Finsberg (a Junior Minister in the DHSS) to BPL which is due to take place on 12th February.

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FEBRUARY

The first document in this section is my letter to Mr. Finsberg dated 2nd February confirming his visit of the 12th February. [The letter enclosed a short document which set out some of the economic considerations for the future working of the laboratory but no enclosure appears in this part of the file - do we have this document?] and this is followed by a letter of the 2nd February to the DHSS dealing with the anticipated out-turn with regard to our expenditure for 1981/1982.

There follows the agenda for the Joint Management Committee Meeting on the 3rd February. **[Where are the Minutes for this meeting?] [There appear to be two papers - PSG 82/1 and PSG 82/2 on the subject of PFC Liberton - where are these?] [There was also a report by Mr. Harley on plasma supply - oral, and it would be useful to know what was said on this subject].**

There follows a letter of the 12th February from the DHSS to Members of the Policy Steering Group for the redevelopment of BPL enclosing some papers for the forthcoming meeting on the 1st March. These deal with points of detail which are not of any particular relevance for present purposes. **[I note that PSG 82/6, which is a letter from MHN giving details for fees and costs allowances, is not included. For the sake of completeness it might be useful to have this if it is decided to leave the letter in.]**

[The next letter in this section is one from myself to the North Manchester **Regional Virus Laboratory dated 16th February in which I confirmed that Dr. Snape would give a talk on the removal of viral contaminants from coagulation** preparation. **[When** was this talk given - was anything prepared in writing by **Dr. Snape? What was the content of the talk? Does it provide evidence of research done by BPL into the removal of viral contamination at that time?]**

There follows a letter dated the 17th February from ASTMS to Mr. Finsberg following up on the views which they had expressed on behalf of the staff at the time of his visit to BPL. Apart from evidencing the fact that the Union had its "say" these documents are of limited relevance and I am not aware of any particular action resorted from the Union's letter.

There follows a Memorandum of the 18th February from Mr. Mallory to myself reviewing the policies set out in document PSG 82/5 which I have referred to

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above. This deals with detailed points in relation to the redevelopment and contains nothing of particular significance for present purposes.

There follows the Agenda and Minutes of the Regional Transfusion Directors meeting on the 18th February. As will be seen from a review of the Minutes very little of relevance came up for discussion. I did comment on the equipment for processing single packs which at that stage was being installed but aside from this the only other point to note in these Minutes is the fact that by this stage the DHSS had ceased to be represented at the Regional Transfusion Directors meetings, attending meetings of the Advisory Committee to the NBTS instead (see paragraph 5 of the Minutes).

There follows a letter from Mr. Godfrey of the DHSS to myself dated 22nd February which deals with points of detail arising out of my response to the Medicines Inspectors report of their visit to PFL on 23rd/24th June 1981. There do not appear to be any particular points raised which are of relevance to the present litigation.

On the 24th February 1982 Mr. Hilton of the Finance Division wrote to North West Thames regarding BPL's cash limits for 1982/3 but apart from giving a general feel for the overall proposed level of funding the documentation is once again of limited relevance for purposes of this litigation.

MARCH

The first item in this section comprises the Minutes of the Policy Steering Group for the redevelopment of BPL which was held on the 1st March. As will be seen from paragraph 4 of the Minutes Mr. Godfrey of the DHSS reported about an approach which had been made by the DHSS to Regional Health Authorities enquiring about their ability and willingness to increase plasma supplies. RHAs had been given an indication of notional targets if self-sufficiency was to be achieved and Mr. Godfrey reported that replies had been received from six authorities all of whom supported the principle of self-sufficiency but had asked for more time to consider how and when they could increase plasma collection within their region. The group concluded that if outstanding replies followed similar lines it would be necessary to build up in stages towards a target figure for self-sufficiency. In paragraph 6 there was a record of Mr. Harley's report to the meeting on the response received from the SHHD following the PFC Liberton

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"experiment". He said that PFC Liberton would not be able to fractionate any substantial quantity of English plasma without the introduction of a three shift working system. Mr. Harley had asked the DHSS Personnel Division to consult with the Scots on the possibility of reaching an agreement on such a system but was not hopeful of obtaining even a preliminary answer before the end of April. The group agreed that in these circumstances the redevelopment of BPL should not be planned on the basis that there should be any anticipated contribution from Liberton. Mr. Harley was asked to seek approval from the Joint Management Committee planning to proceed on the assumption that BPL would process all plasma for England and Wales. The estimated production capacity of the new laboratory could be revised if necessary at a later date if there were a substantial change in Liberton's position. In the event bearing in mind the other points made in the SHHD letter I referred to earlier I do not think that the shift working system was the sole obstacle to increasing capacity. This is borne out by the paper which the DHSS personnel later produced for the Minister (to which I contributed) and on which I comment below. Clearly there was time and a great deal of money involved in any up-grading of Liberton and a good deal of uncertainty as to the economics of this course of action.

As the Minutes record there was discussion of the feasibility study prepared by Matthew Hall and paragraph 9 records the fact that the working party would invite Matthew Hall to prepare "at their own expense" estimates for three possible production levels. The DHSS did not wish to pay Matthew Hall for this work. In practice therefore what was ultimately produced was superficial since there was no reason to expect that Matthew Hall would devote much in the way of resources for which they would receive no payment in the detailed planning assessment of the designs to cater for the three different production levels referred to in the Minutes. The highest of the three proposed production levels (435,000 kg plus 50,000 kg of time expired plasma) amounted to very nearly 500 tonnes of plasma processed in a year. The feasibility study looked at the costing of the plant to fractionate 250 tonnes a year only and the costing of this plant broke the estimate which the Treasury had indicated a preparedness to fund. Nevertheless it was suggested that Matthew Hall should cost (at their own expenses) a facility of nearly double the capacity.

On 5th March I wrote to Dr. Wagstaff at the Regional Transfusion Centre in Sheffield following-up a suggestion put to Dr. Wagstaff by Dr. Cash that there should be a combined working party comprising representatives of the Scottish Regional Transfusion Directors and their English counterparts to look at the

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question of post-transfusion hepatitis and to have, as part of their brief, the compilation of statistics regarding NANB hepatitis in the UK. In my reply to what was actually a general letter to Regional Transfusion Directors in England and Wales I supported the idea of a combined working party particularly in light of the anticipated demise of the MRC Post-Transfusion Hepatitis Committee.

The next two items in this section comprise the agenda and the minutes of the Medical Research Council Blood Transfusion Research committee meeting on the 8th March and it will be seen at paragraph 3.3.2 of the Minutes that it was decided that the Post-Transfusion Hepatitis working party should be disbanded having regard to the fact that "this working party was in a field in which many other groups, both inside and outside the MRC, were active". **[What were these groups at the time?].**

There follows a letter formally inviting Dr. Snape to the Haemophilia Symposium on 13th/14th September 1982 at which he would contribute a talk on the removal of the viral contaminants from Coagulation Preparation. **[Query do we have any notes of this symposium or a copy of Dr. Snape's paper if any?].**

The next document of note in this section comprises the agenda for the meeting of the Scientific and Technical Committee which was due to take place on 16th March. Several of the supporting papers for the meeting appear immediately behind the agenda but none are of particular relevance for present purposes. Indeed there are no particular items on the agenda which are specially relevant for the purposes of the present litigation. [That said we do not appear to have a copy of the minutes of the meeting itself - where are these?].

The next document in this section which is relevant comprises a correction to the minutes of the twelfth meeting of the UK Haemophilia Centre of Directors. This records a statement which I made regarding our plans to increase production at Elstree, initially to 30 million international units, but ultimately with a goal of 100 million international units per annum. I made this statement at the meeting to emphasise that "contrary to certain opinion, the limitation in Factor VIII production lay with the supply of fresh frozen plasma for fractionation." There was at this time still the idea that somehow there was surplus plasma which could be fractionated in Scotland. This was simply not the case. There was also mention of the inactivation of virus by heat and I said the Laboratory had a active programme in this regard targeting hepatitis. **[There should be some documentation in 1981 recording the genesis of this work - cross-refer it here].**

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The next document in this section comprises the agenda for the forthcoming meeting of the Advisory Committee on the National Blood Transfusion Service together with a number of the papers cross-referred to in the agenda. **[Where are the minutes of this meeting?]** Amongst these supporting documents are the minutes of the Working Party on Plasma Supplies for Self-Sufficiency in Blood Products meeting which took place on 18 December 1981 **[are these referred to in the December 1981 section of the proof?]**. These record, at paragraph 3.2, the need to produce Hepatitis-free products in the future and the potential adverse affect on yields of Factor VIII in consequence (heat treatment was in mind and the need to purify Factor VIII to make it more resistant to heat treatment). As we have seen the estimated quantity of plasma needed to achieve self-sufficiency estimated to be 435,000 Kg of FFP and demand (accepting this was uncertain) was tentatively put at 100 million international units per year. Another supporting paper, AC (82) 2, give figures for FFP Supplies to BPL during 1979 and 1981 as well as notional targets for 1982. To help translate these figures 1 tonne of plasma per week equals 10 million international units per year (or at least did based on the yields at the time). It will be seen that in 1979 some 76,000 tonnes of plasma were supplied for fractionation and in 1981 this had risen to 109,000 tonnes (ie a 25% increase). The target for 1982 was to fractionate nearly 132,000 tonnes and this is effectively the MARP 01 planned level of production.

Paper AC (82) 4 was produced by the DHSS and looked at the financial arrangements for Intra-Regional Charging. As the paper makes clear it was thought at the time that there was merit in examining the possibility of charging for blood products in the context of arrangements which would also credit Regional Transfusion Centres with the value of the plasma which they supplied for fractionation. This of course never came to pass but it is interesting to note (see particularly paragraphs 4 and 5) that the DHSS were not particularly enamourned of a state of affairs where blood products were issued free in the circumstances where there were no financial disciplines which might curb wasteful practices in their use. Of course with certain blood products we had sufficient capacity to produce the total required in the country. The Factor VIII concentrate was different in that we had insufficient to service the country's needs and it was unnecessary to think in terms of policing wasteful or indiscriminate use of this particular blood product through a mechanism charging.

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APRIL

The first memorandum in this section is one dated 5th April from myself to Dr. Harvey and others at BPL. It refers to Polyelectrolyte VIIIC. This was a process used to produce very high quality Factor VIIIC (not R). For reasons which were unclear, the process itself resulted in a Factor VIII which did not appear to transmit hepatitis NANB. The problem was that the end product did not appear to be stable and it was clear that further research work would have to be carried out if the idea of carrying it into full production were pursued. The company which had pioneered the process was Speywood but they did not have sufficient funds to carry on with the work and BPL did not have the funds available to evaluate this potential product further. In fact, the process was not the subject of any further development by any other party subsequently so far as I am aware.

[On 14th April 1982 Dr. Rizza wrote to all Haemophilia Centre Directors enclosing a copy of the revised Minutes of the twelfth meeting of the Directors which took place on 9th October 1981. Do we have a copy of these Minutes?]

The next document in this section is a Notice dated 15th April 1982 which was probably intended to inform staff of the temporary arrangements necessitated by the implementation of the final phase of the MARP 01 project. The document is included simply to show the state of progress with regard to the MARP 01 project which, as the notice makes clear, was into its final phase by this time.

The next document is the Annual Report for BPL and PFL which I was responsible for compiling.

In my introduction to the Annual Report I observed that the input of FFP to BPL appear to transmit hepatitis NANB. The problem was that the end product did not appear to be stable and it was clear that further research work would have to be carried out if the idea of carrying it into full production were pursued. The company which had pioneered the process was Speywood but they did not have sufficient funds to carry on with the work and BPL did not have the funds available to evaluate this potential product further. In fact, the process was not the subject of any further development by any other party subsequently so far as I am aware.

[On 14th April 1982, Dr. Rizza wrote to all Haemophilia Centre Directors enclosing a copy of the revised Minutes of the twelfth meeting of the Directors which took place on 9th October 1981. Do we have a copy of these Minutes?]

The next document in this section is a Notice dated 15th April 1982 which was probably intended to inform staff of the temporary arrangements necessitated by the implementation of the final phase of the MARP/01 project. the document is included simply to show the state of progress with regard to the MARP/01 project which, as the notice makes clear, was into its final phase by this time.

The next document is the Annual Report for BPL and PFl which I was responsible for compiling.

In my introduction to the Annual Report I observed that the input of FFP and BPL had increased for the first time in five years and that this was all fractionated to provide Factor VIII with only minimal losses. Output of intermediate Factor VIII concentrate and BPL's other main products increased accordingly.

At that time we had the capacity to fractionate all the FFP which was sent to us but BPL was approaching capacity and it was anticipated that over the next two years the programme to increase regional plasma supply would result in between 150 and 200 tonnes of FFP for fractionation and I was anxiokus that we should not reach a stage where there was more FFP to fractionate than we had the capacity for.

Under the heading of "Quality Control" there was reference to our supplying RIA tewsts for Hepatitis B to all UK transfusion centres. There is also reference to the routine tests carried out by BPL with 16 tests proving positive out of 35,711. Two of these tests related to plasma which in fact tested negative at the relevant Regional Transfusion Centres but positive once the plasma was pooled and tested by us. Fourteen samples proved positive where the plasma came in 5 litre bags. Again these would have been tested at the Regional Transfusion Centre but we found one of the problems with the 5 litre bags was that they did not mix their contents particularly well and if you took a sample from the top of the bag to test, sometimes the virus was at the bottom and was consequently missed. The test which had been used routinely up to that point by the Regional Trans;fusion Centres was the Reverse Passive Haemoglutination test which was not as sensitive as the RIA test BPL developed and employed and therefore one would expect, in a

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very small number of cases, to pick up a positive result using RIA even where a carefully conducted test by the Regional Transfusion Centre failed to identify the existence of the virus in the plasma. As I previously indicated, there were also occasions where infection at a level which should have been picked up by the Regional Transfusion Centres Reverse Passive Haemoglutination test was missed for one reason or another and spotted where RIA testing was used at BPL.

As will be seen from paragraph (iii) on page 11 of the Report, there were a number of visits during the year from Regional Transfusion Centre staff and the programme on these occasions included talks with senior staff; an explanation of BPL and its products and a tour of the production areas. This may be relevant in relation to the suggestion that there was a lack of dialogue between BPL and the transfusion centres.

Under heading "Research and Development Department" there is a list of the various projects which were then under way. In 1981 no time was spent researching inactivation of viruses by heat treatment as will be seen from the Report; this work only really started (in relation to Factor IX) in 1982.

The next item in this section comprises the Minutes of the Meeting held on 31st March of the Advisory Committee on the National Blood Transfusion Service. **[These should be moved and the following comments also moved to the appropriate section of the proof]**.

As will be seen from the Minutes, there was discussion of the progress in formulating arrangements for fractionating plasma from Northern Ireland at PFC Liberton and an endorsement of the figure of 435,000 kg of plasma per annum as the amount necessary to achieve self-sufficiency in blood products in England and Wales. I confirmed (see paragraph 8) that the upgraded BPL now had capacity to process all available FFP.

[The next item in this section comprises the Minutes of the Haemophilia Centre Directors meeting which took place on 9th October 1981. This document and the text that follows should be moved to the appropriate place in the red file and in the proof]. [As will be seen from the Minutes (page 11) Dr. Chanarin proposed that the manufacture of Factor VIII concentrate should be handed over, in toto, to the pharmaceutical industry and the DHSS should withdraw from this activity. There was some discussion of this proposal but there was no enthusiasm for the suggestion! I reported (page 13) on the position with regard to Factor VIII

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production. I indicated that with the completion of MARP 01 we would have an increased capacity which should lead to an ability to provide some 30m. iu of Factor VIII during 1982, and I also made reference to the long-term aim which was to redevelop BPL to produce 100m. iu's of Factor VIII. I also referred to the Laboratory having an active programme concerning the reduction of hepatitis transmission by protein fractions which were unsuited to an activation of virus by heat. **[Can you identify what this programme was and whether it related to Factor VIII?].**

On the subject of hepatitis it will be seen (pages 19 and 20) that with regard to sub-clinical hepatitis (that is to say heplatitis NANB) Dr. Craske reported that it was proposed that there should be multi-centre study of hepatitis in first time treated/seldom treated patients but also went on to say that "this group of patients seem to be running a higher risk of contracting NANB hepatitis whatever the type of material was used for their treatment" which shows a realisation (later to become a certainty) that NANB was as prevalent in NHS concentrate as it was in commercial. It will be seen under the heading "Chronic Hepatitis" on page 20 that Hepatitis B vaccine was on the scene and it was proposed that there should be a clinical trial. There is also reference on page 20 to "Hepatitis-free Factor IX concentrates". This is not in fact a reference to heat-treated Factor IX but to chromatographic separations which was a method of producing Factor IX which was thought to result in its being free of hepatitis. In the event, it was found that this was not in fact the case. Factor IX has for various reasons always been somewhat less infective than Factor VIII and whilst there might possibly have been some reduction in the infectivity of Factor IX using this method of produc;tion, it was later established that it was wrong to consider Factor IX produced in this way as "Hepatitis-free".

There follows the Agenda and some of the supporting papers for the meeting of the Joint Management Committee due to take place on 27th April. **[Where are the Minutes themselves?].**

MAY

The first item in this section is a letter from Dr. Wagstaffe to Regional Transfusion Centre Directors dated 5th May on the subject of the composition of the proposed UK Working Party on post-transfusion hepatitis. As will be seen, he put forward a number of names for consideration including my own and he

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alludes in the letter to the winding-up of the MRC Working Party and suggests that Dr. Gunson, who had acted as chairman of that now defunct group, should become chairman of the Regional Transfusion Directors working Party.

The next letter in th;is section is dated 7th May and is from Dr.l Harris, Deputy Chief Medical Officer of the DHSS, to the BPL/PFL ASTMS Secretary. The letter refers to the substantial increases in the Laboratory's output - with Factor VIII up by 39 and Factor IX by 38, and was written to congratgulate the staff on the performance during the financial year 1981/82. The letter does evidence that we were doing our best (within the resources available) to respond to the need for more Factor VIII and Factor IX.

There follows the Agenda and the Minutes of the Regional Transfusion Directors Meeting which was held on 10th May. As will be seen, the composition of the Working Party on Post-Transfusion Hepatitis was agreed by the Regional Transfusion Directors (see paragraph 12 of the Minutes) but otherwise it is perhaps significant to note that there were no other matters relevant to the present litigation discussed at all. During this period it is interesting to see that self-sufficiency, whilst it was being discussed, was not something which waes considered to be a burning issue and the same can be said of hepatitis NANB. With the redevelopment of BPL underway, Hepatitis B largely a thing of the past, and with some studies underway in relation to Hepatitis NANB (without at this point a proper appreciation of its long-term effects) one may in retrospect see this period as the calm before the HIV storm.

On 13th May I wrote to all Regional Transfusion Directors in England and Wales alerting them to the fact that for a period of about three months commencing in June 1982, there would be a restriction on the supply of Factor VIII and I sent with my letter a note setting out the quantities of Factor VIII which we anticipated during June and the period July to December. As I indicated in the letter, we would continue to receive the usual amount of FFP for fractionation and it was intended that we would catch up once the redeveloped laboratory facilities were restored to fully commissioned working so taht there would be no overall loss of Factor VIII during this period. **[Can you expand a little on what promnpted this restriction - what works were being carried out].**

the next document in this section is a letter from Mr. Mallory, who was the Deputy Director of Administration and Manufacturing of BPL at the time, to Mr. Collins at North West Thames Regional Health Authority dated 14th May 1982

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on the subject of the project management of the MARP 01 upgrading programme. It will be seen tha the programme was running behind time (approximately 18 weeks) and that our view at the time was that blame for this attached to the project management team system. The consequential effects of the problems referred to in Mr. Mallory's letter were, amongst other things, the need to limit the production of Factor VIII, as I previously described.

On 18th May Mr. Godfrey of the DHSS wrote to all members of the Advisory Committee on the National Blood Transfusion Service and enclosed a summary of our production during the financial year 1981/82 and also the parliamentary question announcing the establishment of a Special Health Authority to manage the Central Blood Laboratories. Both papers appear immediately behind Mr. Godfrey's letter.

There follows an extremely good defence, in the form of a letter dated 19th May 1982 by Mr. Collins of North West Thames Regional Health Authority, to Mr. Mallory's letter complaining about the project management system. Many of the points that he makes are perfectly valid; the problem was that the project was generally not operating as either North West Thames or BPL would have hoped and the main point is that irrespective of where the blame lay (if blame attached at all) the problems experienced did interfere with the supply of Fact VIII concentrate for a few months. [Would this have impacted on patients forcing them to switch to commercial brands or is it likely that through accumulated stock and the later catching up with production this would not have interrupted patients treatment with NHS concentrate?]

JUNE

As will be seen from the first item in this section, the Medicines Inspectorate were still visiting periodically and on this occasion the purpose was to look at the changes made in the production unit and to discuss progress in relation to quality control.

This is followed by a memorandum of 10 June recording the Inspector's dissatisfaction with regard to the congested state of the buildings (although partially attributable to the need for free space for building operations at this time). This is followed by the written report of Inspector K.J. Ayling of his visit on 10th June. In the main, the points he raises are points of detail but it will be

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noted at the foot of the first page that there is reference to yet another case where a Regional Transfusion Centre, using the Reverse Passive Haemaglutination test (subsequently replaced by RIA) had failed to pick up an infected 5 litre plasma pack. The Inspector notes that this is yet another reason for speeding up the single donation pack which, of course, we were pursuing in any event in the interests of increasing the supply of FFP.

Following the Inspector's report is another Memorandum from me dated 11th June to Mr. Mallory and others referring to some of the additional criticisms to be found in the Report which I had not been made aware of during the course of Mr. Ayling's visit. This is of very marginal relevance, as indeed is the Report itself, save that it is illustrative of the fact that whilst the laboratory was being redeveloped, we were having to cope with additional criticism and advice from Medicines Inspectorate on top of all the work required by the redevelopment project itself. This is not to say that the Medicines Inspectorate were wrong in their approach but rather to emphasise the obstacles which we were having to overcome in the day to day management of the facility.

The next document is a Memorandum from myself to various BPL personnel dated 14th June which relates to another of the periodic programmes we arranged for Regional Transfusion Directors. On this occasion it was an update on BPL and was a programme arranged to take place at Elstree. Details of the programme, in the form of a timetable, appear behind the Memorandum and again evidences the collaboration and dialogue between Regional Transfusion Centres and BPL.

The next document in this section is a letter from Matthew Hall to North West Thames Regional Health Authority giving some revised budget costs for the redevelopment. Again these are of marginal relevance save to show that various options were still at that stage in the course of being considered and costed.

There follow the Agenda and the Minutes of the Meeting of the Scientific and Technical Committee for the Central Blood Laboratories which took place on 21st June. The meeting was unexceptional save that there is reference, at paragraph (a), to the continuing difficulties we were experiencing in appointing a Chief Engineer. If fact, the Medicines Inspector, in his last report, had observed that we were still lacking a Chief Engineer and that the implications of this were serious. The difficulty (and a perennial difficulty at that) was that we had insufficient funds to attract the right candidate for this and certain other posts. Even today we are without an experienced pharmaceutical engineer. The Minutes

also record that Ministers had agreed to set up a Special Health Authority to take over responsibility for the Central Blood Laboratories.

There follows the Agenda for the Joint Management Committee Policy Steering Group for the redevelopment of the Blood Products Laboratory held on 23rd June. **[We do not appear to have other than one extract from the Minutes - where are the full Minutes?].** There follows an extract from the Minutes of the Meeting indicating that at that time the Group considered that the potential financial benefits of a Laboratory equipped to process 435,000 kg of FFP justified the higher level of capital expenditure. On this basis it was agreed that Mr. Angilley **[of the DHSS?]**, in conjunction with myself, should prepare a detailed appraisal of the various options for submission to the Treasury. In the meantime the DHSS would prepare a paper for the Minister explaining all the various options pointing out the Revenue saving aspects of the proposed level of redevelopment and seeking formal approval for the proposed increase in capital expenditure over that originally authorised on the basis of a plant intended to fractionate 250,000 kg of FFP per annum **[query]. [We appear to have the Angilley paper - see below - but where is the DHSS Ministerial paper - did you ever see this?].**

On 28th June I wrote to the DHSS advising them that we had concluded that the MARP 01 reconstruction had reached a point where it was necessary to effectively shut down production altogether for a period of three weeks (this did not lead to any further cut-back in Factor VIII production beyond that which I had already alerted the Regional Transfusion Centres to expect).

The last item in this section comprises a Report produced by the Blood Transfusion Research Committee of the MRC.

It will be seen at paragraph (c) on page 3 that the work of the Haemophilia Centre Hepatitis Working Group is touched on and their findings that there was more than one sero-type of NANB hepatitis. There is also reference to the high instance of NANB infection on the occasion of the first transfusion of a patient.

JULY

The first letter in this section dated 1 July from Dr. Snape to Dr. Roberts at the Liverpool Regional Blood Transfusion Centre concerns yet another occasion where

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plasma tested for Hepatitis B on receipt and had obviously slipped through the Liverpool testing system.

There follows a Memorandum dated 7th July from me to the various staff who helped with the Regional Transfusion Directors "update" programme showing that the programme went ahead and that it proved successful. A list of the Regional Transfusion Directors who came appears on the next page.

The next letter dated 8th July from Dr. Darnborough at the Cambridge Regional Transfusion Centre to myself indicates that whilst there had been an overlapping period during which 100 RIA testing had not been in operation, Cambridge anticipated that, as from August 1982, RIA would be used exclusively.

The next document in this section is a report on a visit made by Dr. Snape to the Liverpool Regional Transfusion Centre following up on the problems which had arisen with regard to Hepatitis B infected plasma failing to be identified at the Centre before it was sent to BPL for fractionation. The reason the visit was made was that the problem at Liverpool might result in BPL having to carry out additional tests on Liverpool plasma. Dr. Snape's review really speaks for itself in that the two problems which had occurred were the consequence of loopholes which were effectively closed and this enabled Dr. Snape to rescind instructions to re-test all Liverpool FFP before it was fractionated at BPL which was an instruction he had earlier issued in the interests of safety.

There follows a letter of 19th July from the MRC to myself formally advising me of the disbandment of the MRC Blood Transfusion Research Committee. At the time, I found it extraordinary that it should be disbanded and in retrospect the timing was most unfortunate since it was only a few weeks later that blood-related HIV began to manifest itself. Consequent on the disbandment of the Committee, I was also notified that the Working Party on the Factor IX concentrates for conditions other than Christmas Disease, was disbanded and a letter to this effect dated 20th July was sent to me.

I also received a letter on 21st July from PHLS advising me that the quality assessment panel for hepatitis was to discontinue its work. This was the result of financial stringency. The hepatitis testing panel was a mechanism by which the PHLS through its regional laboratories assisted in checking the accuracy of our [and Regional Transfusion Centre] testing.

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There follows a letter from Dr. Snape to Mr. Ayling following up on several points arising out of the Inspector's work and then an NHS draft circular on the manufacture of products, the main message of which, as far as we were concerned, was that if products could not be manufactured more cheaply than the commercial equivalent, then manufacture should cease.

The last document in this section comprises the appraisal of the redevelopment options for BPL which Mr. Angille of the DHSS and which was referred to above. I contributed quite considerably to this paper **[did you do a paper and if so where is this?]** and in particular should be noted that Notice, paragraph 3 which repeats the reasons why PFC Liberton was eventually dismissed as a possible contributor to the fractionation of English and Welsh plasma. The paper quite usefully draws together all the various arguments in favour of redevelopment (see for example paragraph 4) as well as reviewing some of the costing considerations in favour of redevelopment. The conclusion (see paragraph 28) is a recommendation to build a 400 tonne laboratory at a cost which was then budgeted at £21.1 million spread over the years 1982/3 to 1985/6. The uncertainty with regard to plasma supply was reviewed in paragraph 30 and the need to ensure that, at the same time as the BPL was redeveloped, there was an increase in the supply of raw material for fractionation recorded.

AUGUST:

The first item in this section is a letter dated the 3rd August from Dr. Craske to myself in which he indicates his intention to call a meeting of the Hepatitis Working Party to review the results of recent surveys and to consider Dr. Craske's proposals for further work. It is interesting to note (a) that a study of Hepatitis B vaccine was about to start at Oxford and (b) that Dr. Craske had been unsuccessful in trying to obtain finance from the MRC for a prospective study of Factor VIII and IX Hepatitis. It will be seen that notwithstanding this failure Dr. Craske had managed to carry on with a feasibility study for this research at Oxford using funds from the local haemophiliacs society and a grant from commercial sources.

There follows a memorandum from Dr. Smith to myself dated the 4th August in which he reviews various R&D matters and touches, in passing, on the development of methods for the production of coagulation factor concentrates with reduced risk of Hepatitis transmission. The only reference to any work in

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this area is to be found in the third paragraph on the second page where mention is made of Dr. Einarsson who was engaged in research **[into the area of reagents with a view to determining whether these might assist in their removal of NANB ineffective agents]**. As it turned out, the method was not foolproof. **[We were merely keeping reports of this research under review in the hope that the research might lead to something of interest to us]**.

On 11th August Dr. Gunson wrote to me regarding arrangements for the meeting of the first Regional Transfusion Directors UK working party on post-transfusion Hepatitis. This was followed by a report prepared by Dr. Snape on a visit made by three representatives of BPL to the Sheffield Regional Transfusion Centre. The document is worthy of comment since it records that at the time we were visiting Sheffield and five other regional transfusion centres for the purpose of assisting with the security of plasma RIA testing at the centres and with a view to commenting critically on areas of common concern - in particular assessment at BPL of the quality of plasma despatched to BPL. Again, this paper reflects the continuing dialogue between BPL staff and regional transfusion centres on matters of common interest.

There follows the agenda for two meetings, the first of which was to discuss the establishment of the CBLA and took place on the 25th August **[where are the Minutes for this meeting?]** and the second is the agenda for the forthcoming meeting on the 27th September of the UK working party on post-transfusion Hepatitis.

SEPTEMBER:

The first item in this section comprises the haemophilia centre directors' annual returns for 1981 as received by mid-August 1982. These were, as usual, compiled by Dr. Rizza and Dr. Spooner at the Oxford Haemophilia Centre. Total Factor VIII consumption during 1981 came to 65.7 million iu. Of this consumption 35.5 million iu came from Commercial Factor VIII concentrate and 22.4 million iu from the NHS equivalent. Cryoprecipitate amounted to only 7.7 million iu. In percentage terms Commercial Factor VIII concentrate represented 54% of the Factor VIII units used by haemophilia centres in 1981. The trend shown in Fig 1 shows Commercial Concentrate purchases beginning to level off as BPL produced more Factor VIII during the course of 1981.

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The Minutes of the working party to advise on plasma supplies for self-sufficiency of blood products established under the auspices of the Central Advisory Committee for the NBTS appears next in the file. A meeting was held on the 2nd September. The discussions are largely irrelevant for present purposes although it will be seen that plasmapheresis was undergoing a trial at the Bradford Regional Transfusion Centre and this was part of the wider trial which has led to the increasing use of plasmapheresis with consequential improvements in the amount of plasma available for fractionation.

There follows the agenda for the UK Haemophilia Centre directors' Hepatitis working party meeting due to be held on the 13th September and some papers relating to the UK Haemophilia directors' annual meeting which was also due to take place on the 13th September continuing on the 14th September.

The Minutes, which appear next in the file, of the UK Haemophilia Centre directors Hepatitis working party meeting held on the 13th September are of interest. First, it can be seen on page 2 that Dr. Craske reports that the MRC has refused a grant into his prospective study of Factor VIII and Factor IX associated Hepatitis and that the DHSS had no longer any funds available owing to the reallocation of monies to the MRC. Dr. Craske states:-

> "Despite this a preliminary study with the help of funds from the Haemophilia Society had been carried out at Oxford. 32 patients had so far been enroled and 28 of these had been followed for a period of at least 6 months. These were patients with mild coagulation defects who had had less than 2 transfusions of Factor VIII or Factor IX concentrate during the previous year. Nine out of nine patients treated with one batch of concentrate who had had no previous transfusions of Factor VIII or IX developed non-A, non-B Hepatitis with incubation periods of between 25 and 111 days. Some of these patients had received NHS Factor VIII, one US Commercial Factor VIII and the last patient NHS Factor IX."

The Minutes go on to say:-

> "This working implied that there was more than a 90% chance of contracting non-A, non-B Hepatitis after first treatment with

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NHS or US Commercial Factor VIII concentrate. No cases of Hepatitis B had so far occurred."

As matters developed and Dr. Craske's research continued it became clear that 90% should read "100%" and that there was effectively no difference in terms of infectivity between NHS and Commercial Factor VIII concentrate.

On page 3 there was discussion about the evaluation of new brands of Factor VIII or Factor IX where attempts had been made to reduce the amount of virus contaminating the products by biophysical methods. I propose that special batches of Oxfords Factor VIII might be prepared from plasma obtained from a special approved donor panel. **[I believe that what I was proposing was the preparation in small amounts of heat treated product which would of course not be licensed at that point?]. [The Minutes do not seem to suggest that this was the case and I wonder whether instead what was being referred to here was the Oxford "small pool" experiment?].**

The Minutes refer to the "Hepatitis reduced" brand of Hemofil, manufactured by Travenol Laboratories Limited. This was heat-treated product which used **[pasteurisation - that is to say, wet heat - as the method of treatment].**

The Minutes also record that Biotest Laboratories in Germany had recently patented a method for the pasteurisation of Factor VIII and IX by heat in the presence of polysacharrides. In fact there was a German product called Hemate produced by Behringwerke in Germany in about 1980 which, I believe, used dry heat but the product was never licensed and was not to my knowledge introduced into this country. I also recall that the Factor VIII yield for this product was extremely low - around 7% to 10%. Effectively the heat treatment crippled the product.

It was stated at the meeting that the only way to evaluate the preparations for freedom from non-A, non-B Hepatitis viruses was by chimpanzee inoculation (which no one had the funds to carry out) or in a prospective study of susceptible human subjects. In this regard Dr. Craske agreed to revise the prospective study protocol in the hope that this might be used by haemophilia centre directors to evaluate the new concentrate products on appropriate patients. This was really the only way of trying to gauge the effectiveness of these new concentrate products. Again all this has to be put in the correct context ie that Hepatitis NANB was not at that stage considered to be of such importance that

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one would do other than continue to evaluate products as they appeared within the available resources through the good offices of the haemophilia centres. As can be seen from paragraph 4 of the Minutes the Hepatitis B vaccine developed by Merck, Sharpe and Doehne had now been licensed and was being introduced HIV was just beginning to appear but very little was known about it. One sees this from paragraph 5 on page 5 of the Minutes where, under the heading "Acquired Immune Deficiency Syndrome (AIDS)" there is the first reference to the appearance of this:-

> "Following discussions at the Annual General Meeting of Haemophilia Centre Directors, it was agreed by the working party that as the AIDS syndrome had similarities in its epidemiology to that of Hepatitis B virus infection, enquiries would be made by members of the working party to ascertain the likelihood of transmission of the disease by blood or blood products. A further meeting of the working party would be held when more information became available".

One sees therefore that the issue of AIDS was raised, it appears for the first time, at the main meeting of the Haemophilia Centre Directors held at this time. There follow the Minutes of the Advisory Committee on the National Blood Transfusion Service meeting held on the 15th September. It will be seen that PFC Liberton had successfully processed plasma from Northern Ireland and was about to embark upon regular fractionation of this plasma. There is a further reference (see paragraph 13) to the MRC decision to end the NBTS research committee but apart from this little of any relevance to the present litigation occurred.

On 17th September Dr. Craske wrote to Dr. Gunson regarding the forthcoming meeting of the NBTS working party on post-transfusion Hepatitis to take place on the 27th September and it will be noted that aside from attempting to frame the terms of reference Dr. Craske also suggested that the name of the working party should be changed to the UK Working Party On Transfusion Associated Diseases as this would allow discussions of problems which might arise from time to time including Acquired Immune Deficiency Syndrome (AIDS), the epidemiology of which might have implications for the Blood Transfusion practice. Again this shows the development of interest in AIDS as a problem which might have implications for all of us.

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The Minutes of the Regional Transfusion Directors meeting held on the 20th September are next in this section but really contain very little of interest save once again reference to the MRC disbandment of its blood transfusion research committee and proposals to try and carry on its work in some other way.

On the 24th September in the Journal of the **[American Medical Association?]**- Medical News - an article on AIDS was published under the title "Acquired Immuno Deficiency Syndrome cause(s) still elusive" and this obviously would have come to everyone's attention fairly quickly. The article states:-

> "More than a year after the first reports of opportunist infections and Kaposi's Sarcoma among homosexual men and intravenous (IV) drug abusers, the medical community still is baffled by the alarming number of cases of Acquired Immuno Deficiency Syndrome (AIDS)."

It can be seen in the third paragraph that there is reference to the "recent addition of three haemophiliacs ..." in the number of cases of AIDS reported. There is a marginal note against this article **[I am not sure whose handwriting this is]** to the effect that a further two have been reported. The article continues (bottom of the first page):-

> "The three cases of P Carinii pneumonia among haemophiliacs are alarming to some since they suggest the possible transmission of an agent through blood products, although as yet there is no evidence for this. A single contaminated source is not the culprit, however, since no two patients received Factor VIII concentrate from the same lot. Because the concentrate is manufactured from plasma pools collected from as many as 1,000 or more donors, it is impossible to determine whether any plasma from AIDS patients was used".

This probably reflects the then state of knowledge and as will be seen there was a good deal of doubt as to what AIDS actually was and how the three haemophiliacs reported to have contracted AIDS (two of which had died) had in fact become infected.

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There follows the Minutes of the first meeting of the UK Working Party on transfusion-associated Hepatitis which took place on the 27th September. As can be seen from paragraph 3 the terms of reference were not widened to include other specified infections however experience gained in dealing with co-ordination of reports etc of transfusion-associated Hepatitis it was said could be applied to other infections where applicable. This also applied to "Acquired Immune Deficiencies". In short therefore, despite the name of the working party there was tacit agreement that it would keep an eye on AIDS to the extent necessary. Again the meeting should be placed in context and it should be borne in mind that links between AIDS (which had yet to be identified as a virus) and blood products had not yet been made. As can be seen from paragraph 7 it was agreed that the working party should collate data to determine the importance of non-A, non-B Hepatitis in the UK.

The next document in this section is a "draft" of a paper prepared by Dr. Barbara of the North London Blood Transfusion Centre and Dr. Briggs of the Department of Microbiology at the Middlesex Hospital Medical School dealing with the subject of post-transfusion Hepatitis in North London in 1981. The paper essentially identifies the complexity of the investigation into non-A, non-B virus and in particular the problems raised by the absence of any specific test for the virus.

The final item in this section is a document recording notes for the Haemophilia Centre Directors' meeting which were prepared by me **[query]** which cover various domestic issues at BPL with regard to Factor IX production, packaging etc.

OCTOBER:

The first document in this section is a memorandum from Mr. Mallery to myself giving information about the projected issue of Factor VIII vials during the last quarter of 1982 and monthly thereafter. Mr. Mallery had at this time been newly recruited as deputy director in charge of production and administration. As can be seen, we were hoping by the end of the year to be issuing vials at the rate of 8,500 per month.

The next memorandum from Dr. Snape to various BPL personnel dated the 4th October records yet another visit of the Medicines Inspector.

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There follows the agenda for the Joint Management Committee for the Central Blood Laboratories meeting to be held on 5th October and the Minutes of that meeting. As will be seen from paragraph 3 of the Minutes the final stage of the interim redevelopment was due for completion by the end of the current financial year **[December 1982?]**.

We were still endeavouring to appoint a chief engineer at BPL (see paragraph 4 of the Minutes) and the policy Steering Group for the redevelopment of BPL had been advised by the Treasury that it approved the appointment of Matthew Hall Norcain Limited as management contractors for the redevelopment (see paragraph 12). It was recorded that after careful study of a range of options the group had recommended that BPL should be redeveloped on a basis which should make it large enough to make England and Wales self-sufficient in blood products and capable of extracting all therapeutic products from plasma it would receive. It is recorded that approval was awaited from the DHSS Ministers and the Treasury. Aside from this there is nothing else of major importance that arose at the meeting and of course the JMC was at this stage about to disappear and be replaced by the Central Blood Laboratories Authority.

The next item in this section is a paper prepared by Dr. Smith on the 27th October entitled "Strategy for small-pool Cryoprecipitate production in new BPL". The Haemophilia Centre Directors were still advocating the possible use of small pool freeze dried Cryoprecipitate which might carry with it a reduced risk of transmitting Hepatitis in ANB. As Dr. Smith pointed out:-

> "Small pool products are bound to be labour intensive in production and control and to mix uneconomically with large scale processing".

In the event the idea of small pool freeze dried Cryoprecipitate lost favour and was not proceeded with.

On the 13th October I sent a memorandum to Dr. Harvey **[insert position]** entitled "Pasteurisation of Factor VIII". As I indicated I was proposing to call a meeting to set out our plans for studies on pasteurisation in the light of some reported success in this area. **[Where is the paper said to be attached to the memorandum on the subject of non-denatured detergents in the disassociation of aggregation?]**.

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On the 16th October Dr. Craske wrote to me reporting that he thought it likely that there would be sufficient patients enroled to make the trial observation for the incidence of Hepatitis NANB in patients first treated with NHS Factor VIII and possibly IX concentrate possible. He went on to say that he knew I was thinking of making some Factor VIII from our special donor panel and that this product would be well worth trying. **[Is this heat treated product? If not, is it part of the Oxford small pool experiment?]**

The letter dated 29th October 1982 from Keith Gibson at the MRC to Dr. Gunson concerns a request which had been made to secure various samples of serum which were collected for the MRC 1974 prospective Hepatitis study but which had not then been used. The idea was that the Regional Transfusion Directors working party would use this material as part of its studies. In the event it was discovered that all the samples had been lost and therefore cannot be used.

NOVEMBER:

The letter from Dr. Snape to the Regional Transfusion Centre in Birmingham which is dated the 11th November 1982 is a further illustration of the continuing dialogue with the Regional Transfusion Centres on matters of common concern. The letter deals with the use of the BPL RIA test and the objective was to foster the security and improve the quality of the plasma we were receiving at BPL.

There follows a letter dated the 11th November from Dr. Craske under cover of which he circulated material on Acquired Immune Deficiency Syndrome.

He says in the letter:-

> "At Peter Kernoff's suggestion, I wrote to the Project Leader of the team looking into the epidemiology of this disease at the Communicable Diseases Centre, Atlanta, Georgia. He telephoned me last week. The latest information is that there are five haemophiliacs who have been identified with this syndrome, two of whom recently died. All these cases are without the usual association of homosexual practices, drug addiction or treatment with immuno suppressive drugs, which are factors which have been found in other patients acquiring opportunistic infections.

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The hypothesis at present being used to explain the acquisition of these cases, which are in areas of the USA where the syndrome had not been hitherto described, is that one or two patients in the incubation period of the disease donated plasma which has since been used to prepare Factor VIII or IX concentrate. All the haemophiliacs who have had the disease have had severe coagulation defects requiring treatment with Factor VIII. The likelihood is, therefore, that other cases will be identified amongst severe haemophiliacs, though probably at a low prevalence".

As it turned out the last observation was not correct. I think the letter and the paper which it enclosed constitutes the first real recognition of a possible risk of AIDS for haemophiliacs. The paper which follows reflects the fact that at that time the majority of those found to be suffering were homosexual but with a small proportion of heterosexuals and seven haemophiliacs, three of whom also had no association with drugs or sexual promiscuity. On the third page of the paper there is reference to the fear that Hepatitis vaccines manufactured from the plasma of Hepatitis B carriers (who might be susceptible also to AIDS) might carry the AIDS virus. There is a statement to the effect that the Communicable Disease Surveillance Centre in the UK recently reviewed all reports of opportunistic infections associated with AIDS in the UK since 1975 and had found, as yet, no evidence of a recent increase in incidence.

The next document in this section dated the 11th November is a press release announcing the formation of the Central Blood Laboratories Authority. The press release sets out the membership of the Authority which, as I have indicated earlier, was chaired by David Smart.

There follows a paper published in the New England Journal of Medicine entitled "Reducing the incidence of non-A, non-B post-transmission Hepatitis by testing donor blood for alanine aminotransferase". The suggestion put forward in the paper was that blood with an elevated level of alanine aminotransferase might have a high incidence of NANB Hepatitis. The suggestion was that screening to exclude this type of blood might have some benefit in terms of limiting infectivity but because of major uncertainties about the medical consequences of NANB Hepatitis the costs benefit of such policy decision could not be estimated. The paper is not of much relevance for the present purposes.

This is followed by another paper which was published in Transfusion September-October 1982 entitled "Plasma derivatives and viral Hepatitis". A review of this paper does not reveal anything new regarding NANB Hepatitis. There is passing reference on page 350 to heat inactivation and the experience of treating albumin by heat at 60°c for 10 hours which suggested that Hepatitis B was inactivated using this treatment. The article makes reference to studies having been completed and others being currently underway to evaluate the methods to stabilise clotting factors to heating as heat is capable of inactivating both Hepatitis B and the agent of non-A and non-B Hepatitis. However, beyond this the article gives no useful information.

DECEMBER:

The first item in this section is a letter from Dr. Rizza to myself dated 10th December referring to a meeting which had been called to discuss Hepatitis-free/Hepatitis reduced coagulant factor concentrate. The meeting was to take place on the 15th December and was an informal one to talk about ways and means of reducing the Hepatitis NANB virus in Factor VIII.

There follows a letter enclosing the agenda for the Haemophilia Centre Directors Hepatitis working party meeting due to take place on the 19th January 1983 and then the Minutes of the meeting on the 15th December to look at reducing Hepatitis in Factor VIII. I asked for the meeting and had very much in mind at that time the possibility of heat treating Factor VIII and Factor IX. I should emphasise that at that stage our work had nothing to do with HIV.

The Minutes of the meeting record the fact that so called Hepatitis-safe Factor VIII and IX products were beginning to appear on the market and were being used on a named patient basis, that is to say without their having been licensed (a prerequisite of which would be a properly documented clinical trial). There was lack of information from the manufacturers as to quite what was done to the products in order to render them "Hepatitis-safe" and there was considerable concern about the haphazard way in which the products were appearing and were being pressed upon the haemophilia conditions. The conclusion of the meeting was that random exploitation of the haemophilia service by commercial organisations for the study of "Hepatitis-safe" products should be discouraged; that the haemophilia services should create a formal basis for controlled clinical trial of alleged "Hepatitis-safe" products in line with the requirements of the

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Medicines Act. Lastly, that the haemophilia services, PHLS and NBTS should combine resources in a manner likely to advance economic treatment of NHS haemophiliacs with safe products. As the Minutes make clear (see paragraph 3) there was really no proof at that time that the products described as "Hepatitis-safe" were indeed safe. As I have mentioned previously there was concern that heat treatment might alter the immune status of the product (and thrombogenicity was a problem with Factor IX). It was unclear what "heat treatment" had been applied. There follows a further copy of the same Minutes amended in manuscript by Dr. Harvey **[describe his position]**.

The next item in this section is a letter from John Cash dated the 17th December which follows up on the meeting of the 15th which he attended. He advocates that there should be no encouragement given to the commercial manufacturers to hold proper clinical trials for their "Hepatitis-safe" products since, in the event these successfully complete the clinical trials and become licensed, he concludes that the NHS product (inevitably following behind) will find no doctors prepared to look at the product and use it for patients on a clinical trial basis. I confess I found this an extraordinary comment. At the meeting itself John Cash was negative. Towards the end of his letter he refers to "furtive arrangements" with regards to Factor VIII between Dr. Smith of BPL and Dr. Foster of PFC. These were in fact not furtive but quite open and were intended to share knowledge and information about heat treatment experimentation. I concluded at the time that John Cash really wanted all the research to take place in Scotland. In essence I was anxious to find out whether the commercial manufacturers were indeed making a safer product. If so, we needed to know that this was the case and if we could try and replicate whatever they were doing to their product to render it safe.

My letter in reply dated 21st December appears next in this section and records the fact that John Cash had appeared to change his view since the meeting on the 15th December regarding the wisdom of prompting commercial manufacturers to support their claims for their products through proper clinical trials. There is a further letter from John Cash dated 22nd December setting out the FDA attitude to US "Hepatitis-safe" products.

Also on the 22nd December Dr. Craske wrote to me enclosing a paper he had prepared for the MRC Hepatitis vaccine group describing early information about AIDS in the USA. He drew attention to the fact that the latest information from the CDC in Atlanta was that 8 cases of AIDS had occurred in haemophilia A

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patients. All were patients with severe coagulation defects requiring regular treatment with Factor VIII. He said that as yet no information about whether any brand or batch of concentrate was implicated had emerged. He also said that there was 2 cases which had occurred in non-haemophiliac patients which might be related to whole blood transfusions between a year and 18 months prior to the onset of the syndrome.

The document which he enclosed listed various clinical disorders which were associated with AIDS. Also immediately behind this document is a further copy of the paper prepared by John Craske entitled "The Acquired Immune Deficiency Syndrome (AIDS)" which is slightly different from that they have commented on earlier. It bears the date 5th November 1982.

UNDATED:

The first item in this section is a paper entitled "Factor VIII defractionation on aminohexyl sepharose with possible reduction in Hepatitis B antigen". Dr. Smith was the co-author of this paper and it looked at the method of Factor VIII purified chromatography on aminohexyl sepharose. Chromatography removes some virus but, it is now established, not all. It also removes some of the Factor VIII activity. At this stage we were keeping an eye on current developments in this field in case the research held the key to "Hepatitis-safe" products.

There follows an indication of the identity of those who accepted an invitation to become members of the CBLA and then a Scottish paper entitled "Blood products laboratory radioimmunoassay for detection of Hepatitis B surface antigen using antibody-coated beads (BPL-bead-RIA): comparative valuation for blood donor screening". This paper was prepared in conjunction with BPL and related to a modification of the BPL RIA test. The paper evidences the use of the test in Scotland.

The last item is entitled "Third Annual Report on Project Number J/S240/78/7- preliminary results". This was produced by Dr. Craske. Its precise date is unknown but it covers a period from 1st January 1980 to 1st January 1982 and therefore will have been produced at some stage during 1982. It comprises the results, at that stage, of studies of the epidemiology and chronic sequelae of Factor VIII and Factor IX associated Hepatitis in the United Kingdom. Of relevance is paragraph 3 on page 3 entitled "NHS -v- commercial concentrate".

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Dr. Craske said:-

> "In Table 6 (page 18) of the Second Annual Report, the attack rates of Hepatitis in patients treated with only one product in any year was reported. This suggested that non-B Hepatitis associated with NHS Factor VIII had a considerably lower attack rate than that associated with commercial Factor VIII. However, preliminary results of a prospective survey at Oxford have failed to confirm this. Of 5 patients with no previous exposure to concentrate, treated with a mean of approximately 12,000 Factor VIII units of NHS concentrate during one treatment episode, 5 patients so far followed have developed non-A, non-B Hepatitis with incubation periods from 51 - 125 days. Of these, 2 were symptomatic and 3 symptomless ... it is possible that the previously reported lower attack rate associated with NHS concentrate may be due in part to the fact that a higher proportion of non-A, non-B Hepatitis cases associated with NHS Factor VIII may be sub-clinical compared to those associated with US commercial concentrate. These preliminary results suggest that there is a 90% chance of contracting non-A, non-B Hepatitis when first transfused with either NHS or commercial concentrate."

The Oxford studies referred to above were those based on the small pool experiment [is this correct?]. Of course of the conclusions reached by Dr. Craske later developed further still to the extent that 90% became 100% but this evidence is, for all intents and purposes, the end of the fallacy that so far as non-A, non-B Hepatitis was concerned US commercial concentrate was more infective than NHS concentrate.

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JANUARY:

This first item in this section comprises the agenda for the Advisory Committee on the National Blood Transfusion Service meeting on the 10th January and this is followed by the Minutes of that meeting. It will be seen that paragraph 4 of the

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Minutes records the establishment of the Central Blood Laboratories Authority. At paragraph 10 there is a further reference to the MRC's decision to disband its Blood Transfusion Research Committee and an indication to the effect that the CBLA would consider whether the research committee it intended to establish would stimulate and co-ordinate NBTS research with representatives and observers as appropriate from SHHD and the MCR. There is reference at paragraph 11 to the preparation of a report by the Exchequer and Audit Department of the DHSS. The report dealt primarily with the redevelopment of the BPL and in particular the scope for collaboration with the PFC, Liberton and the different prices paid by some transfusion centres for blood bags. I do not recall seeing a copy of this report but it obviously did not recommend any closer collaboration with the PFC. My guess (and it is speculation) is that the costing of the manufacturer of products by PFC as revealed to the Exchequer and Audit Department demonstrated that manufacturing at PFC was a relatively expensive exercise.

One of the papers for this meeting (AC (83) 8) gives information on the supply of FFP as sent to BPL. This shows supplies for 1981 and 1982 and signs of improvement (109,000 kg in 1981, 127,000 kg in 1982). The introduction of the single donation bag was beginning to assist increase in production at this time.

There follows a paper entitled "Review of policy on distribution of blood products for sale on a named-patient basis" which I prepared on the 12th January 1983 as a follow-up to the Haemophilia Centre Directors' meeting in December 1982. This was purely an aide memoir which I prepared for the file to assist me in any later presentations or correspondence. On the first page under the heading "Hepatitis-safe Factor VIII" I record the fact that certain companies, notably Armour, Immuno and Hyland were offering so-called "Hepatitis-safe" material and that production methods for reducing Hepatitis centred mainly on the inactivation of virus by heat in a purified product which had been stabilised by detergent and sugars. I note that none of these products was guaranteed free of transmission of risk of Hepatitis, that methods of treatment tended to carry substantial penalties in yield of product and that the method of treatment employed was not sufficiently close to the existing production methods to enable variations to existing production licences. At paragraph (IV) on page 2 I observe that the methods for inactivation of virus in Factor VIII and Factor IX cannot be considered in parallel. In short you could not assume that Factor VIII and Factor IX were going to react in the same way to the application of heat. Each had to be separately tested and validated. In the event, when we looked into the matter and after overcoming problems of thrombogenicity, we determined to use a heat

treatment regime which was the same for our new concentrate, 8Y, as it was for Factor IX. However, this might not have necessarily have proved to be the case.

My own view was that the commercial products should have been subjected to a clinical trial and then licensed. We did not know for a fact that they had carried out any tests on chimpanzees. In order to obtain a license it would be necessary for the manufacturer to show:-

1. A standardised process to eradicate Hepatitis B (and NANB);

2. How the process worked (otherwise it might appear arbitrary and empirical); and

3. That the process could be reproduced on a standard basis without variation.

None of the commercial manufacturers at this time were describing with any accuracy the type of heat treatment which they were employing or what they were introducing by way of stabilisers as part of their processes. Some of the alternatives like polyelectrolyte, which was a new approach to the separation of Factor VIII from both human and porcine plasma, were not really attracting much attention. In the event no one really used this process or for that matter made much use of porcine plasma. Feiba to which I refer on page 3 had no obvious advantages that anyone could determine and certainly appeared to pass on HIV.

The conclusion, on page 4, refers to two appendices, A and B. Neither accompany the note but Appendix B appears to be the paper produced by John Cash (which I refer to above) in which he touched on the FDA attitude to the new "Hepatitis-safe" products. Appendix A appears to be a document setting out some preliminary considerations aired at a meeting recently at BPL. **[Where is this paper?]**

At this stage we had certainly not heard of any clinical trials being held in the US in relation to the new "Hepatitis-safe" products. In the UK it is relatively straightforward to get such trials under way economically. I do not know what the licence status of these products was in the United States; it was always possible that heat treatment was really regarded as simply a variation to an existing licence for a product.

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Looking at the factors which I summarise on page 4 I have mentioned in relation to paragraph (I) that there was no evidence of a move towards clinical trials in the United States and in paragraph (II) that it was surprising to me that the FDA would accept treatment of Factor VIII and Factor IX on a comparable basis since production of both products would have far different consequences. In paragraph (III) I said that whilst it was accepted that heat might inactivate the virus it might also have other equally detrimental effects on proteins normally present in the concentrates and I was somewhat surprised that the risks appeared to go unrecognised by the FDA. Our thinking was that the application of heat proteins could introduce structural changes and that the changes might be so gross as to destroy the protein we wished to make use of or possibly more subtle detrimental effects, for example, producing new antigens or unfolding the protein to expose antigens. This could induce antibody development against protein itself ie against Factor VIII. So our real concern was whether there was function impairment or a risk of new antigen creation. This is why studies were, we felt, important.

My purpose in calling the meeting in December to which I refer to above was to see what a representative selection of the Haemophilia Directors wanted. I did not want to direct a course of research and development into a product which thereafter failed to gain acceptance. We were, at that stage, focusing particularly on Hepatitis NANB and there was no imperative to improve the product at the time because NANB, in a chronic form, was not that prevalent or life-threatening to make search for inactivation an urgent priority. Hepatitis was simply a problem which haemophiliacs had to accept the risk of for the time being and it was certainly not remotely in the league of HIV.

There follows the agenda for the 187th regional Transfusion Directors meeting which took place on 14th January and immediately behind this appear the Minutes for that meeting. In paragraph E of the second page of the Minutes there is reference to the Blood Transfusion Research Committee and the attempt to graft this committee on to BPL's Scientific and Research Committee when formed. I was not particularly keen on this idea since effectively it was a way of using part of the budget which we had. Aside from this nothing of any great relevance was discussed at the meeting so far as the present litigation is concerned.

Next is a letter from myself to Dr. Wagstaff, the director of the Regional Transfusion Centre in Sheffield dated the 17th January following up on criticism which was levelled at BPL at the meeting on 14 January and in particular the suggestion that plasma supplies which were being improved through the

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introduction of AG.M was not being matched with increased product from BPL. This was not the case and I felt it necessary to put the record straight. The document appearing immediately behind this letter is an extract from Blood Preservation working party documentation which was discussed at the meeting and a lot of what is said on that page is not true. A single plasma pack had been introduced and we had found the change was accepted only with some reluctance by certain regional transfusion centres. It then became necessary to design a larger bag to take the extra volume of plasma resulting from the advent of the use of AG.M. This produced more plasma per donation. Moulds for new bags were expensive, Travenol had designed the old bag, and we arranged for them to produce a new one. As far as yield was concerned, the comments were simply wrong. Together with others I had spent a great deal of time explaining the logic and purpose of a single donation pack and yet here was the working party advocating a five litre pack. On top of all this, some of the members were in favour of AG.M whilst others were not.

At paragraph D in this document there is reference to concern about new methods to produce Hepatitis-free Factor VIII and that these might cause an additional fall-off in yield. This was all very well but it was not particularly helpful to state the concern in the light of the fact that clinicians were interested in the product and if this resulted in a loss of yield well, so be it.

The next paper in the file is entitled "Outline proposal for prospective study of non-A, non-B Hepatitis" which was prepared by Dr. McClelland (from the Scottish Transfusion Service) on the 10th January. I do not recall that this proposal ever managed to get off the ground. The paper concerns transfusion associated Hepatitis rather than Hepatitis in blood products. The hope was to follow up on some research and sampling which the MRC had done in 1974 but, as I have previously mentioned, it transpired that the samples from that time had been lost.

Next in this section is the agenda for the UK working party on transfusion-associated Hepatitis meeting for the 18th January.

The next document in this section comprises the Minutes of the UK Working Party on transfusion associated Hepatitis meeting which took place on the 18th January. I attended the meeting. At paragraph 6.5 there is reference to Dr. McClelland's draft proposal for a prospective study of NANB Hepatitis. This study did not eventually get off the ground. At paragraph 8 there is reference to AIDS and Dr. Craske summarised the current position. Dr. Craske said that he

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would be studying the effects of American Factor VIII on UK recipients and would be examining immunological markers but the field was currently confused. This is a reference to the very early tests which were used on a surrogate basis to try and identify HIV. In effect such tests look for viruses [and other conditions] which might be fellow travellers with HIV so that the existence of those viruses might (but only might) suggest that the individual also had HIV.

There follow the Minutes of the UK Haemophilia Centre Directors Hepatitis Working Party. In paragraph 2 of the Minutes there was discussion of a prospective study of Factor VIII and IX associated Hepatitis and the implications of trials to evaluate Hepatitis risk of "Hepatitis-reduced" Factor VIII and IX. I pointed out the unsatisfactory state of affairs which was then existing where no proper clinical trials were being carried out in relation to the commercially available "Hepatitis-reduced" products.

On page 2 (second paragraph) Professor Bloom is reported as saying that as a result of the meeting which we had had on the 15th December he and Dr. Rizza had written to each haemophilia centre director requesting them not to take part in trials of "Hepatitis-reduced" products on a named patient basis without taking advantage of an evaluation where the powers of the Medicines Commission, under the Medicines Act, could be exercised in the interest of the patient. [What does this mean?]. In the third paragraph on this page I make reference to several of the issues that I touched on in my aide memoir on which I have commented above and speculated that it was likely that Factor VIII activity would be reduced by about 50% as a result of the pasteurisation process (this is what we believed was being used for heat treatment at the time).

In the fourth paragraph it is stated:-

> "In discussion it was suggested that trials on a named patient basis often provided the best means of obtaining preliminary information about a new product. It was pointed out however, that this method did not provide a guarantee of the product under the Medicines Act, and that there was still a danger that a drug firm might use the information contained to create a climate where it appeared unethical to withhold the product from general clinical use."

This was the concern at the time. There appeared to be three possible procedures:-

1. The valuation on a named patient basis;

2. The granting of exemption from a clinical trial certificate by the licensing authority. In the UK, this was the National Institute of Biological Standards. The clinician organised trials prior to the granting of a new product licence. This procedure was not so costly or lengthy as that of obtaining a clinical trial certificate; and

3. A clinical trial certificate. This involved a full application for a new product license with all the trials organised by the manufacturer. The procedure was lengthy and costly.

I said that if all the Haemophilia Centre Directors collaborated the manufacturers would be obliged to follow whatever procedure was adopted. In the event however the product continued to be imported on a named patient basis and proper evaluation proved impossible. We were obliged to continue our research and introduce products against the background of considerable uncertainty as to the effectiveness of the final product largely because HIV became so important and hijacked everyone's attempts to adopt a properly considered and orderly approach towards virus inactivation which might have proved possible in the context in which the original research was started ie targeting Hepatitis NANB.

On page there is reference in the penultimate paragraph to the fact that 10 cases of AIDS had occurred in haemophilia A patients and that none of the predisposing causes such as heroin addiction, promiscuous homosexuality, or treatment with immunosuppressive drugs, were present and all had occurred in areas of the USA where cases had not been found before. All except one patient were patients with severe coagulation defects, 5 had died at this stage. There was a statement to the effect that it seemed possible that Factor VIII or other blood products administered to these patients might be implicated. Further support for this hypothesis had come from a report of 3 cases associated with whole blood or platelet transfusions. 2 were adults who had developed AIDS 14 and 18 months respectively after transfusion to cover operations. In one case, one of the two donors implicated was known to be a young man in his 20s from New York. The third case was that of a 20 month old boy from California who had been transfused with blood platelets at birth. 14 months later he developed

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an AIDS like syndrome. One of the donors of the unit of platelets to this patient was a young homosexual who subsequently developed classical AIDS and died in August 1982.

At this stage there had been no cases reported in the UK and by this stage urgent work was underway, with something of a vengeance, both in the United States and in France. Against this background we adopted a policy of monitoring developments. As reported on page 4 of the Minutes the Americans were keen for the UK Haemophilia Centre Directors to collaborate in reporting cases of AIDS possibly associated with transfusions of US commercial Factor VIII. There had been no cases at that time but Dr. Craske said that he had been sent the detailed protocols of the National Haemophilia Foundation Survey by the Americans. It was suggested that the working party should consider the kind of survey which should be undertaken in the UK. Dr. Craske agreed to draw up a form for the reporting of AIDS cases and to consider what further information would be needed in a retrospective study which was aimed to try and identify possible AIDS related cases which might not have been associated with what was now in the course of investigation in the United States.

The next document in this section is headed "Hepatitis Study" and is dated the 20th January. This briefly summarises results of the study into some 40 patients. These results have to be, once again, viewed with some caution in the light of the unfolding knowledge of Hepatitis NANB. It is interesting to note that 21 patients had received NHS Factor VIII and that of these, 12 had developed Hepatitis (or so it seemed at the time). This represented a 57% "hit" rate although it was subsequently established by Dr. Craske that in fact the "hit" rate was 100%. The Hepatitis referred to would be predominantly NANB.

The next document in this section is entitled "9H4 Pasteurisation of Factor IX concentrate, 24.01.83. This sets out a record of various experiments on the pasteurisation of Factor VIII in a liquid state using a temperature of 60° for 10 hours (we were using the same heating regime as for albumin). The process used sorbital and glycine. We attempted to identify the loss of activity. At worst, there was a 48% loss of activity; at best 27%.

We needed sorbital and glycine as a prop for Factor IX protein if it was to escape damage in the heat treatment process. In this sense Factor IX was different from albumen which needed neither. The problem was that sorbital and

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glycine might also act as a prop for any virus we sought to destroy reducing the efficacy of the heat treatment.

The next few papers relate to a survey to establish the incidence of jaundice in patients. Those involved were clinicians at the North London Regional Transfusion Centre. The material is of limited relevance for present purposes.

FEBRUARY:

The first document in this section is a paper entitled "PFC method for heat-treated Factor VIII concentrate 10.02.83." This details the zinc precipitated Factor VIII product which PFC Liberton were experimenting with at this time. They called it "Factor VIIIZ". The Scots introduced heat treatment of Factor VIII earlier than BPL but they only gave their product marginal amounts of heat. We could not see the point of heat treating potentially ineffectively. It is possible that the treatment given might have reduced HIV but current information suggests that it was unlikely to and the product did not work as far as Hepatitis NANB was concerned. It should be noted that the process itself involved a pasteurisation "wet heat" treatment. Eventually the Scots ended up using dry heat treatment like ourselves.

The next document in this section is a memorandum from Dr. Smith to myself and others at BPL dated 15th February reporting on a visit to the Scottish National Blood Transfusion Service Protein Fractionation Centre, a headquarters seminar which was held from the 10th to the 11th of February. At the bottom of the first page under the heading "other information on virus inactivation" there is "gossip" as to what the commercial manufacturers might be up to. It was thought (but no one had firm information on this) that Hyland's method consisted of heating freeze-dried products; that Cutter were following Behringwerke's glycine-sucrose method; that Biotest were combining PEG and detergent with BPL/UV treatment of a concentrate (not plasma); that Immuno were probably using diethyl byrocarbonate and a new unspecified virucide for Factor VIII. This was all unconfirmed speculation. There is also a description on this page of the work which Scotland were then engaged in and which concentrated mainly on heat inactivation of Hepatitis viruses in coagulation in Factor concentrates using glycine and sorbatol. There was an indication (see page 2) that Scottish Haemophilia Centre Directors had expressed confidence in proceeding to clinical trials with PFC's products without chimpanzee studies which

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were likely to take more than 2 years even if the animals became available. Apparently the Medicines Inspectorate (and Professor Zukerman) were quoted as being quite keen on work with more readily cultured model viruses as markers. This was a means of "spiking" the products with representative viruses and seeing whether the heating process killed those viruses. If it did then there was a possibility (but not a certainty) that the heat treatment might have a similar effect on Hepatitis NANB (at that stage of course the virus was not identified or adequately described and indeed even today, as I have commented above, it is thought there is more than one virus at work and a test for only one of the possible viruses, HCV, has been developed).

On the 17th February Dr. Gunson wrote to us with regard to arrangements for the Central Research Committee it was proposed to establish by grafting it on to CBLA. It was agreed that we would provide a room and a secretariat and Dr. Gunson set out the terms of reference in the committee as he saw them in that letter.

This is followed by a memorandum from Dr. Harvey to myself dated 22nd February which sets out a list of possible "consultants" who might be co-opted on to the BPL research committee (which was really the same committee that Dr. Gunson was referring to in his letter of the 17th February[?]).

This is followed by a note which I prepared dated 24th February and copied to Dr. Harvey entitled "BPL Research and Development Committee". I seem to recall that I had been asked how we would splice in our research and development work with the new NBTS research group and I think this note would have gone to Mr. Armour who was secretary of the CBIA.

As will be seen at paragraph 2 the research projects having the highest priority were listed and item A was "inactivation of transmissible virus in protein fractions".

The next letter in this section, dated 25th February, is the MRC to Dr. Gunson and records the loss of the samples which would otherwise have been used in the Hepatitis study proposed by Dr. Gunson's group.

This is followed by a paper entitled "Development projects relating to Prothrombin Complex". This paper evidences further research work on BPL's part and touches, in several places, on heat treatment (particularly of Factor IX) aimed at

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improving the safety of the products. The paper chiefly evidences the fact that R and D was continuing at this time in a variety of areas consistent with available funds.

On 15th March in a memorandum to Mr. Armour on the subject of the Research and Development Committee of the CBLA I set out some thoughts as to its composition and function.

The next document of importance in this section is re-printed from the British Medical Journal and consists of an article entitled "Treatment of Haemophilia and related disorders in Britain and Northern Ireland during 1976/80: Report on behalf of the Directors of Haemophilia Centres in the United Kingdom" and was written by Dr. Rizza and Dr. Spooner. This sets out the results of the five year survey of the treatment of patients. As the abstract records the survey showed an increase in the number of patients receiving treatment at the Haemophilian centres and a substantial increase in the total amount of therapeutic materials used. Home treatment had become established for severely affected patients and accounted for roughly half the total amount of material used. Most of the information contained in the article can be seen in the material prepared for the annual meetings of the Haemophilia Centre Directors over the five years in question. As will be noted, the last paragraph on page 5 states that cerebral haemorrhage was the commonest cause of death in haemophilia A (29%) whereas Hepatitis was recorded as the cause of death in one patient only out of 89 with haemophilia A who died during the period, and only one patient with haemophilia B (out of 18 who died) during the five years in question.

In his handwritten memo to me of the 23rd March Dr. Harvey (our Head of Research and Development) identified who he would want to see on the Research and Development Committee (external to BPL).

The last item in this section dated 24th March 1983 is a memorandum from myself to Mr. Mallery on the subject of AIDS. This arose from the fact that Professor Bloom drew the attention of the CBLA at their meeting on Wednesday, 23rd March, to the problems which were becoming associated with blood transfusion and blood products administration with the increasing incidence of reported AIDS cases which continued to gain momentum in the United States on a monthly basis. **[Where are the Minutes of the CBLA meeting of the 23rd March?]**

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My memorandum was written against the background of an expectation that as concern amongst haemophiliacs with regard to the AIDS risk heightened there would come, with that concern, the likelihood of a return (albeit on a temporary basis) to the use of cryoprecipitate as a desirable form of treatment. This would clearly have important effects on BPL as far as our source material was concerned and it seemed to me that we needed to begin thinking in terms of converting to the production of small pool freeze dried cryoprecipitate to assist blood transfusion centres which might (albeit that they would be rusty) want to revert to the manufacture of cryoprecipitate which, historically, was something they as opposed to BPL had produced. I proposed a meeting between the key BPL staff to discuss the strategic alternatives. This meeting is dealt with in more detail below.

In the event the anticipated switch to the use of cryoprecipitate as a temporary expedient and as an alternative to using increasing suspect US commercial concentrate never happened. It was a matter for haemophilia clinicians (and to an extent the licensing authority if they thought the US concentrate was unsafe) but neither acted in a way which resulted in the demand for cryoprecipitate increasing.

APRIL:

The first document in this section is entitled "Draft proposals for discussions; TAH follow-up by BTC's; guidelines." TAH stands for transfusion associated Hepatitis and this document followed up on the Committee proposals that there should be a jaundice survey.

Next is a draft letter prepared by Dr. Craske and sent to me under cover of a compliments slip dated the 12th April 1983. The draft letter which appears immediately behind the compliments slip was intended to serve as a covering letter for an enclosed protocol for use in trials of "Hepatitis-reduced" Factor VIII products. The trial proposed was a "pups" trial, that is to say using previously untreated patients. As Dr. Craske indicates in the second paragraph of his letter there were only a limited number of these patients in the United Kingdom in any one year and the hope was that Haemophilia Centre Directors would identify appropriate patients who could then be treated with one of the "Hepatitis-reduced" Factor VIII products which were then available. The next document sets

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out the protocol for the trial. **[What was the fate of the trial - did it get off the ground?]**

The notes of the meeting held on the 18th April 1983 and dated 21st April were prepared by Norman Pettet and record the internal meeting which was held consequent upon my earlier memorandum which suggested we needed to think out our strategy in light of the possible switch to cryoprecipitate and the reaction to AIDS. As the first page makes clear there were a number of uncertainties. There were still no identification of AIDS, no demonstrated link between AIDS and haemophiliacs and insufficient data to assess the extent of any perceived risk. Dr. Snape reported that an association was now being formed between heat treated concentrates in reducing the risk from AIDS. Dr. Smith said that there was at that time little firm knowledge on how effective heat treatment was on NANB virus or for that matter AIDS nor the effect on yield. There were several considerations which had to be borne in mind and these are listed in paragraphs 1 to 4 on the second page of the note. Of particular importance was paragraph 3. What would be the effect if BPL which was only able to produce one half of the UK requirement for Factor VIII at the time had to incur a further substantial penalty with regard to yield arising from heat treatment?

On page 3 there was discussion about the wisdom of moving to small pool (ie small volume pools) and/or small panel (i.e. large volume pools with fewer donors) as a means of producing Factor VIII and IX and the general feeling of those at the meeting was that BPL should go for small panel and heat treated products. However, to an extent we were obliged to adopt a policy of wait and see. We needed clearer signals from the users and those treating them before we could react.

The next document in the section comprises the agenda for the working party on transfusion associated Hepatitis which was meeting for the third time on Wednesday, 20th April and the Minutes of this meeting appear immediately after the agenda. The Minutes record (paragraph 5.5) that Dr. McClelland's transfusion associated Hepatitis study proposal had so far been unsuccessful in attracting funds. At paragraph 7, Dr. Craske reported on his Hepatitis surveillance work in relation to haemophiliacs at Oxford and repeated that of the 9 cases which had been studied where the patient had not received concentrate before all had developed non-A, non-B Hepatitis and of these 9, 7 received NHS concentrate and 2 US product. At paragraph 9 there is reference to AIDS and to the fact that Dr. Gunson would be attending the Council of Europe meeting in May on AIDS

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and blood transfusion. Dr. Craske reported that there was still no cases of AIDS in UK haemophiliacs although there were 6 likely cases in UK homosexuals. Again there is reference to the anticipated increase in the uptake of cryoprecipitate because of AIDS and that this might mean a drop in supply of plasma to BPL. The next pro forma letter dated 25th April was one which I drafted to go to various experts who were not employed within the Health Service but who we hoped to try and attract onto the BPL Research and Development Committee. A list of those who received the letter appears immediately behind. We had a very poor response with most of those we approached being too busy to assist.

The next document of importance in the file comprises a summary of the work of the Regional Transfusion Directors Committee working party on transfusion associated Hepatitis dated the 28th April 1983. As the summary indicates the working party was established on the 27th September 1982 and had by this time met three times.

Under the heading "AIDS" at paragraph 5 appears the following:-

> "The working party has followed carefully the information from the USA on AIDS and has considered the recommendations with respect to donor screening and use of cryoprecipitates. To date there have been no cases reported following transfusion of blood or blood products. It has been agreed that, until further information is available, the working party will not recommend changes to present practices for donor selection or use of blood products."

MAY:

The first document of importance in this Section comprises the Minutes of the 13th meeting of the UK Haemophilia Centre Directors which was held on the 13th September 1982 **[check if we have a copy of these Minutes in the 1982 file]**.

These were made available under cover of a letter from Dr. Rizza on 5th May 1983. There is a paragraph on Acquired Immune Deficiency Syndrome on page 10 recording the fact that the directors had asked Dr. Craske to look into the report from the United States that this syndrome was mainly found in homosexuals but

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included 3 haemophiliacs. At that stage it appeared that there was "a remote possibility that commercial blood products had been involved". Of course the speed with which events were unfolding changed this to a relative certainty within a month or so.

The next two important documents in the file comprise the agenda and Minutes of the Regional Transfusion Directors meeting that took place on the 18th May. **[There is reference at Item 8 in the Agenda to a paper prepared by you dated 18th April 1983 designated RTD(83)7 on the subject of the required growth in plasma supply. Where is this paper?]**

There is reference at paragraph 10 under the heading "AIDS" to Dr. Walford reporting the DHSS meeting on AIDS. I was not involved with any DHSS meetings on this subject and I cannot recall the substance of Dr. Walford's report. Clearly at that stage Dr. Gunson, on behalf of the Regional Transfusion Directors, indicated four courses of action which they could accept:-

1. Questioning of donors at sessions;

2. Sessions to be discontinued in areas of high risk donors;

3. Pamphlets explaining AIDS to donors;

4. Publications in newspapers.

It was agreed that the medical branch of the Gay Society should be contacted and advised that until more was known about the disease, practising homosexuals should be asked not to donate blood. It was also decided that Dr. Davis and Dr. Barbara would draw up an information leaflet on AIDS and circulate this to Regional Transfusion Directors for comments. It was hoped that the leaflet would be ready for printing in 6 weeks and Dr. Walford indicated that she would try and have the leaflet printed through the DHSS.

The next document in the section is headed "Budget - function relationships. Blood products laboratory PESC estimates related to BPL manufacturing requirements". This was developed for a talk which was given to Regional Transfusion Directors by myself. This was in the context of a Travenol sponsored annual symposium. The paper and its supporting documentation was intended to show the future demands for plasma to service the new BPL plant which was then

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due to be commissioned in December 1985 and to have a capacity of 450 tonnes per annum in terms of processing plasma.

There follow the agenda and Minutes of the Central Committee for Research and Development meeting which took place at BPL on the 21st June. Dr. Gunson chaired the meeting and Professor Bloom was also in attendance (he was one of the Haemophilia Centre Directors). Dr. McClelland attended (he was from the Scottish Transfusion Service) and Dr. Stewart from Wellcome was also present. It was explained that the committee was to advise the CBLA on research and development in blood transfusion and related fields.

The Minutes record the discussion on the subject of AIDS (see paragraph 4/83). As recorded in the Minutes it appeared by this stage that AIDS was transmitted through blood and blood products and should accordingly be one of the subjects considered by the committee. The Transfusion Service was considering how to cope with the problem and the DHSS was putting out a circular asking "high risk" donors not to give blood but of course this relied upon the integrity of the donor. A problem at this point was that still not enough was known about AIDS to arrive at any concrete conclusions. The uncertainty lead to the not unusual conclusion that what was needed was an ad hoc group to look at the matter in more detail.

The next document in this section is a memorandum from Dr. Smith dated 23rd June addressed to Dr. Winkelman who was engaged in research and development work at PFL. In the memorandum Dr. Smith requests Dr. Winkelman to lead the project on heat inactivation of viruses in Factor VIII concentrate. The priority is described as "A1" ie most important to BPL/PFL's immediate product strategy. The deadline for draft proposals for the project was set at 15th July.

This really confirms our commitment at that point to progress as far and as fast as possible the development of heat treated Factor VIII. There was no confirmation that heat treatment would inactivate HIV but it had been tentatively identified in the spring of 1983 as a virus (this identification was not confirmed until the spring of 1984 however) and in the circumstances whilst inactivation through the use of heat could not be demonstrated to work and therefore to be a solution we nevertheless concluded that given all the uncertainties, in the absence of any other apparent solution, we should try and accelerate the heat

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inactivation programme which had been tentatively underway to deal with Hepatitis NANB, which was altogether a different and much less urgent problem.

JULY:

The first document in this section is a memorandum prepared by Dr. Craske in his capacity as Chairman of the UK Haemophilia Centre Directors Hepatitis working party dated the 11th July. This sets out various factors to be considered in the selection of Hepatitis reduced products for clinical trials. As I mentioned earlier the decision was to try and set up clinical trials with various of the commercial products which claimed to be "Hepatitis-reduced" to determine their effectiveness. In this memorandum Dr. Craske sets out to classify the various products which were then available and to an extent speculates as to their effectiveness both in relation to Hepatitis NANB and AIDS. He records, at paragraph (III) on page 2, that one suspected case connected with transfusion of Factor VIII had by this time been reported to him the UK. As he states, at the bottom of page 2, since there was no information as to the physical characteristics of AIDS at that time materials used to reduce the risk of transfusion Hepatitis such as heat treatment could not be relied upon to render Factor VIII concentrate manufactured from the same plasma free of AIDS. It will be seen from the first page of his note that there was a considerable amount of uncertainty regarding the commercial products both as to the nature of the heat treatment applied to them and in certain instances the timing of their emergence and availability. In his conclusion Dr. Craske hoped for a Hepatitis-reduced product from the NHS. As he says "since the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received Factor VIII or IX concentrate, a choice will have to be made between using heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non-A, non-B Hepatitis."

This seemed to produce a difficult ethical problem. Of course with hindsight we know that NHS concentrate was also infected with AIDS (although not to the same extent as commercial concentrate from the US) and therefore the choice was not quite as John Craske presented it in his memorandum but at the time the dilemma was a very real one.

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On the 14th July Dr. Gunson wrote inviting me to submit names for inclusion in the ad hoc group to consider the research aspects of AIDS related to blood transfusions. It was proposed that I should be on this group. I replied on the 18th July with my suggestions.

The letter dated 20th July 1983 from Mr. Lamberti **[he is described as Assistant Regional Engineer - but whose?]** to David Kut and Partners evidences that the up-grading of BPL was, subject to various remedial works, nearing completion.

The next document in this section is a memorandum from Dr. Smith to myself and Dr. Harvey entitled "Heating activation of Hepatitis viruses in Factor VIII concentrate". It is dated the 25th July and attempts to set out the current position with regard to heat treatment in the context of the introduction of project proposals for work on Factor VIII and Factor IX concentrate heat treatment at PFL. Dr. Smith indicates that inactivation by heat was chosen as the most promising method of inactivation because of availability - extensive experience with albumin and other concentrates; clinical "acceptability" compared with the use of less familiar agents, eg virucides and probable general application to viruses as yet incompletely characterised (by which he meant, inter alia, AIDS).

He refers in the memorandum to the only fully documented work on heat treatment of Factor VIII, at the end of 1982 being that carried out by Behringwerke. This was a pasteurisation process. He goes on to record the work at PFC Liberton which I have referred to above which did not permit treatment for long enough at high enough temperatures to be effective.

Dr. Smith touches on Haemophilia Centres' concerns about AIDS and states that, although nowhere set out in print, senior clinicians had been told by Hyland and Armour that their method of inactivation was to dry heat the freeze dried vials. Dr. Smith had to speculate as to the extent of Hyland's success in tackling Hepatitis NANB and the implications were that it did not completely eradicate it. He encloses with his report a table showing the effect of heating freeze dried vials of 8CRV (the PFL intermediate concentrate then being manufactured). Results suggested that temperatures between 60°c and 70°c might be possible for 48 hours, 75°c for about 10 hours or 80°c for about 4 hours without losing more than 5% of the Factor VIIIC activity. The work was continuing at the time he produced this report and he concludes

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"provided we make no immodest and unsupportable claims about evidence of Hepatitis safety, or overstate our confidence in this as a long term solution, I believe that many clinicians would be happier to use a dry heated product than the existing one, and it might respectively be offered on that basis".

The next memorandum is one prepared by myself dated the 26th July and is titled "AIDS progress of heat treatment of human plasma products". I believe this is a paper which I prepared for the CBLA and also possibly the ad hoc group on AIDS. Under the heading of "Virus transmission in haemophiliacs" I state that the severity of NANB Hepatitis in haemophiliacs probably associated with the co-existent impaired immune responsiveness of these patients has motivated plasma fractionation organisations to re-examine means whereby the Hepatitis virus can be inactivated in large pool concentrates. My reference to impaired immune responsiveness is not, in fact, to AIDS but to the general lack of immune responsiveness which is particularly a feature of severe haemophiliacs exposed to heavy treatment with concentrate.

Under the heading "AIDS" on the second page I recorded the view current at that time to the effect that the syndrome was likely to include in its aetiology transmission (that is to say its causation) an effective virus and the possible phenomenon of reactivation of an existing virus in individuals concerned. In short, it had been tentatively identified as a virus by this time but the exact mechanism by which it worked in the recipient's body was unclear then and to an extent still is unclear now. The clinical view was that as a virus it might, like Hepatitis, be partially or completely inactivated by heat. The reasons set out under the heading "Means of heat treatment of blood products". Wet heat, which we used in relation to the production of albumin, appeared a less satisfactory route for research than dry heat. The majority of commercial manufacturers appeared at this time to be using a "dry" method of heat treatment. The claims they were making for their products were, so far as we could see, unfounded at that time but nevertheless we felt instinctively that, in the absence of any other obvious serious alternative, we should, in a sense, "run with the pack". As is apparent from the third page of my note we were concerned about yield and we were endeavouring to find a happy medium between an effective heat treatment (or what we suspected would be effective since it was difficult to establish this scientifically) and a method of treatment which did not seriously reduce yield.

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AUGUST:

The first item in this section is a Minute of the Medicines Inspectorate visit to Elstree which took place between the 28th July and the 3rd August. The report covers, in the main, points of detail which are not relevant but once again evidences (see page 5 under the heading "The Centre's Reply") that some of our problems were to do with finance and staffing (although the two were obviously closely related). The memorandum of 3rd August from Mr. Armour to myself, "Heat treatment of human plasma products", suggests that the paper which I refer to above, on the subject of AIDS, was probably produced for the CBLA although it may also have been utilised in relation to the ad hoc group.

SEPTEMBER:

Dr. Gunson's letter of the 26th September lists those who had been invited to join the ad hoc working group on AIDS in addition to myself. He encloses a standard form of letter to be written to those invited to serve on the ad hoc group and records the fact that the terms of reference for the group set up by the central committee for research and development were to "advise the authority [that is to say the CPBL] on research and development in immunohaematology, blood transfusion and related diagnostic and related fields". The agenda for the meeting of the Haemophilia Centre Directors Hepatitis working party to be held on the 14th September is the next document in the section dated 11th August and this is followed by the Minutes of that meeting.

At the bottom of the first page of the Minutes appears the following reference:-

> "In discussion, it became apparent that there was still considerable concern about the possible transmission of an infection related to the Acquired Immune Deficiency Syndrome (AIDS). It was not known whether the inactivation procedures used in various products inactivated the putative AIDS related virus. Any director considering using the commercial products in such a clinical trial would, therefore, have to take this into account when considering the best product to use. It was proposed to discuss this problem at the annual meeting of the Haemophilia Centre Directors".

The Minutes also record the products of commercial Factor VIII were being considered for trials and that these consisted of the dry heat treated Travenol laboratories product and the Armour products. The Travenol product had been granted an exemption from clinical trial certificate and the Armour Laboratories had applied for exemption for their products.

At the top of page 2 of the Minutes there is a record of the fact that from the study that Dr. Craske had been involved in it had been determined that there was a 100% chance of contracting NANB Hepatitis whether the product used was NHS Factor VIII or commercial Factor VIII.

In the second paragraph on this page it is reported that there are two cases of the AIDS syndrome in haemophilia A patients treated with commercial Factor VIII concentrate in the UK. One might say that this is the first documentary evidence of the arrival of AIDS amongst haemophiliacs in the UK. There is also reference to the implications for Hepatitis B vaccine which, as I have explained above, it was believed might carry a risk of AIDS. This eventually turned out to be incorrect.

There follows the agenda and the Minutes for the Regional Transfusion Directors Meeting held on the 22nd September. As can be seen from paragraph 3(A) AIDS leaflets had been issued and centres had been encouraged to use differing methods of distribution. Some were being sent out with call-up cards; some were being handed to donors and others were simply being left at donor sessions for donors to pick up. The DHSS was preparing a further supply of leaflets.

Apart from this there were no other matters relevant to the present litigation discussed during the course of the meeting.

There follows the agenda and some of the supporting papers for the UK Haemophilia Centre Directors annual conference to be held on the 17th October. As will be seen the current situation regarding AIDS was on the agenda and Dr. Craske was down to deal with this. Amongst the papers circulated with the agenda were the annual returns for 1982 and, as will be seen from table 4, BPL were by this stage producing some 31% of the Factor VIII units consumed during 1982. Cryoprecipitate was down to 7%.

It is perhaps constructive to look at Fig.2 which shows the consumption of Factor VIII units over the period 1969 to 1983 and the extraordinary climb in

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consumption is very apparent. The use of cryoprecipitate commercial Factor VIII concentrate and its NHS equivalent are also charted and in many ways this graph brings together the various threads which I have sought to identify during the course of this statement with regard to the pattern of usage and the problems created by the popularity of concentrate.

The next document which was also circulated with the agenda is entitled "Haemophilia Centre Directors AIDS Investigation - surveillance of AIDS cases and patients with blood coagulation disorder". This is up-dated to the 10th September 1983. It records the details of the two cases that appeared to have emerged. One of the two had since died exhibiting the signs of classic AIDS. The other remained in reasonably good health. Both it seemed had received commercial concentrate and it was proposed that suspected batches would be followed up. The batches associated with each case were different and therefore it was concluded that each might constitute a separate "transfusion event".

The next document in this section comprises the agenda for the UK working party on transfusion associated Hepatitis meeting due to take place on the 27th September. Once again AIDS features in the agenda at Item 4. The Minutes of the meeting appear next in the file. Under the heading "AIDS" it can be seen that Dr. Craske summarised the current position. He reported that in the USA there had been 18 Factor VIII related cases although others were being investigated. Approximately 20 blood associated cases were under review. In the UK he said there had been a very low number of cases and these seemed to be mainly "imported" from the US. He mentioned that two of these cases were in haemophilia A patients.

On the third page of the Minutes there is reference to the AIDS pamphlet. Clearly the effectiveness of the pamphlet depended partly on how it was distributed and partly on the integrity of the donor. It should be remembered that at this stage we had no test for AIDS. On page 4 under the heading "Non-specific tests for AIDS" there was some discussion of surrogate tests which might be employed but no firm conclusion was reached. There was a report on Dr. Gunson's attendance at the Council of Europe AIDS meeting. The recommendations set out in paragraph 4.3 of the Minutes on page 4 were fairly straightforward. They were to aim for national self-sufficiency in blood and products and to aim at minimising cross-border transfer of blood stock. It was suggested that there should be an avoidance of the use of coagulation factor products made from large plasma pools and recognition of the fact that this would

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pose problems in the UK due to considerable product losses during the quality control procedures. This time our product loss during the process was somewhere in the region of 25% and I suspect that this figure was higher because our quality control procedures were more stringent than in some other countries. **[Can you expand on this?]**. Nevertheless it was suggested that smaller pools might be used in relation to patients with "low immunity" eg babies or "infrequent users" eg mild haemophiliacs at operations. It was also suggested at the Council of Europe meeting that information on AIDS should be provided to all donors so that high risk donors could exclude themselves. In addition there was a suggestion that physicians and selected recipients should be informed of the potential hazards of haemotherapy so that blood (or its products) would not be given unnecessarily. It must be remembered that up to a point there was scope for limiting or avoiding the use of concentrate. For example, a mild haemophiliac might be treated with cryoprecipitate or simply have the operation he was due to have postponed whilst the risks existed. I think however it is fair to say that by this stage severe haemophiliacs, who had consumed large quantities of Factor VIII, much of it from commercial sources, were almost certainly infected with HIV and there was little purpose (as events turned out) in damage limitation where they were concerned.

OCTOBER:

The first document in this section comprises the Minutes of a meeting of the MRC working party on AIDS which took place on the 10th October. This particular group had just started its work. There were no representatives of the transfusion centres or any member from BPL sitting on the working party but the DHSS were represented and in fact I recollect that it was a DHSS initiative to get the group started. The terms of reference for the working party are set out in paragraph 2 and in essence comprise the review of scientific knowledge and research on AIDS in the UK and abroad, the encouragement of contact and co-operation between research workers in the field and the provision of advice to the Medical Research Council on the current state of knowledge in the field and on topics for research. As is apparent from paragraph 3(a) entitled "Clinical" there was difficulty in establishing a marker or markers which would identify an individual as a sufferer. Under the heading (See "Aetiology") it will be seen from the comments recorded there that there was still doubt as to whether HIV, as it became known somewhat later, was a totally new virus or a familiar one that had developed new properties. It will be seen that there is mention of retroviruses

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(HIV turned out to be a retrovirus) and reference also to HTLV which was the original description given to the HIV virus identified in the United States. As will be seen from paragraph 7 the DHSS were effectively identified as having a liaison role between national and international groups and from paragraph 9 that there were three specific grant applications for investigative and research work in the area of AIDS which were reviewed. The working party did not have the power to approve grant applications, merely to comment upon them. You can see that there various applications were passed on to the Systems Board for consideration.

[There follows a letter from myself to Dr. Barbara dated 11th October, commenting upon the draft Minutes of the UK working party on transfusion associated Hepatitis. I mention in that letter the possibility that a test like TPHA might be performed on source plasma at the Transfusion Centres in an attempt to identify donors at high risk to AIDS - can you explain what TPHA is? There is reference to BPL possibly "requiring" this sort of test to be performed on source plasma. What became of this tentative proposal?]

There follow some detailed comments on the Medicines Inspector's Report of the July 1983 visit. These were prepared by Mr. Mallery and are fairly detailed. They are of limited relevance for the purposes of the litigation but again demonstrates the continuing involvement of the Medicines Inspectorate in the up-grading of BPL and it will be seen from the following document, a letter of the 13th October 1983 from Mrs Gibson to the Secretary of CBLA, that CBLA were provided with a copy of the report arising out of the inspector's visit between the 28th July and the 3rd August in light of the fact that the CBLA was now responsible for remedial measures.

There follows the agenda and the Minutes for the meeting of the CBLA Central Committee for Research and Development in Blood Transfusion working group on AIDS which took place on the 14th October. This was the first meeting of the group since it was established and it was noted that a few days earlier the MRC working group had met and given that Professor Bloom was a member of the CBLA Research and Development Committee as well as sitting on the MRC working group on AIDS. It was thought that he might usefully form the link between the two.

In paragraph 3 of the Minutes there is reference to the leaflet "AIDS and how it concerns blood donors" and to the distribution of this by regional transfusion

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centres. Unhappily (but fairly typically) there seemed to be no co-ordinated approach as to how the leaflet was circulated. Some sent leaflets out the donor card/letters, others had them available at sessions. My own feeling was that it was all a bit amateurish and I expressed the view that persons experienced in marketing/advertising would be able to give advice on getting the information to the public and I said I thought their methods might be more effective.

It can be seen from paragraph 3.1.2 of the Minutes that the use of surrogate tests was discussed. The general view of the meeting was that it would be preferable to investigate the use of anti-HBc screening rather than TPHA. [Can you explain the difference between the two]. [The Minutes do not really record any conclusion as to what was to be done about surrogate testing. As far as you were aware, what work was done in this area, what conclusions drawn and what would have been required to introduce surrogate testing?].

At paragraph 3.2.1 of the Minutes there is reference to the use of plasma pools containing small numbers of donors and I explained the investigations which were currently being carried out in this regard at [PFL]. The use of small pools appeared, on the first occasion we used the product to treat patients at Oxford, to have the advantage of not passing Hepatitis NANB to the recipient. However, whilst the experiment started well it finished badly and all our subsequent attempts to minimise infectivity by using small pools on these patients failed and they all became infected with Hepatitis NANB. The Minutes state:-

> "If one could extrapolate from results with respect to non-A, non-B Hepatitis to those which may be expected for AIDS the concept of small donor-pool material, with a group of donors where there was a greater chance to obtain more information, might have considerable advantages. It was noted, however, that this would, if implemented, require a reconsideration of plasma supply for self-sufficiency in blood products".

[Although the Oxford experiment later proved that small pools were no protection against Hepatitis NANB what further consideration was given to the use of small pools to assist in relation to AIDS? In hindsight it would seem Hepatitis NANB was so prevalent that no one was safe and the small donor pool offered no protection. However, infection with AIDS at least amongst the English/Welsh donor base appears to have been very markedly lower and small pools probably would have afforded protection - what is the position in this regard?]

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Lastly, it will be seen on the fourth page of the Minutes that I made reference to dry heat treatment of Factor VIII and Factor IX with regard to non-A, non-B Hepatitis. I was referring to US work which had been published when I said that dry heat treatment of Factor VIII and Factor IX had not initially been encouraging from the studies on chimpanzees.

There follows the Minutes of the meeting on the 17th October of the Advisory Committee on the National Blood Transfusion Service. This was chaired by Dr. Harris, the Deputy Chief Medical Officer at the DHSS. At paragraph 15 there is reference to the redevelopment of BPL and that this was on schedule and the project costs were fully in hand. Subject to what I say below this was at the time broadly correct but of course the timetable and costs later spiralled. There was discussion (see paragraphs 16 to 19) of the need to dramatically increase the supply of FFP if self-sufficiency was to be achieved. I explained at the meeting that we had mounted a campaign to make the Regional Health Authorities fully aware of the role of BPL and the long term benefits to the authorities of immediate investment in plasma procurement **[can you give details of this?]** and the DHSS representative said that they would discuss CBLA what assistance might be given by the Department in reaching RTO's **[who are these?]** In fact, this assistance never came.

Beginning at paragraph 27 of the Minutes there is reference to the work of the CBLA Central Research Committee on blood transfusion and haematology which had just been established. It was explained that at the first meeting in June the committee had set up the working group on AIDS and that the discussions in this group had centred on two main topics (1) the use of surrogate tests and (2) measures which might be taken to minimise the risks following the transfusion of blood products prepared by pooled plasma. With regard to the former it was stated, correctly, that there was no test for AIDS but that certain tests had been shown to give positive results with greater frequency in AIDS patients. There were limited studies being undertaken and a survey of two studies, one at Bristol and one at North London was to be carried out. [What were these studies **concerned with and what did CBLA do in relation to them?]** As to the latter we were at that stage engaged in the small pool experiment which it was thought, if successful, might lead to it possibly being employed as a safeguard in relation to AIDS.

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There follows a copy of the agenda for the forthcoming meeting of the Central Committee for research and development of CBLA which was due to take place on the 7th November and then the agenda for the meeting of the advisory committee on the National Blood Transfusion Service due to take place on the 17th October. [We do not appear to have the Minutes of this meeting although there were reports (oral) on AIDS and CBLA research - can we obtain the Minutes?].

The papers appearing immediately behind the agenda are I think documents which were circulated with the agenda. The first relates to the regional purchase of commercial blood products. The paper is not particularly relevant save possibly that at paragraph 8 under the heading "Current experience" there is once again some emphasis placed on the fact that clinicians treating haemophilia patients had the freedom to prescribe the products they considered were appropriate and there was concern about compromising their clinical judgment in circumstances where a Region decided to purchase, on a bulk basis, a particular make of Factor VIII.

Also amongst these papers will be found a table setting out the supply of FFP to BPL which showed that the pro-rata system was beginning to have an effect. In 1982 we had received 127,000 kg whereas in the first six months of 1983 we had already received 73,000 kg. Annualised this showed a reasonable increase over the previous year.

The next few documents in the file comprise copies of papers which were circulated at the meeting of the UK Haemophilia Centre Directors which took place on the 17th October. **[We do not appear to have the Minutes of this meeting - where are they?]**

Amongst these documents will be found a report on the work of the UK Haemophilia Hepatitis working party.

At paragraph (a) under the heading "Prospective studies of Hepatitis in infrequently treated haemophiliacs" there is repetition of the fact that the results of Dr. Craske's work confirm the risk of contracting NANB Hepatitis was 100% on first exposure whether NHS or commercial Factor VIII was used.

At paragraph B under the heading "Evaluation of the infectivity of heat treated Factor VIII using a protocol based on the prospective study, since no tests for non-A, non-B Hepatitis are yet available" there is reference to the need to

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encourage Haemophilia Centre Directors to participate in the study. The report states:-

> "An internationally based trial was started with Travenol product, and then Armour product will be available for evaluation in the next 3 months. However, the problem of AIDS has over-shadowed these developments, as the ethical problem of exposing mild haemophiliacs to commercial material must be considered by each director."

This really identifies quite clearly the problem which was faced at that time. There was an ethical dilemma which I have touched on earlier but aside from this the momentum of AIDS very quickly eclipsed the idea of carrying out detailed studies on products which might potentially offer protection.

The next document sets out the factors to be considered in the selection of Hepatitis reduced products for clinical trial and is a document which has been commented upon earlier having been first written by Dr. Craske in July.

Next will be found tables setting out the incidence of acute Hepatitis in haemophilia patients. As will be seen from Table 1 there were 206 cases out of a total of 4,060 patients treated ie just over 5% of patients treated developed acute Hepatitis.

There follows a paper on the subject of the Hepatitis B vaccine which was under trial at Oxford about this time and which, as I have previously indicated, came under suspicion for a while as possibly being infected with AIDS. The remaining papers in this section are not particularly important.

NOVEMBER:

The first document in this section comprises the Minutes of the Central Committee for Research and Development meeting that took place on the 7th November. Paragraph 11 refers to the working group on AIDS in relation to blood transfusion. There is reference to the MRC working group and to action taken by the DHSS in respect of community health councils **[what was this?]**. At paragraph 11.2.2 it is stated that the committee welcomed the action taken with

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respect to the investigation of the use of surrogate tests and the committee looked forward to Dr. McClelland's report. **[What was this report].**

At paragraph 11.2.3 of the Minutes there is a record of my reporting to the committee that a dry heat treated product (this was Factor VIII) was available at BPL and that I had approached the haemophilia directors as to how they wished to proceed with its use. What I had done was to phone up some of the directors, I spoke to Dr. Gunson, Dr. Delamore (Sheffield) and Dr. Jones **[anyone else?]** to advise them that we now had a product available for trial. The Minute continues:-

> "Professor Bloom commented that the product obtained from UK plasma was more acceptable for use in a trial than the imported products. The question of embarking upon a trial of the BPL material was discussed and the difficulties with respect to the limitations of available patients was noted. However, the fact that within a relatively short time the commercial companies may introduce such a product which, with its attendant publicity may place the haemophilia directors in a dilemma with respect to the treatment of their patients, led the committee to recommend to the CBLA that the BPL heat-treated Factor VIII should be subjected to clinical trials as soon as possible".

This was in fact what we endeavoured to do. A protocol was developed for discussion and agreement with the Haemophilia Centre Directors but this took a long time and in the meantime those Haemophilia Centre Directors I approached showed no immediate enthusiasm to use the new BPL product on a trial basis and our efforts in this regard culminated on our securing 3 patients only **[where were these?]** on which to try out the new heat treated product. In the event our efforts to obtain a proper trial of the product through 1984 were unsuccessful and the problem of AIDS developed to the point where by the last quarter in 1984 it was clear that, notwithstanding the veracity of the information obtained from the treatment of the three patients who agreed to use heat treated product in 1984 we would have to introduce the heat treated product even though we did not know whether it worked for Hepatitis NANB or HIV.

The next document in this section is a letter from me to the DHSS dated 11th November in which I address the statement in the Minutes of the Advisory Committee on the NBTS that the redevelopment of BPL was on schedule and the

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project costs were fully in hand. I commented that what I had said at the time was that, in line with the fast track method being used by Matthew Hall and agreed as necessary by CBLA and the DHSS, project costs were under control with a regular report being made to the DHSS. I went on to say that during discussion two points were made, the first being that some escalation in capital costs due to process equipment were being considered against an ultimate function to achieve revenue savings in manufacturing, and the second being that no doubt the Chairman of CBLA would be discussing the BPL redevelopment with Ministers at their meeting in November. In short, I thought that the comment attributed to me in the Minutes was somewhat too emphatic.

There follows a memorandum from Mr. Mallery to myself dated 22nd November which again deals with points of detail in relation to the inspector's report on the July/August visit.

Next are the Minutes of the CBLA meeting on the 23rd November 1983. **[We do not appear to have seen any CBLA Minutes prior to this - where are these Minutes?]**.

At paragraph 91.1 it is recorded that Dr. Harris reported that the Chairman of the MRC's committee on AIDS had welcomed co-operation with the CBLA's working group on AIDS and it had been agreed that Minutes of the two committees meetings would be exchanged. It was also noted that Dr. Gunson would be invited to meetings of the MRC committee at times when his expertise could be valuable.

There is reference at paragraph 92.3 of the Minutes to the problems which we had experienced during 1982 which led to a shutdown of production on Factor VIII at one point. The Minutes state:-

> "Dr. Gunson raised a question with regard to the hold-up last year of Factor VIII production and whether or not it had been recovered as many RTC's had to buy its supplies during this period. Dr. Lane said that the requirement for Factor IX was now occupying time and plant which could otherwise be used for recovering the position on Factor VIII; he could thus not guarantee that the Factor VIII shortfall could be made good during the next year".

[This appears to suggest that there was a marked knock-on effect from the shut-down of production in 1982. What were the problems with regard to Factor IX? What was the extent of the shortfall during this period? Was it ever recovered?]

At the top of page 5 of the Minutes it will be seen that CBLA endorsed the recommendation of the Central Committee for Research and Development that clinical trials of the heat treated Factor VIII which we had developed at BPL/PFL should commence as soon as possible. As I have explained above, our preparedness to manufacture this and willingness to make it available was not matched with any real enthusiasm from the Haemophilia Centre Directors to use it.

DECEMBER:

The first item in this section is an article reproduced from the British Medical Journal for the 10th December 1983. The title of the article is "Non-A, non-B Hepatitis after transfusion of Factor VIII in infrequently treated patients". This confirms what Dr. Craske (one of the authors) had been saying in the various meetings on the subject ie that where non-A, non-B Hepatitis was concerned there was no difference between the infectivity of NHS or commercial concentrate. **[Where is the rest of the article].**

Next in this section is a letter sent by the director of the Centre for Infectious Disease, Atlanta (CDC) to Dr. Watt at PFC in Scotland arising out of his participation in the WHO meeting on Acquired Immuno Deficiency Syndrome. **[When did this take place and did anyone from BPL or any regional transfusion or haemophilia Centre Directors attend?].** The letter encloses a draft of a paper which attempts to assess the situation in the world as at December 1983. The paper itself is of general interest [and would have been freely available to those sitting on the various AIDS working parties at the time].

The next document in this section is dated the 14th December and is a memorandum from Dr. Smith to myself, Dr. Harvey and Dr. Snape. This relates to the new heat treated Factor VIII which had been developed. Dr. Smith points out that PFL aimed to produce the first batches of dry heat treated Factor VIII at the end of January 1984 for projected release at the end of February. As I had previously indicated the trial idea faltered but the memorandum also makes reference to our possible use of haemophilia dogs as part of the testing regime

[did this ever happen?] and the possibility that Dr. Rizza who had accumulated patients for the small-panel Factor VIII experiment at Oxford might be willing to use a heated Factor VIII on a similar basis without a clinical trial certificate or formal exemption **[did this ever happen? If not, why not].**

The next document in the section is my memorandum to Dr. Smith in reply to his of the 14th December. In that memorandum I approved the idea of experimental work in haemophilia dogs and asked him to produce a full statement of costs and more programme details.

UNDATED:

The first item in this section is a paper which I prepared entitled "Plasma supply - National Blood Transfusion Service" and is designated RTD(83)7 **[track down the regional transfusion directors' meeting where this paper was presented and cross-refer].**

The paper was intended to bring all the threads together (that is to say the information regarding BPL's development, likely future capacity and requirements for plasma to inform Regional Transfusion Centre Directors of what was required for the future. As will be seen from page 10 of the paper to develop the national projections further a document was in preparation **[where is this - who produced it?]** which asks regional transfusion directors to draw up a five year plan aimed at supplying regional blood transfusion service needs and the projected plasma supplies required for BPL. In this way we hoped to galvanise Regional Transfusion Directors into producing plans which would ultimately lead to sufficient FFP for BPL and to think now about the cash implications of this so that appropriate provision could be made.

I would draw attention particularly to Figure 3 which shows what was required in terms of FFP to supply a maximum input of 444 tonnes using a mixture of SAG.M and plasmapherises to boost the ordinary supply of FFP.

There follows another paper which I prepared in 1983 for the Travenol symposium for the National Blood Transfusion Service. This dealt with the value of SAG.M systems in the provisions of plasma products. Again, the idea was to educate the service in the advantages of using SAG.M which, if accepted by clinicians,

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would have a major impact on the plasma procurement by NPTS and of course supplies of FFP to BPL.

The next document in this section is an important one and is entitled "Proposal to develop a "Hepatitis-safe" Factor VIII concentrate." This is Mrs Winkelman's proposal which she was asked to prepare by Dr. Smith as a matter of urgency back in July. The proposal is undated but was presumably delivered within the timescale required by Dr. Smith. Dr. Winkelman's conclusion was that heat inactivation looked the most promising approach for research because:-

1. It was likely to be of broad application ie conditions which inactivate the exceptionally robust HB virus were likely to inactivate other blood-born viruses.

2. The treatment was cheap, relatively easily controlled, recorded and scaled up with precision.

3. There was extensive experience with other successful pasteurised proteins such as albumin which offered regulatory and clinical acceptance than the use of novel or unfamiliar chemical virucide.

The fractionation of plasma from small pools of "accredited" donors was also an option looked at by Mrs Winkelman (see paragraph 2.4). **[Mrs Winkelman states that schemes for comprehensive small-pool fractionation have already been proposed for the new BPL, and some of the possibilities are summarised in paragraph 2.4. What happened with regard to this idea?].**

As will be seen at paragraph 3 of her proposal Dr. Winkelman expanded on the idea of pursuing research into inactivation of virus by heat and I gave the go-ahead for this research once I had seen the proposal. **[Is this formally recorded anywhere?].**

The next document in this section is entitled "Working group on AIDS in relation to blood transfusions". It is undated and I believe it was a paper produced for the CBLA working party on AIDS by someone from Scotland. I am not sure whether it is a 1983 document. **[There is reference to screening tests having been developed by Dr. Richard Tedder in collaboration with Dr. Robin Weiss based on competition radioimmunoassay. When was this test developed. What use was made of it?].**

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1984

JANUARY:

The first document in this section is a memorandum from Dr. Smith dated 3rd January 1984 headed "Proposal for special preparation - 8CRV pasteurised dry". At that time it was clear that Factors VIII and IX had been heated by means of pasteurisation and dry heat. There was an active programme during 1983 at a time when HIV and its association with haemophiliacs was only just becoming a real entity. There is a certain element of urgency evidenced in the BPL literature. This was not, however, the case amongst the various Committees comprising National Blood Transfusion Service Representatives and Haemophilia Centre Directors, the one exception being Dr. Craske. By the end of 1983 we had a heat treated product and we recommended to the Research Committee that the BPL product be the subject of clinical trials. We were only a matter of months behind the schedule adopted by companies such as Travenol. We were adopting a proper approach regarding the new heat treated products: there may have been no validity in claims that HIV was inactivated by heat. The proposal contained in Dr. Smith's memorandum is for 8CRV pasteurised dry. We tried to set up a protocol for clinical trials of heat-treated intermediate concentrate but this had still not been done by the end of the year. However, as of summer 1984 we had 8Y and the need for a heat-treated intermediate product had passed. At the time Dr. Smith's memorandum was written, it was still nothing more than a presumption that HIV was a virus. We were therefore operating in the dark.

It was "inferred" from publications, patents, discussions etc that Behringwerke were heating product in solution with glycine and sucrose and that both Armour and Hyland were dry heating. Hyland had taken the decision in May 1984 to issue only dry-heated Factor VIII in future although heating had almost certainly been introduced to combat NANB Hepatitis. **[Do we have Hyland's literature?]**. It was only an "unsupported hope" that the transmissible agent of AIDS, if any, was heat sensitive. Dr. Smith comments in paragraph 1.1 that:-

> "Faced with the understandable anxieties of patients over AIDS and the insinuations of commercial producers, the Haemophilia Centres feel the need to offer at least some hope that NHS products will carry a reduced risk of transmitting AIDS".

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Paragraph 1.3 is also worthy of comment. It was assumed that virtually all patients receiving either commercial or NHS Factors VIII or IX for the first time would contract infection with NANB Hepatitis. Although the incubation period and severity would differ, the long-term sequelae were equally feared. Turning to paragraph 1.5, reference to "our late start" is not to be misunderstood. The documentation for 1982 and 1983 indicates our concern over the desirability of heat treatment and the need to do it properly. It had been generally agreed that the product should not be put at risk for NANB Hepatitis inactivation. However, for AIDS the picture was very different: the virus was perceived as an undesirable element in the product. Dr. Smith's aim for the heat treatment of 8CRV was to subject it to the maximum temperature for the maximum time, compatible with a less than 10% apparent loss of Factor VIII activity and the appearance of no other undesirable characteristics. The results of Dr. Smith's tests showed that the loss of Factor VIII when heating at 60°c for 72 hours, was acceptable. However, losses at 70°c were heavier and such treatment had a significant adverse effect on solubility. It was known that heating at 60°C did not kill the NANB Hepatitis virus and therefore higher temperatures were required. However, the effect of heating at 80°c was to lose more than 25% of the Factor VIII **[activity]**. Preliminary work had also been carried out in Edinburgh to show that higher temperatures were needed. Dr. Prince in New York considered that heating at 68°C was only marginal. However, most people found it impossible to subject their existing products (with limited tolerance to heat or pasteurisation) to a more severe level of heat. At the top of page 5 Dr. Smith says that in the absence of T/t profiles for the inactivation of HB and NANB Hepatitis, 8CRV should be heated for 72 hours at 60°c. **[What are T/t profiles?]** Dr. Smith wanted our product to be tested by Dr. Rizza by the end of February 1984, to see whether it had a normal half-life in Vivo **[what exactly does this mean]**. There were fewer problems experienced with the heating of Factor IX, because of the lower levels of fibrinogen.

The next letter on file is dated 3rd January 1984, to Dr. Thomas Reeder in the Liver Unit at the Royal Free Hospital. He was conducting a lot of work into Hepatitis at the time.

The next document is a very lengthy report I prepared on the BPL covering the period April 1982 to April 1983 and from April 1983 to December 1983. The report itself is dated 16th January 1984 and it was to coincide with CBLA's first year of management. The only mention of HIV is on page 39, on which I shall

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comment below. The summary to the report is set out on pages 2 and 3. Reference is made to the expenditure of £2.5 million on modernisation and extension of the existing buildings. The Minister had allocated £1.3 million for refurbishment: I had said all along that £2.5 million was required to do the minimum job. Annual Factor VIII output had doubled to 30 million iu and Regional Blood Transfusion Centres had doubled the input of fresh frozen plasma. I referred to the development of the new production building which had commenced on site at Elstree in April 1983 and said that it would cost in excess of £21 million. Reference is made in the summary to the inactivation of Hepatitis virus, but not to the inactivation of HIV. The rest of the report comprises individual departmental notes, on which I shall reserve comment. It is, however, worth looking at Table 2 on page 19 which shows the units of products despatched for clinical use during 1982/1983. There was an increase of about 4,000 units of Factor VIII over and above the figure for 1981/82. The figures on Table 5 show products despatched for clinical use during the period April to December 1983 and demonstrate a further increase in units of Factor VIII of about 18,000.

Mention is made at the bottom of page 38 of efforts made to reduce the transmission of viral diseases. In particular, it is stated that Factors VIII and IX continue to transmit NANB Hepatitis to susceptible patients (believed to be those receiving large-pool concentrates for the first time). The report also adds:-

> "There is considerable interest in the possible transmission of Acquired Immune Deficiency Syndrome through intravenous concentrates".

Efforts to date had been directed at pasteurisation of Factor IX (Factor VIII presented more problems) but the report does go on to say that conditions had been established for heating concentrates in the dry state.

Whilst discussions continued as to the means of inactivating virus in Factor VIII, Dr. Smith's memorandum dated 16th January 1984 directed attention to a Hepatitis-safer Factor IX concentrate and the associated problem of thrombogenicity. Throughout this period, our approach to heat treatment was focussed on NANB Hepatitis. That was our objective. Experience suggested that it was a tough virus: if NANB could be inactivated, the treatment would affect a number of other less robust viruses. It was still not, however, known that HIV was a virus. Also, at this time we were not aware that it was weak. However, positively

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to inactivate NANB Hepatitis, we would have been pushing the product to its limit any way. Dr. Smith in his memorandum says that:-

> "We should be doing our best to get the safest concentrates to the most important patients - those seldom or never treated before and the younger patients who might benefit most from less frequent insult with infected material".

The tenth meeting of the CBLA took place on 25th January 1984. **[Where are the documents attached to the agenda?]** Following the visit of the Medicines Inspectorate **[when?]**, Dr. Harris, whilst accepting the inadequacies of the present BPL site, suggested that the main concern was to take all reasonable steps available at the present time to improve matters. The position with Scotland at that time was that John Watt was no longer director of the PFC Liberton. Mr. Smart reported that the Scottish BTS was likely to have a surplus of Factor VIII and that it may be possible to use some of their surplus stocks at the time of the BPL transition to the new factory. It transpired that Scotland had one "job lot" of 2 million i. u. which we subsequently distributed. I will comment on this later. The only other matter of note arising from these Minutes is that it was agreed to hold a special meeting of the CBLA on 22nd February 1984 to discuss research and development.

A meeting of Regional Transfusion Directors also took place on 25th January 1984. AIDS was only mentioned at that meeting in the context of the introduction of AIDS leaflets at donor session. Clearly, the Regional Transfusion Directors were not getting too excited over AIDS!

The last document in this section is the Minutes of the second meeting of the Working Group on AIDS in relation to Blood Transfusion, held on 27th January 1984. The meeting was chaired by Dr. Gunson and I was one of those present. **[Do we have Dr. McClelland's paper?]**. Consideration was given to carrying out tests to pick up markers of Hepatitis which in turn may be related to AIDS, a "fellow traveller" in the epidemiology. In other words, those in high risk groups would be identified. The cost benefit of approaching those donors implicated, was to be considered in the light of the following:- first, that AIDS was not "grabbing people by the neck" and secondly the NHS was not wishing to lose large numbers of blood donors. **[Do we have a copy of the WHO paper: "AIDS, an assessment of the present situation in the world"?]**. Very little arose out of

yes

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these Minutes, although in all fairness there was very little that the Group could do at the time.

FEBRUARY:

The first document in this section is a letter from Dr. Delamore to Dr. Gunson dated 3rd February 1984 which relates to the proposed "Northern Centres' Trial" of NHS heat-treated Factor VIII concentrate. The paper which follows is a protocol for the study of heat-treated Factorate, Armour's product. This was an indication of what the commercial manufacturers were doing by way of heat treatment. The protocol is dated May 1983.

The draft document following the WHO meeting on AIDS in Geneva was circulated to members of the CBLA under cover of Mr. Redhead's letter of 10th February 1984. **[Dr. Lane has this document at Elstree]**. The agenda for a Special Meeting of the CBLA to be held on 22nd February 1984 was circulated on behalf of Mr. Armour, on 14th February 1984. This was a special meeting on the subject of research and development. Attached to the agenda is a copy of BGRL's report. **[Where is Dr. Lane's report?]**.

On 28th February 1984 the third meeting of the Central Committee for Research and Development in Blood Transfusion took place. The meeting was chaired by Dr. Gunson and I was one of those present. The establishment of a protocol for the Northern Centres' Trials to be conducted by Dr. Delamore was reported to the meeting. There was also a report on the Minutes of the second meeting of the Working Group on AIDS, which we have seen above. Recapping very briefly, nothing much had come out of that meeting apart from the possibility of surrogate testing which it was hoped would provide significant numbers of positive results in the majority of patients suffering from AIDS. The tests used would be for Hepatitis B core antibody. At this point, HTLV antibody had been identified, but the test facilities were still very primitive. In paragraph 4.2 I reported on Dr. Rizza's study of Factor VIII prepared from pools of Plasma obtained from a panel of plasmapheresis donors at Leeds. In 18 patients, short-incubation NANB Hepatitis appeared to be absent. With Factor VIII obtained from plasma from randomly collected donations the attack rate was 100%. The implications would have been immense, in terms of the amount of plasma required, if significance had been attached to the results.

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Paragraph 4.4 demonstrates that discussions were taking place with commercial manufacturers about the implications of AIDS. However, the system of reporting the input of an AIDS patient into a donor pool was merely conducted on an informal basis.

The documents which follow, to the end of this section, form the CBLA's response to the Medicines' Inspectorate visit in August 1983.

MARCH:

On 8th March 1984, Dr. Kernoff sent me a copy of a draft paper he was to present at the Haemophilia Society Residential Seminar on 10th March. The paper is headed "Blood products and their problems". The paper touches on a number of areas of concern: heavy reliance in the NHS on imported commercial blood products; the inability of the transfusion service to meet the plasma requirements of the country; lack of co-ordination between the policy makers and those implementing the policy at regional blood transfusion service level; the emphasis placed on the collection of whole blood, rather than its separate components. Dr. Kernoff does on a couple of occasions cite the Scottish experience, by way of comparison: he says that Scotland is not dependent on imported commercial plasma products and that its administrative system gave rise to fewer problems.

Dr. Smith's memorandum of 14th March 1984 summarised the current position with regard to both small-pool and dry-heated Factor VIII product. The small-pool product was destined for particular users, who could be suitably followed-up. A batch of small-pool heated products had been used at the Middlesex Hospital in February and early March 1984. Of those batches heated, some vials of unheated product were kept back, for the purpose of quality control testing in tandem with the heated portion of the batch. This was a clinical quality control exercise. Another approach under discussion was to release half the files in a batch unheated and to bring out the remaining vials (heated) at a later stage on the same patients to complete the study.

I was requested by Mr. Armour on 13th March 1984 to up-date the CBLA on the heat treatment of human plasma products. I refer in my reply to a project file prepared for the CBLA's R&D meeting on 22nd February. **[Do we have the project file?]** I wanted more time before I put a report to the CBLA.

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The next document, prepared for the benefit of the Advisory Committee on the National Blood Transfusion Service sets out the experience of the first six months of the "AIDS leaflet". The returns for the 14 regions throw up remarkable variations in the use of the leaflets. Clearly there was no homogoneous policy to develop communication with donors and potential donors. However, we relied on a more coherent policy. By way of illustration, Tooting, the largest region, distributed a very small number of leaflets in comparison with some of the smaller regions.

Dr. Rizza sent to Dr. Cash on 23rd March 1984 a copy of the protocol for "Trials of Hepatitis reduced Factor VIII concentrate in the NHS - assessment of residual infectivity", a document produced by the Hepatitis working party. **[Do we have Dr. Cash's letter of 13th March 1984?]**

Dr. Smith's memorandum of 28th March 1984 sets out an attempt to do what was a very limited trial on heat-treated 8CRV for the potential reduction of NANB Hepatitis infectivity. Despite its limited nature, it was the only way in which a proper control on the heat-treatment process could be carried out.

This is followed by my paper prepared for the benefit of the CBLA entitled "Phased redevelopment of BPL: unresolved interim capital requirements". **[Where are the annexes?]**.

The eleventh meeting of the CBLA took place on 28th March 1984. **[Where are the attachments to the agenda?]** Dr. Harris' comments at the bottom of page 2 in relation to plasma supply, are characteristic of the shambles at that time. Nothing else of note arose from the meeting with the possible exception of the record of the fact that Mr. Fowler, MP, had laid the foundation stone of the new factory at BPL on 23rd March 1984. It was believed that the factory would be due to open in two years' time. **[Do we have a copy of Mr. Fowler's speech?]**.

A memorandum was circulated to all UK Haemophilia Centre Directors on 29th March 1984 setting out details of the products currently available. Three companies were using dry heat treatment for their products and one company was producing a wet heat product. Mention is also made of trials conducted on a German product manufactured by Behringwerke which was known to inactivate Hepatitis B but gave rise to considerable loss of yield. On the NHS side, NHS Factor VIII was available from specially selected donor panels monitored for abnormal liver function tests, Hepatitis etc. One brand of heated NHS Factor

VIII was shortly to be available from PFC, Edinburgh and a second, manufactured at Elstree, was to be available later in the year.

Clinical trials had only been completed on one product, the "Hemofil HT" Factor VIII, which was subjected to "dry heat" treatment. On first exposure to the product, there was still a 63% attack rate of NANB Hepatitis and I recall there was more or less a 100% attack rate on second exposure. The only mention of AIDS in respect of these products is in relation to the putitive risk from plasma imported from the USA.

APRIL:

The first document under this heading is a note prepared by Dr. Gunson headed "Surveillance of AIDS in relation to Blood Transfusion". A meeting had taken place on 4th April between Dr. Gunson and representatives from the CDSC (Communicable Disease Surveillance Centre). There had been no obvious liaison for reporting AIDS to the PHLS or to contacting the NBTS where a patient diagnosed with AIDS has stated that he or she received a transfusion of blood or blood products. The purpose of the meeting, therefore, was to develop the liaison and to set out the policy and procedure for implementation.

The agenda for the ninth meeting of the Advisory Committee on the National Blood Transfusion Service was circulated on 6th April 1984. The meeting was scheduled to take place on 10th April 1984. **[Where are the attachments? Do we have the Minutes?]**.

The meeting of the Regional Transfusion Directors took place on 11th April 1984. AIDS was the subject for discussion at Item 4(c) of the Agenda. The importance of discouraging high risk groups from donating blood was recognised, together with the particular need to carefully assess plasmapheresis donors.

The next document is Dr. Wallington's application to the MRC for support for a research project aimed at evaluating screening tests for antibody to Hepatitis B core antigen as a screen to exclude blood donors who present a high risk of transmitting AIDS. Under the heading "Purpose of proposed investigation" Dr. Wallington states that the causative agent of AIDS is unknown. However, a number of non-specific abnormalities are found commonly in AIDS cases and healthy people belonging to groups where the risk of developing AIDS is high.

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Antibodies to Hepatitis B core antigen (anti HBc) are the commonest abnormality. He continues:-

> "The purpose of this project is to evaluate whether this identifies blood donors belonging to groups where the risk of developing AIDS is high and therefore the risk of transmitting AIDS is high".

Under the next heading, Dr. Wallington attempts to identify those high risk groups whose lifestyle exposes them to special risk. He adds that although the cause of AIDS is unknown, its epidemiology suggests strongly that an infectious agent is responsible. The idea of testing for anti HBc was that it could be an indication of past as well as present infection. **[Do we have the articles referred to in Appendix 1, page 7?]**.

On 19th April 1984 Dr. Gunson sent me some interesting news briefs reproduced from the American Association of Blood Banks (AABB). The news briefs are dated April 1984. It is interesting to note that the Americans were conducting similar discussions on the use of anti HBc testing as a surrogate marker. However, opinions were divided: Aaron Kelner of the New York Blood Centre said:-

> "We are not convinced that AIDS is transmitted by blood transfusion ... the evidence is still very shaky".

This is a very interesting comment to be made as late as April 1984. On the second page of the article under the heading "AIDS update" the last paragraph is worthy of particular mention. It was reported that there was an apparent decrease in the use of Factor VIII by 30% with a corresponding 30% increase in cryoprecipitate use. However, at the same time it was reported that there was a foreign case of AIDS in a haemophiliac who had been treated only with cryoprecipitate.

MAY:

The first document in this section is the Minutes of the 14th meeting of the UK Haemophilia Centre Directors held on 17th October 1983. These were circulated by Dr. Rizza on 9th May 1984.

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Dr. Snape attended the meeting on my behalf. It was reported on page 9 of the Minutes that we were looking at methods for making Factors VIII and IX safer, with regard to the transmission of Hepatitis. We hoped that not more than 10 per cent to 15 per cent of the Factor VIII yield would be lost in the making of the virus free products. It was further agreed at the meeting that the BPL should go ahead on a limited basis with a new product for clinical trial. The trial would be on a named patient basis. Dr. Craske then reported on the use of commercial "virus free" products. It was clear at that time that the problem was "far from solved" and there was an urgent necessity to follow-up patients who received these products. Dr. Chisholm, from Southampton, commented that certain patients refused to use commercial Factor VIII concentrate, in the light of the AIDS scare. Professor Bloom replied:-

> "There was no need for patients to stop using the commercial concentrates because at present there was no proof that the commercial concentrates were the cause of AIDS".

After some discussion, it was agreed that patients should continue to be treated with NHS or commercial concentrates and that they should not be encouraged to change over to cryoprecipitate. Reference is also made by Dr. Craske to two cases of AIDS in haemophiliacs in the United Kingdom. He was proposing a form of follow-up for three years of patients who had received "suspect batches" of concentrate. **[MOVE TO OCTOBER 1983 PART OF THE PROOF].**

The next document sets out the results, updated to 15th May 1984, of the patients who had received special batches of Factor VIII through the study being conducted in Leeds **[plasmapheresis donors?].** The results showed that even with small, special batches, patients contracted NANB Hepatitis. There was therefore no reason to commit huge resources into small pool sizes. **[Note: patients identified by name].**

The next documents in this section are the agenda and the Minutes for the 12th meeting of the CBLA held on 23rd May 1984. **[Do we have the submission to the DHSS and the documents referred to in the agenda?]** It was reported to the CBLA that a trial was to take place in the Northern Centres, of BPL heat treated Factor VIII and that it was hoped to commence this trial by late summer. The protocol for the trial had now been agreed. The key point on page 4 of the Minutes emerges during the reporting of Dr. Wallington's application to the MRC for a grant (for performing non-specific tests). Dr. Gunson reported that it now

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seemed most likely that an HTLV virus was the causative agent of AIDS. Collaboration with the MRC working party on AIDS was the next move, looking for antibodies against the "AIDS agent".

The next document in this section is in fact the letter from Dr. Tyrrell, Chairman of the MRC working party on AIDS, to Dr. Gunson, referred to in the Minutes of the meeting above.

The 9th Meeting of the Advisory Committee on the National Blood Transfusion Service was held on 10th April 1984. The meeting was chaired by Dr. Harris and I was one of those present. AIDS was the subject of discussion under paragraph 10. Amongst the reported cases of AIDS, reference is made to two haemophiliacs. Mention was made of the AIDS leaflet, directed at blood donors. The six month trial of the leaflet had been conducted at the discretion of the Regional Transfusion Directors, but the Committee now recommended that Ministers should issue the revised leaflet (in the course of preparation) with a donor call up card in all regions. However, greater significance should be attached to paragraph 12, where Dr. Harris assured the meeting that the DHSS was liaising closely with the MRC, CBLA and HEC **[Health Education Council?]** on the subject of AIDS.

The question of plasma supply to the BPL was also discussed at the meeting. In mid 1983 Regional Transfusion Directors had been confident of increasing the supply of plasma to BPL, to attain a level of self-sufficiency. However, a recent survey of Regional Transfusion Centres made it evident that because of resource constraints within the regions directors were now "less optimistic" of attaining their targets. By 1984 the issue of plasma supply was clearly beginning to cause tension.

[ACR has removed document headed "Cost commentary - May 1984"]

JUNE:

The first document in this section is a memorandum from Dr. Smith dated 1st June 1984. This is a status report on the stocks of small-pool Factors VIII and IX in late May 1984.

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The letter from Mr. Perry, Scottish National Blood Transfusion Service to Mr. Pettet dated 8th June 1984 relates to the arrangements for the "decanting" of excess stocks of PFC, Edinburgh Factor VIII to the CBL for subsequent distribution to Regional Transfusion Centres in England and Wales. The first position taken by the Scots was to supply a total of between 7 million and 9 million iu to the BPL. However, it was stressed that a "regular supply commitment" could not be made. The manuscript notes on the letter are in Norman Pettet's handwriting.

The "with compliments" slip is written by Dr. Smith and relates to the protocol for the Northern Centres' Trial.

Dr. Smith's letter of 22nd June 1984 to Dr. Delamore enclosed the draft protocol for the "Northern Centres'" study of "Hepatitis-reduced" Factor VIII concentrate, 8CRV"H". Reference is made in his letter to the small pool trials conducted at the Oxford Haemophilia Centre. The results showed that the infectivity of those batches for NANB Hepatitis was already significantly diminished. One batch given to two patients did not appear to transmit Hepatitis and two other batches had given less than the expected 90% to 100% attack rate. However, it was not possible to attach too much significance to these results, because of the variability of batch performance. The protocol is a revision of Dr. Craske's model protocol dated 22nd March 1983.

A special meeting of the CBLA took place on 27th June 1984 to discuss, in the main, the redevelopment of the BPL [ACR has removed earlier documents relating to "the fast-track system" of building].

JULY:

The first document in this section is a letter from Dr. Craske to Dr. Smith, dated 5th July 1984. The letter is important in that it conveys the fact that heat treatment was not at that time creating enormous confidence. None of the heat treated commercial products were providing an indication that NANB Hepatitis was adequately dealt with. He reports in the letter that two patients first treated with Armour heat treated Factor VIII contracted NANB Hepatitis 2 to 3 weeks after their first transfusion with the material. He continues:-

"I do not see that the information at present available suggests that we should not proceed with the study of NHS "Hepatitis-reduced" Factor VIII material, but I thought that you should be aware of the results of the use of the Armour material. This case is being reported to the Medicines Division of the DHSS and the relevant batch of Armour Factor VIII has been withdrawn from the trial".

The next letter is from Dr. Smith to Dr. Colvin at the London Hospital. The letter relates to a specific patient who had received NHS heated Factor VIII concentrate. This was the kind of case that Dr. Smith was examining to establish the incidence, or lack thereof, of NANB Hepatitis from NHS heat-treated concentrates. [Query relevance and note: named patient].

A meeting of Regional Transfusion Directors took place on 11th July 1984. Even at this time, AIDS had very little prevalence in the Minutes. It was reported that Dr. Gunson had approached the Medical Defence Union who had advised that if a patient had been given "at risk" blood, it was sufficient for the general practitioner to be informed in confidence.

Dr. Smith up-dated me by way of a memorandum on 11th July 1984 on the cases where individual patients had received NHS heated concentrate. One of Professor Stewart's patients had passed the 12 week mark without showing any signs of Hepatitis. Another patient, of Dr. Colvin, was to be followed vigorously over the next two months. Dr. Smith thought the results were encouraging, particularly in the light of "poor performance from competition".

The 13th meeting of the CBLA was held on 18th July 1984. **[WE ARE MISSING THE ATTACHMENTS TO THE AGENDA]. [DO WE HAVE A COPY OF THE BPL BROCHURE RELATING TO THE LAYING OF THE FOUNDATION STONE CEREMONY?].** Under the heading "Any Other Business", I reported on the work being carried out as a result of the identification of the HTLV virus as the causative agent of AIDS.

[IS DR. LANE'S INVESTMENT APPRAISAL FOR THE BLOOD PRODUCTS MANUFACTURING UNIT, RELEVANT].

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AUGUST

The first document to be noted in this month is a letter from Dr. Harris dated 31st August which was a circular addressed to a number of people including myself, inviting participation in a meeting to take place in October to consider the implications of two recent developments in relation AIDS. These were the recent isolation of HTLVIII and LAV (it was still a little unclear at that time that these were in fact just different names for the same virus) which appeared to be closely related to AIDS and the development in the United Kingdom of a radioimmunoassay technique for the detection of the HTLVIII antibody. A meeting was really intended to talk about the introduction of testing for HIV. The meeting was to be convened under the Chairmanship of Dr. Michael Abrams who was head of the Department's Medical Division dealing with Scientific Services.

The remaining item in this section which is of significance appears to be one of a number of appendices to the annual Haemophilia Centre Directors' Report. This one is entitled "Incidence of Hepatitis in Patients with Congenital Coagulation Defects treated by U.K. Haemophilia Centres during 1980-83". It is interesting to note from Table 1 that over the period in question, some 258 patients, amounting to some 5.6 per cent of those treated, developed acute hepatitis and that by far the highest proportion of cases of hepatitis were of the NANB variety. This is a significant number of acute hepatitis cases demonstrably linked with hepatitis NANB and was one of the reasons for the increasing interest in the very early 1980's in the idea of heat treatment, notwithstanding the very effective screening out of hepatitis B during the same period.

SEPTEMBER

The first document in this section (which is very poor copy), gives some details of patients who had received special batches of Factor VIII. **[This is part of the Oxford small pool experiment and, as I have indicated previously, was an experiment which in the event proved unsuccessful in protecting recipients from hepatitis NANB].**

In his memorandum to me of the 6th September, Dr. Smith made some comments arising from the Haemophilia Centre Directors Hepatitis Working Party meeting which took place on the 5th September. He refers to the fact that hemofil HT had apparently been unsuccessful in eradicating hepatitis NANB through heat

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treatment, and had recorded a 63 per cent attack rate in European trials. He commented that a similar heat treated product from Armour had resulted in three cases (out of three treatments) of hepatitis NANB, one of which was severe. Clearly at the meeting he summarised our own experience with regard to small-pool Factor VIII as well as the two patients who had agreed to participate in clinical trials and were receiving dry-heated batches of our intermediate concentrate. He comments with regard to the reports of chronic hepatitis in haemophiliacs which had been put together by Dr. Craske for tabling at the Haemophilia Centre Directors annual meeting later in the month, that these were somewhat suspect in accuracy as was a lot of the patient data in circulation.

[Do we have the Haemophilia Centre Directors Hepatitis Working Party minutes for 5th September 1984?]

By his letter of the 7th September, Mr. Perry the acting Director of the PFC in Edinburgh, confirmed that 2,123,500 iu's of Factor VIII concentrate would be delivered to BPL on Friday, 14th September. This amounted to 8,320 vials each with an average content of 230 iu per vial. He comments at the end of his letter that as he had previously mentioned, we should not plan on any additional quantities being available and in the event this was sound advice since we received no further Factor VIII concentrate. This concentrate was not heat treated. **[Do we know whether it was in fact issued?]**

There follows the agenda and a number of appendices for the 15th meeting of the U.K. Haemophilia Centre Directors which was due to take place on the 27th September. As will be seen from appendix A (the annual returns for 1983), there were 4,745 haemophilia A patients undergoing treatment at the various Centres, representing well over twice as many patients as were receiving treatment in the mid 1970's. The trends are perhaps best summarised by quoting from page 2 of appendix A:-

> "The total amount of Factor VIII used to treat haemophiliac patients in 1983 was 68.6m units and rises to 71m units if the amount of Factor VIII used in the treatment of haemophilia A carriers and Von Willebrands disease is included (table 5). If the amount of material used to treat all Factor VIII deficient patients is adjusted to allow for the amounts which might have been used by Centres who have not yet sent in their returns, the total amount of Factor VIII used in the U.K. in 1983 would be approximately 76m units. From fig.2 it will be seen that the amount of

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NHS concentrate used by Centres has increased and the amount of commercial FVIII has decreased, as has cryoprecipitate. The average amount of Factor VIII used for the treatment of haemophilia A patients remains at nearly 33,000 units per patient. More than half of the Factor VIII used in the management of haemophilia A patients was used for home treatment (table 6)."

Table 13 gives an analysis of the cause of death in the 29 haemophiliac patients, 3 Christmas disease patients and 3 Von Willebrands disease patients who died in 1983. 10 (35 per cent) were due to cerebral haemorrhage; 7 of those were patients more than 50 years of age. Other types of haemorrhage accounted for a further 2 deaths. There was one death from AIDS, 3 from cancer and 3 suicides.

Appendix E is Dr. Craske's attempt to try and produce some information as to the likely number of haemophiliacs "at risk" as a consequence of receiving treatment from the same batches of blood products as those used to treat the two haemophiliac AIDS cases which were known about at the relevant time. The conclusion reached is that some 600 patients were at risk having been treated with the same batches as the two AIDS cases but it was not known which of the relevant batches over the five year period which was taken for the purposes of the study were infected with the virus.

Mr. Pettet's letter of the 12th September, a circular letter to Regional Transfusion Directors deals with the arrangements for an "up date" meeting which we held at BPL on the 18th September. As the timetable and agenda make clear, the plan was to show those attending around the new factory which was, of course, in the process of being built and to discuss various matters of common interest but, of particular relevance to the present litigation, plasmas procurement and supply, plasmapheresis trials and the supply of Scottish Factor VIII. In addition, of course, the BPL development was a general topic of discussion.

There follow three documents recording the allocation to the various Regional Transfusion Centres of the Scottish Factor VIII received at about this time. This exercise was overseen by Mr. Pettet.

There follows a revised agenda for the 18th September "up date" meeting and then the notes of the meeting itself. It will be noted that under the heading "Item 5", it was announced that issues of the Scottish Factor VIII would be made

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during September/October and would form an addition to the normal pro-rata allocation to the relevant Regional Blood Transfusion Centres.

Next in this section is the agenda and the minutes of the CBLA meeting which took place on the 26th September. It will be noted from the minutes that there is no mention of AIDS and that the Authority did not really discuss anything which was directly relevant to the present litigation. The redevelopment work was continuing at that point and there were concerns regarding the levelling off (or so it seemed at the time) of the supply of Fresh Frozen Plasma. It is interesting to note Dr. Gunson's comment (see paragraph 69.2) that the requirement for Factor VIII was, by that time, in excess of 100m. units per year. The comment was made in the context of our seeking collaboration with Travenol on production of cloned products, but it is further evidence of the enormous growth over the previous ten years of consumption of Factor VIII.

The last item in this section is a copy of an article which appeared in the Lancet on the 29th September which was on the general subject of recovery and inactivation of infectious retroviruses added to Factor VIII concentrate. The conclusions were that retroviruses might well have a possible role in AIDS (HIV was found to be a retrovirus subsequently), and that in freeze dried material (lyophilised), heating at 68°c. for several hours did produce inactivation in substantial quantities of infectious mouse retroviruses. This pointed the way to heat treatment and the article examines the effective heat treatment on a number of marker viruses.

OCTOBER

The first item of note in this section is a letter from Dr. Perry at PFC in Edinburgh indicating that he had some 2,000 vials of Factor VIII (460,000 iu) at PFC which had failed to meet their defined finished product specification. He said that, bearing in mind the tentative evidence that was emerging in relation to the infectivity (AIDS) status of commercial product, Haemophilia Directors in England and Wales might consider that the use of this "sub-specification" product was preferable to the use of commercial concentrate and he enquired whether BPL would be interested in taking a supply. In the event I wrote on the 1st November confirming that just as we would not wish to send out batches of our product which failed our quality control test, we would really have to take the same line in relation to Scottish product. **[At this stage clinicians had a**

reasonable range of products available to them and by this stage, enough information for them to make as informed a choice as anyone as to which to use. In retrospect, it is probably the case (with the possible exception of the Armour product) that the commercial heat treated products were safe from the standpoint of HIV. Unheated NHS Factor VIII concentrate whether English or Scots was not, as we now know. Accordingly, in hindsight, the release of sub-specification in Scottish product (or for that matter product from BPL/PFL) would not, I believe, have assisted in the reduction of the incidence of AIDS cases. Additionally, of course, many were by this point already infected through the use of unheat treated commercial concentrate in earlier years].

In my letter of 1st October to Mr. Perry, I tackled an issue he raised in a letter to me of the 26th September on problems they were experiencing in the manufacture of Factor IX. Dr. Perry had suggested that two of his staff might liaise with our own on the problems they were experiencing, and as I intimated, in my letter of the 1st October, we were also experiencing a fairly mixed bag of results from our work on Factor IX in terms of heat treatment. This is evidence of collaboration with Scotland.

There follows the agenda and the minutes for the 193rd Regional Transfusion Directors meeting held on the 10th October. Again, there was no mention of AIDS.

The next document of significance in this section is a memorandum from Dr. Snape to Dr. Smith and Mr. Wesley entitled "Definition of a Programme for the Manufacture of Dry-Heated Coagulation Factor Concentrate". This records the fact that I had asked those concerned to give urgent consideration to the possibility of introducing as routine a dry-heating step in the finishing of Factor VIII and IX concentrate. As the memo records, this step would be aimed principally at eliminating AIDS infectivity whilst accepting that it may have less effectiveness in terms of preventing NANB hepatitis transmission. [What prompted this at the time - is it by any chance associated with the discovery announced at around about the same time in a forum attended by Dr. Smith that the AIDS virus was heat labile?]

The next document is a copy of an update on AIDS published in the Morbidity and Mortality Weekly Report for October 20th 1984. This is an important milestone document. The report which is entitled "Update: Acquired Immunodeficiency Syndrome (AIDS) in persons with Haemophilia", begins by setting

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the scene in terms of the number of haemophilia cases where AIDS have been reported. It is interesting to note from the text which is quoted below there were no cases reported in 1981, 8 in 1983 accelerating to some 29 in 1984. The report states:-

> "Reports of haemophilia-associated acquired immunodeficiency syndrome (AIDS) in the United States were first published in July 1982. Since then, the number of U.S. patients with underlying coagulation disorders who develop AIDS has increased each year. In 1981, 1 U.S. case was reported; in 1982, 8; in 1983, 14; and, as of October 15th, 29 cases have been reported in 1984 for a total of 52 cases".
>
> "Three patients are known to have had risk factors for AIDS other than haemophilia. These 52 persons reside in 22 States. Only 10 States have reported more than 1 case, and no State has reported more than 8 cases."

Later in the report, it is stated:-

> "CDC has investigated the blood product usage of the majority of these cases. In 9 cases, Factor VIII concentrates had been the only blood product reportedly used in the five years before diagnosis of AIDS."

Of particular importance, is the advice recorded on page 591 of the report:-

> "The Medical and Scientific Advisory Council (MASAC) of the National Haemophilia Foundation (NHF) has recently issued revised recommendations for the therapy of haemophilia. Two physicians treating patients with haemophilia, they recommend that (1) cryoprecipitate be used in Factor VIII deficient new born infants and children under 4 years of age, and in newly identified patients never treated with Factor VIII concentrates; (2) Fresh Frozen Plasma be used in Factor IX - deficient patients in the same categories; and (3) desmopressin (DDAVP) be used whenever possible in patients with mild or moderate haemophilia A. The majority of haemophilia patients do not fit in categories (1) through (3). For these patients, MASAC recommends that, "because heat-treated products appear to have no increase in untoward effects attributable to the heat treatment, treaters using coagulation factor concentrates, should strongly consider changing to heat-treated products with the understanding that protection against AIDS is yet to be proven". They

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also recommend that all elective surgical procedures for haemophilia patients be evaluated with respect to possible advantages and disadvantages of surgical delays."

Lastly, the report notes:-

"Although the total number of haemophilia patients who have thus far developed clinical manifestations of AIDS is small relative to other AIDS risk groups, incidence rates for this group are high (3.6 cases/1,000 haemophilia A patients, and 0.6 cases/1,000 haemophilia B patients)".

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In a memorandum of the 26th October from Mr. Prince to Mr. Wesley, the practical requirements to begin dry heating of Factor VIII and Factor IX on a relatively large scale basis were described. This followed a meeting between Dr. Harvey and Dr. Smith on the 16th October which was prompted by my request that we move to heat treated products without delay.

There follows a report prepared by Dr. Smith entitled "Unheated Heparin VIII: Progress Report May-October 1984 (8Y1-8Y9)". This is really a summary of the work on the 8Y project up to that point. As the first paragraph under the heading "Background" makes clear, the idea of 8Y had to some extent sprung from the heparin precipitation which had been done in connection with research into pasteurising Factor VIII concentrate. It was clear that 8CRV and HL were unsatisfactory candidates for vigorous heat treatment, and the 8Y project was aimed at producing a product which overcame the problems and, in essence, had a greater purity.

NOVEMBER

The first significant item in this section comprises the agenda together with some supporting papers and then the minutes of the 10th meeting of the Advisory Committee on the National Blood Transfusion Service held on the 8th November. I attended this meeting. So far as the support papers are concerned, the only one of interest is paper AC(84)13 which gives details of the formation of the Advisory Committee on the National Blood Transfusion Service Working Group on AIDS and sets out the composition of the group. I was a member of the group together, inter alia, with Dr. Gunson, Dr. Rizza, Dr. Mortimer and Dr. Tedder. Dr. Craske was a co-opted member and it will be seen that there were

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representatives from the Scottish Home Health Department and the Scottish National Blood Transfusion Service in addition to three representatives of the DHSS.

With regard to the minutes, paragraph 7 under the heading "AIDS Cases reported by CDSC", there is reference to Dr. Smithies reporting that by the end of October 1984, 88 cases and 37 deaths had been reported to the Communicable Disease Surveillance Centre. Of these, 75 per cent were homosexuals, and 3 were haemophiliacs but none were associated with blood transfusions. He indicated that over 300 cases were anticipated by the end of 1985.

Under the heading "AIDS Leaflets", (paragraphs 8 and 9), there is reference to the Committee's advice on the adoption of a uniform system of distributing the revised NBTS leaflet and this advice had been accepted by Ministers with the consequence that leaflets would shortly be distributed to Regional Transfusion Centres for issue individually to every donor. This was an improvement on the haphazard, differing methods, which Regional Transfusion Centres had hitherto employed in distributing earlier leaflets.

The terms of reference of the AIDS Working Group were reported in paragraph 10, and the terms of reference were:-

> "To consider the implications for the NBTS of testing blood donations for antibody to HTLVIII and to report."

With regard to AIDS testing, paragraph 11 of the minutes contains reference to Dr. Smithies' report that the Middlesex Hospital and the Chester Beatty Laboratory were testing for HTLVIII antibody using a radioimmunoassay method. Pilot screening at a Regional Transfusion Centre was one of the points to be considered by the Working Group which had just been established at its meeting on the 27th November. I enquired about the Gallo and British Isolate availability and was advised by Dr. Smithies that the U.S.A. had been approached for permission to use the Gallo Isolate in the U.K.; some progress had been made on the British Isolate, but the position would be clearer by the time the Working Party met on the 27th November. Dr. Gunson commented that 5 American companies were licensed to use the Gallo Isolate to develop tests. **[This refers to the need to have samples of the virus, then called HTLVIII, (or antibodies to the virus?) in order to develop a test. Gallo was the American researcher**

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responsible for isolating the virus although parallel work had also been done in France].

In a letter to me of 8th November, Dr. Harris, responding to a letter I had written on the 12th October indicating our intention to heat treat Factor VIII, replied:-

> "As far as your proposal to heat treat Factor VIII is concerned, I would hope that you would bring this to the attention of the Advisory Group who might wish to consider if the evidence for inactivation of HTLVIII by heat is sufficient to warrant taking this step, particularly if a screening test can be made available. There may also be implications for the adequacy of the proposed plasma supply if heat treatment affects the yield of Factor VIII harvested which both CBLA and the Department would need to have clarified. I trust that you will furnish both the Department and the CBLA with full details of this proposal."

satisfactory commercially available

At this time we were pressing ahead with heat treatment in any event. It seemed to me that whilst there were penalties involved, the risks of transmission of HIV were such that heat treatment should be employed even if it turned out to be a temporary expedient. There was no test for HIV at the time, but we knew from our research work on heat treatment which originated from our desire to eradicate hepatitis NANB, that heat treatment was feasible and, in the longer term, the development of a superior product (8Y) carrying less penalty in terms of loss of yield and greater possibilities of virus inactivation because of its tolerance to heat, was beginning to look a firm possibility.

Dr. Harris' reaction to our news suggested that he was getting hold of the wrong end of the stick in apparently focusing on the question of whether screening tests would be enough.

Next in the file is a letter from Dr. Kernoff to me dated 8th November enclosing a copy of a paper which he had prepared in conjunction with others entitled "High Risk of Non-A Non-B Hepatitis after a First Exposure to Volunteer or Commercial Clotting Factor Concentrates: Effects of Prophylactic Immune Serum Globulin". Again the paper emphasises the virtual 100 per cent hit rate Non-A Non-B irrespective of whether commercial concentrate or NHS concentrate was used. In the summary, Dr. Kernoff's says:-

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"After a first exposure to Factor VIII concentrates, 9/9 British patients treated with U.S.-derived commercial products, and 10/12 treated with British volunteer (NHS) products, developed acute Non-A, Non-B (NANB) hepatitis. Hepatitis following commercial products was more severe, and of shorter incubation. ... after a first exposure to NHS Factor IX concentrates without ISG, 4/4 patients developed short incubation NANB hepatitis; 1 also contracted prolonged incubation hepatitis B."

Several points arise from this. First it will be seen that there is reference to the apparently more severe hepatitis communicated by commercial products. As I have indicated elsewhere, this severity was, in one sense, more apparent than real - where hepatitis NANB was concerned, in that research showed that the long term chronic aspects of hepatitis NANB infection were, largely speaking, the same as between commercial and NHS concentrate.

There follows the agenda and minutes of the CBLA Central Committee for Research and Development in Blood Transfusion meeting which took place on the 9th November. It is interesting to note at paragraph 8.2 under the heading of "Developments with respect to AIDS", that Dr. Tedder reported to the meeting that the causative agent of AIDS was now known to be a retrovirus which was called "HTLV3". There was reference to the work to develop test kits and, in particular, that there were five U.S. companies which were currently licensed to develop a test. Dr. Tedder expressed the view that Porton, Unilever or Wellcome Diagnostics were the only firms in the U.K. with capacity to be involved in this work. The Chairman, Dr. Gunson, suggested that test kits would be available for sale by the end of the year but in practice this did not prove to be a correct prediction. The first licenced and commercially available test (Abbott) became available in about March 1985.

Dr. McClelland made reference to the dreadful problem which they had experienced in Scotland with one batch of Factor VIII which was found to contain HTLVIII in August 1984 having been fractionated in November 1983. The virus attack rate on this product looked like being as high as 80 per cent. The remainder of the product had been withdrawn but the effect was salutary in the extreme.

At paragraph 8.3 of the minutes under the heading "Trials of Heat Treated Factor VIII manufactured at BPL", there is reference to my report and our work in this regard. I explained the work which had been done with regard to heat treatment

of Factor VIII with particular reference to our new 8Y product which I then estimated was approximately a year away. Of course with this product our anticipation with regard to loss of yield was that this would not be that great. I referred to the fact that the CBLA had, in March, agreed to finance trials of the BPL heat treated Factor VIII (this was of course the heat treated intermediate concentrate rather than 8Y) and that a draft clinical trial protocol for the Northern Centres had been circulated. There is a reference at the bottom of page 2 of the minutes which reflects, to some extent, a rather odd feeling which I had coming away from the meeting at the time;

> "After further discussions, it was agreed to recommend to the CBLA that the Director should commence dry heat treating material currently being produced, whilst existing methods to obtain a better yield so that wet heat treatment might be feasible. It was also agreed to recommend that trials of heat treated Factor VIII should continue, but be extended to take into account anti HTLV3".

The odd feeling to which I refer above was that I was being sent back by this meeting to the CBLA to get approval for heat treatment whereas in fact, as far as I was concerned, we were well embarked on our work in this regard rendering the idea of obtaining CBLA's consent, somewhat otiose.

There follows a memorandum from Dr. Smith to Dr. Harvey dated the 12th November entitled "Options for Heat Treatment of Coagulation Factor Concentrates". As the first paragraph indicates, the memo was intended to survey the products which had been developed to meet the demand for safer concentrates, what stage they were at, what they were expected to achieve, and when they might provide clinical products first from PFL and then from BPL.

In paragraph 1.1, Dr. Smith comments on the "Restricted-pool "Intermediate" Specific Activity Concentrate, HCRV". **[This was the Oxford experiment where plasma obtained from restricted plasmapheresis pools was used to manufacture 8CRV which in turn was used in patients who had not been treated before or not for about two years. As Dr. Smith indicates, there was evidence of a reduction of about 50 per cent in the incidence of hepatitis NANB suggesting only one or two carriers may affect a pool of about 1,000 donations but, as Dr. Smith pointed out, whilst donors were usually selected from panels of experienced donors thereby reducing the chance of a donor at risk for AIDS donating blood, the risk**

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was not eliminated. Realistically, we could not expect more than about 1m. iu per year from this method of manufacture as we were then organised].

In paragraph 1.2, Dr. Smith comments on the dry heating of 8CRV and HL and in particular, the results of our use of this in connection with three patients in 1984. All three had received large doses of dry heated 8CRV and none had contracted hepatitis or AIDS up to that point.

Dr. Smith summarises our then knowledge of the merits of dry heating on page 2 where he says:-

> "Dry-heating of other commercial Factor VIII concentrates is said to result in negligible losses of VIIIC, but incompletely published results of clinical trials suggests that the incidence of transmitting NANBH is reduced only by about 30 per cent. The concentration of infective particles in commercial plasma pools may of course be higher than in our pool. Publications by Cutter suggest that the heating conditions usually used will kill many logs of several viruses, including retroviruses and one strain of NANBH, but may give borderline kill when the titre is very high.
>
> Considering the lack of good clinical data, convincing chimpanzee data or any hard data on AIDS, and with a suspicion that virus kill (and Factor VIII loss) might vary greatly between batches or even between vials because of minor variations in moisture content, dry-heating has not been considered at PFL as more than a stop gap. Very recent data on inactivation of HTLVIII spiked into Factor VIII concentrate, possibly five logs kill after 24-48H at 68°, make dry heating attractive as an immediately practical and minimally invasive way of reducing the transmission of AIDS, if not NANBH".

In paragraph 1.3, Dr. Smith addressed the work which we had started in earnest in July of developing the new 8Y product. As he indicates in the second paragraph on page 3, our initial heat treatment work on 8Y suggested no significant loss of Factor VIIIC or any other important quality after 72 hours at 72°. The signs were encouraging and this information really prompted the decision at about this time to concentrate on developing 8Y using the heat treated intermediate concentrate as a stop gap only.

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The next document is another technical memorandum this time produced by Mrs. Winkleman on the stability of 8Y intermediate, and this simply records the progressing experimentation with regard to 8Y.

There follows a memorandum from Mr. Prince to Mr. Wesley which summarises the equivalent requirements for heat treatment of Factor VIII which again evidencing our gearing up for heat treating product at BPL.

Next in this section are some minutes of an internal meeting which are dated the 19th November, but relate to a meeting which had taken place on the 13th, to consider the various options for heat treatment of Factor VIII. This really followed on from Dr. Smith's memorandum of 12th November setting out the options for heat treatment of coagulation factor concentrate. As will be seen from paragraph (vi) on page 2 under the heading "Target Date for Implementation of Heat Treatment", we had agreed that every effort would be made to start heat treatment as soon as possible. The provisional target date was 1st April 1985 for the issue of heat treated Factor VIII intermediate concentrate. In the event, this target was met and of course we were producing heat treated product **[and issuing it?]** prior to April.

In a memorandum of 20th November from Dr. Smith to myself, Dr. Harvey and Dr. Snape entitled "Clinical Use of Dry-Heated Restricted-Pool 8CRV", Dr. Smith raised an issue which we were in danger of losing sight of in the rush to produce and issue heat treated Factor VIII. We had the dry heat treated restricted pool 8CRV and some stock of this remained for issue, and with it the possibility that we could derive very useful data from those who received treatment with this product. Dr. Smith was anxious not to lose the opportunity which the existence of this stock presented, and in the memorandum set out, those categories of patient who might be used for the purpose of receiving this limited stock of heat treated Factor VIII and who, because of the type of patient, could yield helpful data from a standpoint which might then be utilised in relation to future products.

There follows a document entitled "Report on EEC Workshop on AIDS held at Institut Pasteur 20-22nd November 1984". This records the pattern of AIDS cases in Europe at that time and also mentions that some 6,000 cases have been notified in the U.S.A. This compared with some 559 in Europe, 88 of which were in the United Kingdom. It is recorded that 3 haemophiliacs had developed clinical AIDS.

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It will be noted on page 3 under the heading "Sero-Epidemiology" that there is reference to the work at the PHLS Virus Reference Laboratory and by the Middlesex Hospital/Chester Beatty Group which suggested that in the United Kingdom, that approximately 10 per cent of homosexuals with multiple partners and 20-30 per cent of the most promiscuous homosexuals were anti HTLVIII positive. 30 per cent of haemophiliacs overall but some 70 to 80 per cent of those receiving regular doses of commercial Factor VIII concentrate, were also HTLVIII positive.

This shows that by the autumn of 1984, a very large proportion of severe haemophiliacs who had, because of the severity of their condition, been receiving regular doses of commercial Factor VIII had sero converted.

The next document in this section is a paper prepared by the PHLS Communicable Disease Surveillance Centre entitled "Acquired Immune Deficiency Syndrome Surveillance in the United Kingdom September 1981 to November 1984." This may be regarded as something of a landmark document. Although the document bears reading in its entirety, it will be noted that on page 3 in the second paragraph under the heading "Blood and Blood Products", there is reference to blood being donated by two patients who had subsequently developed AIDS and that red cells and whole blood had been given to two patients from that donated, and the blood had been used to produce Factor VIII concentrate subsequently received by over some 391 patients with haemophilia. At this stage there were still only three haemophiliacs who developed full blown AIDS although, I suspect, there were already a number of cases where AIDS was in the process of manifesting itself and were therefore not yet confirmed.

In a memorandum of the 22nd November from Dr. Snape to myself he recorded a report of increased frequency of mild to severe reactions to our heat treated intermediate Factor VIII concentrate as reported to him by Dr. Aronstam (Lord Mayor Treloar College). The reactions were typically tachycardia, chest pain, flushing, pounding headache. In the note, Dr. Snape speculated about the possible cause of this since the reaction did not appear to be batch or dose related so as to give any sort of lead or pattern as to the cause, and he could only conclude that the reactions described would be consistent with reactions to non-specific plasma protein contaminants present in current batches of HL at higher level than was previously the case. **[Did this problem persist to an extent or was this an isolated incident?]**

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The next document in this section is an internal memorandum from Dr. Smith to various other personnel in BPL dated 23rd November on the subject of the heat treated intermediate product 8CRV covering the week commencing the 26th November. Again, Dr. Smith was attempting to utilise PFL's restricted-pool heat treated product in such a way as to obtain valuable clinical information before all NHS Factor VIII was issued in a heated form.

The next memorandum in this section is dated the 26th November and is from Mr. Wesley to myself and deals with the equipment which we had to procure to heat treat Factor VIII. The equipment was initially intended for the heat treatment of the intermediate concentrate but was subsequently used for 8Y. HL was released up to August 1985 at which time 8Y effectively took over (having been phased in over some months). The product which was left over at this stage was effectively scrapped apart from some very small batches which were used for specific **[research]** purposes.

There follows the agenda and some of the papers for the meeting of the Working Group on AIDS which took place on the 27th November. **[Where are the minutes of this meeting?]** Amongst the questions to be discussed at the Working Group as will be seen from the last page of the briefing document designated WGA/84/2, was whether heat inactivation of HTLVIII should be used in preparation of Factor VIII even if donations were screened for antibody. It would seem from my manuscript note at the bottom of this page which reads:-

> "In relation to testing for AbHTLVIII cost - comment short of money due to poor financial control by your Authority".

Dr. Abrams refers to a point I raised about having the necessary financial resources to introduce testing at BPL which produced the response from Dr. Abrams that if we were short of money, it was effectively our own fault.

There follows the agenda and the minutes for the CBLA meeting held on the 28th November. This records (page 3) that with regard to the trials of heat treated Factor VIII manufactured at BPL, there was approval, following this, to spend £72,000 for ovens to heat treat the Factor VIII.

Aside from this routine, reports on the redevelopment of BPL and other housekeeping matters, nothing else of significance in relation to this litigation was raised during the course of the meeting.

In my letter of the 28th November to Mr. Smart, I recorded my objection to the remarks made by Dr. Abrams of the DHSS during the course of the Advisory Committee Working Party on Aids meeting on the 27th November. I took great exception to an unsolicited comment that it was due to poor financial control of CBLA that we had insufficient funds to develop an antibody marker test for HTLVIII. **[What became of the objection]**.

There follows a memorandum from Dr. Smith giving further information on dog infusions of Factor IX concentrate which was of course the separate line of research we were pursuing in relation to Factor IX at the time.

DECEMBER

The first item in this section comprises a report from Dr. Smith to myself on his visit to PFC Edinburgh on 29th/30th November. He notes, in relation to Factor VIII, that PFC have come under clinical pressure to "supply something or they will buy U.S. heated concentrate" with the consequence that they were recalling large batches of Factor VIII and subjecting these and their current stock (approximately one year) to dry heat. He states "Their concentrate will not stand 24 hours at 70° and the exposure is much briefer, shorter than they or I would be happy about". **[Presumably we would say with regard to recall that (1) we did not have the heating capacity to recall and heat treat, and (2) that - apparently unlike the Scots - we would not be happy with the quality control aspects of this exercise. Leaving point (1) aside for the moment, what would we say about the Scots programme of recall and reheating with regard to quality control - had they got it wrong or was their product one where this made more sense?]** Both PFC Edinburgh and ourselves were using dog infusions as a way on checking the safety and efficacy of heat treated Factor IX.

At this time I decided to promote a joint meeting between the Haemophilia Reference Centre Directors, the Blood Transfusion Service Advisors and the Plasma Fractionation staff at BPL on the subject of AIDS and the management of haemophilia with the intention of obtaining an expression of opinion from those intimately involved with the problem as to the nature of the product which they wanted from BPL for the future. The agenda for this meeting is contained in a circular letter which I prepared, dated 4th December, which appears next in this section.

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The next document in the section is entitled "AIDS - Newcastle Policy December 1984" and was a document which I believe was brought down to the meeting from Newcastle and sets out the policy being followed in that region at the time. I think that it is fair to say that, even at this stage, clinicians were still not sure about the wisdom of using U.S. heat treated commercial product so far as HIV was concerned.

The next document of significance comprises the minutes of the meeting on the 10th December. As will be seen from the list of attendees, the meeting attracted a good group of people including three virologists (Doctors Mortimer, Craske and Tedder) and a number of Regional Transfusion Centre Directors, Dr. Gunson, Dr. Rizza and Dr. Smithies from the DHSS. At my request, Professor Bloom chaired the meeting.

The first part of the discussion was taken up with a review of the situation as it was at the time with regard to the development and application of HTLVIII testing. As will be seen from the second page of the minutes, Dr. Craske advised that the reagents which were necessary for tests were available on research basis only and that substantial resources would be required to enable the proposed workload of testing on a wider scale to be undertaken. It was said that it was considered that to know the antibody status of every haemophiliac would be advantageous in determining the regime for treatment, but in view of the limited resources, it was impossible to do routine tests at that time. The DHSS listened to these comments and, through Dr. Smithies, gave an indication that they would take all the various points back for consideration. In connection with blood donor testing, there was a statement to the effect that testing of donors required either (1) mass commercialisation of a British test or (2) application of a current commercial test. There was confirmation that testing would be introduced at two Centres early in 1985, but Dr. Gunson advised that it would be preferable to test all donors. If resources were limited, however, he observed that it might be better to concentrate on major "risk" centres, and I suspect that he had in mind North London. There were concerns expressed by Dr. Tedder about the pace of test advancement and that this was so fast that the scientists were left to introduce a test as soon as possible. There was also concern about the lack of financial support from the DHSS.

Two observations were made under the heading "Significance of HTLVIII Antibody Tests" which are of interest. First, it had been noticed that some patients did

not produce an antibody to HTLVIII with the effect that an infected batch of concentrate might not always be open to detection by the antibody test being developed. **[Was this in fact a correct observation - if so, it does support still further the argument that donor testing was not an adequate protection in contrast to heat treatment of blood products].**

On the fourth page of the minutes under the heading "Advice to Patients and Donors", there is reference to the Newcastle policy being discussed and in addition the following reference appears:-

> "All concentrate is now heat-treated commercial; advice was sought on the use of non-HT Factor VIII and Factor IX. There was obviously a long discussion as to whether persons found to be positive were to be informed and differing views were expressed. It was said that each clinician should decide for each case depending on the facts of the case but in general, to provide information if asked for."

Under the heading "Factor VIII Concentrates", it was agreed that HT product should be given to all patients, if freely available, to include those found to be antibody positive. In the case of antibody negative patients, it was agreed that from now on, treatment should be with HT material.

Dr. Kernoff commented that as some 70 per cent of haemophiliacs were now positive, it might be considered irrelevant if one tells or does not tell the results of testing. **[This seems an extraordinary comment for him to have made. Do you recollect it?]** There was, as the minutes show, discussion about the balance to be struck between the increased safety of Factor IX when it was heat treated against the possible downside of heat treatment in the form of increased thrombogenicity.

In the balance of the morning session, there was considerable discussion of the merits or otherwise of heat treatment but in summary, the Chairman said that one had to accept, for the present, that it was difficult to avoid the argument that non-heat treated product constituted a risk.

In the afternoon, the Chairman began the session by outlining the current position with regard to the commercial supply of heat treated Factor VIII. Cutter, Harmer and Travenol were dry heated preparations whereas Alpha was a

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wet heat treatment concentrate. He said that Hoechst were also supplying a preparation.

I explained the work which had commenced in 1984 on heat treatment and that the two objectives at that time were to produce a product which achieved inactivation of non-A, non-B hepatitis, and one which was acceptable for general use with non transmission of virus. Research and development with these objectives in mind had progressed and now coincided with the AIDS problem which was being faced. I explained the current stage which had been reached in research and development. From the discussions, there seemed to be general agreement that the BPL heat treated product would be accepted for use (this being the intermediate heat treated concentrate at that time). It was made clear, however, that heat treatment brought with it a 15 to 20 per cent loss in terms of output.

On the page 9 of the minutes, there is reference to Dr. Savage raising the problem of haemophiliacs who had only received NHS product. Until then HT material was available, the alternatives were commercial HT or non-HTNHS material. It is recorded that opinions varied as to whether non-heat treated NHS product would be used. The Chairman suggested that it be left to individual treatment centres to determine their policy. I said under the circumstances, BPL would not issue non-heat treated product in December unless this was as a result of a specific request being made. Vials which had not been used should, I said, be returned to BPL as the BPL policy was not to re-issue vials previously sent to users in line with regulatory requirements. Any vials returned would probably be destroyed or put to research use. I explained that some heat treated material would be available for clinical trial purposes, but the bulk would not be available until April. We required three ovens to heat the product, one was already in use and the remaining two were expected to be delivered in March. It was generally agreed that priority for NHS heat treated material would be given to children and past users of NHS material. **[Was any recommendation for the return of unused non-heat treated Factor VIII put in writing at any stage?]**

As the minutes make clear on the last page, it was intended, following the meeting, to issue recommendations for the treatment of patients and this in fact was what occurred. **[Do we have those recommendations?]**

The next item in this file is a detailed report dated the 12th December prepared by Dr. Smith addressed to myself, Dr. Snape and Dr. Harvey entitled "Dry-heated

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Factor VIII Programme". It reflects the anxiety which we had to press on as fast as possible with the production and supply, through general issue, of heat treated Factor VIII. The reference to HT1 and HT2 are to, in the first case, heating at 60° for three days and, in the second case, heating at 70° for one day. HTIII refers, in effect, to the 8Y product. As indicated, small-pool unheated 8CRV was to be withdrawn unless specifically requested by clinicians otherwise we would experiment with each batch of 8CRV, heating 10 vials on a trial basis to ascertain whether the total batch would be suitable for heating. Some batches proved to be, others not. As Dr. Smith indicated in his note, heated batches would not be disqualified automatically if they fell below the 200 iu/vial level, since clinicians seemed willing to use more vials if necessary. As will be seen, at the same time as we were making plans to heat 8CRV, the 8Y project was progressing and we were heating trial batches of 8Y scaling up the amount of our production as we went.

In appendix 2 (page 8), there was some suggestions made by Dr. Smith for the priority of assignment of heated Factor VIII. **[Did you in fact ever issue any instructions/recommendations to Regional Transfusion Centres/Haemophilia Centres prioritising the use of the limited NHS heat treated Factor VIII?]**

The next item in this section is an important circular letter which we sent to Regional Tranfusion Centres. The letter is from Mr. Pettet and is dated the 14th December. It explains, at some length, the origin of our heat treated product, the new product development programme which had been initiated about a year ago, and the fact that it was hoped the new product (8Y) would be available by mid 1985. The letter made clear that the interim arrangements were to heat the existing product but that, as a consequence of heating, we would not be able to meet the present issue level of NHS product. We stated that if Regions decided to continue using non-heat treated Factor VIII on a selective basis, then this could be made available on request. It was stressed:-

> "Under the present circumstances, then, supplies of non-HT Factor VIII will <u>not</u> be Regionally distributed in December for January 1st 1985. It is our intention to avoid issuing product unlikely to be used, which if returned to BPL would not be available for further use under present regulatory guidelines. The present stock of some 15,000 vials of Factor VIII concentrate will be looked at as to their suitability for heat treatment. It is requested that each Region determines the policy to be adopted by each Haemophilia Treatment Centre with regard to the use of

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non-HT concentrate and forwards this information to BPL as soon as possible. Only then can we determine how best to distribute the limited supplies of HT product which would be issued on a named patient/clinical trial basis requiring detailed follow-up data collection. It is reiterated that until April 1985 the HT product cannot replace the present issue level of non-HT product."

We also touched on the situation with regard to Factor IX which was described as "somewhat more serious". It was explained that priority for heat treatment had been given to Factor VIII and in the meantime, non-HT Factor IX would continue to be available. We touched on the doubts about the suitability of Factor IX for heat treatment in view of the risk of thrombogenic reactions and alluded to the fact that discussions were in progress as to how best to treat haemophilia B patients. **[What did this refer to?]**

To an extent, the contents of the letter to Regional Transfusion Directors is reflected in Mr. Pettet's memorandum to me of the 18th December in which he confirmed the despatch of the circular letter and that as far as possible, batches of our intermediate concentrate still in stock were being considered for heat treatment, although it was known some would not be suitable.

The next note in the section which is in the handwriting of John Williams (BPL's Process Manager), is addressed to "Peter" which is in fact Peter Prince. It is entitled "HL Development" and deals, inter alia, with the slight differences in fribrinogen levels between the Oxford and Elstree products which was significant in that this was the sort of information which required to be published with the product.

The next item of significance in the section is a memorandum dated the 20th September from Dr. Smith to Dr. Snape and Mr. Pettet entitled "Some unpolished suggestions towards a leaflet for Heated HL and 8CRV". This was a draft of a package insert explaining a little more about the heated HL and 8CLV product. **[Was anything like this actually produced for inclusion with the product?]** The details given in the draft obviously reflect what we knew at the time and, in particular, Dr. Smith says:-

> "We have then heated the concentrate under conditions which will probably kill the virus which transmits AIDS and may well prevent or reduce the transmission of non-A, non-B hepatitis..."

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The note obviously foreshadowed the appearance of the new 8Y product in 1985.

The next item in this section is an article printed in the Lancet on the 22nd December entitled "Blood Transfusion, Haemophilia and AIDS". This is something of a landmark article, and bears reading in its entirety. It makes clear that the large scale development of antibody tests to exclude donors who are HTLVIII antibody positive was the most immediate spin off from the virological advance in 1984. The article indicates that 52 haemophilia associated cases of AIDS had been reported in the U.S.A. (including two in haemophilia B patients, and two in patients with other clotting disorders), and three in the U.K. There is reference to the fact that in the U.K. unheated large-pool concentrates, even those prepared from voluntary donations, have transmitted non-A, non-B hepatitis, and in addition, first generation heated concentrate had similar transmitted the disease. The article also touched on the advice which had been coming from a number of sources as to how haemophiliacs should be treated against the back drop of AIDS crisis. There is reference to the National Haemophilia Foundation recommendations regarding desmopressin and cryoprecipitate.

There follows a leaflet from the Haemophilia Society giving general information about AIDS and, to an extent, the ideal method of treatment. It is interesting to note that there is a statement to the effect that the haemophiliacs should ask their Centre Directors to make heat treated product available as soon as possible. The leaflet summarises current practice at major Haemophilia Centres as being the use of cryoprecipitate in deficient new born infants and children under 4, the use of Fresh Frozen Plasma in Factor IX deficient patients wherever possible, and again desmopressin where this can be used. There is reference to the fact that heat treated Factor VIII had become available in the United States over the past few months and was not in universal use there. In fact I think it is true to say that by this stage it was also readily available for those who wanted it (subject always of course to finance) in the U.K. as well.

UNDATED

The only relevant item in this section is the revised AIDS leaflet which was issued towards the end of 1984 and was available to donors. Of course this approach still relied on voluntary exclusion by people who might otherwise have the virus and the task which lay ahead during 1985 was the introduction of

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effective screening for AIDS and, as far as BPL were concerned, the introduction of the new 8Y product with its high tolerance to heat.

1985

JANUARY

The letter from Peter Kernoff dated 7 January addressed to Directors of Haemophilia Centres supplied by NBTS Edgware concerns a meeting which had been arranged for 18 January, the main purpose of which was to discuss problems related to aids in haemophiliacs and to attempt to reach a uniform policy regarding the use of heat treated concentrates. Representatives of the NBTS Edgware and myself on behalf of BPL were duly present. The letter then sets out the agenda for the meeting. **[There appear to be no Minutes for this meeting, were there any?].**

On 9 January Dr. Smith sent a memorandum to myself, Dr. Snape and Dr. Harvey attaching the third edition of the documents relating to the clinical use of heated 8CRV and HL. Throughout 1984 the clinical trial documentation had been drafted, considered and revised and the documents that accompanied Dr. Smith's memorandum represented the latest and final version of the documentation. Although, even at this stage, he was endeavouring to keep the idea of a proper clinical trial alive, the fact is that events had overtaken us and from January 1985 onwards heated 8CRV and HL were issued on a named patient basis without clinical trials having been carried out or for that matter, being carried out with the aid of this documentation. Non-heat treated product was only issued on specific request by this time. In the event, the protocol and associated documentation was amended and used for 8Y which was introduced on a clinical trial basis by the Spring of 1985 and was the sole product issued after September 1985.

Next in the file is a copy of the Haemophilia Centre Directors Aids Advisory document which we were sent on 9 January. The document was for general advice and assistance of Haemophilia Centre Directors and was circulated to them all. The authors were predominantly Professor Bloom and Dr. Rizza. By this time, as the background statement on the first page makes clear, there had been three reported aids cases in the UK involving haemophiliacs and 52 in the United States. HTLV III antibody tests were available from PHLS and from the

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Middlesex Hospital Medical School. **[What were these tests and how long had they been in use by this time? My understanding is that the first test - the Abbott test - was not licensed for use until the Spring of 1985, was this test and/or others in use earlier?].**

There is a statement to the effect that it was probable that the HIV virus had been incorporated into at least one BPL and one Scottish batch of Factor VIII. [If this has not been dealt with previously, can you expand on the circumstances and timing of this?].

At this time, as the note makes clear, evidence was accruing that the HIV virus was heat labile but there was minimal data from "spiked" concentrate being heat treated. The author speculated that the HIV virus or as they called it at the time HTLV III, was inactivated by dry heat at 68 degrees for 24 hours. However, it was felt unlikely that this process completely inactivated hepatitis NANB. Loss of yield from dry heat treatment was put at 15% whilst wet heat (pasteurisation) was said to be probably more effective but the loss of yield was up to 50%. Koate HT, Factorate HT and Travenol Hemofil were all identified as dry heat treated with Alpha Profilate as wet heat treated. There was reference to Immuno also having treated preparations at this time. As to Factor IX, heated products from the commercial suppliers were identified as Profilnine (from Alpha) Konyne (from Cutter) and Immuno. However, the efficacy and thrombogenicity of the products was unpublished. Since aids was perceived to be less common in Christmas Disease than in Haemophilia A, the authors gave no firm recommendation regarding heat treated Factor IX.

As indicated, at that time BPL could dry heat 30% of its output from 30 January 1985 onwards and we anticipated doing the rest within about two months when two more ovens were installed to supplement the existing one **[in operation at PFL?].** As the authors pointed out, extensive clinical trials had not been undertaken. The position in Edinburgh was that from that moment on, Scottish Factor VIII would be dry heat treated for supply to Scotland and Northern Ireland.

The authors then set out the options as they saw them in order of preference:-

(i) heated UK concentrate (but still with hepatitis NANB risk)

(ii) single donor cryoprecipitate or FFP

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(iii) heated imported concentrate (again still with the hepatitis NANB risk)

(iv) unheated UK concentrate

(v) unheated imported concentrate (almost certain to be contaminated).

For haemophilia A patients needing Factor VIII, it was suggested that "virgin" patients", i.e. those not previously exposed to concentrate and children should use cryoprecipitate or heated NHS Factor VIII (if available). Severe and moderate haemophiliacs previously treated with Factor VIII were recommended to use heat treated NHS Factor VIII, if available, or heat treated US commercial Factor VIII. With regard to Haemophilia B (Christmas Disease) patients were recommended to use fresh frozen plasma or NHS Factor IX concentrate if essential. Mild Christmas Disease sufferers were again recommended to use fresh frozen plasma if possible and otherwise NHS Factor IX and severe and moderate Christmas Disease sufferers previously exposed to Factor IX concentrate were recommended to continue to use NHS Factor IX. The uncertainties are well illustrated by the statement on page 3:-

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

In the notes at the bottom of the third page there is an indication that BPL could not take back for reissue unused, unheated concentrate. The reason for this was quality control. We had no idea of the status of products which had

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been issued some time ago and how they had been handled during transportation and storage. In these circumstances we would not be willing to heat-treat products which had been out of our control for some time and reissue it. Aside from this, and on a more practical basis, we simply did not have the capacity. At that stage we had only one oven for heat treatment at PFL and were still awaiting two more ovens which we would use to full capacity when they were commissioned.

On the testing front (see page 4) it was recommended that patients should be tested for the presence of the HTLV VIII antibody. Those who tested positive should be informed, reassured and counselled regarding transmission to spouses etc. Against the background of this recommendation it does seem strange that in certain of the claims as pleaded by the Plaintiffs, some were not tested for quite some time and a few, who tested positive, appear to have been informed only months, sometimes years later.

It will be noted that the advisory document is dated 14 December 1984 and that the observations made in the document had been discussed and recommendations made in consultation with myself, Dr. Cash, Dr. Gunson, Dr. Mortimer, Dr. Tedder and Dr. Craske as well as others.

We did not introduce heat treated Factor IX until October 1985 (and at that time went over completely to heat treated Factor VIII at one time, in contrast to the position with regard to Factor VIII). The reason for this was that we had to reformulate the Factor IX product and ran into problems with regard to thrombogenicity. The product itself needed more extensive testing than Factor VIII because of this and this delayed its introduction. That said, Factor IX did appear to be less infective when it came to HIV and the reticence about using heat treated Factor IX is apparent from the advisory document.

The general uncertainty may also be seen from Dr. Jones' letter to me of 14 January. He was the Haemophilia Centre Director for the Northern Regional Haemophilia Service based in Newcastle Upon Tyne and in his letter he indicated that after discussion with colleagues about using heat treated Factor IX, he had decided to change once the stocks of NHS unheated Factor IX were exhausted.

There follows a letter from Dr. Kernoff at the Royal Free Hospital Haemophilia Centre to Dr. Snape dated 15 January indicating a preparedness to participate in the clinical studies we were hoping, notwithstanding the turn of events, to

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pursue in relation to our new heat treated product. His letter enclosed a list of the patients which he wanted to treat with our new product. It was necessary, given the product itself was not licensed, to issue it only a named patient basis. In practice this meant that the patient had to be identified by the Centre requiring treatment and the Factor VIII would be specially labelled for that patient's use only before despatch. There are a number of letters which follow on from this from various haemophilia centres identifying the patients they required supplies for. These letters remain in the files for the time being but having explained the reason for the identification of the patients to be treated, I do not propose to comment specifically on any further letters of this sort.

On 16 January Dr. Harvey sent a memorandum to me which enclosed an abstract of the proposed preliminary study on the use of BPL heat treated Factor VIII which was to be put on the notice board at the forthcoming Spring meeting of the British Society for Haemostasis and Thrombosis which was being held in Edinburgh on 26 March 1985.

The abstract appears immediately behind the memorandum and summarises the new product which had been prepared by PFL (this was heated at 60°C for 72 hours). It was intended that there be an oral presentation on the subject at the meeting. **[Did this happen and if so who gave it?]**

As part of our Factor IX development, Dr. Harvey wrote to me on 16 January on the subject of using dogs for the trial of the new heated Factor IX concentrate. His memorandum contains the essential costing details and we went ahead with this as part of our research during 1985 before we introduced the product in October.

The memorandum of 18 January from Mr. Prince **[what was his post]** to Mr. Wesley **[what was his position]** records the strategy for Factor VIII production at that time. As will be seen, we planned to heat-treat all batches of HL (as the BPL product was known) even if this brought the activity of the files down as low as 160 iu per vial as a consequence.

On 18 January Dr. Gunson wrote to Norman Pettet at BPL to advise him that his region **[specify region]** had decided that all commercial Factor VIII concentrate to be used for the present would be heat treated and he cancelled the allocation of non-heat treated material which we were proposing to issue to him in January, February and March.

On 21 January Dr. Smith prepared a memorandum for myself and others at BPL reporting on the clinical use of 8CRV heated to 60°C for 72 hours which had been the subject of a study in 1984 using three Factor VIII deficient patients who were bleeding or were undergoing elective surgery. This was the limit of the trial we had managed to achieve during 1984 and Dr. Smith's paper summarises the result of the trial and the effect of heat treatment on the product itself. There seemed to be no untoward effects as a result of using the product. Of course the effectiveness with regard to Hepatitis NANB and HIV of this treatment could not really be assessed back in 1984 as neither had an accepted test available but we did not subsequently find any evidence of hepatitis NANB or HIV manifesting itself in these patients.

This is followed by a memorandum from Mr. Prince to Mr. Wesley and others at BPL reporting on the first 600kg 8Y batch. At the same time as we were manufacturing heat treated 8HL and 8CRV, we were of course developing 8Y and this memorandum reports on the scaling up operation we were running at the time to produce larger batches. The intention at that time was to double production to 1,200kg batches. On 23 January Norman Pettet, the Product Services Manager at BPL wrote to Dr. Gunson at the Manchester Regional Transfusion Centre and copied the letter to Haemophilia Reference Centre Directors, Regional Medical Officers in England and Wales, the DHSS, Mr. Armor at CBLA and Colonel Deacon at The Army Blood Supply Depot. In that letter he explained the progress we were making towards producing heat treated Factor VIII. He confirmed that since 14 December BPL had issued restricted amounts of non-heat treated Factor VIII only to those regions that had indicated that this material would be used until supplies of heat treated Factor VIII became available from BPL. He anticipated that from some 15,000 vials of labelled non-heat treated product it was expected that approximately 9,000 would be used between January and April.

With regard to heat treated product, he explained that the results of our investigations had showed a loss of between 20% and 25% of the original activity was in the vial resulting from heat treatment and that vials could therefore be assumed to have an average of between 165 and 185 iu per vial.

He explained that all batches processed since December had been subjected to heat treatment and would be released as heat treated Factor VIII. Extra equipment (in the form of two ovens) would be available by March and it was estimated that for the period January to April BPL could make available between

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12,000 and 15,000 vials of heat treated Factor VIII for use on a named patient basis. Mr. Pettet pointed out that some vials were already being made available for pre-trial evaluation and that Dr. Snape, Head of Quality Control, would be writing to all haemophilia centres advising them of the protocol to be followed in the use of heat treated Factor VIII issued from BPL.

The letter drew attention to the fact that a new formulation of product was undergoing pilot production trials (this was 8Y) and was eventually intended to replace the heat treated 8HL and 8CRV product. In view of the loss of yield, the balance of the letter was deducted to explaining how pro rata would be operated in the circumstances.

There follows the Agenda and the Minutes of the Regional Transfusion Directors Meeting held on 23 January.

At the bottom of the page it will be seen that the meeting of the Aids Working Party which took place in November was reported upon and that the Regional Transfusion Directors considered this was an unproductive meeting, there being as yet no new leaflet, new finance and no positive move towards full donor screening. I think this is perhaps a fair characterisation of the meeting in question [this was the last Regional Transfusion Directors Meeting that I attended since I was not invited again]. My own views were that the introduction of testing ought to be accelerated [what discussion/consideration surrounded the possible introduction of testing in BPL in advance of the tests which were eventually introduced at Regional Transfusion Centres?].

At paragraph 7 of the Minutes under the heading "AIDS" there is a record of the discussion which took place on the subject at the meeting. Dr. Gunson gave information regarding the publication of a new leaflet which was then due to come out on the 1st February. Dr. Contreras was asked to report on the status of HTLV III testing but as yet there was no date for availability of test for a pilot study. There is reference to the anti-core test being evaluated at Edgware on stored samples. There is reference to a fact that most commercial companies were approaching Regional Transfusion Directors with regard to tests (the tests being of the ELISA type). The preference within the NBTS was said to be for an RIA technique. It was said that the DHSS should be pressed to make any test available to the community before its use in blood donor screening otherwise it was felt unsuitable donors would be attracted (simply to get a free test).

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I reported on the heat treatment of Factor VIII and also expressed the view that as I saw it, the anxiety on the part of the Haemophilia Society, was not for testing but for effective heat treatment of Factor VIII.

The letter of 24th January which appears in a standard form and was to be written by Dr. Snape to Regional Transfusion Centre Directors and others whose names appear on the sheet immediately behind the letter, concerned a particular batch of Factor VIII, batch HL3186, which had been contaminated by an aids patient who deliberately gave blood; some grotesquely misguided protest at the lack of action on aids as he saw it. The letter was an attempt to try and obtain all unused vials made from this batch **[what was the result?]**.

The next document is a pro-forma letter prepared by Dr. Snape and intended for circulation to the Haemophilia Centre Directors. The letter gives information on BPL's proposals regarding the supply of heated Factor VIII concentrate. It also invited Haemophilia Centre Directors to put in writing requests to BPL for stocks of heated Factor VIII concentrate for use in the treatment of named patients (this being the only basis on which we could issue the new product without its being licensed). Dr. Snape explains that the intermediate heated concentrate was a dry heated variant of the concentrate previously supplied and that it would be generally available for the coming three to four months. The amounts involved would be in the region of 50 to 60 per cent of what would otherwise have been supplied as unheated concentrate (this reflected the losses we were expecting to encounter in the heating process). He also pointed out that heating reduced the level of activity in each vial with the consequence that one could expect an average content of 186 iu per vial. The solubility of the product was marginally impaired, but Dr. Snape indicated that resolution should be achieved within 10 minutes if the vials of dried concentrate and water for injections were pre warmed to about 30°c. He went on to make it clear that our improved higher purity concentrate (8Y) would be available in limited quantity from April onwards and that it was anticipated that all issues of Factor VIII would be in this form by June 1985. In the event, it was September. He said, in relation to 8Y:-

> "In addition to improved specific activity (and a consequent improvement in solubility), it is anticipated that this product will tolerate sufficiently extreme conditions for viral inactivation as to address the problem of inactivation of hepatitis viruses as well as inactivation of HTLV III."

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Again in relation to 8Y, Dr. Snape pointed out that the product was not licensed (and by implication that this too would have to be issued on a named patient basis). He sent with his letter a copy of the protocol for use of the new product. We wished to build up sufficient information to enable us to obtain a product licence, and we were seeking the assistance of the Haemophilia Directors in this regard.

On the 25th January, Mrs. Winkleman and Dr. Smith produced a report giving details of their attempts to improve the dry heating behaviour of 8HL (the Elstree intermediate concentrate) and 8CRV (the Oxford equivalent). This really summarised their work in this field which, by this stage, was largely complete and had resulted in our being able to dry heat a reasonable quantity of the intermediate concentrate pending the full scale introduction of 8Y. Although a technical document, it is reasonably clear from what is said, that dry heating was not a particularly easy exercise when handling our intermediate concentrate.

There follows a letter from Professor Hardisty to myself dated 25th January 1985, enclosing a copy of a letter he proposed to send to the Guardian in response to one written by Mrs. Harrison expressing anxiety about the sufficiency of supplies of British heat treated Factor VIII. Professor Hardisty is the head of the department of Haemotology and Oncology at the Great Ormond Street Hospital for Sick Children. The draft letter he enclosed (and which I slightly amended in manuscript), was uncontroversial. It indicated that aids was first described early in 1981, and that the first case in haemophiliac was reported to the CDC in the United States later in 1981. He makes it clear that it was not until 1984 that the causative virus was identified and that in the meantime, the heat treatment of Factor VIII had been introduced in an attempt (he says unfortunately at that stage unsuccessful) to prevent the transmission of hepatitis, but goes on to say that there was no rationale for its use to prevent aids until this had also been shown to have been caused by a virus. He went on to say that the virus appeared to be more sensitive to heat than the hepatitis B virus, and quarrelled with a statement presumably made by Mrs. Harrison after discussion with Great Ormond Street Hospital that "only minute quantities **[of NHS heat treated Factor VIII]** would be ready in April". He explained that steps to replace old unheat treated concentrate by April/May were under way, and went onto say that there was no evidence that heat treated American concentrate carried the risk of aids.

There follow a series of documents which are in effect type written and

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handwritten records of stock held at around 28th January 1985. These would appear to be of very limited relevance.

The last document in this section is a copy of my reply to Peter Jones' (Newcastle Haemophilia Centre Director) request for heat treated Factor IX. I pointed out that this would not be available until animal trials had been completed. **[At the end of this letter (which is unsigned) there is a line of text reading "Can I also comment on the draft typescript of your text on aids and the blood". What does this refer to and did you ever comment?]**

FEBRUARY

The first two items in this section comprised the agenda and the minutes for the CBLA meeting held on the 1st February 1985.

By this stage Dr. Harris, the Deputy Chief Medical Officer, decided against attending. I should point out that Dame Phillis Friend was the Chief Nurse (and therefore technically representing DHSS along with Mr. Williams).

The first paragraph in the minutes of particular relevance is 4.3 which records a fairly lengthy discussion prompted by Professor Bloom on the subject of the distribution of heat treated Factor VIII concentrate. Professor Bloom had obviously not read too closely the letter which had been circulated by BPL (and written by Dr. Snape) setting out for the general information of Haemophilia Centre Directors the arrangements which were to apply to the distribution of heat treated intermediate concentrate and thereafter 8Y. I explained in some detail the arrangements which we were applying and the problems which had been experienced due to the fact that not all intermediate concentrate could be satisfactorily heated and that even when it was, there was a distinct reduction in activity. This had consequential affects on the pro rata system of distribution. As the minutes record, the CBLA agreed to proceed with Factor 8Y from April and authorise the use of small amounts which were then available for protocol trials. It was agreed that Dr. Gunson and Professor Bloom would advise the Director of BPL of their views on relevant matters.

At the foot of page 2 of the minutes, there is a manuscript note of my own which is really just a comment arising out of some suggestion that doubts have been expressed regarding the safety and efficacy of BPL products. The comment

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was to the effect that if there were doubts about heat treated commercial concentrate, why did the DHSS not put a stop order on BPL's heat treated HL and 8CRV.

There was reference at paragraph 5/85 to the position with regard to plasma supply and the fact that heat treatment would reduce the Factor VIII yield with consequential requirement to ensure the plasma supply was adjusted accordingly. Dr. Gunson was pushing plasmapheresis, as the minutes make clear, but in addition for the appropriate central funding for plasmapheresis. Of course plasmapheresis had been around for some time, it was simply a question of securing sufficient funds to increase its use.

There was reference in the same section of the minutes to the fact that some Haemophilia Directors were apparently going over to commercial heat treated Factor IX. I reported on the current progress of our Factor IX work.

There was some reference to the redevelopment of BPL (paragraph 6/85) and by this stage, it will be seen that the Minister had allowed £35.35m. for the project (the Minister by this time was Mr. Kenneth Clarke).

Lastly, there was some discussion (see paragraph 8/85) of an RIA test for HTLV III. I was keen to pursue the idea that CBLA develop an RIA test for the aids virus. The meeting were generally agreed that it was vital that British tests should be developed as soon as practicable. In the event, we were never authorised to proceed with the development of our own test and instead Wellcome were in effect allowed a free hand to develop the test which was eventually was introduced in October 1985 in preference to the earlier U.S. Abbott test. As will be seen from the minutes, Dr. Stuart (of Wellcome) absented himself during the discussion of this particular item.

There follows a memorandum of the 1st February from Mrs. Winkleman to Peter Prince enclosing some test results on the 8Y product.

The next document of importance is a memorandum of the 4th February to Dr. Snape to Mr. Prince and Dr. Smith on the subject of batches of heated Factor VIII intermediate concentrate which had found to have a particularly low activity per vial (less than 150 iu). Dr. Snape indicates that he was not, at least for the present, approving the labelling and subsequent clinical use of these

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batches. **[What happened to these? In view of the shortage of heated product, were any low activity vials issued?]**

The next letter in the file is dated the 4th February and is a circular letter from Professor Bloom addressed to all the Haemophilia Reference Centre Directors. The letter was intended to follow up on our circular to Haemophilia Centre Directors and reflected the fact that David Smart, Chairman of CBLA, had suggested to Professor Bloom at the meeting of the CBLA on the 1st February, that he liaise with me about any aspects of our proposed course of action which he thought merited this.

I regarded the letter as somewhat unfortunate, since (1) we had gone to the trouble of circularising all the Haemophilia Centre Directors who in consequence would have been well aware of what our proposed course of action was, whereas Professor Bloom's opening paragraph suggested that what we proposed was known to a few Reference Centre Directors only who had the benefit of my confidence and advice. This really reflected that Professor Bloom had not properly read the material which we had sent out. However, (2) Professor Bloom suggests that there were various alternative courses of action open with regard to the interplay between heated intermediate Factor VIII and 8Y when in fact we were already committed to the course of action we were pursuing, i.e. producing as much heat treated Factor VIII intermediate concentrate as we could manage over the next few months, but with the intention of introducing the demonstrably superior 8Y product as soon as practicable by scaling up production from April onwards. I do not recall ever hearing from Professor Bloom with Haemophilia Centre Directors' views as a consequence of his writing to them. **[There is an indication that there is to be a meeting of Haemophilia Reference Centre Directors on the 18th February. We have no minutes of this meeting. It is suggested in Professor Bloom's letter that this would be the forum in which to discuss his characterisation of the alternatives. Did you or anyone from BPL attend this meeting?]**

There follows a retyped and revised version of the stock list for Factor VIII as at 1st February 1984, and the second page dated 28th January 1985 which is clearly intended to be part of the same document despite the date. These documents are of marginal relevance.

The next document of significance is a printed report headed "Oxford Haemophilia Centre" which gives results of the small pool unheated concentrate exercise which

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had been carried out at Oxford. This was really an update of results of treatment which had taken place quite some time before. As will be seen from the results, small pool treatment was not offering the protection against hepatitis which had been hoped for. For example the second batch referred to at the bottom of the first page of the paper was used to treat six patients and all developed hepatitis.

The next document in the file is an extract from Hansard giving details of a written answer provided by Mr. Kenneth Clarke to a question concerning the timetabling of the introduction of British heat treated Factor VIII, and the redevelopment of BPL so that self sufficiency could be achieved. The answer given by the Minister obviously used the 1984 returns (it was said that we were supplying almost half the National Health Service consumption of Factor VIII). These returns would have been the Haemophilia Centre Directors' returns so clearly the DHSS had access to them and making use of material from the Haemophilia Centre Directors. The answer also indicated that redevelopment of BPL was on schedule to open January 1986, but in the event, serious problems were experienced and commissioning was delayed for several years.

A further circular letter prepared by Dr. Snape and dated 7th February intended for distribution to all Haemophilia Centre and Regional Transfusion Centre Directors appears next in the file. It was intended to keep everyone advised of the steps we were taking to distribute heated intermediate purity Factor VIII concentrate. Dr. Snape indicated that the first despatches would be possible in late February and subsequently at monthly intervals thereafter. As the letter makes clear, consignments on a named patient basis would be sent to the Regional Transfusion Centre for onward distribution. Dr. Snape took the opportunity to address the question of the availability of heat treated Factor IX concentrate and made it clear that having regard to the thrombogenicity problem, heated Factor IX concentrate would be subjected to extended safety testing, including assessment in a dog model, prior to its release for clinical use. He reported that the work was progressing and we confidently expected to be in a position to begin general issue of heated Factor IX concentrate during July. In the event, Factor IX concentrate for clinical assessment was issued at around this time but the full issue of the product (and corresponding discontinuance of the unheated Factor IX concentrate together with recall of old stocks) did not occur until October 1985.

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Mr. Pettet's letter of the 7th February to Professor Bloom at the Haemophilia Reference Centre at the University Hospital of Wales (and also sent to six other Haemophilia Reference Centre Directors) followed up on their agreement to participate in a safety and efficiency trial of the heat treated Factor VIII intermediate concentrate. Although this is quite late in the day, we were still trying to get information on these products, notwithstanding that we were already well advanced with the development of the 8Y product. Immediately behind the letter will be found the protocol documentation for the use of the heated intermediate concentrate which, suitably adapted, was later used for clinical trials of the 8Y product.

Also on the 7th February, Dr. Snape wrote a memorandum to me which he copied to Dr. Smith on the Haemophilia Directors Hepatitis Working Party meeting on the 6th February. **[We do not appear to have the minutes of this meeting - are they available?]** Dr. Snape attended in my absence and Dr. Smith was also present at most of the meetings. It is clear from the memorandum that they took the opportunity of explaining once again what we proposed with regard to the supply of intermediate product and its subsequent replacement by 8Y. There is reference to Peter Kernoff arguing that profilate (wet-heat treated) would, at the moment, be the material of choice in virgin patients, given indications of freedom from transmission of non-A, non-B. This was in fact a personal view which he was expressing at the time. Profilate is not really a wet-heat treated product in the strict sense, be that as it may, it later transpired that profilate transmitted hepatitis NANB.

[Note that Chris Ludlam reported on the experience of treatment with one batch of Scottish Factor VIII used to treat 32 patients. 15 sero converted in 3 to 4 months; 1 patient sero converted after 9 months, whilst 16 remained negative for HTLV III AB - consider the implications of this when (if) it becomes necessary to identify batches which might have been infected with HIV].

The memorandum indicates that various ~~hepatitis~~ Haemophilia. B (Christmas disease) patients had sero converted. Dr. Snape commented that the data strongly suggested infection by one or two batches, but in any event, a significant number of HTLV III infected Christmas disease patients had been treated with only NHS Factor IX which strongly argued for haste in the manufacture of heated Factor IX.

Finally Dr. Snape reports that Eric Preston presented strong evidence based on paired liver biopsy results with a time interval of five years between biopsies, of

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progression of haemophiliacs to increasing severe forms of liver disease, arguably attributable to repeated exposure to NANB hepatitis virus. The data was to be presented to the annual meeting of the Haemophilia Centre Directors.

The next document of significance is a letter to Dr. Rizza at the Oxford Haemophilia Centre in a format which was also used for circularising the other participating Haemophilia Centres dealing with the practice to be followed in using the new 8Y heated concentrate. This set out details of the intended clinical trials and enclose the protocols for use which, as I have indicated previously, were originally formulated for use in connection with our heat treated intermediate concentrate.

On 12th February, Mr. Pettet, the Product Services Manager, prepared a pro-forma letter to be sent to Regional Transfusion Directors explaining the proposed method of allocation of heat treated intermediate Factor VIII concentrate. He advised "the allocations in the previously supplied pro-rata issue sheet for January-June 1985 (non HT product), will be used. However, as supply of HT-Factor VIII is limited until April, we are only able to supply 50 per cent of the monthly allocation."

On the 15th February, Dr. Smith wrote to Professor Bloom enclosing copies of the documents which at that stage had been sent to Dr. Rizza, Kernoff, Jones, Hill, Colvine and Winsley (the Haemophilia Centre Directors) in relation to the clinical testing of the new 8Y product. (This documentation comprised the protocols for that testing). The idea, as his letter makes clear, was to, inter alia, follow up on a long term basis the clinical records to ascertain whether there was any communication of NANB hepatitis and/or HTLV III.

The next document, which is an internal memorandum dated 20th February from Mr. Prince to Mr. Mallory entitled "Heat Treatment of CF Products in New Building", identifies a shortfall between our ability to heat products after delivery of the ovens which we were then awaiting, and our final estimated production once the redeveloped plant was commissioned. He identified that oven capacity would have to be increased further. **[In the event this was done in time for the commissioning of the new factory]**.

On 21st February, Professor Bloom replied to Dr. Smith thanking him for his letter and the forms regarding the 8Y concentrate. He said "I am very grateful to receive this information which at least keeps me in the picture and will avoid

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any embarrassment to me in various committee discussions in the future. I admit that sometimes in the past, I have been rather in the dark about the products that BPL have on line. It is only within the last few weeks that I have come to realise what the term "8Y" meant. You can imagine that as a member of CBLA and Chairman of the Haemotology Centre Directors, I have occasionally been handicapped by this lack of information and therefore especially grateful to receive your helpful letter." This is tacit admission that on occasions Professor Bloom simply did not listen to what was said in the various meetings that he attended or read material which was sent to him. 8Y was hardly a secret. Professor Bloom had by this time written a rather unsatisfactory letter to the Lancet which was, inter alia, critical of BPL and again evidenced a "from the hip" action on his part which was all the more mystifying because clearly Professor Bloom did not grasp what was going on. Professor Bloom apologised for any embarrassment that the piece may have caused. **[Do we have a copy of the offending letter or letters written by Professor Bloom to the Lancet?]**

This is followed by a memorandum dated 22nd February from myself to Mr. Armour, Secretary of CBLA, with a copy to the Chairman, David Smart. In this memorandum I drew attention to the recent correspondence in the Lancet by Professor Bloom. I said "You have seen copies of this correspondence and realised that adverse criticism of the NHS product is made in an area which the writer himself admits is theoretical, non-specific and unsupported by scientific data - hardly a scientific approach for a leader in the British field of haemophilia care."

I pointed out that as from the 1st February when he attended the CBLA meeting, Professor Bloom knew the response which we at Elstree were making to the problem of creating a more satisfactory Factor VIII concentrate than that which we presently had on offer which seemed to me all the more extraordinary given that his criticisms in the Lancet concentrated on a product he knew we were close to withdrawing. I deprecated the fact that a member of the authority should have written on a subject where he had access to privileged information at all, but the more so because the content of his correspondence was so wide of the mark.

The next item in the file is a reprint of a letter from Glen Pearce of the Washington University School of Medicine that appeared in the Lancet on the 23rd February. The letter is a follow up to the correspondence which had obviously been taking place on the subject of heat treated blood product. It said

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little which was new but it will be noted that he maintains that most haemophiliacs in the USA and Europe are sero positive. I am afraid that this was indeed the case by this time and was the reason why Haemophilia Centre Directors were well advised to target the relatively scarce resource of NHS heat treated product during the early part of 1985 to virgin patients or other categories who might benefit rather than using the product on those who were already infected with HIV.

The next document of importance is a letter from Dr. Snape to Dr. Duncan at the DHSS dated 28th February, in which he sets out, in some detail, the approach which BPL was adopting with regard to the manufacture and issue for clinical use of heat treated concentrates of Factor VIII and Factor IX. **[In the letter he apologises for failure to write sooner and suggests that this was a cause for embarrassment - what was the background to this?]** It was necessary to keep the Medicines Division advised of our approach both in relation to 8Y and the new heat treated Factor IX which was imminent, since the protocols which we were using would later form, together with other information, the basis of licence applications for the products. We needed to ensure that the approach we were proposing to follow was satisfactory to the Medicines Division so that we could feel reasonably happy that if all proved well, our licence applications would be granted at the appropriate time. **[Is this correct?]**

There follows a draft of the data sheet which we prepared to go to Haemophilia Centre Directors with the heat treated HL and 8CRV products. Under the heading "Warning", the following is stated:-

> "It has been reported that cases of Acquired Immune Deficiency Syndrome (AIDS) have been seen in haemophiliacs receiving blood and/or Factor VIII and other concentrates. The benefits of treatment should be carefully weighed against the risk of transmission of virus before the product is used. Unpublished evidence suggests that the heating conditions used may activate HTLV III added to similar concentrates, (1) but this remains to be confirmed by prospective studies. At least partial inactivation of NANBH virus(es) by heat is likely (2)(3) and heat inactivation of some model retroviruses has been described (4)."

The references referred to were:-

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(1) Centres for disease control. Update: acquired immuno deficiency syndrome (AIDS) in persons with haemophilia. MMWR33, 589-91(1984).

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

(3) Mozen et al. Heat inactivation of viruses in AHF concentrates. WFHXVI TH Congress, Rio de Janerio, 1984.

(4) Levi et al. Recovery and inactivation of infectious retroviruses added to Factor VIII concentrate. Lancet P72-3, September 29, 1984.

MARCH

The first item in this file is a useful paper put together by Brian Combridge of BPL, and Dr. Barbara of the North London Blood Tranfusion Centre on the subject of the "Effective Screening of Serum Donations for HBsAg at English Regional Transfusion Centres by Immunoradiometric".

Brian Combridge outlines the history of testing thus:-

> "Since 1970, pooled plasma received at the BPL from these Centres (i.e. the Blood Tranfusion Centres) for the processing of coagulation and other plasma protein fractions, has been screened for the presence of HBsAg. Initially screening was by discontinuous immuno-electroosmophoresis (a first generation test) followed by reverse passive haemogglutination techniques RPHA (2nd generation tests). Since 1979, however, all incoming plasma pools have been screened by a 3rd generation immunoradiometric test."

Table 1 in the paper shows the chronology of usage of the 1st, 2nd and 3rd generation tests by both the BPL and the Regional Transfusion Centres and shows the number of positives found by BPL on re-testing. It is very significant that the number of positives found by BPL on re-testing have dropped to zero by 1984 when both the Regional Transfusion Centres and BPL were using the same RIA

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test. The 3rd generation RIA test had been in use at BPL since 1979, and this really coincides with the period when it can be said that hepatitis B, through the screening at the BPL and the use of 2nd generation tests at the Regional Transfusion Centres (gradually replaced through the period by RIA testing) largely solved the problem of hepatitis B.

My memorandum of 4th March to Mr. Armour records, in the context of arranging a short scientific production seminar relating to Factor 8Y, that 8Y had by this time been launched into trials successfully.

There follows an internal memorandum from Dr. Snape to Dr. Harvey entitled "Establishment of a R & D Virology Facility" which simply records the fact that there is a continuing interest in and necessity for such a facility, but problems with regard to obtaining adequate provision for it. We now have such a facility and I suspect that the memorandum is therefore of questionable relevance.

The next document of significance in this section is a circular letter written by Mr. Pettet to Regional Transfusion Directors and Haemophilia Reference Centre Directors on the 19th March setting out more details of the arrangements being implemented for the issue of the heated intermediate Factor VIII concentrate. He reiterates that the amounts to be made available will be approximately 50 per cent of those which would otherwise have been supplied as unheated concentrate, and also points out that the response to an initial request for named patient submissions has been slow. In the circumstances he suggests that in the interests of supplying the heated concentrate as soon as it becomes available, Regional Transfusion Directors should liaise with their Haemophilia Treatment Centres to determine an agreed system of allocation wherever possible meeting the restrictions for named patient use as required under the licensing arrangements and regulations. [Did this mean that **where it could, BPL issued suitably labelled bottles but otherwise issued the product to Regional Tranfusion Centres and left it to them to ensure that appropriate names were submitted to them before the product was released?**] Mr. Pettet's letter also makes reference to the anticipated introduction of 8Y in June/July, and advises that clinical trials are under way, and that the results were encouraging. He said:-

> "In addition to improved specific activity (and a consequent improvement in solubility) it is anticipated that this product will tolerate more aggressive conditions for complete viral inactivation."

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There follow a number of data sheets giving information about 8Y which was then in the course of testing. But of particular interest is table IV entitled "Viral inactivation of other Viruses in BPL by heat treatment" which shows a high kill rate virus (although of course we could not test its effectiveness in relation to hepatitis NANB or HIV for which there were no tests available at the time).

The next document of importance in this section is a paper which I prepared and is entitled "Licensing Arrangements for Heat-Treated Factor VIII and Factor IX". The paper was essentially prepared for the file, since there was very little we could do about obtaining product licenses until we were established in a new and satisfactory manufacturing facility. By this time the prospects of our being installed within a reasonable timescale appeared to be reducing. **[There is a suggestion that with regard to Factor 8Y, an abridged licence application would be developed and that it was expected to have delivered the licence application by June 1985. Did this happen?]** and IX (Heat treated)

The next document in this section which is of importance is a summary of a telephone conversation which took place between Dr. Snape and Dr. Finlayson of the office of Biologics in the United States. The telephone call took place on the 21st March 1985. The purpose was to enquire about the current position with regard to Aids tests. This followed the FDA approval of the Abbott HTLV III AB test. In the course of the conversation, Dr. Finlayson gave information about the approach adopted where an HTLV III AB positive result was obtained in relation to a donation. Interestingly, Dr. Finlayson said that there was concern expressed by US manufacturers, which he obviously viewed with moderate disbelieve, that a policy of excluding HTLV III AB positive donors from HBsIg donor panels would decimate the donor panel unacceptably. This refers to hepatitis B vaccine donors. He also said that manufacturers where, on the whole, assuming that the conditions of the Cohne ethonol fractionation method used to produce the vaccine was destructive of HTLV III virus. As I have indicated, it later transpired that the vaccine did not contain the Aids virus. **[Check carefully that this is the correct interpretation to put on the record of the telephone conversation].**

There follow the agendas for the forthcoming meeting of the Central Committee for Research and Development in Blood Tranfusion which was due to take place on the 2nd April, and the agenda for the CBLA meeting to take place on the 27th March. These are followed by the minutes of the CBLA meeting on that day.

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The minutes record at paragraph 23.1 that Wellcome had approached CBLA to assist in distributing the HTLV III test that they were developing. **[What happened about this - did we participate in any trials or provide any assistance?]**

Although plasma supply and the redevelopment of the BPL were further discussed, little of any significance emerged. There was reference at paragraph 30/85 to a paper I prepared on heat treatment of Factor VIII and Factor IX - Licensing. **[I believe this is the document which I refer to above as having originally been prepared for the file - is this correct?]**

There were no other matters of relevance to the current litigation discussed at the CBLA meeting.

becomes 8Y

The next document of significance in the file is a progress report on 8Y related research work covering the period October 1984 to March 1985. This seeks to summarise the scale up and production work which followed the research work that had resulted in "unheated heparin VIII" which had been referred to in the previous progress report prepared by Dr. Smith. In this paper Dr. Smith outlined the results of the work which Mrs. Winkleman was engaged upon and which had led to full quality control having been completed on 5 batches of PFL 8Y on both unheated and heated samples. The encouraging result was that no significant changes had been found after heating other than the expected 5 to 10 per cent loss of Factor VIII C activity.

The next item in the section is headed "Haemophilia Information Exchange - Aids Update/March 1985". This is in fact a U.S. document prepared by the National Haemophilia Foundation and seeks to give some basic information on Aids. At paragraph 22, the question of whether heat treated products offer protection from Aids is addressed, and the reply is interesting:-

> "It is not known for certain if the heat treatment of concentrates has eliminated their potential to transmit AIDS. It is, however, becoming apparent that some viruses are heat sensitive. There is now preliminary evidence that HTLV III is quite sensitive to heat treatment processes used to treat concentrate.
>
> For this reason, NHF's Medical and Scientific Advisory Council has recommended that heat treated concentrate should be strongly considered for patients now on Factor VIII concentrate. The same advice has been

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given for recently released heat treated Factor IX concentrate. The Centers for Disease Control in Atlanta has endorsed these views."

It is interesting to see that even in the United States a degree of caution is apparent when it comes to advocating the use and effectiveness of heat treated Factor VIII.

The next item in this file is a circular letter sent out by Dr. Galbraithe, the Director of PHLS to various PHLS Laboratories asking them to report all newly detected persons with the HTLV III antibody and, at the same time, to group these under one of the categories set out in his letter. The pro-forma documentation for use by the Laboratories appears immediately behind.

APRIL

The first item of importance in this section comprises the minutes of the Central Committee for Research and Development meeting which was held on the 2nd April. At paragraph 4/85 under the heading "AIDS", there are two sub-headings; "Introduction of Anti HTLV III Testing in BTS" and "Use of Heat Treatment on Factor VIII and Factor IX Preparations". It is recorded in paragraph 4.1 that two firms have been licensed by the FDA for an HTLV III test. **[What was the second company apart from Abbott?]** The concerns for the BTS were outlined by Dr. Gunson in the following terms:-

"(a) Obtaining a proper evaluation with the U.S. tests on donor population would be difficult, and the U.K. might have to consider doing its own.

(b) The implication of the test was not really known. A positive test indicated that donor had been exposed to virus may exhibit no signs of illness. Implications regarding transmission to others or personal health could not be determined at present.

(c) Whilst persons in a high risk group were currently being asked not to donate blood, some might be attracted to donor sessions simply in order to be tested, if the BTS introduced a test unilaterally.

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(d) If tests were not introduced simultaneously in the U.K., public concern was possible if certain regions fell behind schedule."

It was reported that evaluation studies for the tests had been set up. In effect the DHSS and the PHLS were involved in this exercise and CBLA had no part to play. As will be seen, the Chairman asked about testing in the haemophiliac population and Dr. Rizza and Professor Luzzatto informed the Committee of tests they had carried out in Oxford and at the Middlesex Hospital, and the results of these had confirmed the importance of evaluation. **[Presumably they were using the Abbott test at the time?]**

In relation to heat treated products, I reported our hopes that the heat treated Factor VIII which we were producing would deal with HTLV III. I reported on the work we were carrying out on 8Y, and the problems which we had run into with regard to Factor IX, where there was an elevation of thrombin activity consequent upon heat treatment. Dr. Rizza reported that his initial usage of the new 8Y product suggested there were no adverse side reactions. He was proposing to continue with longer term experiments with respect to the investigation of transmission of non-A, non-B hepatitis.

In his letter of the 4th April to Dr. Kernoff of the Haemophilia Centre at Royal Free Hospital in London, Dr. Smith reported on stage 1 of the clinical trial of 8Y. These were effectively the first test results and appeared satisfactory for our purposes.

This is followed by an internal memorandum from Dr. Smith to myself dated the 4th April 1985, on the subject of heated Factor IX concentrate.

As Dr. Smith makes clear in the first paragraph of his note, we had determined that there must be a programme of animal testing before releasing any modified Factor IX concentrate due to the problems of thrombogenicity. By the time the memorandum was written, these experiments were under way.

In paragraph 2.1, Dr. Smith identifies the problem which had arisen and which caused the delay (albeit a fairly slight one) in the heat treated Factor IX development programme. During the early stages of experimentation, the NAPTT test [for thrombogenicity] was employed and indicated that there was no significant problem with regard to the presence of thrombin. However, when, quite late in the research programme, the full range of tests acquired by the

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British Pharmocapoeia and the European Pharmocapoeia were applied to the product, to our surprise it emerged that heating had led to an increase in the free thrombin to a level which was above that which we considered acceptable. The result did surprise us since the additional tests required by the British Pharmacopoeia and European Pharmacopoeia were not thought to have any physiological significance and that any particular problems in the area of thrombin would have been thrown up by the NAPTT tests.

The discovery of this problem at a late stage reinforced the need, once the problem had been tackled, to use dogs in experimentation before clinical trials were commissioned. Dr. Smith's memorandum indicates the technical solution which was employed to protect the heat treated Factor IX from thrombin generation during heating (effectively with the addition of pasteurised AT III). **[What is this?]** The programme for dog infusions is dealt with at paragraph 3, and at paragraph 4, Dr. Smith sets out some alternative courses of action aimed at securing as earlier release of the heated Factor IX for treatment of patients as possible, having regard to the problems of testing to ensure safety and efficacy. Pending a decision (which was anticipated would be taken at BPL on the 8th May) the interim policy was summarised at paragraph 5. Dr. Smith indicated that PFL would aim at the most rapid possible provision of a finished 9D (as the heated Factor IX was called) plus AT III for dog infusions in clinical trial (and potentially the most pressing treatment of little exposed patients).

It was decided not to interfere with the planned dog infusions due to take place during April of one batch of 9D minus AT III, but Dr. Smith indicated that the second trial product would be 9D plus AT III (in light of the thrombin problem which had revealed itself). The difficulty was that we had embarked upon the dog trials using the product which later revealed itself as having more thrombin than we wished, and we were effectively having to change course part way through the trial using the revised heated Factor IX adapted to reduce the generation of thrombin.

Mr. Prince's memorandum to Dr. Harvey and others at BPL dated 10th April, records the installation of the two heat treatment ovens which we had been waiting for in order to accelerate production of heat treated Factor VIII and IX, and also records the fact that they were in the process of being commissioned and validated.

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There follows a letter from me to Dr. Collins at the Regional Transfusion Centre in Newcastle dated the 12th April 1985, acknowledge receipt of the agenda for the forthcoming meeting for the Regional Transfusion Directors to be held on the 17th April. The only point to note is that I commented on the absence, both in this agenda and its predecessor in 1985, of any reference to the questions of plasma supply and self sufficiency. They appear to have dropped out of sight as issues which struck me as rather odd.

The next document of importance in this section is a memorandum from Mr. Prince of BPL to Mr. Evans of PFL on the subject of the 8Y process. This deals with points of detail arising out of problems in "sieving" of fibrinogen/fibronectin precipitate during the 8Y production process. Since the equipment necessary for this purpose required to be obtained quickly, Mr. Prince asked that PFL investigate as a matter of urgency, how the removal of the precipitate might best be achieved.

There follows a further memorandum of the same date from Mr. Prince to Mr. Mallorey setting out equipment requirements in relation to the heat treatment of Factor IX. He also addresses the programme which would typically operate in relation to the heat treatment of Factor IX and how this would fit in with the heat treatment of 8Y.

The next document which is particularly relevant is a note of a PFL Working Party meeting on the introduction of heat treated Factor IX. This appears to have been the first meeting of its type and took place on the 16th April. Those attending include Dr. Smith. The purpose of the meeting was "to do for Factor IX what we had done for Factor VIII (but faster)".

The meeting concluded that the scientific evidence so far showed that 50 UL of AT III to Factor IX added to Factor IX added to Factor IX enabled heating at 80° for 72 hours without detrimental affects as far as thrombin was concerned. A decision was taken to proceed with this level of additive and, as will be seen on the second page of the note, the effect of this on the dog trial programme suggested that this would be complete in time to allow for clinical trials by the end of May or the beginning of June.

There follows a memorandum from Dr. Snape to Dr. Smith dated the 16th April commenting on Dr. Smith's memorandum of 4th April. This dealt with points of detail and again reflects the anxiety to keep up the pace of work on Factor IX.

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The next document of significance in this section comprises the minutes of the meeting of the Regional Transfusion Directors on the 17th April 1985.

As will be seen at paragraph 7, there was reference to BPL's heat treatment of Factor VIII. However, I was not present at the meeting and, as will be seen, the Chairman indicated he would write to me requesting up to date information on the position with regard to heat treatment.

On page 2 in the fourth paragraph, there is reference to a recent Aids meeting attended, by amongst others, Dr. Smithies. I do not know what this refers to.

At paragraph 7 on page 3, there is reference to appraisal work to be carried out on the Aids test which it was planned to introduce in October (this was the Wellcome test). As will be seen, the DHSS and PHLS were involved in arrangements for this.

The next document of relevance is a record of the meetings of the PFL Working Party on heated Factor VIII on the 29th March and the 18th April. The note records various points of detail which were arising out of the continued work on 8Y. It will be seen that the clinical trial results were described as very encouraging. I should also mention that we filed a patent application for 8Y on the 7th March.

In his memorandum of 18th April 1985 to me, Dr. Snape confirmed the solution to the thrombin problem which had been decided upon in relation to heated Factor IX. As will be seen, it was decided to add 50 units of antithrombin III per litre of diluted concentrate which would be effective in guaranteeing the compliance of heated concentrate with a fibrinogen clotting time limit of 6 hours at 37°c. He sought my authority to institute the appropriate change (which I subsequently gave).

There follows a memorandum from Dr. Snape to Mr. Pettet on the subject of the issue of heat treated Factor VIII concentrate. The memorandum identifies two potential problems. First that the Sheffield Regional Transfusion Centre did not appear to have received any heated Factor VIII. The suggestion was that there might be some problem in the Trent Region but the consequence was that the Nottingham Haemophilia Centre had not received its agreed allocation of heated Factor VIII. The second problem had arisen at Lewisham Transfusion Centre

where it appeared that one batch of heated Factor VIII had arrived with no indication as to how this was to be distributed to individual Haemophilia Centres.

[Can you comment on these two problems and also address any other complications which may have arisen and for which BPL might be accused of failing to do their best to assist the fair distribution of heat treated concentrate? There is a suggestion that Haemophilia Centres may not have properly co-ordinated their use of the relatively scarce amounts of NHS heated concentrate in such a way as to ensure that those patients who would properly benefit from treatment got heat treated product. With this in mind, we need to tackle any suggestion that BPL may have created problems in distribution.]

The next document of any significance is a memorandum from Mr. Prince to myself and others at BPL dated 24th April confirming that the Pickstone oven No.2 had been satisfactory validated and was in use producing 8Y. Oven No.1 was recorded as having been run several times but not achieving as tight a control over temperature as No.2. Further modifications/adjustments might therefore become necessary and Mr. Prince recorded that validation of the machine would continue as rapidly as possible.

On 26th April 1985, Dr. Fraser wrote in response to my letter querying the absence of plasma procurement and self-sufficiency from the agenda for the Regional Transfusion Directors' meeting, indicated that in fact these topics were discussed under the general heading of Heat Treated Factor VIII in the January and February meeting. He also indicates that the DHSS were conducting another survey on plasma procurement within the Transfusion Services and that the Transfusion Service was awaiting the result of the survey.

The next important document in this section comprises a "Preliminary Report of Studies on the Heat Inactivation of Factor IX Freeze Dried in the presence of Virus Markers - Virus Studies" prepared by Paul Harrison, BPL's Virologist. As the introduction makes clear, the study, in the absence of information on the nature of the agent(s) responsible for non-A, non-B hepatitis, concentrated on marker viruses believed to have similar properties. The studies to which the report refers chose polio virus as a marker. Given the lack of resources at the time, the test was really about all that could be managed and was really not nearly as stringent or as far reaching as we would have liked. **[We really needed to have appropriate equipment to do more extensive work with hazardous**

pathogens and I think it is therefore fair to characterise the exercise which was carried out as a very limited one.]

Another American publication entitled "AIDS Center News" which sets out in very general terms, recommendations on the approach to clinical management of haemophilia patients at risk for Aids or the Aids-related complex. Whilst the publication is of general interest, it contains little if anything which can be considered new. Again, however, it is interesting to note the relative tentativeness with which the issue of what constitutes the best and safest treatment is dealt with. See in particular paragraph 18 where, in response to the question "Is there an increased risk of developing Aids from the use of concentrate as compared to the use of cryoprecipitate or fresh frozen plasma?" the response is:-

> "To date, there is no specific evidence indicating that there is a greater risk with concentrate than with cryoprecipitate or fresh frozen plasma. While most of the patients with haemophilia who have developed Aids have been treated with concentrate, the proportion of persons with severe haemophilia treated exclusively with other products is so small that this observation is expected from the relative use pattern. Many Centers are currently studying this matter in an intensive fashion, and more information may be available in the future.
>
> The Medical and Scientific Advisory Council of the National Haemophilia Foundation has recommended that cryoprecipitate be used instead of Factor VIII concentrate under certain circumstances. For example, the exposure to fewer blood donors suggest that it is prudent to avoid concentrate, unless medically indicated, in patients with mild haemophilia. Similar guidelines should be applied to mild Factor IX deficient patients, where fresh frozen plasma has been used instead of concentrate.
>
> It should be noted that there is no evidence that AIDS is associated with any specific blood product or manufacturer."

[Is there some way that we can obtain the National Haemophilia Foundation recommendations?]

The last item in this section comprises a standard form of letter from Dr. Galbraithe, Director of the PHLS, to physicians in genito-urinary medicine

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thanking them for participation in the national surveillance scheme, and the further steps to be taken in relation to this exercise.

MAY

The first two items in this section are memoranda dealing with technical adjustments to the 8Y process. This is followed by a note of heated and unheated stocks of intermediate Factor VIII concentrate and 8Y as at the 2nd May.

The next important document in this section is a letter written by Mr. Pettet to Dr. French, the consultant dermatologist at the Department of Dermatology in Queens Medical Centre, Nottingham. The letter sets out in some detail the problems which were encountered in the initial issue of heat treated Factor VIII intermediate concentrate. Mr. Pettet explains in the letter that, initially, it proposed that the product would be issued direct to Haemophilia Treatment Centres on a named clinician/named patient basis. For this purpose we had requested a list of patients to be submitted to BPL to enable this exercise to proceed but the response from the majority of the Treatment Centres was very slow with the consequence that by mid-March BPL had received lists for only just over 50 per cent of the Treatment Centres. At the relevant time, Mr. Pettet explains, through efforts at BFL, BPF and BFL were in a position to issue heated Factor VIII on a limited basis and the new ovens had been installed which allowed greater heating capacity from 1st April. In consequence, at the beginning of March, the CBLA having been given advice by the Transfusion Service and the Haemophilia Reference Centres to issue heated Factor VIII on a regional pro rata basis through the Transfusion Centres proceeded to do so. **[How was this advice received - where do we see this evidenced?]** Mr. Pettet points out that it was apparent that the urgent need for NHS product outweighed the need for a full protocol follow-up and in any case many Centres were unable to fulfil its requirements. Accordingly, on the 18th March supplies of heated products were despatched to Regional Transfusion Centres for distribution to Treatment Centres who had supplied lists of patients by that date. Clearly there had been a problem in relation to Dr. French's patients since Mr. Pettet indicates that his letter of 13th March (presumably listing patients for treatment) arrived too late for inclusion in the issue list sent to the Sheffield Transfusion Centre from which Nottingham would have drawn its products. Mr. Pettet advises Dr. French that BPL should be in a position to issue an allocation of heated Factor VIII to each

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Transfusion Centre at between 50 per cent and 60 per cent of that for unheated product for May and June and that by July the new 8Y product would begin to replace the intermediate. He ends by saying that the present heating methods appear to have no effect on the NANB virus, at least from the published studies so far but in fact as our later studies showed the heat treatment we were applying to the BLP/BFL products worked so far as any NANB was concerned.

BPL/PFL

The next document of significance is a memorandum from Dr. Snape to myself dated 7th May in which he advised me that Peter Kernoff **[insert his position]** had indicated that he might imminently decide to discontinue the use of unheated NHS Factor IX treatment for his Christmas decease patients. Seemingly there had been one case that Dr. Kernoff had treated where he was absolutely confident that only NHS Factor IX had been used but the patient had become sero positive for HGV III antibody. As the memorandum indicates, they were presently evaluating the heated Factor IX produced by Alpha Therapeutics but their preliminary studies showed a tendency to raise FPA levels in some patients. **[What is this?]**

HTLV.

The next relevant document in the section comprises the report prepared on the PFL working party on introduction of heated Factor IX second and third meetings which had taken place on the 2nd and 16th May. The information contained in the memorandum is largely technical but it will be seen that dog infusions were underway at this stage and seemed to be proving satisfactory.

There follow the Minutes of the CBLA meeting on the 22nd May. As will be seen plasma supply was again subject to discussion (see paragraph 43/85) and Dr. Gunson reported that a meeting had been held to consider data received by the DHSS from the Regional Transfusion Centres on projected volumes of plasma to be supplied over the next four years. **[The Minutes of the relevant meeting are said to be attached as an appendix but they are not.]**

Certain shortfalls in four areas were identified and the recommendations made during the course of the previous plasma supply meeting were endorsed. Progress in the redevelopment of BPL was reviewed. At paragraph 50/85 there was reference to the Secretary of CBLA having had a six monthly meeting with representatives of the Haemophilia Society at which the Haemophilia Society had expressed some concern to the joint Parliamentary Secretary of State about the BPL Factor VIII and IX. There is reference to a reply outlining the facts having

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consequently been sent to the DHSS. **[Do we have a copy of this reply and what was this all about?]**

There were no other matters of any relevance dealt with at the meeting.

As will be seen from the memorandum for Dr. Harvey to various personnel in BPL dated 23rd May and entitled "Coagulation Factors - Development Project Teams" we were, by this stage, putting together teams to assist in the scaling up of production of 8Y and details of these teams appear immediately behind the memorandum in the file. The last item in the section comprising a memorandum of Dr. Smith to Mr. Prince and Dr. Snape entitled "Manufacturing of 8Y" (dated 31st May) again evidences the continuing work on 8Y at this time and indeed this was a feature throughout the period as we increased the level of production to that permitted by the buildings we were then occupying.

JUNE

The first item in this section is a letter from the Harrogate General Hospital dated 3rd June dealing with the receipt by the Hospital of 50,000 units of heat treated BPL Factor VIII. Affecting the somewhat unsatisfactory distribution procedures which were eventually resorted to and on which I touched earlier this letter evidences a typical problem where the Factor VIII was passed on by the Transfusion Centre but minus the associated protocol and paperwork that resulted and begun to be used for two patients who were HTLV III antibody positive. The Doctor in question, Dr. McEvoy, seeks guidance in the letter as to whether the heated products should be withdrawn from the two patients who are HTLV III positive.

There follows some further handwritten stock records showing the amount of heated Factor VIII, 8Y and unheated Factor VIII held by BPL as at 4th June.

Two memoranda dated 5th and 6th June respectively, the first from Mr. Montgomery to Mr. Prince and the second from Mr. Prince to Mr. Montgomery record the problems which we ran into in commissioning one of the heat treatment ovens. **[Did this result in problems with regard to the supply of heat treated Factor VIII?]** Dr. Snape's reply to Dr. McEvoy appears later in this section in the form of a letter dated 13th June. He passed on proper copies of the protocol and pointed out that the original protocol did not cater

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specifically for the follow-up of HTLV III antibody positive patients. As he says, "It was assumed that, in the trial phase at least, the heated NHS concentrate would be used primarily in HTLV III antibody negative patients." However as Dr. Snape points out in the letter the final decision on patient management was for the Doctor to make. For a patient who was already HTLV III antibody positive there was little to choose between heated NHS intermediate purity concentrate and heated commercial concentrate. We certainly did not indicate in the documentation which we sent out with the heated Factor VIII concentrate that should not be used for HTLV III positive patients although clearly the best use of what was a scarce resource was best made by identifying those categories of patients who might benefit from what appeared to be a safer product than the unheated one.

There follows a record of the PLF working party on heated Factor VIII concentrate fourth and fifth meetings which had taken place on the 30th May and 13th June and again this reports the progress with particular reference to the Factor IX with added AT III. Dog infusions continued. This is also picked up in a letter from Dr. Smith to Dr. Prowse at the Blood Transfusion Centre in Edinburgh written on the 14th June.

The last item of relevance in the section comprises another circular from the World Haemophilia Aids Centre in Los Angeles. This records the approval of the HTLV III antibody detection test by the FDA and states that "test kits to screen for the presence of HTLV III antibody were approved March 2nd 1985 by the US Food and Drug Administration (FDA). Three firms, Abbott Laboratories, Electro-Nucleonics Inc. and Litton-Bionetics have been licensed to market the kits. Two other Companies have applied also for FDA approval to produce the test".

The circular goes on to state that the American Red Cross immediately signed an agreement with Abbott and announced plans to begin phasing in the assay within days. Nationwide implementation was anticipated to take from two to six weeks. It records that government officials had stressed that the new blood test would have to be used cautiously since it was neither aeroproof nor a diagnostic test for AIDS. There is an interesting edited note at the end of the relevant section which reads "Readers are cautioned that this antibody test is a good screen for blood and blood products but is a poor test for diagnosis for patients. "It screens blood not patients"".

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Clearly the case of the introduction of the test in the US was in very considerable contrast to the timetable followed later in the UK.

JULY

The next document of significance is a paper prepared by Dr. Smith entitled "A New 'Virus-Safer' Factor VIII Concentrate of High Specific Activity". The paper was probably prepared as a briefing document for a CBLA meeting. It sets out basic details regarding the 8Y product but in the course of doing so, Dr. Smith says:-

> "Unheated concentrates made from the plasma of unremunerated donors in England and Wales have so far caused a very much lower incidence of HTLV III infection than most U.S. concentrates, but the incidence of NANBH transmission is almost as high."

As I have previously indicated, this still represents our general view.

The next document in this section is a similar summary prepared by Dr. Smith in respect of Factor IX. He touches upon the fact that laboratory tests had shown that a small amount of thrombin was released from Factor II present in the Factor IX as a consequence of heating, and that although the concentration of thrombin produced was not thought to be physiologically significant, we had taken the step of adding, as a precaution, a very small amount of antithrombin III before freeze-drying and heating. He goes on to state:-

> "All Factor IX concentrates also carry the risk of inducing thromboembolism in a few categories of high risk patients, e.g. those with liver damage or undergoing extensive surgery. Laboratory tests have been developed to measure the content of "activated" factors in concentrates, but these tests do not confidently predict untoward clinical side-effects. Any new concentrate, or new processing stages added, e.g. to inactivate viruses in the concentrate, should therefore be tested in animals before clinical trials; the preferred animal model in the U.K. is post-infusion detection of minimal DIC in dogs.
>
> The new concentrate 9A, dry heated after addition of AT III, has now been shown to be even less reactive than the parent 9D in the dog DIC

model. Clinical trial of immediate safety and efficacy has been planned in five Haemophilia Centres, to start on 12th July. Preliminary arrangements have been made, subject to satisfactory safety trials, to proceed to treatment of patients susceptible to NANBH and HTLV III transmission, starting in August. Current production of Factor IX concentrate in PFL and BPL has been easily adapted to incorporate the addition of AT III and heating in the ovens developed for heating Factor VIII."

This effectively summarises the position we were in at the start of July. A few pages further on, there is a summary of Factor VIII units issued during the course of 1985. The summary is dated the 9th July 1985. It reveals that we had issued 3.9m. iu of unheated Factor VIII against 4.3m. iu of heated during this period. The 3.9m. iu of unheated Factor VIII would only have been issued at special request.

Next in this section will be found the minutes of the CBLA Central Committee for Research and Development in Blood Transfusion meeting held on the 9th July.

Of relevance in these minutes, is a section on Aids (see paragraph 10/85). The Chairman (Dr. Gunson) said that there were five company tests now available for anti HTLV screening but that in his view, until a proper evaluation of the tests had been carried out within PHLS and the BTS, the introduction of the tests should not be used for routine screening of blood donations. BTS were, as yet, unaware of the most effective test as far as false positive results were concerned. It was reported that 6,000 donor samples were due to be tested at Edgware and Manchester and the results would be analysed as the studies continued. Six PHLS Laboratories in addition to PHLS Colindale were being set up as Reference Laboratories.

Professor Bloom, speaking in his capacity as Chairman of the Haemophilia Centre Directors, said that whilst he appreciated the need for a proper evaluation of the tests as a representative of "users", his immediate priority was the protection of recipients from Factor VIII and he therefore considered that any undue delay in the introduction of the tests would be unreasonable.

I made the point, in the context of the possibility that any excess plasma products we might produce could be released onto the commercial market, that these would require licensing by the FDA and this in turn would lead almost

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certainly to an FDA requirement that there be routine screening of donations by an FDA approved test for the HTLV III antibody. Dr. Gunson's reaction was that it was possible that an FDA approved test was not necessarily the most appropriate for the BTS.

At paragraph 10.2 in the minutes, I reported progress with regard to the heated Factor VIII and Factor IX concentrates (probably using Dr. Smith's two memorandum on which I have commented above). I described the Factor VIII as "virus-safer". Our problem continued to be that we could not show the efficacy of viral kill in relation to HTLV III. By and large this sort of experiment requires you to start with 6 logs of virus per cubic meter, and with HIV you could not get anywhere close to this level in patient plasma. This required spiking with extra virus **[which we did not have]**. Our assumptions regarding the effect of heating on HTLV III at this time had therefore to be based on the effect on a marker virus. Information which had come from Edinburgh suggested that heating **[at a similar level and for a similar length of time as ourselves]** killed 4 logs of vaccina which is recognised to be an especially tough virus which withstands a lot of heat. Given that the information we had regarding HTLV III at the time suggested that it was altogether a more fragile virus we had some reason for confidence that heat treatment was working for HTLV III, but of course we could not describe our Factor VIII heated concentrate as "safe".

The next document of importance in the file comprises the minutes of the Regional Transfusion Directors' meeting which took place on the 10th July. At paragraph 5 of the minutes there is, under the heading "AIDS", a description of the then state of affairs with regard to the introduction and evaluation of testing at Regional Transfusion Centres. As will be seen, it was appreciated from the comments made that there was media pressure to get on with testing, and it was at that stage hoped shortly to begin the NBTS testing in the valuation exercise to determine what tests should be adopted. There was quite a lot of discussion about the need to agree on the appropriate counselling procedures and practices to be introduced at the time testing began, across the board.

At paragraph 13 of the minutes I am quoted, under the heading of "Factor VIII" as summarising the position at that time with regard to the issue of Factor VIII. The minutes state:-

> "Up to April, non-heat treated material was issued; then between April and August, material was heat treated. In September the issue of the

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new product (8Y) will begin. Clinical trials appear satisfactory and a provisional license is likely to be granted in the late summer."

I should add an extra veneer to this statement in that heat treated material was only issued on request. Additionally at about this time I seem to have been somewhat caught up with the idea of applying for a licence. I can only think that I had in mind a clinical trial licence, since as matters then stood, we needed (a) a new building, and (b) a relatively long track record of use of the product before we could get a production licence.

The next document of importance is a summary of the PFL Working Party on heated Factor VIII concentrate, 6th and 7th meetings which took place on the 27th June and the 11th July. This mainly contains points of technical detail. Progress was entirely satisfactory at that stage, and indeed it is fair to say that the only real "hiccup" was caused by the discovery of additional thrombin in the heated Factor IX at the start of the year.

On 15th July, Mr. Perry the Director of PFL wrote to me suggesting exchange of information with regard to the clinical evaluation of our respective heat treated products. The Scot's Factor VIII product was heated at 68° for 24 hours. I would only comment that here again we see England and Scotland going entirely their own way. One might say, given what had been achieved with regard to 8Y, that there would have been some sense in PFC asking whether they could make 8Y rather than incurring further time and cost on developing and testing a product which seemed to be inferior.

The next document in this section which appears worthy of comment comprises the minutes of the CBLA meeting which was held on the 24th July. There is a note at the end of paragraph 61/85 which reads: "The latest position in regard to anti-HTLV III testing in the NBTS was noted" which suggests that there was a discussion about the topic. Since Dr. Gunson was at the meeting, it was likely that, given his central role in this, he took the opportunity of up-dating members of the Authority on progress.

A few pages further on will be found a paper entitled "Evaluation of the MARP.01 Programme and other Capital Expenditure Projects between 1981 and 1983". This paper designated CBLA85/39 makes clear that the total cost of the MARP.01 project at 1985 prices came to £3.038m. which may be compared with the original £1.3m. that the Minister authorised. The value of the product which this

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investment produced we calculated at £12.257m. so it was clearly money well spent.

There follows a copy of the information sheet which we issued to Haemophilia Directors and Regional Transfusion Directors in England and Wales in July 1985 on the subject of 8Y. The information sheet gives full particulars of the heating to which the concentrate has been subjected. With regard to virus activation, we said:-

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

With regard to distribution and targeting of patients, we said this:-

> "Factor 8Y will be issued through Regional Blood Transfusion Centres, unless special provisions exist by agreement for product to be sent direct to the Haemophilia Centre. Allocations to the BTS will observe the pro rata requirements for distributions agreed between BPL and the BTS except for 8Y required to fulfil the special needs of clinical trials to provide information for product license application.
>
> It is recognised that, until the new production unit at Elstree is completed, output of 8Y will meet about one third of current demand for concentrate and, for this reason, attempts have been made to define those patients likely to benefit most from the security inherent in 8Y.
>
> Therefore Haemophilia Centre Directors are being asked to compile lists of their patients considered "at risk" and most Centres have complied. It is the considered view at BPL that, where possible, liaison between Haemophilia Services and the BTS should aim at directing 8Y to these patients, using the existing framework of distribution and supply.
>
> Haemophilia patients who are HTLV III AB negative and have no history of hepatitis are being identified as suitable persons to comply with clinical trial requirements. This treatment group is under separate discussion between the trial Centres and BPL."

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There follows a letter to Regional Transfusion Directors confirming that 8Y would commence issue in September 1985 at the level of 7,500 vials (250 iu) per month. The letter was written by Mr. Pettet.

The last document in this section of interest comprises a letter dated 31st July 1985 written by the consultant at the Doncaster Health Authority to various other doctors, including Dr. Fraser at the Bristol Regional Transfusion Centre, and Dr. Wagstaff at the Sheffield Regional Transfusion Centre on the subject of counselling and management of those who tested positive for HTLV III. This merely reflects the concern that testing should go hand in hand with counselling which was the general concern of all of those involved in the Blood Transfusion Service.

AUGUST

The first few documents in this section give details of the publicity we put together on 8Y and the heat-treated Factor IX for the British Society for Haemostasis and Thrombosis Annual General Meeting which was to be held between the 25th and the 26th of September. The documentation is in the form of an abstract and in the case of 8Y the publication was going to be by means of a poster and in the case of Factor IX an oral presentation.

SEPTEMBER

[The first item in this section comprises a page from the British Medical Journal published on the 10th August. There is a letter entitled "HTLV III haemophilia, and blood transfusion" - only a very small part of which is reproduced - can we get the remainder since it seems to be relevant].

The next document of any significance is an internal record of the PFL Working Party on heated Factor IX concentrate 8th and 9th meetings which took place on the 1st August and the 10th September. Again, the content is mainly technical but as will be seen from the final paragraph, the issue of 98 haemophilia centres was poised to take place by this time.

On the 18th September a further meeting of the CBLA took place and the Minutes are the next significant document in this section. However, the only

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reference to issues which are relevant is to be found at paragraph 87/85 of the Minutes where there is a short reference to Mr. Williams (from the DHSS) enlarging upon the Government's action in asking health authorities to draw up plans for a nationwide AIDS counselling service. Beyond that the meeting did not deal with anything relevant to the present litigation save to say of course that the redevelopment of BPL was a continuing exercise at this stage and was accordingly always the subject of discussion at the CBLA meeting.

The next paragraph which merits comment is a document entitled "Interim Report on Survey of HTLV Antibody in Haemophiliacs in the UK" and is dated the 27th September. The authors are Dr. Rizza and Dr. Spooner at the Oxford Haemophilia Centre. This is very useful in that it gives a summary of the survey of patients tested for HTLV III in August 1985. Of course this was all, in effect, too late since we were by this stage heat-treating Factor VIII and poised to distribute heat-treated Factor IX. At the relevant time returns had been received from 81 of Haemophilia Centres (74 per cent). A total of 2,570 patients had been tested. 44 per cent of haemophilia A patients tested were found to be positive and the prevalence in severe haemophilia A was 59 per cent. The prevalence of HTLV III antibody in patients suffering from Christmas disease was, however, much lower with only 6 per cent of those tested testing as positive. Since there is nothing in Factor IX which makes it less likely to transmit HIV this would seem, as I have said earlier, to be evidence supportive of the contention that blood products made from English and Welsh donations would have been inherently safer than the equivalent commercial product where the raw material came from US donors.

The next document on which I shall comment in this section is a re-print from the answer of 28th September where a piece was published by Dr. Kernoff and others on the subject of wet-heating. The letter proposes that wet-heating might be safer than dry-heating on the basis of study of 18 patients which had been undertaken. However, 4 were treated with the same batch of Profilate heat-treated Factor VIII produced by Alpha Therapeutic and they caught NANB Hepatitis. We have, so far, had no evidence that anyone treated with 8Y has caught NANB Hepatitis with a consequence that the conclusions of the authors of the letter have in retrospect been shown to be wrong.

At the end of this section is an AIDS pamphlet produced by the National Blood Transfusion Service dated September 1985. In a real sense this was "closing the

stable door after the horse had bolted" since the solution for haemophiliacs had already been devised.

OCTOBER

The first item to draw attention to in this section is the information sheet dated October 1985 on the heat-treated Factor IX concentrate. This confirms that from October heat-treated Factor IX concentrate would replace the previous product and the information sheet gives details of the heat treatment. The information sheet states:-

> "Clinical trials at specified haemophilia centres are now in progress to gain evidence of reduction or elimination of viral transmission, particular NANBH virus transmission. Further assurance is sought over freedom from risk of viral transmission."

The next page in the section is a pro-forma letter which Dr. Snape wrote to Regional Transfusion Centres requesting them to return unheated Factor IX type 9D concentrate now that the heat-treated Factor IX concentrate was available. Amazingly some haemophilia centres failed to return their unused unheated stocks. As I previously mentioned we did not recall unheated Factor VIII in view of the more complex situation existing in relation to the supply of Factor VIII.

First, we were unable to supply the same proportion of heated Factor VIII concentrate as we had previously been able to supply as unheated Factor VIII. Some clinicians made an informed choice to keep using the unheated Factor VIII for a variety of reasons. Second, at the time unheated stocks were still available on request there was a choice which the clinician could make to use commercial heat-treated product. In contrast the English and Welsh requirements for Factor IX concentrate had been solely left from products made at BPL/PFL and in the circumstances there was only very limited use of other rival commercial products. Accordingly a clean break could be made in relation to Factor ~~VIII~~ IX since we controlled the supply but this was not possible for the reasons given in relation to Factor VIII.

Although one of the next items in the section entitled "Notes of the Regional Transfusion Directors' Meeting Blood Products Laboratory 2 pm, Tuesday, 8th October 1985" suggests (see item 1) that we were close to commissioning the

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new factory, so close in fact that documentation for this was being prepared, in reality it was quite different as it later transpired. We were certainly encouraged by Matthew Hall in the belief that commissioning was likely to take place about 3 months later than originally planned but the reality was that the slippage was much greater and commissioning was still some way off. Nevertheless, at the time I addressed the Regional Transfusion Directors' meeting it seemed to be reasonably imminent and I gave them details of what we hoped our production would comprise. Dr. Smith reviewed the history of the development of Factors 8Y and 9A.

On page 8 of paragraph 5 there is discussion of two AIDS cases who had donated blood in the northern region. The plasma donations deriving from these sources (5 in all) had gone into many blood products. This included 5 batches of Factor VIII, all of which had been issued and used as non heat-treated, 3 batches of Factor IX, all of which had not been issued and 9 batches of albumin (all heat pasteurised at 60°c for 10 hours).

Dr. Snape drew attention to other similar cases that had been notified in the last few months and said that the implications for BPL were of concern as many batches might have to be withdrawn from release. **[Was any record kept of the enquiries which resulted from transfusion centres identifying HTLV III positive donations which were already in the system? Can Dr. Snape assist in giving more information regarding the tracing of "hot" plasma and blood products?]**

In the Minutes of the Regional Transfusion Directors Meeting which took place on the 9th October there is again reference to AIDS on page 2 at paragraph 4. It is said that the HTLV III screening is in hand and the training of staff complete. All Regional Transfusion Centres were to start full testing by the 14th October 1985. The issue of what should happen with regard to untested donations was raised. It was agreed that wherever possible back-testing would be carried on in-date material. It was felt important that BPL should accept and process FFP and time expired plasma for heat-treated products which might not have been tested. I stressed that such material must clearly be identified and BPL given notice. **[What happened with regard to BPL testing?]**

Although heat-treated Factor VIII concentrate was poised to be released in October the PFL Working Party on the subject continued to meet at the Minutes of the 10th meeting which was held on the 15th October appear in this section.

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Again, the contents of the memorandum is technical. By this stage, the party were effectively tying up loose ends of the research.

The proforma letter prepared by Mr. Pettet dated 17th October shows that we set up a clinical trial for heat-treated Factor IX at the same time as switching to issuing the product replacement for the unheat-treated version.

[There is an agenda for the 16th meeting of the UK Haemophilia Centre Directors to be held on the 21st October 1985 in the file. Where are the minutes of this meeting?]

The last document in this section comprises a note by the DHSS for the Advisory Committee to the National Blood Transfusion Service. This describes the publication of the AIDS leaflet in September and the contents of that leaflet. It goes on to give a brief history of HTLV III antibody testing. The note states that in February 1985 the Department alerted Regional Health Authorities to the need to fund the introduction, later in 1985, of routine testing for HTLV III antibody of all blood and plasma donations. The Department funded a two-stage evaluation of various commercial test kits; the first stage at BHLS was completed, the note states, in July 1985, and the field work of the second stage involving two Regional Transfusion Centres was completed in September 1985. The note says that preliminary advice arising from the second stage had been given to Regional Transfusion directors. It is confirmed that routine screening of all blood donations was introduced in a co-ordinated manner from the declared date of 14th October 1985.

NOVEMBER

This information is again reiterated in the Minutes of the Advisory Committee on the National Blood Transfusion Service meeting held on the 6th November (see paragraph 7 under the heading "Acquired Immune Deficiency Syndrome"). As will be seen from the relevant paragraph the Communicable Diseases Surveillance Centre showed 241 AIDS cases with 134 deaths.

On page 3 under the heading "Self sufficiency", paragraph 11 records that I reported progress on the BPL project and said that commissioning would be gradual. I expressed concern about maintaining a quarantine supply of plasma. Mr. Williams of the DHSS advised the meeting that the plasma supply situation

seemed to be improving, with the forecast being a supply of 400 tonnes against 435 tonnes demand. It was agreed at the meeting that the DHSS would continue to monitor the conversion of regions' firm promises into action plans for plasma production. At this stage, therefore, it can be seen that the DHSS were playing a rather more decisive role than historically had been the case in encouraging increases in plasma supply to keep BPL functioning.

The next document in this section comprises the Annual Returns for 1984 which were given out at the UK Haemophilia Centre Directors' meeting held on the 21st October. These were forwarded to us on the 12th November 1985.

There are several points of interest in the Annual Returns. First, as to the number of patients on the treatment by this stage there were 4,918 haemophilia A patients known to Haemophilia Centres as at 31st December 1984. At the bottom of the first page it is recorded that the amount of NHS concentrate used by centres had increased and the amount of commercial Factor VIII had decreased and that for the first time since 1974 more NHS concentrate than commercial concentrate was used. This really reflects the MARP01 upgrading with the consequent effect on output. On page 2 it can be seen that the average consumption of Factor VIII approximated to 34,000 units per patient.

It is interesting to look at Appendix D(I) in these papers - UK Haemophilia Centre Directors Hepatitis Working Party Report 1984-85. Under the heading "Introduction of heat-treated Factor VIII" it is recorded that Travenol "dry" heat-treated concentrate showed little or no reduction in associated cases of Hepatitis and that Profilate "wet" heat-treated products had, as I have previously commented, passed on NANB Hepatitis to one of the batches used in the test. There is reference to a recent report of a case of HTLV III infection after transfusion of heat-treated Factor VIII. **[Do you know whether this was Armour product?]** Also interesting are the comments under the heading "Chronic non-A, non-B Hepatitis". John Craske, the author of this particular document, states that the recent report from Sheffield on the follow-up of patients with chronic liver disease and repeat liver biopsy shows that previous reports of relatively benign sequelae after acute non-A, non-B Hepatitis may have significantly underestimated the risk of serious chronic liver disease. Further evidence is the increasing knowledge of the seriousness of Hepatitis NANB which was only dimly glimpsed in the early 80s.

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Item 9 (Appendix G) is also interesting. This is a paper prepared by the UK Haemophilia AIDS Group entitled "Surveillance of cases of AIDS and AIDS-related illness". The paper records that there were, by that time, 10 cases of AIDS in haemophilia A patients and 1 in haemophilia B together with 1 in a spouse of a haemophilia A patient. By August 1985 there were 834 HTLV III antibody positive haemophilia A patients giving an accurate incidence of 1.1% for AIDS itself. Three of the AIDS cases occurred in patients with mild haemophilia where the exposure to high risk blood products occurred on one or two occasions only.

There is reference on the second page to identification of HTLV III infection associated with batches of Factor VIII, especially HL3186. There is a statement to the effect that Dr. Snape and Dr. Spooner together with Dr. Craske would review the latest information with regard to possibly affected batches at Manchester during the immediate future. It is stated that there appeared to be five identifiable batches of Factor VIII associated with HTLV III infection. **[What detailed information exists regarding Dr. Snape's work in this regard?]**

The next document in this section meriting comment comprises the Minutes of the CBLA meeting which took place on the 20th November. There is reference at paragraph 98/85 under the heading "Production" to a report on the production and issue of BPL products (the report identified as CBLA 85/53). **[Do we have a copy of this report anywhere?]** There is a reference to a fall in plasma volume processed, presumably by this stage however this is somewhat irrelevant **[query]**.

DECEMBER

The earliest documents in this section comprise correspondence from PFC in Edinburgh proposing a joint programme of research into HTLV inactivation. **[What became of this?]**.

This is followed by a letter dated 13th December from Miss Rawlinson, the Principal Scientific Officer of the National Blood Transfusion Service, reporting on the HIV tests carried out in November. This was, I believe, the first of the monthly reports which she has done on a monthly basis ever since. The total number of tests carried out in October were given as 187,147 with 3 confirmed positives. As will be seen two sorts of kit were being used at the time, the Wellcome test kit and the Organon test kit. The latter was dropped fairly

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quickly because of the number of false positives it gave. **[I thought that the introduction of testing was delayed to enable the Wellcome test to be universally introduced - what is this Organon test?]**

There follows the Minutes of the meeting of the Central Committee for Research and Development held on the 19th December. At paragraph 14.2 of the Minutes it is recorded that HTLV III antibody testing was underway and that all but four of the regional centres were using the Wellcome test. It was recorded that the MRC had set up a sub-committee of the working party on AIDS to carry out an epidemial logical research programme on the transmission of HTLV III virus.

UNDATED

The only document of any real significance in this section is an undated document prepared by Dr. Smith and Dr. Snape entitled "Changes in PFL fractionation section since last inspection". This was prepared some time in 1985 and seeks to summarise the changes which have occurred at PFL over the four years from 1981 when the Medicines Inspectorate inspected PFL. It is also descriptive of the work which was then currently underway at PFL.

The balance of the section comprises principally data sheets on our products which I have commented on, in the main, elsewhere. The very final document in this section is a fact sheet on AIDS but directed towards Blood Transfusion Service staff rather than the general public.

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