[DRAFT NO 5 DATED 10TH DECEMBER 1990]

HIV HAEMOPHILIA LITIGATION

DRAFT PROOF OF EVIDENCE OF
RICHARD SPENCER LANE

I, RICHARD SPENCER LANE, M.B., B.S., M.D. (London), M.R.C.P., F.R.C. Path, WILL SAY as follows:-

1. I am the Director of the Bio Products Laboratory which changed its name from the Blood Products Laboratory on **[insert date P1]**. Throughout my proof, I shall refer to it hereafter as the Blood Products Laboratory ("BPL"). I became Director in September 1978 (having been appointed Director designate with effect from 15th April 1977). In my capacity as Director, I am responsible for the day to day management of BPL and the Plasma Fractionation Laboratory ("PFL") and report to the Chief Executive (Mr. Bernard Crowley) and the Chairman (Mr. Ronald Wing) of the Central Blood Laboratories Authority ("CBLA") which has been responsible for the operation and management of BPL and PFL since 1st December 1982, and who are presently my employers.

2. I held various house appointments in paediatrics, medicine and surgery between 1959 and 1961, at which time I became Senior House Officer in pathology at the West Middlesex Hospital. Between 1962 and 1966, I was a research fellow

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in haematology in the Department of Pathology, Royal Maternity and Samaritan Hospitals, Glasgow, and between 1966 and 1973, was employed as Scientific Officer at the Medical Research Council Experimental Haematology Unit at St. Mary's Hospital Medical School, London. From **[P2]** 1969 to [ ] 1970 I spent time as a Senior Fellow of Medicine in the Department of Haematology and Medicine at the University of Washington, Seattle and at King County Central Blood Bank in Seattle, U.S.A. Between 1973 and 1975, I was lecturer in haematology at St. George's Hospital, London and between 1975 and the date I took up my appointment as Director designate at BPL, I was a Consultant Haematologist to the North East Thames Regional Blood Transfusion Centre, Brentwood in Essex.

3. I belong to the World Health Organisation Expert Advisory Panel on human blood products and related substances. I am a member of the International Society of Blood Transfusion ("ISBT") panel of experts on computerisation and automation in blood transfusion. I am a member of the Department of Health Advisory Group on Hepatitis and its Working Party on Anti-D and I am also a founder member of the British Blood Transfusion Society. I am also a member of the Department of Health Advisory Committee on the Viral Safety of Blood ("ACVSB").

I. INTRODUCTORY BACKGROUND

BPL

4. BPL has been established at Elstree since 1954 but I understand that its history goes back to 1943 when the Medical Research Council ("MRC") Blood Filtration Unit moved from the London County Council Laboratories at Carshalton to the Lister Institute of Preventative Medicine at Chelsea. With associated research on the preservation of human blood plasma and serum, large amounts of

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plasma were prepared for freeze-drying in the MRC plant at Cambridge serving military and civilian needs. Continuing under the joint management of the MRC and the Lister Institute on behalf of the Ministry of Health the title of the Filtration Unit was changed in 1946 to the MRC Blood Products Research Unit and the Unit pursued work which had already begun there on preparation of plasma fractions for clinical use. In addition, it continued the production of dried plasma in plants which were moved to Chelsea and Elstree following the closure of the Cambridge Unit.

5. Between 1954 and the commissioning of the present, much extended, manufacturing facility during 1987/1988, the Laboratory at Elstree underwent successive development to increase production of freeze-dried plasma to meet post-war National Health Service needs and enlarge facilities for plasma fractionation. It was managed on a day to day basis by the Lister Institute for the Ministry of Health (as it then was) which provided financial support for its operations through the agency of the MRC. The Lister Institute held the lease for the main site at Elstree.

6. Throughout its operations, BPL has been maintained and developed by direct financial support from the Ministry of Health (later the Department of Health and Social Security and now the Department of Health, collectively referred to hereafter as "DOH"). However, throughout its involvement with BPL, the Lister Institute acted as the employing authority for the staff working at BPL. Management of BPL was a complex affair involving the MRC who, on behalf of the DOH, maintained responsibility for policy, budgetary approval, planning and building developments, etc., until the early 1970's. Thus an extension to BPL which was commissioned in 1962 was controlled by the MRC.

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7. Growth and requirements for blood products arising from the development of new fractions, plasma protein fraction and dried antihaemophilic globulin (AHG or Factor VIII), resulted in the need for a further extension of BPL which commenced planning in 1965 and was commissioned as a new Large Fractions wing to the complex that already existed in 1972. By about this time, the MRC's role in management was diminishing as production became the dominant purpose for the facility replacing the earlier research based laboratory. The 1972 extension was built with the Lister Institute acting as the client body for the purpose of the building operation on behalf of the DOH. In 1975, the Lister Institute took over full responsibility for the administration of BPL on behalf of the DOH.

8. Within months of completion of the 1972 extension, the need for a further extension to the BPL facilities became evident. Pressures of under capacity coupled with outdated concepts of production enshrined in earlier building designs pointed to a completely new building being required. A vital and preliminary need was for a pilot process laboratory to examine new technology and process methods, outside main production. Plans were first submitted in 1975 but, although the need was strongly supported, in the event, approval in principle for a pilot laboratory was not given until 1990 by the DOH.

9. In September 1978 for commercial reasons, the Lister Institute ceased operations at Elstree. After realising its capital resources, the Institute returned to the support of basic research through a newly constituted trust body.

10. The closure of the Institute had immediate and far reaching consequences for BPL, and a series of significant events followed rapidly. The North West Thames Regional Health Authority ("NWT") met the interim need to take over as the legal employing Authority on behalf of the DOH. To secure BPL at Elstree, the DOH negotiated the acquisition of the whole Elstree site and

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buildings from the Lister Institute and completion of this acquisition took place during September 1979, the existing leasehold reverting back to the DOH. The acquisition of the land which surrounded the very small site on which BPL had been located removed a primary spacial constraint on the extension and redevelopment of BPL.

11. The management of BPL also altered in that the DOH and NWT now handled policy, planning and financial affairs through a Joint Management Committee ("JMC") for the DOH and had its first meeting on the 13th December 1978. With this new management group, came the conclusion of the existing advisory management body which was called the Advisory Sub-Committee on Blood Products and Blood Group Reference Laboratories of the Central Committee of the National Blood Transfusion Service. The JMC was further assisted by the formation of a Scientific and Technical Committee, and the Finance Sub-Committee, which were both set up during 1979.

12. The first Director of BPL, Dr. (later Sir William) Maycock, retired (in September 1978), and I replaced him as Director of BPL.

13. Although this is dealt with in greater detail below under the general heading of "Self-Sufficiency", I would mention at this stage that shortly after I became Director of BPL, the Medicines Inspectorate carried out a detailed inspection of the BPL facility in April 1979 (and subsequently the PFL facility), and reported that the Laboratory was seriously sub-standard as a pharmaceutical manufacturing factory. There followed a period of uncertainty during which basic and essential up-grading which had been planned prior to the Medicines Inspectorate visit was postponed, re-planned, modified and then approved prior to 1982, at which time CBLA took over responsibility for BPL and PFL, and before

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the DOH approved the building of a completely new manufacturing facility which, after certain difficulties, was eventually commissioned during 1987/1988.

PFL

14. I refer to the proof of evidence of Dr. Smith for further detail regarding the history of the PFL located at Oxford.

15. In the decade leading up to 1964, Professor R.G. Macfarlane and Dr. Rosemary Biggs developed a unit in Oxford with special expertise in blood coagulation. The unit developed a world reputation in haemophilia diagnosis and treatment. In 1964, Professor Macfarlane proposed that a Haemophilia Centre should be set up on the Churchill Hospital site in Oxford and that this should comprise a Coagulation Research Unit administered by the MRC, a clinical unit administered by the Oxford Hospital Board of Governors, and a laboratory for the fractionation of plasma which was to become PFL. Because of similarities with BPL, it was proposed that BPL should manage PFL on behalf of the Lister Institute.

16. New premises on the Churchill Hospital site were completed in 1967, and PFL was managed by Dr. Ethel Bidwell, a leading scientist who worked in Dr. Biggs' unit, and under the overall directorship of Dr. Maycock who was already administering the BPL. As with BPL, the funding of PFL was provided directly by the DOH.

17. These arrangements lasted until the closure of the Lister Institute in 1978 and over this period the PFL made a major contribution to the production of freeze-dried Factor VIII for the treatment of haemophilia A, and Factor IX for

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the treatment of the related disorder haemophilia B. Dr. Bidwell retired in 1981 having worked, together with myself, to rationalise activities at BPL and PFL. Following the commissioning of BPL's new production facility by 1988, the role of PFL has changed to provide pilot process capability in the continuing absence of a similar facility at Elstree. The Oxford Haemophilia Centre ("OHC") developed in parallel with PFL (and much of PFL's product has been directed to OHC), has thrived and is the largest Centre for the treatment of haemophiliacs in England and Wales.

CBLA

18. Both BPL and PFL together with the Blood Group Reference Laboratory ("BGRL") (whose activities are not relevant for present purposes) have, since 1st December 1982, been the responsibility of the CBLA. The CBLA presently comprises members who are as follows:-

Chairman:	**Mr. Ronald A. Wing, CBE FPS.** A member of the East Yorkshire Health Authority, Past Chairman of Sanoffi, a pharmaceutical company. Recent past President of the Association of British Pharmaceutical Industries.
Vice Chairman:	**Sir Vernon Seccombe, JP** Past Chairman of the South Western Regional Health Authority. Retired Electrical Contractor.
Members:	**Mr. Roderick Braithwaite.** A Management Consultant.
	Dr. Brian W. Cromie. Retired Chairman of Hoechst Pharmaceuticals U.K. Retired Chairman of Arthur Cox Pharmaceuticals. Chairman of Waverley Pharmaceuticals and a Director of Charter House Venture Fund Management Ltd. He has also served on the Medical Commission and the ABPI.
	Mr. Hamilton Dempsey, FPS. Chairman of Advertising and Design Associates.

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Dr. Peter Kernoff.
Director of the Haemophilia Reference Centre at the Royal Free Hospital and School of Medicine.

Miss Katherine Mellor.
A partner of Elliot & Co and Past President of the Manchester Law Society.

Mr. Colin Walker, OBE.
Chairman of East Anglia Regional Health Authority.
Managing Director of a farming company.

19. Under the Chairmanship of Mr. R. Wing the Senior Executives responsible for the day to day management of BPL and PFL are as follows:-

Mr. B. Crowley:	Chief Executive
Dr. R. Lane:	Director of Operations
Mr. B. Savery:	Director of Finance and Administration

Dr. T. Snape is Factory Manager.

20. The staff of BPL number approximately 380 and in the case of PFL about 30.

21. The first Chairman of the CBLA was Mr. R. D. Smart, who came to the CBLA with experience in pharmaceutical manufacturing: until 1982, he was the Commercial Director of Glaxo Holdings Limited. The then Secretary of State for Social Services, Mr. Norman Fowler wrote to Mr. Smart on 17th November 1982 (document no. 1569) setting out the CBLA's task which was to provide an effective management body for the three Central Blood Laboratories - the BGRL, the BPL and the PFL. The Central Blood Laboratories Authority (Establishment and Constitution) Order 1982 ("the 1982 Order") (Appendix 1) specifies the main functions of the CBLA. CBLA was established as a Special Health Authority and was to perform on behalf of the Secretary of State the functions specified below

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and such other functions as the Secretary of State might direct the CBLA to perform on his behalf:-

"(a) The provision of laboratories for the manufacture of blood products and other purposes;

(b) The preparation of plasma fractions for therapeutic, diagnostic and other purposes;

(c) Research and development in plasma protein fractionation and for other purposes;

(d) The manufacture of blood grouping reagents and other related reagents."

22. The various Committees established by the CBLA to deal with specific aspects of the management of BPL/PFL are outlined in Appendix 2.

THE NATIONAL BLOOD TRANSFUSION SERVICE ("NBTS")

23. This was constituted in 1946 from an amalgamation of the emergency transfusion services during the 1939-45 war. Initially the NBTS was centrally administered. In 1948 administration was delegated to the Regional Hospital Boards as part of the hospital and specialist services provided under Section 3 of the National Health Service Act 1946. There are 14 Regional Transfusion Centres (RTC's) in England and Wales (one in each Region except the South East and the South West Thames Region which is served by one Centre). Some regions have sub-centres. The RTC's in England are administered by the Regional Health Authorities ("RHA's") and financed by RHA's from the Regional financial allocation

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from the DOH. In Wales the transfusion service is administered by a District Health Authority ("DHA") on behalf of the Welsh Office.

24. Each RTC has a medically qualified consultant as a Director who is responsible to the RHA or DHA for blood transfusion services. The Director has supporting consultant and other medical staff, a lay administration and specialist staff for donor organisation, nursing and for the provision of laboratory services.

25. The corner stone of the NBTS has always been voluntary blood donors. In 1977, there were approximately 2.5m. donors on panels maintained at RTC's. At present the number is 2 million. A significant reduction in donors has followed the concern about AIDS. Also a **realise???** in other European countries, e.g. France. Although the NBTS underwent considerable functional changes over the period from its inception, throughout the period which is relevant to this litigation the organisation changed relatively little. It was, in effect, a loose confederation of 14 RTC's, regionally financed, which varied considerably from region to region and were neither controlled nor financed in the same way as BPL/PFL. There were effectively four links with the DOH:-

(a) There was a part-time Consultant Adviser on Blood Transfusion to the DOH.

(b) There were periodic (about 5/6 times a year) meetings of Regional Transfusion Directors. This "body" was not constituted statutorily. The meeting carried no executive function and although its purpose was, in part, to advise the Consultant Adviser, it served as an unofficial, informal mechanism for exchange of information between constituent units of the NBTS and the DOH.

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(c) A Central Committee for the NBTS was formed by the DOH on the recommendation of the Committee on the Future of the NBTS (1974) (the Reid Committee), which proposed terms of reference and the constitution of the Central Committee both of which were accepted by the DOH.

The terms of reference were:-

> "To keep under review, the operation of the National Blood Transfusion Service, including the Blood Products Laboratory and the Blood Group Reference Laboratory, in England and Wales and to advise the Department of Health and Social Security and the Welsh Office on the development of the service."

The part-time Consultant Adviser and two elected Regional Transfusion Directors were members of this Committee. The Committee included representatives nominated by the Royal College and other members in various specialities of medicine. The Chairman was the Deputy Chief Medical Officer of the DOH.

(d) There were regular meetings of the Regional donor organisers under the chairmanship of a senior administrator of the DOH. This particular Committee existed largely to review publicity material for blood donor recruitment, since much of this material, which was of a high quality, was produced separately by the DOH in conjunction with the Central Office for Information ("COI").

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26. I think it is fair to say (and indeed this is summarised in a memorandum which was produced in June 1977 as a submission to the Royal Commission on the NHS (document no. 554)) that the organisation which existed within the Transfusion Service during the period which is relevant to this litigation, limited the development of the national aspects of the service. The RTC's were poorly represented centrally as described above, and the Central Committee itself was only an advisory committee to the DOH and, on national or any other aspects of the Transfusion Service, the DOH was not (for procedural reasons) able to instruct Regions on the allocation of finance to RTC's. The RHA's were not necessarily involved in national policy-making for the NBTS, although central policies might require RHA's to commit allocations of extra funds from Regional budgets to finance development at RTC's.

HAEMOPHILIA

27. The term haemophilia characterises a group of conditions which have mainly a genetic basis and which result in a tendency to abnormal bleeding. Bleeding may be severe and be life threatening or cause severe morbidity. The bleeding is caused by a reduction in plasma levels of certain specific proteins which assist in the normal process of blood clotting. There are two main types, haemophilia A and B where the deficient proteins are Factor VIII and Factor IX respectively.

28. Haemophilia was described as abnormal bleeding in families in the 2nd century but the main defect was not characterised until nearly 100 years ago. Haemophilia B was not described as a separate condition until 1952. The clinical symptoms of haemophilia A and B are similar.

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29. Both haemophilia A and B are genetically sex-linked recessive bleeding disorders. The incidence of haemophilia is approximately 1 : 10,000 of the worldwide population, of which some 20% is of the haemophilia B type. Female haemophilia is extremely rare and probably represents marked expression of the carrier state. The genetic state may arise by spontaneous mutation in an estimated 30% of new cases.

30. The frequency and severity of bleeding in haemophilia may be predicted from the level of clotting factor in the plasma. Less than 1% of normal clotting activity may be associated with severe and frequent bleeding which occurs internally in many sites: however, the crippling effects of repeated bleeding into joints and muscles is a characteristic of the condition.

31. The control of bleeding by blood transfusion was demonstrated in 1840 but until 1964, when the preparation of cryoprecipitate was first described, effective treatment was limited by volume restrictions imposed by blood or whole plasma transfusion. During the past twenty years, successive improvements in the large scale preparation of purified potent freeze dried concentrates of Factor VIII and Factor IX have made the control of abnormal haemophiliac bleeding both more effective and safe. Whereas, untreated, a severe haemophiliac could have expected death or severe disability by the end of the third decade, new haemophiliacs can now anticipate a controlled active life of near normal length without unacceptable periods of hospitalisation.

32. Improved treatment has been paralleled by better diagnostic means and clinical management. The future holds the potential benefits of recombinant DNA-produced clotting factors and the possibility of gene-replacement.

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COAGULATION FACTORS: PREPARATION AND USE

33. BPL/PFL only fractionate plasma collected by the fourteen Regional Blood Transfusion Centres in England and Wales. Blood consists of a cellular component in an aqueous solution of proteins and salts known as "plasma". Blood is donated either as whole blood or as plasma collected by means of plasmapheresis. In plasmapheresis, the donor's plasma and red cells are separated at the time of donation and the red cells returned to the donor during the process of donation. Plasmapheresis enables the donor to safely donate more plasma than can be obtained from whole blood donation. UK practice permits a regular blood donor to donate up to three donations of whole blood a year. In contrast, up to 12 litres of plasma (approximately 20 donations) may be given in a year by plasmapheresis because the donor retains the red cells.

34. The raw material for BPL and PFL comprises outdated plasma from blood which has exceeded its shelf life of up to 35 days and Fresh Frozen Plasma ("FFP") which constitutes over 95% of source materials for fractionation. For the purpose of manufacturing Factor VIII and Factor IX only FFP can be used. Factor VIII and Factor IX concentrates produced from FFP by BPL/PFL and commercial manufacturers, were not the only method of treatment for haemophiliacs. Particularly during the 1970's and now, in exceptional circumstances, cryoprecipitate has provided an alternative treatment. Indeed this was the principal product used to treat haemophiliacs for a long time. BPL/PFL have never produced cryoprecipitate for treating haemophilia patients. This has always been produced by Blood Transfusion Centres. Cryoprecipitate is produced by freezing and the controlled thawing of plasma and, as I describe below, forms part of the fractionation process generally employed in the purification of Factor VIII concentrate.

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35. In contrast to the treatment of haemophilia using plasma transfusions or infusions of cryoprecipitate where, for reasons of injection volume, the product of only one or a small number of donors could be used to treat a patient, the manufacture of concentrates involves the pooling of FFP necessary for the efficient separation of the various proteins in the plasma. The concentrates of coagulation factors prepared from large plasma pools have the advantage of batch consistency and assayed potency.

36. In fact the fractionation process used to produce Factors VIII and IX, was not geared solely to production of these two factors, but enabled BPL and PFL to produce, from the same pool of plasma being fractionated, a number of other products which like Factors VIII and IX, were made available to the NHS for treatment of patients. At all material times, freeze-dried Factors VIII and IX concentrates together with immunoglobulin and albumin were the principal products produced by BPL and PFL.

37. Up to 1978, the intermediate Factor VIII concentrate produced at BPL was coded 8IP and from 1978 to 1985 was re-coded HL. During this latter period the equivalent product at PFL was coded 8CRV ("cooled reduced volume"). The intermediate concentrate freeze-dried Factor IX was coded 9D. These intermediate purity products were replaced by high purity freeze-dried heat treated Factor VIII concentrate called 8Y and freeze-dried heat treated Factor IX concentrate coded 9A in 1985.

38. The change which the availability of freeze-dried Factors VIII and IX concentrates brought in the treatment of haemophiliacs became marked during the 1970's. In the early part of the decade, cryoprecipitate was used in the majority of cases for the symptomatic or elective treatment of bleeding. Gradually as the scale of freeze-dried Factor VIII concentrate production at BPL and PFL

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increased through the 1970's augmented over the same period by the importation of similar products from commercial manufacturers in the United States, the demands of haemophilia care rapidly increased the forecast for national use of concentrates. In particular, it enabled severe haemophiliacs to lead near normal lives by using Factor VIII concentrate in a prophylactic manner to prevent the occurrence of bleeding.

39. Neither Factor VIII nor Factor IX were without risk. From the beginning, it was known that blood and its derivates - plasma, cryoprecipitate and concentrates were sources of hepatitis B virus transmission. Additionally, Factor IX gave rise to problems from various thrombosis in a small minority of patients. Towards the end of the 1970's, it became clear that there were other types of hepatitis virus which both plasma and plasma products could transmit. In a small proportion of patients Factor VIII and Factor IX were rapidly neutralised by antibodies (immune inhibitors to the infused protein). That said, the risk of fatality resulting from the use of the products prior to the discovery of HIV was low, and the risk-benefit ratio was clearly in favour of their use, for without them, in severe and moderately affected haemophiliacs early fatality was common and morbidity was severe.

40. The fractionation process is complex and I would refer to the Statement of Dr. Smith for a detailed description of the work carried out on the processes currently in use at BPL/PFL. Appendix 3 sets out a diagrammatic representation of the process of manufacturing HL or 8CRV which may be simply described as follows below.

41. Plasma separated from whole blood by centrifugation or by plasmapheresis is not sterile but is collected aseptically into closed sterile containers. Blood Transfusion Centres are required to test all plasma to exclude markers for

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hepatitis B virus and for antibody to HIV 1: this is standard procedure throughout the NBTS which has been extended as from June 1st 1990 to include the marker for antibody to HIV II. In accordance with specifications, tested plasma found non-reactive to the above viral markers, is frozen to -40°C and, with appropriate documentation, is despatched in the frozen condition to BPL or PFL. A later section of my Proof deals with blood transmitted viruses in greater detail.

42. FFP is currently collected and transported in single donation containers (although previously, tested plasma was pooled into 5 litre containers prior to freezing and despatched to BPL/PFL). Plasma is maintained frozen at the Fractionation Centres in documented quarantine for a minimum of three months before use.

43. At the start of fractionation, donations of frozen plasma constituting a batch of up to 3,400 kilos or 3.4 tonnes are removed from containers, crushed, thawed and pooled. Batch size has increased from 100 kilos (in the mid-1970's) to the current level above. There are on average 3½ donations per kilo. Accordingly some 15,000 plasma donations may be represented in a defined batch of product.

44. Plasma is thawed to 0°C. and at this temperature some protein stays in suspension and can be removed by centrifugation. This protein fraction is cryoprecipitate. The process of cryoprecipitation concentrates the Factor VIII. Cryoprecipitate is re-dissolved and unwanted proteins are removed by additional purification steps, leaving highly purified Factor VIII in a condition suitable for final formulation.

45. The proteins left in solution after cryoprecipitation include Factor IX which can be removed selectively by its adherence to a solid phase resin.

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Further treatment of the resin releases a purified Factor IX in a form suitable for final formulation.

46. After final formulation, both Factor VIII and Factor IX are made bacteriologically sterile by filtration, undertaken in pharmaceutically controlled operation facilities. The filtered product, after being filled into vials, is freeze-dried by a process known as lyophilization. Following lyophilization the vials are closed and sealed.

47. Since 1985 both Factor VIII and Factor IX freeze-dried products have been subjected to heat treatment in the dry state at 80°C for 72 hours which are conditions shown by clinical use to inactivate hepatitis and human immuno deficiency viruses.

48. Plasma pools, intermediate products and final products are required to be tested for markers for hepatitis B and antibody to HIV 1 at the Fractionation Laboratories and by the National Institute of Biological Standards and Control ("NIBSC"). After testing, the vials are inspected and packed. After release by the Quality Department and NIBSC products are distributed to Regional Transfusion Centres.

BATCH MANUFACTURING RECORDS

[David Donald is to set out details of the batch manufacturing records and incident recording systems]

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HIV

49. It is currently believed that two strains of the HIV virus (HIV 1 and HIV II) are responsible for human immunodeficiency syndrome, AIDS. We are presently concerned with HIV 1. HIV II is a rarer variant.

50. HIV infection can be transmitted in blood, plasma, seminal fluid, and vaginal secretions, although there does not appear to be a sufficiently high level of the virus present to enable it to be transmitted by tears and saliva. HIV infection can therefore be transmitted by the injection of contaminated blood or blood products.

51. HIV can also be transmitted by heterosexual and homosexual contact and drug abuse.

52. Once the virus has entered the host's system, it binds to the specific cell receptor (CD4) which is present on T lymphocytes and other cells in the immune system. The virus enters the lymphocytes and under certain conditions which are still not completely understood, will result in a significant reduction in their numbers.

53. A decline in the CD4 or T cell sub-set will cause a reduction in cell-mediated immunity and in other functions concerned with modifying and controlling the production of antibodies.

54. The host usually develops antibodies to the virus (known as seroconversion) although the effect of these antibodies on viral replication is not clear.

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55. It is believed that the period between infection with HIV and seroconversion is in the region of three months but it may exceed this time in some individuals. However, after seroconversion, the virus can stay quiescent in infected cells for a period of months/years. A variable period of time may elapse between HIV infection and the development of clinically overt acquired immune deficiency syndrome or its clinical precursors. It is not yet understood what factors may precipitate the rapid increase in viral replication leading to the profound decline in the immune competence of the host.

56. The initial infection by HIV virus may be accompanied by a mild glandular fever like illness. The onset of overt AIDS may be preceded by an intermediate stage of immunological abnormalities, described collectively as AIDS Related Complex ("ARC"). AIDS is characterised by opportunistic infections and increased susceptibility to certain malignant conditions: current methods of drug treatment appear to give a measure of symptomatic relief, but this is transient and early death is the usual outcome.

II. THE PLAINTIFFS' CLAIMS

57. The claims advanced in the Re-Amended Main Statement of Claim ("MSC") against CBLA are grouped under six headings, vis:-

(a) Self-Sufficiency and the Blood Transfusion Service;

(b) Manufacture of Non-Heat-Treated Concentrates;

(c) Heat Treatment;

(d) Screening of Donors and Testing for HIV;

(e) Hepatitis Risk and/or Risk of Other Viral Infections;

(f) AIDS Risk.

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58. It may be convenient for the purpose of this proof of evidence to deal with each heading and the allegations grouped under it in turn. I have, however, dealt with non-heat treated concentrates and heat treatment under the one heading "Heat Treatment".

SELF-SUFFICIENCY AND THE BLOOD TRANSFUSION SERVICE

OVERVIEW

59. In essence, the argument developed by the Plaintiffs is that had England and Wales been self-sufficient in Factor VIII concentrate, fewer haemophiliacs would have required imported commercial Factor VIII concentrate which carried a higher risk of contamination with HIV.

60. Throughout the 1970's and 1980's, England and Wales was self-sufficient in relation to Factor IX, since the demand for this product, used to treat haemophilia B patients, was much lower reflecting the lower incidence of this form of haemophilia.

61. My own opinion is that the Plaintiffs contention is probably correct. In a way the data that has emerged with regard to the relative extent of HIV infection amongst haemophilia B sufferers treated exclusively with NHS Factor IX produced by BPL/PFL suggests that pro rata there was a lower incidence of infection when compared with the rate of infection of haemophilia A sufferers who used commercial U.S. Factor VIII concentrate. So far as we are aware, there is little difference between Factor VIII and Factor IX in terms of their inherent potential to transmit HIV when manufactured from infected donations of plasma, and the quantity of Factor IX required to treat severe haemophilia B sufferers is comparable with the quantity of Factor VIII used by haemophilia A sufferers.

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Nevertheless, the pro rata incidence of HIV infection amongst haemophilia B sufferers is lower and I believe reflects:-

(a) the temporal, geographic and demographic aspects of the spread of AIDS which appeared in the United States before spreading to the United Kingdom and Europe:

(b) the fact that Factor IX was manufactured exclusively from plasma which was voluntarily donated in the U.K. generally by categories of person who were less likely to be carriers of the virus than the paid donors who provided plasma used for the production of commercial Factor VIII.

62. However, with regard to (b), there is a further point which it is important to make to dispel the impression that I am in agreement with the Plaintiffs' arguments. Because of the chronology associated with the emergence of HIV and the length of time that it takes to achieve "self-sufficiency", it would be necessary to plan and build a manufacturing facility during the mid-1970's for production to have reached anything like the level necessary to satisfy the needs of the haemophilia A sufferers by the late 1970's when HIV, (as it is now known), appeared. The planning and financing of increases in the supply of FFP would have required a similar timetable. In short, any decision to pursue self-sufficiency as a goal, could only have been taken at a time when HIV was unknown and, therefore, on the basis that self-sufficiency was not just desirable but necessary for some other reason. The Plaintiffs suggest that such a reason was the risk presented by hepatitis and contend that, as with HIV, U.S. commercial Factor VIII concentrate manufactured from plasma donated by paid donors was inherently more dangerous than the equivalent NHS product manufactured from voluntarily donated plasma. For the reasons given under the

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heading "Hepatitis" below, my view is that this is fallacious. Additionally, hepatitis is very different indeed in terms of risk when compared to HIV.

63. In the 1970's, self-sufficiency was considered desirable but it was not seen as an imperative in that external alternative sources of supply were available.

64. By the 1st December 1982 when CBLA took over responsibility for BPL, approval had already been given by the DOH for the building of an entirely new manufacturing facility, and for the up-grading of the existing facility to provide maximum achievable interim capacity until new facilities were complete. Arrangements were also well in hand to ensure an adequate supply of FFP from Transfusion Centres to match the manufacturing capacity. From 1982 until the commissioning of the new manufacturing facility by 1988 the supply of FFP from Blood Transfusion Centres to BPL/PFL and the capacity to fractionate, were broadly in balance.

65. In these circumstances CBLA cannot be responsible for a failure to achieve self-sufficiency aside from the fact that, in common with their predecessors in managing BPL/PFL, they did not control the Transfusion Service and, more importantly, the funds necessary to substantially increase production.

66. It is correct to say, as the Plaintiffs do, that even today England and Wales are not self-sufficient in Factor VIII, if one takes this to mean the total consumption of Factor VIII concentrate rather than the ability of BPL/PFL to supply Factor VIII to those who want to use this product rather than a commercially produced alternative. The DOH have, I believe, reviewed the notion of self-sufficiency, but that is another matter; after the introduction of heat treatment and testing for HIV in 1985 in relation not only to NHS products but

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also commercial products, self-sufficiency ceases to have any relevance to the matters in issue.

67. Nor do I believe that any decision taken during the period from 1978 to 1982 when NWT were responsible for BPL would have made any difference to the scope of the problem now faced by the Plaintiffs. If at the time NWT took over from the Lister Institute in 1978 a decision had been taken to rebuild the manufacturing facility, it would not have been ready in less than three to four years (based on our subsequent experience after 1982), and would only have been commissioned in about 1981/82 at the earliest. It is my opinion (see my comments under the heading "AIDS" below) that by this time, the majority of severely affected haemophiliacs who were using the largest quantities of commercial Factor VIII throughout the latter part of the 1970's, had already become infected with HIV.

68. In my opinion, to aim for self-sufficiency with a view to achieving it before the emergence of HIV would have to have involved taking a decision to do so (and starting to implement this) by the mid 1970's and, as I describe below, against the background of inability on the part of all those concerned to make any accurate assessment of what "self-sufficiency" really equated to and a complete lack of any knowledge of HIV or the risk it was to present some 8 years later.

SELF-SUFFICIENCY IN DETAIL

69. It is probably worthwhile beginning by cross-referring to Appendix 4 which appears at the end of my proof of evidence. This chart compares the actual production achieved by BPL/PFL in each of the years from 1973 to 1990 with the estimates of the requirements for Factor VIII made in each of those

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years by various parties, and the total consumption of Factor VIII over the same period.

70. A second document, marked Appendix 5, sets out the various terms used over the relevant period in the context of measuring/estimating production and consumption having regard to the fact that, particularly during the early 1970's, the output from BPL/PFL and predictions as to likely demand for Factor VIII, were expressed in a variety of different ways.

71. For the purposes of my proof of evidence, it is perhaps sensible to distinguish the period 1973 to 1977 from the period 1978 to 1985. I was not of course employed at BPL until 15 April 1977 and, therefore, the comments set out below, insofar as they relate to most of the first period, are derived from an examination of the documents with the benefit of my background knowledge as a consultant haematologist working in the North East Thames Regional Blood Transfusion Centre. Throughout the second period, I was Director of BPL with the consequence that I have first hand knowledge of the events relevant to the issue of self-sufficiency. The end of 1985 has been taken as a cut-off, for whilst self-sufficiency had not been achieved by then, I believe that it had ceased to be relevant to the issues in the present litigation as the introduction of HIV screening/testing and the heat treatment of Factor VIII concentrates, meant that coagulation products, whether NHS or commercial, were (subject to the aberration of the Armour heat treated Factor VIII product), safe.

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1973 TO 1977

72. Self-sufficiency was considered a desirable objective from about the early 1970's for several reasons. First, the World Health Organisation advocated that countries should pursue the objective of self-sufficiency. **[Dr. Lane will speak to Harold Gunson re supporting documentation]**. This gave countries security of supply and the ability to control the standard of the product. From the point of view of England and Wales, another reason why self-sufficiency appeared desirable was the economic one. There was a general belief (although it has to be said there were no hard statistics in support of this) that it was more economic to manufacture Factor VIII through the state owned BPL/PFL than to purchase commercial product on the open market. However, it was a feature of much of the discussion regarding the "pros" and "cons" of self-sufficiency during the 1970's, that neither the DOH nor BPL/PFL could accurately cost production at the BPL/PFL, principally because these undertakings were not organised on an orthodox commercial basis. For example the "cost" of the raw material was not known. From the point of view of the Regional Health Authorities who were the recipients of Factor VIII concentrate produced by BPL/PFL, the economics were clearly in favour of using "free" issues of Factor VIII produced by BPL/PFL rather than devoting part of their budget to the purchase of commercial Factor VIII. Since BPL/PFL were, however, fractionating FFP produced by Transfusion Centres funded by Regional Health Authorities, there was a cost involved and it is not correct to characterise the NHS concentrates as truly "free". At no stage during the period 1973 to 1985 was any system put in place for charging Regional Health Authorities for the product they received from BPL/PFL.

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73. So, as I have mentioned earlier, at the start of the 1970's, self-sufficiency was seen as desirable but not immediately essential. A number of major obstacles lay in the path of pursuit of this objective, however.

74. First, there was no proper financial co-ordination to implement policies covering the activities of Blood Transfusion Centres who were the source of the FFP, BPL/PFL who fractionated to produce Factor VIII, and the Haemophilia Centres at which clinicians responsible for the choice of Factor VIII for the treatment of haemophiliacs were located.

75. The DOH funded the National Health Service and these funds were distributed through the Regional Health Authorities. From their allocations, the Regional Health Authorities had, amongst other things, to fund their Regional Blood Transfusion Centres as well as the Haemophilia Centres located in certain hospitals within their region. DOH policy was that Regional Health Authorities were to all intents and purposes responsible for allocation of budgets, and the DOH would not intervene in the exercise of their discretion. However, at the same time, BPL and PFL were funded directly by the DOH which closely controlled all but very minor expenditure. Whilst the Regional Health Authorities controlled the Blood Transfusion Centres, the fact was that in 1973 and for some years thereafter, there was no discernable benefit to them, demonstrable in terms of cost savings, flowing from their expenditure at their Transfusion Centres to increase the supply of FFP for fractionation at BPL/PFL. Moreover the Regional Health Authorities had no direct control over the funding of BPL and PFL and with it any expansion in their capacity to fractionate. There was no direct correlation between the FFP Regional Transfusion Centres provided to BPL and the amount of Factor VIII which they received back after fractionation (this came later as I shall describe below).

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76. The practice of the DOH in leaving Regional Health Authorities to determine how they should spend the funds allocated to them through the National Health Service and the distinct reluctance of the DOH to interfere in any way with the Regional Health Authorities autonomy in this regard, created difficulties in striking a balance between increasing the supply of FFP at any given time, requiring funding by the Regional Health Authorities, and increasing the capacity of BPL/PFL to fractionate it, dependant upon the willingness of the DOH to make the necessary finance available if it was to be increased. Only in theory was the possibility of co-ordination ever present.

77. As appendix 4 shows, the output of BPL in 1973 was roughly equivalent to 2m. iu per year of Factor VIII concentrate, reflecting its essential origins as a Laboratory and not a manufacturing facility.

78. At the time, as a file note (almost certainly prepared by someone in the DOH) dated 21st November 1973 reveals (document no. 96), Dr. Maycock's responsibilities as Consultant Advisor to the DOH were: responsibility for dealing with communications with Regional Transfusion Centres, Regional Hospital Boards and generating ideas, implementing and developing various products including Factor VIII; secondly, representing the National Blood Transfusion Service internationally, involving liaison with overseas blood transfusion services (all of which he did "with the staff of one, no finance and no vested power or authority"), and thirdly, as Director of BPL and Superintendent of the Lister Institute at Elstree.

79. What was "self-sufficiency"? The reality proved difficult to forecast. The problem lay in estimating the future requirements of the increasing haemophiliac population for Factor VIII. Modest increases in the production of Factor VIII concentrate in the early 1970's were concomitant with increasing

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availability of commercial Factor VIII concentrate provided by U.S. manufacturers. At the start of the 1970's, cryoprecipitate was used to treat severe haemophiliacs in the vast majority of cases, but by the end of the decade most if not all severe haemophiliacs were using Factor VIII concentrate, which completely eclipsed cryoprecipitate as the treatment of choice. Haemophilia Centre Directors were under pressure from their patients to prescribe Factor VIII concentrate, and what they could not obtain from BPL/PFL via the Regional Transfusion Centres which were supplied with the NHS product, they sought and, in the main, received funds from Health Authorities to purchase from commercial manufacturers. The DOH took the view that it was acceptable to purchase commercial Factor VIII, provided it was paid for out of the Regional budget.

80. Accordingly throughout the 1970's, estimates of Factor VIII use were constantly increasing.

81. First, throughout this period, there was uncertainty (inherent in the nature of the material and the processes in use) as to what was actually being produced at any given time. Plasma is variable in quality and resultant predictions of Factor VIII yield were unreliable.

82. Secondly, in terms of trying to estimate demand, a great deal of treatment during the early 1970's was carried out using cryoprecipitate. There was no real exactitude in estimating how many international units of Factor VIII were to be found in any given bag of cryoprecipitate (indeed the nature of the plasma from which it was derived meant that this could vary quite considerably as explained below). Moreover, there was a tendency (since no one knew precisely how many units of Factor VIII were in any bag of cryoprecipitate) to over treat a patient suffering a bleed with the consequence that the amount of cryoprecipitate used was not necessarily an exact guide to what patients actually

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required. Indeed, arguably, it was a wasteful use of plasma for this reason. Against this, however, cryoprecipitate did not lend itself to prophylactic treatment and therefore usage was depressed.

83. Lastly, the fractionation process always involves a compromise between the yield of Factor VIII at the end of the process and the purity of the product. From the point of view of the recipient, the purer the product the smaller the volume of extraneous proteins and contaminants the individual has to inject (in addition the solubility of the product is improved with the consequence that it can be reconstituted for injection more rapidly). Against this, however, a purer product reduces the yield from the source plasma. This was a consideration when, during the period 1982 to 1985, work was carried out on heat treatment of Factors VIII and IX. In particular, to avoid damaging Factor VIII concentrate, it was necessary to increase the purity of the product with consequential loss of the Factor VIII yield. Refinements to the process from 1985 onwards have materially improved the yield of the new product 8Y, but output was depressed when 8CRV and HL were heat treated as a prelude to the introduction of 8Y and during the early period 8Y was manufactured.

84. The underlying problem (in retrospect) is that those involved were sometimes thinking of different things when considering self-sufficiency. For Dr. Maycock and some of those in the DOH, self-sufficiency was considered to mean the amount of plasma and concentrate produced from it which was <u>needed</u> to treat haemophiliacs in the way they were treated using cryoprecipitate. For others (particularly some clinicians) it was the amount <u>wanted</u> by their patients to lead as near normal a life as possible. Estimates arrived at on either basis were, as we now know, wrong.

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85. It is apparent from a memorandum written by Dr. Waiter of the DHSS to Dr. Raison dated 28th December 1973 (document no. 106) that home treatment with Factor VIII concentrate was beginning to be considered following studies both in Oxford and Newcastle indicating a general preference for such treatment. In the same year, proposals were being put forward for introduction of a new Factor VIII "intermediate" concentrate which was to become the Factor VIII product produced at BPL until the introduction of 8Y in 1985. It was, in effect, a cleaned up cryoprecipitate which was freeze-dried.

86. It appears from a memorandum produced by Dr. Drummond Ellis of BPL on the 6th March 1973, (document no. 70) that it was recognised that in BPL there was scope to increase production of Factor VIII at BPL to somewhere in the region of 10,000 doses per annum (equivalent to approximately 2m. iu per annum), but that any further expansion would require some investment.

87. It is reasonably clear from the documentation from this period, that Dr. Maycock and others were giving thought to a more radical increase in production. For example, his paper BPP(73)1.9 circa. 20th June 1973, (document no. 82) examines the possibility of increasing donations of plasma (FFP) to be devoted to the manufacture of Factor VIII to 250,000 per year yielding (on his figures) 62.5 tonnes of plasma and, in turn, 20m. iu per year. In hindsight, the yield figures appear ambitious. The <u>current</u> likely estimate from that volume of plasma is 12.5 m. iu.

88. On 20th July 1973, there was, it seems, a special meeting of Regional Transfusion Directors which was chaired by Dr. Maycock at which consideration was given to ways of increasing the supply of FFP for fractionation. It appears that an expert group had determined at about that time that additional demand would be the equivalent of about 400,000 donations annually. The minutes refer

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only to donations but translating these (adopting a reasonable basis for conversion) into plasma would give a figure of approximately 75 tonnes of plasma which in turn would (realistically) yield in the region of 16m. iu. Consideration was given to ways of increasing the supply of FFP and these included increasing the number of donations devoted to the treatment of haemophilia, and increasing the use of concentrated red cells in place of whole blood for transfusion. In many cases, concentrated red blood cells would do equally well as a transfusion of whole blood, but clinicians resisted these due to their high viscosity. In addition, collection of FFP required the commitment of the blood donation for that purpose, limiting its clinical use in other ways, i.e. as whole blood or for production of cryoprecipitate. The 400,000 donations appears as the earliest of many targets, but in the same minutes it can be seen that Regional Transfusion Directors attending the meeting agreed that they would by 1975, reach a target of 250,000 donations per annum for fractionation! By December 1973, it appears the goal posts were already moving, since there is reference in the letter from Dr. Stratton to Dr. Biggs dated the 7th December 1973 (document no. 99) to the fact that Dr. Biggs felt that there was a need to fractionate between 547,540 and 750,000 donations annually.

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1974

89. Moving into 1974, I can summarise, from a review of the documents, that the year was one taken up with discussions about the need to increase the production of Factor VIII and although the then Health Minister, Dr. David Owen became involved, not much was achieved. The focus was very much on 1975 and the steps which might be taken during that year.

90. An important meeting appears to have taken place on the 31st January 1974. It was an ad hoc meeting which brought together Directors of the Haemophilia Centres and Directors of the Regional Blood Transfusion Centres. BPL was represented by Dr. Maycock. The meeting endeavoured to reach some conclusions regarding the number of haemophiliacs in the United Kingdom and what was best for their treatment, and how much material was likely to be needed to treat them. The minutes of the meeting (document no. 117) referred to Dr. Biggs introducing an MRC Working Party report mainly concerning the numbers of patients with haemophilia and the amounts and varieties of Factor VIII likely to be needed for their treatment. She noted that the report suggested the need for material derived from 500,000 to 750,000 donations annually. This equates to approximately 40m. iu. At page 5 under the heading of "What kind of material was best for Treatment", it was said:

> "It was generally felt that larger supplies of concentrated preparations were required now and urgently and some felt it was rather meaningless to ask doctors if they would prefer freeze dried concentrate to cryoprecipitate when no freeze dried concentrates were available to them."

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91. Dr. Maycock is reported as having said that his own survey of the amount of material required for treatment of haemophilia obtained figures very similar to Dr. Biggs' figures. There was reference to the fact that plasmapheresis was already being carried out on a large scale in some Centres, but that the "processing" of more blood to obtain plasma for Factor VIII would require more staff, equipment, mobile vans with cold storage facilities, etc., and this would add to the Blood Transfusion Centres' costs. The minutes then say (page 7):-

> "Dr. Waiter [DHSS] could give no statement as to how this extra expense would be met but she said that it should in the first instance be referred to the DHSS. She made the point that the purchase of commercial AHG [Factor VIII] was already costing the DHSS a lot of money."

At page 8 in the minutes the following statement appears:-

> "It was stressed that home therapy was becoming more accepted and widespread and was improving the quality of patients' lives. Cryoprecipitate was not ideal for home therapy from many points of view. Some Directors were buying commercial AHG [Factor VIII] for use in home therapy."

92. Although plasmapheresis was available, the problem was that there were no facilities to fractionate additional plasma if collected. It was not just a question of fitting out mobile vans to obtain the plasma. Funds were required for investment in a new fractionation plant and this required a policy decision by the DOH. Although Dr. Waiter indicates that the purchase of commercial Factor VIII was already costing the National Health Service "a lot of money", the DOH were

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not, so far as I am aware, increasing regional funds specifically for the purchase of commercial Factor VIII.

93. Dr. Maycock obviously felt that if 40% of the total blood collected (some 0.75m. donations) by Regional Transfusion Centres were used as concentrated red cells (as opposed to 8% at the time), sufficient plasma could be obtained to enable BPL to operate at its full capacity, and he wrote to Regional Transfusion Directors on the 12th June 1974 asking them to consider this. Dr. Maycock is reported as saying, during the course of the Haemophilia Centre Directors' meeting held on the 1st November 1974, that about double the amount of NHS concentrate had been made in 1974 as in 1973, and that he believed BPL had the capacity to increase Factor VIII production by 7 to 8 times, but would require new equipment as well as more plasma to achieve this. It would seem that about that time BPL was fractionating approximately 1,600 litres of FFP per quarter (approximately 3m. iu's per annum).

94. Towards the end of the year, there was a meeting of the Haemophilia Centre Directors on the 1st November 1974, which obviously involved discussion of targets. On page 10 of the revised minutes (document no. 162), Dr. Maycock refers to a target which the Expert Group, which advised the DOH, has set for the annual production of Factor VIII concentrate equivalent to production from 275,000 donations by 1975. This is broadly equivalent to 55 tonnes (or 55,000 litres) of plasma and would, roughly speaking, have produced some 11m. iu.

95. It is interesting, however, that this is well below Dr. Biggs' estimates as to what was required by haemophiliacs. Dr. Maycock touched on an ability to increase capacity, but also the necessity for new equipment as well as more plasma if this was to be achieved.

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96. Mr. Watt, the Director of the Plasma Fractionation Centre in Scotland at the time, chipped in on two occasions with comments relating to Scotland. His tendency in these meetings (as I discovered when I was employed by BPL), was to talk either in terms of what Scotland aimed to do (rather than what it was doing), or to try and score points wherever possible by stressing how much more advanced Scotland was compared with England and Wales. In practice this was not too difficult given the disproportionate amount of money per capita which Scotland was receiving and spending on its transfusion service and associated fractionation installation at this time and for some years after.

97. On the 24th December 1974, the DOH wrote to the Regional Health Authorities (document no. 169) summarising the position in relation to increasing production of Factor VIII and albumin as they saw it. With regard to Factor VIII, they stated that there was an immediate need to provide more Factor VIII concentrate equivalent to about 275,000 blood donations annually. They stated that the current output from BPL was limited by the amount of plasma supplied by Regional Transfusion Centres and advocated an increase in the number of blood donations which were used in the form of concentrated red cells from a figure below 10%, to 40%. The cost of providing the necessary facilities such as additional equipment and staff for Regional Transfusion Centres to separate more plasma from whole blood to meet the proposed increased usage of concentrated red cells, was estimated at £0.5m. The letter made it clear that in the DOH's view it was considerably cheaper to produce blood products within the NHS than to buy them from commercial sources. The letter concluded by indicating that £0.5m. would be earmarked as finance for increasing production of plasma, and invited RTC's to estimate their requirements "with the primary aim of making the NHS self-sufficient in AHG" (i.e. Factor VIII concentrate) in two to three years. This is an interesting comment, since there appears to be no suggestion by

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Dr. Maycock (rather the reverse) that all that was needed was an increased supply of FFP to BPL.

98. With regard to targets, it is interesting to note that on the 30th December 1974, Dr. Maycock actually wrote to Dr. Biggs (document no. 170) to pick up one point in the minutes of the Haemophilia Centre Directors' meeting on the 1st November. He states that the target of 275,000 donations was set by Dr. Biggs at the first meeting of the Expert Group advising the DOH and not by himself.

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1975

99. As is apparent from the MSC (pages 25 and 26), Dr. David Owen, then Minister of Health, made statements in Parliament to the effect that finance of £500,000 to increase the production of Factor VIII was to be made available. As previously explained, the bulk of this money was earmarked for the Transfusion Centres to boost the supply of FFP. BPL eventually received some £58,000 for the purchase of additional equipment. Although the stated intention of the Minister was to make the United Kingdom self-sufficient in two or three years, a one-off payment with a view to producing Factor VIII from some 275,000 donations was clearly not sufficient, without continuing investment, to increase the production of Factor VIII beyond this figure.

100. Following the DOH's decision to earmark £500,000 to increase the supply of plasma, there was a special meeting of the Regional Transfusion Directors held on the 19th February 1975 (see the minutes - document no. 185) which Dr. Maycock chaired. Unfortunately the various appendices cross-referred to in the minutes do not appear amongst the papers in CBLA's possession. **[Dr. Lane will obtain from Brentwood RTC [P5]]**. The minutes record at page 2:-

> "Dr. Maycock said that it was proposed to follow the recommendations of the ad hoc Advisory Group **[the "Expert Group"]** that met in 1973 and 1974, that is to say, Factor VIII concentrate would be prepared from at least 275,000 donations and cryoprecipitate would be provided from about 100,000 donations."

Later on the same page, there is reference to the use of concentrated red cells and the following comment in this regard:-

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"The rate at which the target of plasma derived from 275,000 donations was attained, would largely depend on the ease with which hospital clinicians would accept concentrated red cells. To overcome this difficulty, Dr. Cleghorn (one of the Regional Transfusion Directors) proposed that a smaller amount of plasma should be taken from a greater number of donations so that clinicians would be presented with containers of blood more closely resembling whole blood than concentrated blood cells."

101. This foreshadowed a discussion which was to continue for some time on the subject of the amount of plasma which could safely be removed from whole blood donations without compromising their safety or acceptability for use as concentrated red cells.

102. It is clear that throughout 1975, there were a number of internal meetings held at BPL to discuss the requirements for increasing capacity to the level of 275,000 donations annually. These took place on:

11th March	(document no. 189)
20th March	(document no. 191)
8th April	(document no. 198)
15th April	(document no. 199)
5th May	(document no. 203)
10th July	(document no. 218)
12th September	(document no. 233)
26th September	(document no. 237)
27th October	(document no. 248)
20th November	(document no. 254).

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103. On the 17th March 1975, there is an interesting memorandum passing between Mr. Brandes and Mr. Alexander (both in the DOH) (document no. 190) which was copied to Dr. Maycock. In paragraph 2 of the minute, there is reference to the equipment required at BPL as part of the boosting exercise (3 Sharples centrifuges) and in paragraph 4, a fairly revealing comment;

> "4. Much effort will be required of the Regional Transfusion Directors, some of whom may not see eye to eye with their clinical colleagues treating haemophiliacs. For example, some Haemophilia Centre Directors envisage home prophylaxis, whereas the present proposals are based upon home treatment of a bleed when it occurs. Other Haemophilia Centre Directors, apparently, are not fully persuaded of the practicability and value of home treatment."

104. This, I believe, gives some clue to the mismatch between the "target" of producing Factor VIII from 275,000 donations and what was actually required. My belief as previously indicated is that Dr. Maycock and the DOH were concentrating on what was believed to be the appropriate level of production to treat patients <u>when a bleed occurred</u>. Use of Factor VIII for home prophylaxis (which was to become the norm) was a significant factor which may in part explain some of the discrepancies between what BPL actually resolved to produce (and could reconcile with their capacity) and what others estimated was actually needed. I should also add that in paragraph 5 there is a reference to the Factor VIII yield from plasma being in the order of 30% to 40%. This is frankly absurd even at the time this memorandum was produced. At the time yields would have been in the region of 20%, and I am somewhat puzzled as to why figures which were obviously very optimistic were not challenged by Dr. Maycock at the time, since he obviously received a copy of the memorandum and his manuscript note gives no indication of disagreement with this part of the text.

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105. Also in May 1975, there was a meeting of the Scottish National Blood Transfusion Service ("SNBTS") Directors and Haemophilia Directors held on the 6th May 1975 (document no. 205) and it is interesting to note the comments made about yield:-

> "... they had found it difficult to come to any firm forecast figure on the yield of Factor VIII from a given quantity of plasma. Processing of plasma including separation, freezing, storing and thawing resulted in a variable loss of activity. Assay before fractionation showed an average of 600 units Factor VIII activity/litre, but the range was wide. The process of fractionation causes further loss and the ultimate yield may be as low as 250 units/litre rather than the 400 units previously hoped for. The freeze-dried preparation now issued has activity of 200 units/vial being reconstituted to 15 mls."

Once again, this underlines the difficulties in any estimating exercise.

106. Through July and August, it is apparent that the debate as to what was the safe level of plasma to be extracted in preparation of concentrated red cells continued (the range being somewhere between 150 ml. to 180 ml.).

107. There is an interesting internal DOH memorandum dated the 30th September 1975 (document no. 240) which appears to have been produced (together with the draft letter to Jim Lester, M.P. which is attached), against the background of a number of questions of comparative costs of treating patients by AHG concentrate and cryoprecipitate, having been raised chiefly in parliamentary questions. The author of the memorandum suggests there is no precise way of comparing costs of AHG and cryoprecipitate, but says that NHS production costs

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for AHG are about half the commercial cost. He concludes "however these figures are not reliable and should not be quoted." The draft letter which is attached, states that the advice from the Expert Group was to the effect that it would be necessary to process the plasma from about 350,000 blood donations in England annually to produce sufficient Factor VIII for treatment of patients suffering from haemophilia. **[We need a copy of the Expert Group's advice - Dr. Lane to obtain from Oxford Haemophilia Centre [P6]].** The letter states that the plasma from some 75,000 donations would be used to provide cryoprecipitate and from approximately 275,000 donations to provide AHG concentrate which, it is said, is now the preferred therapeutic agent. The letter continues:-

> "I hope that in about a year we will be able to meet some $^2/_3$ of the present requirements and that within two years we may be able to reach the target recommended to us by the Expert Group. Meanwhile, of course, Health Authorities are free to purchase AHG concentrate from commercial firms when individual cases merit it."

108. In October there is a list of the equipment ordered for the purposes of the 275,000 donation target and the cost is shown as £55,723.

109. On 14th November 1975 (document no. 253), Dr. Maycock wrote to six Regional Transfusion Centres (Brentwood, Edgware, Bristol, Birmingham, Leeds and Sheffield) asking for permission for Dr. Drummond Ellis of BPL, who was in charge of the preparation of Factor VIII concentrate, to visit the Centres to exchange information with those concerned about the preparation of FFP, the forecast rate of increase and related problems. This does tend to show, apart from Dr. Maycock's attendance at Transfusion Directors' meetings, that there was dialogue between BPL/PFL and the Transfusion Centres.

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1976

110. This year was yet again punctuated by confusing statements as to "targets" for the achievement of self-sufficiency. However, before attempting to make some sense out of the various figures which emerged during the course of the year, there were several developments which should be referred to which have a bearing on the whole issue of self-sufficiency.

111. First, and perhaps most important, the Secretary of State decided that the manufacturing standards in the NHS units should be no lower than those in commercial firms. Accordingly, Crown exemption from the provisions of the Medicines Act 1968, was waived. Reference to this is to be found in the minutes of the 163rd meeting of the Regional Transfusion Directors which took place on the 6th October 1976 (document no. 395). The announcement of the Department's intention to waive immunity was in fact contained in a circular (HSC(IS)144 at Appendix 6 (and document no. 6/1). As recorded in the minute, the apparently straightforward decision to waive immunity under the Medicines Act 1968 was somewhat qualified:-

> "To give effect to the direction of the Secretary of State Crown Exemption from the provisions of the Medicines Act had been waived. However, these provisions, in particular as regards licensing matters, were being applied administratively with suitable modifications to take account of the NHS situation. RTC's were asked to submit through RHA's brief details of their production activities, premises, etc. It was unlikely that licenses as such would be issued, but some form of written authority might be given. Meanwhile, RTC's could continue to engage in manufacturing activity. When a RTC had been inspected by the Medicines Inspectorate, the Department would write to the RHA pointing

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out any shortcomings and seeking the RHA's proposals for remedying them and a timetable for their completion."

112. The same approach was adopted in relation to BPL/PFL. It is apparent from Dr. Maycock's report on the BPL (document no. 366) that manufacturers' licence and product licence applications for Factors VIII and IX had been submitted for Oxford and Elstree; applications had been submitted during March 1976. No response was received until November 1976 following an informal visit to BPL in October. Dr. Maycock says at page 7:-

"It is not unlikely that the accommodation of both laboratories will be criticised and, in certain respects, found inadequate. Both were designed before the Medicines Act was passed, and therefore several years before those responsible for applying this Act had formulated the criteria to be met."

He continues:

"The design of BPL was virtually fixed by 1965 and later altered in the interests of economy. The general concept of the Laboratory is therefore nearly 12 years old."

113. The Medicines Inspectors did not arrive to formally inspect BPL until April 1979. Their inspection was, as I describe below, to have a profound affect on the elusive goal of self-sufficiency.

114. A second development was that as from the 1st December 1976, NHS Factor VIII concentrate was delivered to the Regional Blood Transfusion Centres in an amount proportional to the number of patients treated at the Haemophilia

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Centres of that region in 1974. It was agreed that NHS concentrate should be given as a matter of priority to patients allergic to cryoprecipitate and to those who were already on home treatment with NHS concentrate. (See minutes of the meeting of Directors of Haemophilia/Associated Haemophilia Centres and Blood Transfusion Centres held on 15th December 1976 - document no. 450). Up until that point, I think it is fair to say that distribution was somewhat ad hoc. The documentation from the early 1970's reveals correspondence from clinicians on behalf of individual patients seeking supplies direct from BPL, and there seemed to be no established and formalised procedure adopted with regard to the distribution of concentrates, particularly one which encouraged Blood Transfusion Centres to increase their supplies of FFP to BPL.

115. The scheme introduced with effect from the 1st December 1976 was a prelude to a later arrangement which I was instrumental in introducing after I became Director of BPL which we called "pro rata". Under this scheme, Regional Transfusion Centres had Factor VIII concentrate returned to them in a quantity which was pro rata to their contribution of FFP to BPL for fractionation. It was not until this stage was reached that Transfusion Centres saw a proportionate return and, therefore, reward for their individual efforts in increasing the supply of FFP to us. This subsequently had an effect in increasing the supply of FFP and the drive towards self-sufficiency.

116. There had been debate during the year as to whether Factor VIII produced by BPL/PFL should be sent to Regional Transfusion Centres for despatch to Haemophilia Centres or direct to the Haemophilia Centres. In the event, the decision reached was that both commercial and NHS products should be handled by the Regional Transfusion Centres which was probably the correct decision, particularly in the light of the pro rata system which we later introduced. The decision was not implemented with respect to the commercial product since,

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Haemophilia Centre Directors continued to obtain product directly through hospital suppliers.

117. The last background point to mention is that a Working Party was established under the auspices of the Regional Transfusion Directors to consider "the quality of cryoprecipitate prepared at RTC's and relevant factors" and on 26th July 1976, (document no. 322) Dr. Maycock wrote to me asking me to become a member of the Working Party. It might be thought (with some justification) that cryoprecipitate, which was by this stage quite obviously not the patients' choice of treatment, was rapidly diminishing in importance. This was certainly the case but in fact the principal purpose of the Working Party was to obtain a more accurate idea of the number of international units which the usage of cryoprecipitate actually represented. The result of this exercise was never going to be particularly accurate, but it would provide more reliable data for use in estimating current and future usage and planning production to meet this.

118. Turning to the targeting of the level of production needed to achieve self-sufficiency, there were a number of discussions during 1976 which revealed a more realistic assessment of what was needed. First, it is interesting to note, in January 1976, that Dr. Ethel Bidwell (then in charge of Oxford PFL) in her note entitled "Production of Factor VIII Concentrate" (document no. 266) was beginning to do her arithmetic on the basis of yields which were far closer to what I would consider realistic. In paragraph 4 of her note, she indicates that after all the processing and sampling losses had been allowed for, yield was probably no more than 200 iu per kilogramme of plasma on a large scale, and 240 iu per kilogramme of plasma on a small scale (e.g. PFL). She estimated that severely affected patients on home therapy might require up to 25,000 iu per year with average consumption being in the order of 12/15,000 iu per year, and the number of patients requiring treatment at around 3,000. In fact, severe haemophiliacs

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reached the stage of using between 40,000 and 50,000 iu of Factor VIII concentrate when available, and so her usage figures were lower than they should have been. However, on the basis of these figures, she was forecasting a requirement for Factor VIII to be manufactured from 970,920 donations to meet current requirements then estimated. Her assessment was that collectively Oxford, Edinburgh and Elstree could manage to fractionate Factor VIII from about 593,340 donations. This was greatly in excess of the 343,100 donations planned for the following year and obviously short of her estimate for what was actually required.

119. The point does not appear to have been lost on Dr. Maycock for in a meeting held at the DOH on the 11th March 1976 (document no. 273) to consider Factor VIII production, he commented (paragraph 2) that the UK "target" was in fact one set by the Expert Group on the Treatment of Haemophilia in March 1973, and that there were those who now thought that the target should be considerably higher. From this minute, it is clear that Dr. Maycock accepted the net yield at Elstree as being approximately 200 iu per litre of plasma. Typically, Dr. Watt from PFC in Scotland suggested that Edinburgh's yield was in the region of 30% to 35% and that their aim at Edinburgh was to achieve a 70% yield. Not only was the yield of 30% to 35% much higher than I would have expected was possible at that time, but 70% was, frankly, ludicrous on any view. For the same reason, I would be suspicious about the costings contained in the same document where Mr. Watt (again trying to go one better), suggests that the Scottish product cost 4.2p. per iu against the NHS product which seems to have been estimated (I am not sure how) as costing 6p. per iu.

120. This obviously led to Dr. Maycock preparing a paper entitled "The Preparation of Factor VIII to provide 35m. iu per year" in July 1976 (document no. 332). The figures in this paper look rather more satisfactory than some of

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those appearing in Dr. Maycock's earlier calculations, although a 30% yield which he assumes is still, in my view, too high. 20% would have been closer to the real yield. The paper sets out various permutations for production to reach 35m. iu per year, but this, interestingly, was at the lower limit of Dr. Biggs self-sufficiency range of figures, and Dr. Biggs' calculations appear to produce a requirement of about 45m. iu (although this may be a UK wide figure). At the time of course BPL had only just embarked on the programme to increase production to some 14m. iu.

121. In June 1976, Dr. Drummond Ellis produced a memorandum entitled "Possible further expansion of AHF Production at Elstree" (document no. 304). This is a first stab at a paper exercise to determine the implications and consequences of increasing production to a target of 25m. iu per year. In the conclusion, it will be seen that Dr. Ellis says;

> "expansion to this level of production (25m. iu Factor VIII per year), would cause serious overcrowding of facilities unless some additional building work done... It should be noted that the existing AHF facility was not designed for the work being done and that it might be undesirable just to add extension."

122. Dr. Drummond Ellis appears to have concluded that a limited expansion (say 30% to 40% increase) was possible without buildings being extended, but only as a stop gap measure and even this increase would require additional freezing and freeze drying capacity. He identifies an improvement in yield as being another way of increasing production without the problems associated with a new building. The picture at this stage was of a facility which had some potential to improve production (if yield could be increased), but very little further scope, without additional expenditure, to manage a significant increase.

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123. On the 26th July 1976, the Blood Transfusion Directors, Regional Scientific Advisers and Haemophilia Centre Directors met. It is apparent from the minutes of that meeting (document no. 321) that Dr. Maycock said he had a target of producing 15m. iu of Factor VIII per annum. This was of course the target for what could be achieved as a consequence of Dr. Owen's £500,000 injection, and by this stage it had effectively slipped by a year in terms of implementation. Dr. Rizza appears to have commented, in relation to what had emerged as the realistic self-sufficiency target of 35/40m. iu, that he wondered how the target of 15m. iu had been originally decided. Dr. Biggs is reported as saying that the Haemophilia Directors had never supported a target of 15m. iu of Factor VIII. Looking back at this correspondence, one is driven to the conclusion that 15m. iu was never an agreed target in the sense of a self-sufficiency target or, for that matter, any other type of target. It was simply a "target" defined by reference to BPL's capacity, and the available FFP as enhanced by the modest £500,000 injection of cash in 1976.

124. Figures which appeared in August (see document no. 336) "Factor VIII available (England and Wales): January - June 1976", (produced by DOH) revealed usage in the first six months running at about 10/11m. iu, of which some 5½m. iu were in the form of concentrate. An accompanying chart suggested current needs at about 33m. iu (being the actual and estimated consumption for 1976). A memorandum prepared by Mr. Dutton of the DOH dated 3rd August 1976 and addressed to Dr. Waiter of the DOH (document no. 338) is a fairly accurate estimate of the then prevailing position. Mr. Dutton notes that, despite estimates suggesting that the use would be somewhat lower, haemophiliacs were already using some 35m. iu per year in one form of Factor VIII or another. Taking all forms of Factor VIII production, he estimates the total at 31m. iu per year of which 12m. to 15m. iu are in the form of concentrate produced in England and

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Wales. One comment to make in relation to Mr. Dutton's memorandum is that he seems to ignore the fact that cryoprecipitate was ceasing to be the treatment of choice. As Dr. Bidwell commented to Dr. Maycock in September (her memorandum of the 13th September 1976 - document no. 370);

> "I do not think the Haemophilia Centre Directors will be satisfied to have half their concentrates applied as "cryo", but the decision about this is a political decision involving finance, not our decision."

125. In a letter from Dr. Biggs to Dr. Maycock of the 21st September 1976 (document no. 378), Dr. Biggs picks up on a statement made by Dr. Maycock at the meeting in July to the effect that he had a target of 15m. iu of Factor VIII and questioned whether Dr. Maycock can have had such a target for 1977. Dr. Maycock says in his reply to Dr. Biggs on the 28th September (document no. 394) that he cannot remember precisely what he did say at the 26th July meeting, but it is clear from the balance of that letter, that he is really talking in terms of capacity to produce not a target in the sense Dr. Biggs means it.

126. In October at a special meeting of the Transfusion Centre Directors and the Haemophilia Reference Centre Directors to which government representatives were deliberately not invited, the "target" was again raked over and Dr. Biggs and Professor Blackburn concluded that there was probably a need for 40m. iu of freeze-dried Factor VIII to match the requirements of haemophilia patients and, moreover, that this estimate was likely to be a minimal one and superseded in practice. There was reference to the fact that by this stage, five commercial companies had licences to supply Factor VIII concentrate in the UK, and comment was made to the effect that it would be surprising if Doctors and patients did not come to prefer these very convenient preparations in preference to cryoprecipitate. Dr. Maycock referred to the Group of Experts' "target" fixed in

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1973, and to the fact that this appeared to have multiplied three times since 1973.

127. Ultimately it is difficult to say that this meeting achieved anything, save possibly that it might, through Dr. Maycock, have brought to the attention of the DOH the fact that the demand for Factor VIII concentrate was accelerating very fast, and that the days of cryoprecipitate were numbered. Estimates of demand then current showed a requirement of at least 40m. iu (the preference being that this be satisfied by Factor VIII concentrate).

128. Following that meeting, Dr. Maycock in a handwritten memorandum headed "Sheffield 22/10/76" (document no. 404) attempts to try and work through the implications of a requirement to produce 40m. iu per year. The last page of this particular document is interesting. Clearly the idea that 40m. iu was to be the target was pointless. It was, as far as anyone could tell at the time, the existing not the future demand and any planning exercise needed to look well beyond existing usage to future demand and plan accordingly. The graph sketched out at the foot of the last page, suggests that Dr. Maycock believes that the demand would flatten out quite considerably, notwithstanding the extraordinary steep climb to the level of consumption as it then stood. This was unfortunately entirely bogus. In my view there were no grounds for believing that the demand would follow the pattern shown on the graph. My first attempt at estimating likely demand when I joined BPL in 1977, produced a figure of 120m. iu as a target we needed to aim to meet within a few years, and this was an exercise only a year later than Dr. Maycock's. My preliminary calculations were referred to in the "Stop Gap" paper in 1978 (referred to below). In the event in 1989/90 we issued 72m. iu (but did not achieve self-sufficiency), although estimates of use exceed 100m. iu.

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129. Dr. Maycock's calculations lead to the conclusion that with an additional £25,000 it might be possible to increase production to somewhere in the region of 35m. iu of Factor VIII concentrate per annum, but it is not clear how this conclusion was reached.

130. The first draft report of the Working Party on Cryoprecipitate was produced in November 1976, and the report concluded that further work was necessary, but identified the significant difference in Factor VIII levels in cryoprecipitate produced at different Transfusion Centres. The overall range of mean values was from 56.6 iu to 113.5 iu per dose of cryoprecipitate.

131. Summarising 1976, the year appears to have been dominated by the continuing cryoprecipitate debate, the implementation of increases in production facilitated by the £500,000 injection of finance, and debate about the "target" necessary to achieve self-sufficiency and the confusion sown in all this by "targets" which related to capacity to produce rather than volume necessary to achieve self-sufficiency and to what was <u>needed</u> rather than what the patients and clinicians <u>wanted</u>. Throughout the debate, there is no intervention from the DOH. At the time the mis-match between what was being achieved (with a struggle), what was required to meet the current self-sufficiency requirements in <u>concentrate</u> and what, had anyone looked beyond current usage, would be necessary to achieve self-sufficiency for the future was all too obvious. Decisive action would have been required (backed by considerable funding) to plan a facility which would be ready by the end of the decade, and of a size which would leapfrog sufficiently far ahead to cater for the burgeoning demand for Factor VIII concentrate.

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132. I joined BPL as Director Designate on the 15th April 1977 which enables me to speak with more authority with regard to events after that date than before. I should point out, however, (and this will be apparent from many of the minutes of the meetings between April 1977 and September 1978), that Dr. Maycock kept me very much in the background. He continued to attend Transfusion Directors meetings, etc., as representative of BPL/PFL without me, and although, as I explain below, I was given some specific work to do in planning for the "Stop-Gap" proposals to further up-grade the BPL facilities, it was not until Dr. Maycock's retirement in September 1978 that I found I was able to exert much influence or control over BPL/PFL.

133. Before I joined in April, there were a few significant events. It will be seen from the documentation that on the 13th January 1977 there was a meeting of the Haemophilia Centre Directors at the Middlesex Hospital in London (minutes - document no. 486). The meeting was very well attended with Dr. Sheila Waiter representing the DOH. Dr. Ethel Bidwell was present on behalf of PFL, Dr. Rosemary Biggs from the Oxford Haemophilia Centre, and Dr. Drummond Ellis on behalf of BPL. It is also worth noting that Dr. Drummond Ellis prepared a short note of the essential points emerging from the meeting (document no. 484). Since there were some interesting comments made on behalf of the Plasma Fractionation Centre ("PFC") at Liberton near Edinburgh in Scotland, I think it is worthwhile putting these in context.

134. In about 1974/75, approximately £400,000 was spent on enlarging the Scottish fractionation capacity at PFC Liberton. Mr. John Watt, Director of the PFC who was involved in planning the extension to the PFC, specified a final fractionation plant which had the capacity to fractionate 6,000 litres of FFP per

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week which was in excess of that officially defined. Against insufficient budget provision, the capacity of the manufacturing plant was maintained at the expense of other essential elements e.g. warehousing and final processing. He proceeded with the extension of the fractionation plant at this capacity although the ancillary equipment and buildings could not support its effective utilisation in full. It is believed the view was held that further funds were available should the plant be required to be extended to its full potential capacity at a future date.

135. A number of interesting points emerged during the course of discussion if the minutes are accurate. Dr. Kirk commenting on the trial of prophylactic treatment of haemophiliac patients at Alton, said that the Factor VIII needed to treat a patient on prophylaxis (rather than on "demand" therapy) was of the order of 100,000 iu a year. In terms of numbers of patients, Dr. Biggs is reported as saying that the number of known haemophilia A patients in the UK had now exceeded 3,000. There appears to have been a statement to the effect that the Blood Transfusion Service could supply sufficient plasma for fractionation to provide a minimum of 14m. iu of Factor VIII per annum, although I am bound to say that at the time, so far as England and Wales were concerned, there was not yet enough FFP being provided to keep BPL at Elstree working to capacity.

136. An interesting discussion on targets for Factor VIII requirements took place. Dr. Holman (Lewisham Hospital, London), commented that the Directors had for years said that they wanted concentrate instead of cryoprecipitate and in these circumstances asked whether it was true that the DOH was making no provision for expansion. Dr. Waiter on behalf of DOH said that the target for Factor VIII requirements had shifted over the years; "The DHSS had understood that the capacity at Liberton, Elstree and Oxford was adequate". Curiously nobody at the meeting appeared to challenge this statement. Dr. Waiter continued

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by saying that the stated capacity of the Centres could accommodate a target of 50m.iu. Dr. Biggs retorted that the target had not shifted. The first estimate given in recent years was 40-50m. iu (Dr. Biggs in 1974). Dr. Biggs was not certain where the lower targets had come from.

137. In the second paragraph on page 11 of the minutes, Dr. Biggs says that it would be difficult to forecast Factor VIII usage if supply were unlimited and neither patient nor Doctor had to pay for the product. Doses could well be increased and prophylaxis could become popular. She continues, "The estimate of 40-50m. units per year made by the HCD's and the MRC Working Party, concern a minimum reasonable need". At the top of page 12, Dr. Drummond Ellis from BPL said that the maximum capacity for Elstree (including a proportion made in Oxford) was 14-15m. iu. It will be noted that Dr. McDonald from the Royal Infirmary, Glasgow, said that Liberton had the capacity to make 60m. iu per year. He added that to reach this target the Centre would need about £25,000 for new capital equipment and money for extra running costs including payment for staff operating a 24 hour shift system. This figure was nonsense, but was not apparently challenged in the meeting if the minutes are correct. As I shall describe below, it subsequently became apparent that Scotland was not in a position to make any real contribution to the requirements in England and Wales for Factor VIII concentrate, but at this meeting a comment was made that it seemed as if Liberton had capacity to supply Factor VIII for the whole of the United Kingdom. In fact Dr. Waiter said, at page 12, that the DOH together with the Scottish Home and Health Department ("SHHD") were planning the supply of Factor VIII on a UK basis:

> "Plans had been made to divert plasma from south of the Border to Liberton when Mr. Watt was ready to receive it. It was planned that the Factor VIII made from this plasma would return to Centres south of

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the Border. Agreement in principle had already been reached between the DHSS in London and the SHHD."

In fact, so far as I can tell, whatever plans the DOH may have had, nothing ever came of them.

138. It will be seen that the minutes referred to a discussion regarding the supply of Factor IX as well as the position in relation to Factor VIII. At page 18, Dr. Ethel Bidwell noted the increasing demand for Factor IX (by 1976 nearly 10,000 bottles were being used per annum), and commented on the possibility that prophylaxis use of Factor IX might impose a strain on supply. The general consensus appears to have been that such prophylactic treatment involving Factor IX as was then underway, did not materially increase present requirements.

139. One other development which can be traced back to this meeting in January 1977, was the establishment thereafter of the Haemophilia Centre Directors' Working Party on the Incidence of Hepatitis in Haemophilia which was organised and run by Dr. John Craske.

140. During March, it is clear from the correspondence that there was an exchange of products between Oxford and Edinburgh with a view to Edinburgh conducting some quality comparisons on batches of Factors VIII and IX.

141. It has been agreed that Edinburgh would receive up to 25 tonnes of English out-dated plasma for fractionation on an annual basis. An experimental fractionation to stable plasma protein solution ("SPPS") showed significant differences between specifications of Scottish HPPS and BPL plasma protein fraction ("PPF") - 4.5% human albumin solution. No further fractionation of BPL outdated plasma was entertained.

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142. On the 22nd March 1977 (document no. 515), Dr. Maycock replying to a letter from Dr. Smith concerning the purchase of commercial Factor VIII, referred to the use of Factor VIII at the level of 15m. iu per annum, and added "I think it will be very difficult for the UK to produce this quantity in the form of concentrate which the clinicians seem to want" (i.e. high purity Factor VIII like Hemofil).

143. It will be seen that on 20th May 1977 (document no. 542), Dr. Gunson on behalf of the National Blood Transfusion Service, sent a memorandum entitled "The National Blood Transfusion Service: its present status and proposals for re-organisation" to the Royal Commission on the National Health Service. This was a submission which embodied comments and views of all the Directors of the Regional Transfusion Centres (including myself in my former capacity prior to joining BPL). As it transpired, it had very little impact. The thrust of the document was that there was a lack of central co-ordination within the National Blood Transfusion Service. The Central Committee was only an Advisory Committee to the DOH and had no executive financial status. Reference is made on page 3 of the submission to the formation of the Central Committee for the National Blood Transfusion Service which was on the recommendation of the Reid Committee. It has been said that Reid initially advocated a central Transfusion Service with a National Director, but this was not accepted as it was contrary to then current government devolution policy. Notwithstanding the submission, the problems identified in it persisted, and it was only in 1988 that a National Directorate for the NBTS was established, reporting to the Director of Operations of the NHS Executive Committee. (The National Directorate remains mainly advisory and without regional executive authority).

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144. I have mentioned previously that there appears to be a disproportionate amount of money spent on the Scottish Blood Transfusion Service and this discrepancy in funding is exemplified on page 9 of the submission. In 1975/76 expenditure on the National Blood Transfusion Service in England and Wales was £15.8m. for a population of some 49m. compared with expenditure of £3.5m. in Scotland where the population was only 5.5m. It was stressed (see page 10) that a central organisation for national planning was essential if the NHS was to receive sufficient blood and blood products. The proposal at the bottom of page 10 was for the establishment of an executive committee or board to replace the Central Committee. The recommendation was not followed.

145. Under cover of Dr. Gunson's letter of the 22nd June 1977 (document no. 550), I received a copy of the final version of the report of the Working Party on the Quality of Cryoprecipitate in England and Wales which was dated June 1977. (I have commented above on the draft which was produced in November 1976). The statistics in the report show that approximately 15% of the total number of donations of blood collected each year were at that time committed to the production of cryoprecipitate.

146. At the World Federation of Haemophilia Congress (23rd June 1977) (document no. 551), there were figures given for the requirements for Factor VIII for haemophiliacs in the United States. The paper states that the requirement for US haemophiliacs was 354m. iu. This works out at 20,000 iu per patient per annum. This was twice the amount being used in Oxford at about this time (although usage was increasing). However, out of the total of registered haemophiliacs, approximately 50% were actually in treatment which brings an actual consumption figure up to around 40/45,000 iu per annum. Back in the January meeting of the Haemophilia Centre Directors, Oxford estimated usage at

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between 11/12,000 iu per patient, whilst Dr. McDonald on behalf of Scotland suggested that usage there was in the region of 6,700 iu per patient.

147. In September, Dr. McDonald of the Royal Infirmary Glasgow wrote to Dr. Maycock (document no. 577) as follows:-

> "With reference to our previous discussion and correspondence, you will recall I was invited by the National Haemophilia Directors to arrange a meeting between representatives of the Scottish Home and Health Department, the DHSS, Haemophilia Reference Centre Directors and those concerned with fractionation, to discuss the problem of the availability of plasma, fractionation, and the availability of Factor VIII products.
>
> From the replies I have received, it would appear there is no great enthusiasm for such a meeting and therefore I have no alternative but to indicate to you that this meeting will now no longer take place."

148. Also in September, a report was produced on BPL, for the Advisory Sub-Committee on Blood Products and Blood Group Reference Laboratories of the Central Committee for the National Blood Transfusion Service for the year ended July 1977 (document no 594). Some of the points made in the report (to which I contributed) are relevant in the context of self-sufficiency.

149. In Dr. Maycock's opening paragraph, he alludes to the fact that during 1976 there were no formal discussions or actions taken in relation to the future of BPL, save for the initiation of a feasibility study for a pilot chromatography laboratory (which was never commissioned even as part of the new facility in the 1980's). He says:-

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"The "stretched" capacity of BPL will be reached about the turn of the year. The experience of the past year suggests that thereafter the Laboratory will continue to work in an atmosphere of uncertainty about future developments."

"There are no means at present of matching future fractionation potential with the potential availability of plasma collected by RTC's and of relating both to therapeutic demand. This is a projection of the fact that since it was opened, BPL has had no means of controlling its "raw material". Under the present scheme or organisation, although plasma is sent to BPL by all RTC's, there has never been, with one exception, any means of influencing its volume apart from persuasion. The exception was the introduction of the scheme for providing fresh plasma for Factor VIII concentrate which was made possible by the central provision of money and central co-ordination. The present method of operation will become more difficult if the scale of fractionation grows. What is needed is a programme in which each region would be responsible for carrying out planned growth pattern within an essentially co-ordinated plan for the NBTS in England and Wales. Without this, or something like it, it will be difficult to plan the future of BPL and PF Lab.

"It would at least dispel the feeling of uncertainty at BPL if DHSS were to say whether or not it intends to secure its investment (the magnitude of which has not been disclosed) in PFC at the expense of developing its own fractionation potential in NBTS.

"Hitherto communication between BPL and PF Laboratory with DHSS and RTC's has been, in some ways, simplified by the fact that the BPL

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Director was also Consultant Adviser on Transfusion to DHSS. The need to formulate channels of communication for his successor is urgent."

150. The capacity which Dr. Maycock refers to above was 1,000 litres of plasma per week.

151. In addition, Dr. Maycock said:-

"Also creating uncertainty at BPL is the unfortunate situation in which the problems of BPL as they relate to NBTS in England and Wales, seem to have become entangled with the problems of PFC Liberton, the design size and development of which were carried forward entirely independently apart from an agreement in principle, that it should fractionate 500 litres time-expired plasma weekly, and prepare 10,000 containers of Factor VIII concentrate. Planning the future of BPL should not wait until the problems of PFC have been resolved."

152. It was at my insistence that this paragraph was inserted. The indecision as to whether or not to redevelop BPL in line with what was clearly required by this time, was becoming confused by DOH intentions to utilise PFC Liberton to some extent, a state of affairs which was not helped by exaggerated claims made by the Director of PFC Liberton for its operational capacity.

153. My main contribution to the report was in the form of appendix A1 which outlined certain changes I wished to bring about concerning the method of sending FFP to BPL and the preparation of Factor VIII concentrate.

154. The main theme of my paper was the desirability of RTC's abandoning their approach of producing 5 litre bags of pooled plasma in favour of single

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donation packs of frozen plasma. There are several reasons why I advocated this, and they are set out on page 3 of appendix A1. In essence, however, 5 litre pooling (made up of plasma derived from 20-30 donations) operated on an "open" system which involved greater workload, more equipment and carried a greater risk of contamination than single plasma donations obtained using a "closed" system of plasma collection. Additionally it was believed that a dedicated plasma collection system would boost the potential supply of plasma for fractionation, and would resolve difficulties associated with hepatitis B testing of plasma pooled in 5 litre containers. These problems are considered in greater detail below.

155. My conclusion was as follows:-

> "Critics of change will argue that the cost of revising the present facilities will be large but, because it is agreed that considerable sums of money will have to be spent over the next ten years to rebuild and re-equip the Blood Products Laboratory, it will be wrong to limit the potential of this investment by the installation of old technology and plant in new buildings. Thus it must be repeated that, during the next four years, the problems of technology and plant must be resolved. The effects of shortage of finance can be mitigated in several ways which this paper seeks to show:
>
> (a) by integrated policy within the NBTS (i.e. Regional Centres and BPL) to avoid reduplication of expenditure;
>
> (b) improving yield within BPL;

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(c) changing the Department's attitude to free-spending on expensive commercial imported alternatives to the NBTS - produced therapeutic fractions and serological reagents;

(d) adhering to the Department of Health's principle that the Health Service shall make all possible attempts to become self-sufficient.

The Director Designate of BPL hopes the Central Advisory and executive bodies will re-affirm their intent to make the NBTS self-sufficient. In turn, the NBTS can help by integrated planning made possible through central co-ordination."

156. My report generated limited response from the DOH. Steps were taken to phase out the 5 litre packs in favour of single donor plasma packs, and a new system of hepatitis testing was considered for BPL.

157. On the 10th October 1977, the second draft of the report of the Working Group on Trends in the Demand for Blood Products (document no 602) was produced. The Working Group on Trends was set up in 1977 by the DOH to consider long term planning in the NBTS. The brief of the Working Group was to give broad estimates for the likely demand for blood products over the next 5 to 10 years.

158. The second paragraph on page 2 of the report reiterates David Owen's self-sufficiency policy stated two years previously. In the same paragraph, there is a bold statement that the "demand for blood products does not necessarily reflect the need for them." The implication is that demand was equivalent to need plus wastage. Self-sufficiency is expressed to be targeted at need rather than demand. We have seen in earlier documents that DOH policy was to allow

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clinicians freedom to manage the treatment of individual patients. . This being the case, it should be demand met by NBTS otherwise clinicians would necessarily use imported product. I proposed that charging for NBTS product would result in more effective use and lessen the problem of non-administration of the product **[P8]**. Dr. Maycock would in no way have supported this contention. It should be noted that the Working Party was working at the same time as the study going on in America to which I have made reference above. Paragraph 6 deals with estimates for Factor VIII production but there appear to be some discrepancies amongst the numbers. In any event, the estimates are based on 1 iu per capita per annum. The point is made at the top of page 4 that up to 70% of the available Factor VIII was lost in collection, storage and processing of plasma. In industry at that time, the aim was generally for a 20% yield: some very high purity product had a yield as low as 7%. The report concluded by saying that considerable further investment in collecting, testing, processing and premises would be required to achieve the target. There is also talk of an additional major investment for increased fractionation capacity.

159. On the 25th October 1977, an important meeting took place at BPL between representatives of BPL and the DOH (notes on which are document no 612). Dr. Maycock, myself, Mr. Bailey and Mr. Vallet were present on behalf of BPL, and Mr. Parrott, Mr. Dutton, Dr. Waiter and Mr. Cleasby on behalf of DOH. The original stimulus for the meeting was the receipt by BPL of letters from Sheffield RTC and West Midlands RHA containing proposals which would involve BPL in processing greater quantities of plasma for the production of Factor VIII concentrate. Although BPL could process one extra plasma pool per week, this would be carried out in unsatisfactory accommodation which the Medicines Inspectorate would be likely to condemn and it was therefore considered that the meeting could usefully be broadened to consider future production problems at BPL generally.

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160. In the second paragraph of the minute, the DOH make it quite clear that no commitment could be made at that stage to any specific solution. In paragraph 3, I summarised the three main problems, vis:-

(a) the continuing pressure to produce more Factor VIII concentrate with BPL having almost reached the limit of its present production capacity;

(b) the implications of the recommendations of the Working Group on Trends which pointed to a substantial expansion of the existing production of Factor VIII and, for that matter, albumin over the next 5 to 10 years;

(c) the application of the Medicines Act to the NBTS and the probability that a number of processing units in RTC's and in the BPL itself, would not meet the standards being demanded by the Medicines Inspectorate, particularly in relation to open systems for handling blood and plasma.

161. In paragraph 4 on the second page, the scene is set by Mr. Parrott explaining the DOH's thinking on future planning for BPL:

"Although the Department fully accepted the desirability of having the activities of RTC's co-ordinated among themselves and with the Central Laboratories, it would not be possible to instruct RHA's how to develop their RTC's. However, it was agreed that whatever happened at BPL would tend to influence RHA planning of their own services."

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162. Mr. Parrott also refers to "low-cost selective development". I would comment this was not in line with Dr. David Owen's objective as stated two years previously, that self-sufficiency should be pursued. It is also worth noting that the wheels were beginning to turn in Mr. Parrott's mind as to the advisability of reliance on the Scottish plant. However, his manuscript amendment refers to "not being totally reliant" on the Scottish PFC at Liberton. At this stage Mr. Parrott had not yet been to Scotland. It is noted in the minutes that the value of the Factor VIII product produced by BPL/PFL alone was some £1.3m. annually.

163. The conclusion of the meeting was that BPL should draw up a list of options for future development, bearing in mind the DOH constraints. The commencement of the "Stop Gap" programme may be traced from this meeting, and a paper put together by myself, Dr. Drummond Ellis and other BPL staff, entitled "Stop-Gap Requirements for Factor VIII Production in 1978-1982" was circulated in December.

164. Indeed it was on the 20th December 1977 that Dr. Maycock circulated the first "Stop-Gap" paper. The paper (document no 631) was presented to Mr. Parrott of the DOH. The proposal was to increase Factor VIII production by raising the amount of plasma processed from 1,200 litres to 2,400 litres per week over a four year period. In simple terms, we were looking for a doubling of donations of FFP. This was intended to improve supply while a new building/development was being looked at.

165. The paper dealt with the <u>immediate</u> requirements for increasing Factor VIII production, set against the background of the longer term target for Factor VIII of 1iu per capita as published in the Trends Working Group report. One of the first elements in the Stop-Gap programme was an increase in the pool size from 300 to 600 litres; a large pool size is more efficient in terms of

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manufacturing practice. Thawing became a continuous process. Stage 2 of the programme gave consideration to phasing out 5 litre pooling. With the system of single donations, each donation could be frozen immediately. BPL required development support for a single plasma pack from the principle manufacturer at that time, namely Baxter Travenol.

166. I am bound to say that the report itself was prepared without knowledge of DOH's intentions so far as Elstree was concerned, particularly with respect to the planned use of PFC Liberton.

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1978

167. 1978 saw the closure of the Lister Institute and its replacement, so far as the day to day management of BPL/PFL was concerned, by NWT. Looking back at 1977, the total number of Factor VIII units used during the year was some 48,433,605 in various forms (see Haemophilia Centre Directors' annual returns dated 18th October 1978 - document no. 793). Total plasma fractionated by BPL during 1977 amounted to 144,537 litres (report to the Advisory Sub-Committee on Blood Products and Blood Group Reference Laboratories of the Central Committee of the National Blood Transfusion Service for the year ended July 1978 dated 8th September 1978 - document no. 770). BPL had produced a total of 46,005 containers (each of 250 iu) of Factor VIII concentrate during the course of 1977 compared with a total for 1976 of 23,786 containers. So production of Factor VIII concentrate had increased from 5.9m. iu per annum to 11.5m. iu. Against this, as the meeting of the Haemophilia Centre Directors held on 24th October 1977 records (document no. 611), BPL was beginning to reach its peak of production at 14m iu worth of Factor VIII per annum by late 1977, against the need for 50m. units of Factor VIII concentrate per annum.

168. In the context of providing estimates of expenditure under the PESC system, Mr. Dutton wrote an interesting memorandum to Mr. Harris (both were DOH personnel) on the 14th February 1978 on the subject of BPL (document no. 661). There are some key passages in the memorandum which repay reading in full. However, the memorandum clearly shows an appreciation that BPL was nearing capacity and that whilst the Stop-Gap package had been received, the doubts about BPL's ability to meet the requirements of the Medicines Inspectorate as well as the targets emanating from the Trends Working Party report, all indicated that important policy decisions (and their financial implications) had to

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be made and addressed. In particular, paragraphs 2 and 3 are worth referring to:-

> "2. Before I deal with the individual points in your minute, may I say that however necessary it may be to regard BPL as a "fringe body" for other purposes we must be realistic about what would happen if a policy of no growth were applied stringently for very long.
>
> "3. If BPL should fail to provide the blood products which the NHS needs, hospitals will buy the commercially available product usually at greater cost to the NHS. In short, a no growth policy applied to BPL would only be realistic if a similar embargo were placed on any expansion in the use of blood products. While one accepts the imposition of cash limits on health authorities means that some aspects of their activity must be subject to no growth and some possible cut-back, there is no evidence to suggest that the stringencies are affecting the inclinations of clinicians to use more (and more sophisticated blood products) as their usefulness becomes apparent."

169. An important meeting took place on the 13th March at BPL (notes-document no. 674). This was a very high level meeting to discuss the financial arrangements for developing BPL. It is to be noted in paragraph 2 that "quite apart from eventually meeting the Trends target, there is an urgent need to produce more Factor VIII and albumin...", attention was focused on both short term developments, for 1978/9 and for the longer term "stop-gap" proposals. Reference is made at the top of page 2 to an increase in plasma supply from RTC's resulting in "sufficient extra Factor VIII to make appreciable inroads into NHS purchases of the commercial concentrate." The note largely speaks for itself, but in general the need to improve efficiency at BPL and the need to take

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positive steps was recognised. In fact three days later Mr. Dutton sent a note to Mr. Parrott (document no. 677) which shows that things were starting to move within the organisation. The third paragraph of Mr. Dutton's note says:-

> "Mr. Harris informs me that if we are prepared to give sufficient divisional backing, he is prepared to add to the bids a sum of £200,000 to cover the most which might conceivably be spent on "stop-gap" and other necessary developments in the year 1978/9".

170. On the 17th April 1978, the closure of the Lister Institute was announced and my report to Professor Mollison (document no. 688), for the Management Sub-Committee, attempted to address the implications of this. I viewed the Lister's closure as a unique opportunity for the development and future of BPL. In particular, I saw an opportunity to buy all or part of the Lister site to facilitate the development of BPL. I recognised that a decision would have to be made quickly in order that the Lister staff could be advised of the position. In the event, two thirds of the staff left preferring to take redundancy payments (although a number promptly rejoined!). I raised the question of the replacement of the Lister Institute as governing body. I was rather anxious not to see BPL subsumed into some other group, for example the Public Health Laboratories Service ("PHLS"), but to remain as separate and distinct as possible.

171. The closure of the Lister Institute was important for a number of reasons. It jeopardised the status of the 1978/9 budget which had not yet been agreed. Stop-gap proposals needed review because the future of existing buildings was unknown. Activities had, therefore, to be diverted to such questions as the future of the site, the future of the BPL and the question of long term management. As the position presented itself, operations could have ceased. Dr. Maycock was retiring in six months time. It was possible that the DOH would

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perceive an immediate need to resort to Scotland for Factor VIII concentrate if the Scottish figures were to be believed. As it turned out, the closure could not have come at a better time as far as I personally was concerned. The Department decided to buy the Lister site, to maintain the security of BPL, to keep staff and obtain temporary management arrangements.

172. At a meeting which took place on the 31st May 1978 between representatives of BPL including myself and Dr. Maycock and representatives of the DOH, the general problems arising from the closure of the Lister Institute were reviewed (they were particularly acute in some areas where we shared staff with the Lister) and, as will be seen from the minutes of the meeting (document no. 710), that, although contrary to existing policy, consideration was given to creating a Special Health Authority to take over the running of the BPL. It was proposed that an RHA should be encouraged to take over the day to day management role on behalf of DOH for an interim period.

173. On the 5th July, there was a meeting of the Regional Transfusion Directors (document no. 732). As I recall, this was the first meeting of the Regional Transfusion Directors which I was permitted to attend, notwithstanding that I had been Director Designate for over a year by this time. As will be seen, those attending included representatives of the DOH. The meeting began with a short tribute to Dr. Maycock, since this was the last meeting he would be attending before he retired in September (he had been knighted in the birthday honours list in June). I proposed that there should be a working party to look into possible methods of increasing supplies of FFP, and the implications for BPL, and this was accepted. As will be seen from Mr. Parrott's (DOH) comments, there was a general note of caution sounded regarding any financial consequences arising from an examination of new methods of harvesting FFP. The Committee which this gave rise to became known as the "Single Bag" Committee in that it

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recommended using single donation plastic bags in place of the 5 litre bags. Its formation and work was criticised by Scotland.

174. Anticipating some developments that I comment on below, I think it is worth making the point that so far as FFP production was concerned, three opportunities presented themselves during the period relevant to this litigation. The first was that resulting from the David Owen £500,000 injection. This enabled BPL to effectively double its production of Factor VIII concentrate from 5m. to 11m. iu per annum in the targeted period (1976 to 1977). The second was the development of optimal additive solutions permitting blood to be totally separated resulting in an increase of 30% in recovered plasma volume from each donation. The third opportunity to increase FFP could have resulted from more use of plasmapheresis, enabling donors to donate a greater plasma volume. The introduction of single plasma donations and pro rata return to RHA's of products in relation to volume of plasma supplied to BPL were further contributory factors.

175. On the 1st September the third meeting of the Haemophilia Centre Directors and Blood Transfusion Centre Directors took place (document no. 768) and I attended on behalf of BPL. I used the meeting as an opportunity to touch on the question of distribution arrangements with regard to Factor VIII concentrate. I recorded the fact that the existing arrangement was that RTC's received Factor VIII concentrate on the basis of the number of treated haemophiliac patients reported to PFL Oxford, but commented that this particular method was not the only one available. As indicated above, introduction of the pro rata regional incentive scheme would relate Factor VIII supply to RHA's plasma supply to BPL/PFL.

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176. September also saw the publication of the report to the Advisory Sub-Committee on Blood Products and Blood Group Reference Laboratories of the Central Committee of the National Blood Transfusion Service, (document no 770), in respect of BPL for the year ending July 1978. This was effectively Dr. Maycock's last report and possibly because of this, Dr. Maycock used the report for his valedictory statement, which I reproduce below.

177. First, as one will see from reading the "General" section of the report, "Stop-Gap" had by this time been under discussion since the 25th October 1977 and it had reached the point where the services of an architect would be necessary to proceed further. (I should also mention for completeness, that external management consultants had reviewed the Stop-Gap proposals as well). As Dr. Maycock indicated, the "Stop-Gap" concept envisaged a two phase increase in capacity over about 4 years and would ultimately lead to an effective doubling of output of Factor VIII concentrate and albumin.

178. On pages 6 and 7 of the report, there are details with regard to the production for 1977 and, as will be seen, the total plasma fractionated came to 150,000 tonnes, and in terms of Factor VIII, BPL produced approximately 13.2m. iu. In effect, Dr. Owen's £500,000 had resulted in an increase of nearly 300% of BPL production in 1976. In 1978 as capacity was reached, growth in output was reduced so that the increase was limited to nearer 15%. This was achieved by BPL with only £58,000 capital investment out of the £500,000 made available to the NBTS.

179. In retrospect, however, the Owen initiative rebounded on the Service in that it supported growth in <u>demand</u> for Factor VIII but only a basis for limited supply and growth in <u>output</u> from NBTS and BPL sources. The growth at BPL

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focused attention on the effects of transition from a development laboratory to a manufacturing enterprise, now seriously below pharmaceutical standards.

180. The problem was that the basic infrastructure of BPL remained one which was appropriate to a laboratory engaging in research and relatively small scale production. The buildings dating back to the 1950's were old, small and not appropriately designed for manufacturing. In 1979 the Medicines Inspectorate condemned the facility. However, whilst still inadequate, it was now a facility making a significant contribution to the increasing requirements of haemophiliacs for Factor VIII concentrate. In retrospect it would have been less disruptive to the NHS if the consequences of inspection had been met in 1976 when the Licence Application to manufacture was submitted to the DOH.

181. In his conclusion, Dr. Maycock said:-

> "There is perhaps a moral to be drawn from the building history of the present BPL.
>
> "1954 building: planned in 1949-1952 mainly as a civil defence project to prepare freeze-dried large pool UVL irradiated plasma, the preparation of plasma which was abandoned during erection of the building in favour of a return to freeze-dried ten donor small pool plasma. The potential value of plasma fractions had not been appreciated in any countries, and a combination for fractionation was included only as an after thought.
>
> "1962 extension: a make and mend operation which by moving the bacteriology and enlarging the small-pool plasma laboratories, relieved some of the pressures on the laboratory which were becoming intolerable.

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"1972 extension: this enlargement originated from the relatively immense need for immunoglobulin to prevent rubella in exposed pregnant women. Later it was decided that the plan should include means for meeting the estimated needs of Factor VIII concentrate and, later still, that the building should accommodate means for fractionating all plasma and that freeze-dried small-pool plasma should be replaced by albumin and PPF. It is now known that estimates for Factor VIII concentrate and albumin concentrate on which the plan was based were totally inadequate. Planning, completed in 1965, was affected by the severe constraints imposed by the site and, in spite of these impediments, reductions in floor space were nevertheless imposed by the Department."

Dr. Maycock concluded:

"It takes at least four to five years to plan and build accommodation for plasma fractionation or any other large laboratory. It is thus impossible for a fractionation laboratory to respond quickly to a new demand unless it has unused space at its command and unless it has been designed in a manner and use its techniques which allow flexibility in its accommodation and in the adjustment of production methods. I suggest two proposals concerning the BPL which will succeed "Stop-Gap" and provide accommodation that meets requirements in the Medicines Act 1968:

"Firstly, the redevelopment of BPL should have a capacity greater than that needed to provide for the latest estimates for plasma fractions available during the planning stage.

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"Secondly, DHSS should take a long term view and consider a new BPL as a valuable investment which will save the Department much money."

182. In October 1978, a letter was written by the DOH to NWT setting out proposals for the management of BPL by NWT (document no. 781). The key paragraph in the letter provides:-

"The RHA has agreed to undertake a number of administrative, financial and personnel functions on the Department's behalf. It has also become the employing authority for all staff, and thus presumably fully responsible in law for the administration of the laboratories. However, the RHA's responsibilities will, in practice, be limited and the Department will retain responsibility for policy and for some management decisions. In these circumstance we suggest that the Department and the RHA should form a joint management committee; this would be in keeping with our recognition of the laboratories as an entity distinct from other Blood Transfusion Laboratories run by the region, and of the shared responsibilities of the region and the Department."

183. The JMC's terms of reference are set out in the same letter and reflect the continuing involvement of the DOH in the affairs of BPL.

184. Also in October 1978, we revised the budget for 1978-79 to reflect some important alterations to the Stop-Gap project. Being released from the space constraints imposed by the Lister Institute which had earlier limited the Stop-Gap proposals, impending acquisition of the whole Estate now necessitated a review of redevelopment plans and associated budgets. The revised plans and budget were submitted to the DOH.

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185. The first meeting of the JMC was held on the 13th December 1978 (document no. 819). Dr. Harris, Deputy Chief Medical Officer, said that:-

> "the purpose of this Committee was to oversee the management of the laboratories in which task they would be assisted by advice from experts whenever needed."

On page 2 of the minutes, the tasks of NWT are set out and are indicative of personnel functions. The DOH was to provide central funding and to receive advice through the JMC to enable it to formulate policy. On page 3 there is a discussion relating to the purchase of the Lister site. On the question of finance under the new arrangements, I was to undertake financial work in connection with the running of BPL and PFL Oxford with effect from the 1st April 1979. It was also agreed at the meeting that a Finance Sub-Committee should be set up. Reference is made on page 5 of the minutes to the requirements that the manufacturing activity at the laboratories complies with the provisions of the Medicines Act. BPL was, as I describe below, visited by the Medicines Inspectorate in early 1979. On page 6 reference is made to the establishment of the Scientific and Technical Committee for the Central Blood Laboratories which was set up shortly after and included representatives from industry on it. Professor Mollison agreed to be Chairman of the Scientific and Technical Committee.

186. By way of conclusion with regard to the events of this year so far as they relate to self-sufficiency, I would refer to the minutes of a meeting of the Working Party in Haemophilia (which is in fact a local group in North East Thames Region), which met on the 29th November 1978, and, amongst other matters, discussed the question of likely requirements for Factor VIII concentrate. The minutes (document no. 807) record the views which I had formed by that

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time, i.e. that we really needed a facility which could produce at least 100m. units of Factor VIII concentrate per annum. It was considered that £15m was needed in the short-term to upgrade BPL to meet the estimated growth in demand for Factor VIII.

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1979

187. In terms of self-sufficiency, by 1979 it was too late, (having regard to the four to five years it would take to plan and build a new facility), for a decision in this regard to have made any difference if, as I would submit, the majority of severe haemophiliacs were infected with HIV before 1985. That said, 1979 saw the Medicines Inspectorate carry out their inspection of BPL's facilities in April, and the publication of their findings severely criticising virtually every aspect of the BPL facility in the summer. From my discussions with the Inspectors during the course of their initial inspection, I was fairly clear in my own mind what the outcome would be even before their report was available, and this prompted me to press for a decision by the DOH on the future of BPL.

188. Unfortunately the recommendations of the Medicines Inspectorate bore resource implications which the DOH considered might be in conflict with budget allocations set aside for implementing Stop-Gap. Stop-Gap arrangements were held up while priorities were reviewed against a background of limited financial resources. Eventually it was agreed that Stop-Gap plans accommodated many of the Inspectorate's recommendations, but limited budgetary expenditure required a reduction in the original proposals.

189. The year opened with my producing a paper entitled "The Function of Stop-Gap and Phased Redevelopment of the Blood Products Laboratory" (document no. 836). I prepared this paper for the benefit of the [Sub-Committee (of the Central Committee) [P9]]. In the summary, I set out the production limit for the new Laboratory as being 120m. iu of Factor VIII per annum. The required commissioning date was 1984. The projected needs of Factor VIII concentrate were considered on page 11. Total use of Factor VIII in 1977 was 48.5m. iu which should be viewed against the Trends Working Party level of 60m. iu for use

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by the mid-1980's. Factor VIII use was therefore in a period of rapid growth. The use of cryoprecipitate was hard to assess although some data suggested a decrease in cryoprecipitate use between 1976 and 1978. I commented, at page 12, that:-

> "gradually increasing numbers of haemophiliacs diagnosed and treated, expected increase in life span and associated increased incidents of concomitant illness and surgery, a move towards home therapy and prophylactic care all suggest a continued growth in Factor VIII use".

190. From page 13 onwards, I considered both the short term and the long term requirements for an increased plasma supply to BPL. In the longer term, I was advocating a serious appraisal by an expert group of techniques of plasmapheresis. On page 16 I reviewed what I saw as the inequality of the arrangements for plasma collection and the distribution of the finished product, and I suggested that Regions supplying large amounts of FFP should receive Factor VIII in return on a pro rata basis and, for that matter, the albumin attributable to their source material.

191. On the 26th March 1979, the first meeting of the Scientific and Technical Committee for the Central Laboratories took place at Elstree (document no. 859). The meeting was chaired by Professor Mollison. The notes of the meeting are a fairly comprehensive review of the position at that time and what was required. In the middle of the fourth paragraph on page 2, the notes record:-

> "after discussion, it was agreed that if clinicians were to retain freedom to treat their patients in the way that was considered most suitable, it

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was possible that eventual requirement **[for Factor VIII]** might well approach the 100m. iu per annum mark."

192. Both Stop-Gap and the need for more radical redevelopment of BPL were discussed and, at the conclusion of that part of the meeting, it was agreed that Mr. Smart would prepare a comprehensive report following discussion of the requirements with myself which members could consider at their next meeting.

193. On the 23rd to the 27th April 1979 inclusive we were visited by the Medicines Inspectorate, Mr. Flint, Dr. Purvis and Dr. Holgate. From my discussions with the Inspectors during the course of their visit, my expectation that they would be severely critical of the facility was confirmed by their comments. So much so that, on the 2nd May 1979, I wrote to Mr. Dutton at the DOH (document no 868) setting out my observations on their visit prior to the publication of their first formal report.

194. The second paragraph of my letter summarises my thoughts at the time:-

"Mindful of the shortcomings of the existing system and somewhat contrary to the previous Director's feelings, I both welcome and encourage this inspection, since I believe it is quite contrary to good manufacturing practice to use a privileged situation to hide the considerable deficiencies of BPL. In addition and also contrary to the previous Directors' views, I believe that Medicines Division, through their Inspectorate and acting on behalf of the Secretary of State for the Health Service, have a responsibility to assist a Central Health Service Production Laboratory like BPL to carry out its function in the best possible way."

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195. At the top of page 2 the letter identified the three major problems then facing BPL. First, the deficiencies and constraints of the building; secondly, problems arising from both quantity and quality of staff because of BPL's inability to compete with industry terms and conditions, and thirdly, the fact that the Laboratory was in a stage of transition from a "cottage industry" into a major production process, moulded along commercial industrial lines. I should perhaps point out that the context in which the Inspectors' visit took place was the Department of Health and Social Security Health Service Circular (interim series) document HSC(IS)144 "Application of Medicines Act 1968 to Health Authorities. Blood Transfusion Service" (Appendix 6).

196. I revised my earlier paper entitled "The Function of Stop-Gap and Phased Redevelopment of the Blood Products Laboratory" in May 1979 (document no 878), with the intention that it should be provided to the DOH and the JMC. The document really served to collect together our thoughts and plans starting with Stop-Gap in its various incarnations between 1977 and 1978 and, building on this, the proposals for a phased redevelopment at BPL.

197. Although we did not have the Medicines Inspectorate's report on their visit in April 1979 (another was planned in July), I had, as I have explained above, a fair idea from my discussions with them as to the outcome of their first visit. I had promptly written to Mr. Dutton of the DHSS on the 2nd May setting out my concerns and, anticipating that there would be no immediate financial response (indeed there was none), I thought it best to put forward my paper with a view to focusing everyone's attention on the issues we had to face up to.

198. Of course we now had the additional land that we needed for expansion. I had previously mentioned at a meeting of the North East Thames Regional Haemophilia Group the idea that 100m. iu would, realistically, have to be the

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target of any redeveloped BPL. In my paper, however, I increased that figure to 120m. iu (I was working on the basis of some 2,000 patients each using approximately 50,000 iu per annum plus a small margin). The figure was also based on the Council of Europe recommendation for albumin of 200 kilos per 1m. of population, and I had in mind that with Factor VIII, US published figures at the time showed annual usage running at some 40,000 to 50,000 iu per treated patient. In planning for 120m. iu, I was trying to avoid what seemed to have been the pattern in the past of always aiming for the lowest current usage as a target with the inevitable consequences, and instead to aim sufficiently ahead of current usage to be more certain of hitting the target when an enlarged facility was commissioned. In the event, it seems likely that usage will reach the 120m. iu level this year (1990).

199. I believe the paper repays reading and is largely self explanatory. One or two points can be made, however. First, I commented on page 10 on the deficiencies which we suffered in management, and I have earlier indicated that the legacy which we had from the early 1970's was a staff of scientists rather than pharmaceutical manufacturing managers and engineers. I have to say that ten years later we still have no Chief Engineer and the problem throughout (as I have mentioned above) has been that we have been unable to offer salaries and terms and conditions which are competitive with those in the private sector. The present Factory Manager, Dr. T. Snape, was in fact originally employed at Oxford and trained by BPL to occupy his present position.

200. It will be noted that on page 12 the intermediate target was 90m. iu which I thought was likely to be the usage by the mid-1980's. In fact in overall usage terms, this level was reached in 1987, but in terms of concentrate, this level was reached in 1989. I also estimated that it would require 375,000 litres of plasma to produce 90m. iu but of course this was later proved incorrect when we

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were obliged to develop a purer product which would withstand heat treatment with a corresponding reduction in yield as purity improved. We were later able to recoup most of the lost ground in terms of yield as between our current product 8Y and the 8CRV and HL it replaced, by refining the manufacturing process. I believe that our estimates of yield in the 1970's were not made on the same basis and were not that accurate: any comparison of the differential would therefore be inappropriate.

201. My paper was actually tabled at the Scientific and Technical Committee meeting held on the 7th June 1979 and at the same time a report prepared by Mr. R.D. Smart was tabled (document no 880).

202. Mr. R.D. Smart was, at the time, a Director of Glaxo Holdings. He subsequently became the first Chairman of CBLA. He was brought onto the Scientific and Technical Committee (a sub-committee of the JMC) when it first began and his appointment coincided with views I had expressed to Dr. Harris about the need to have guidance from experts in pharmaceutical manufacturing. The result was that Mr. Smart was approached by the DOH and initially joined the Scientific and Technical Committee subsequently progressing to membership of the JMC itself before being appointed Chairman of the CBLA when it took over the management of BPL and PFL in December 1982. He ceased to be Chairman in December 1988 when he retired.

203. I think his paper really speaks for itself and, as one would expect from his background, he concentrated on the financial aspects using such preliminary financial data as was available at the time.

204. Immediately behind his paper are a number of miscellaneous pages **[where are they? [P10]]**. The page headed "BPL re-Development" sets out a quick and

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robust costing based on simple linear calculations to give an overall order of magnitude costing. As will be seen on page 4, the overall cost was estimated to be somewhere in the region of £20m. On the strength of this, when the new BPL building was sanctioned, the Junior Minister (Mr. G. Finsberg) authorised expenditure of about £20m. but without contingencies. The authorisation overlooked the fact that the provisional estimates from DOH were based on 1978 figures and moreover, that they were on the basis of up-grading an existing building, not on a green field site development. Matthew Hall who undertook the construction of the new BPL facility were aware of the provisional estimates early in the course of their negotiations with the DOH, and when their tender was submitted, it reflected a cost which was fairly close to this figure. By the time the new building was commissioned, overall building costs were in the region of £50m. although it has to be said that the building was larger and more comprehensively equipped than the one which Matthew Hall originally tendered to build and much of the increased cost was based on changes in preliminary design and specification, some of which reflected the appearance of AIDS as a transmissible disorder.

205. The Scientific and Technical Committee met on the 7th June 1979 and those attending included DOH representatives and Dr. Gunson representing the NBTS. However, there were no representatives from the Haemophilia Service present. As will be seen from the minutes (document no. 882), my paper on the continuation of Stop-Gap and the phased redevelopment of BPL was discussed. Dr. Holgate reported on the visit made by the Medicines Inspectorate and pointed out that a few more days would be necessary before the exercise was complete. He drew attention to the fact that it would be some time before the Inspectors' report would be available but that it was already apparent that substantial deficiencies had been found and many improvements would be required. On page 5, Dr. Tovey (who had succeeded Dr. Maycock as Consultant Adviser to the DOH)

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drew attention to the problems in the Transfusion Service in providing plasma necessary to support even the "Stop-Gap" proposals, without significant additional investment.

206. As will be seen from the third paragraph on this page, discussion eventually led to the conclusion that the DOH should proceed to prepare a complete appraisal of the various possibilities open and their cost effectiveness for consideration by the Committee in September, and that this should precede any approach to Ministers regarding the future of BPL. It seemed to me at the time that matters were still drifting and likely to continue to do so for some months, and I expressed the hope that there would be an early decision in principle on the development of BPL.

207. The JMC met on the 13th June 1979 and its minutes (document no. 884) are of importance. At paragraph 4 on page two of the minutes, Dr. Harris, the Deputy Chief Medical Officer with joint responsibilities for NBTS/BPL and Medicines' Division, outlined the contents of the Inspectors' Report and Recommendations (I had not seen the latter). The minutes record his evaluation of the basis of the report and status of the recommendations as they applied to a Crown exempt organisation. The Minutes record that:-

> "Dr. Harris described the status of the Report which the Department would eventually receive. The Report would be scrutinised by a Departmental multi-disciplinary committee to establish whether the basis of the Report was valid. Appropriate action would then be decided upon and, if necessary, Ministers would be consulted. It was always open to the factory or laboratory reported upon to challenge the validity of the Inspectors' findings. It was not for the Inspectors to decide what should be done to put matters right, and what was or was not appropriate if

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there was no question of the safety of the product at issue. Documentation and environmental control were however both matters of great concern to the Inspectors since they had a direct bearing on the quality of the finished product".

208. I do not believe that Dr. Harris was taking issue with the Inspectors' right to make recommendations: he was merely pointing out that because of the BPL's Crown Immunity status, it wasn't necessarily the case that the recommendations would have to be noted.

209. In the next paragraph I comment on the findings of the Inspectors, but my comments at this stage were without the benefit of having seen a copy of the recommendations, based only on discussions with the Inspectors during the course of their visit.

210. At the top of page 3, there is a significant comment:

"While the possibility had to be faced that there might be no more money available to make any radical changes at BPL for perhaps three or four years, everything possible had to be done to improve the state of affairs from within whatever money was available."

211. This foreshadowed what came to pass. On page 4 of the minutes under the heading "The Scientific and Technical Committee", there is reference in the third paragraph to Stop-Gap. I argued in the course of the meeting that Stop-Gap was the only way forward and embodied much of what the Inspectors wanted to see changed. Buildings and procedures were inadequate, but there was no reason why they should not be tackled together provided that financial resources were available to meet requirements in the short-term (2 to 3 years).

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Capital budgets could only be agreed on a year to year basis notwithstanding that a project like Stop-Gap had to be implemented over the short-term. It will be noted at the foot of the page there is reference to NWT being asked to become the client for the purpose of contracting with appropriate parties for the Stop-Gap project. Perhaps not surprisingly when NWT were approached over this, they wanted to re-examine the original costings (which delayed matters further) and they were not prepared to become involved unless the totality of the funding (not just the current year) was guaranteed. In the event, DOH agreed to this.

212. John Harley wrote to me on the 13th July 1979 (document no. 885) to put a hold on capital expenditure pending publication of the Medicines Inspectors' report and resolution of its the implications. Mr. Harley said that it was likely that the Medicines Inspectors would require some up-grading of the facilities at BPL and that there was no money allocated for this. In the circumstances he suggested that the situation might have to be faced where we were obliged to choose between up-grading and going ahead with the Stop-Gap programme. On this basis, he directed that we should avoid incurring any further Stop-Gap expenditure until the financial position had been clarified. As stated above I considered that Stop-Gap would almost certainly cater for many of the Medicines Inspectors' points whilst, at the same time, being an important stepping stone towards a redevelopment of the facility. This point was pursued during the coming months.

213. On the 8th August 1979 (document no. 897), I wrote to Dr. Holgate at the DOH commenting on the DOH decision to put a temporary halt on all developments, and sought to draw attention to the fact that various aspects of the Stop-Gap programme would take care of many of the important recommendations and requirements of the Inspectorate. In that letter I urged that consideration be given to initiating some of the Stop-Gap work before the

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end of the financial year. I recorded the fact that the current state of affairs made me vulnerable as Director. I had been given specific responsibilities for quality control and product safety which I could not discharge in the face of a freeze on capital expenditure intended to improve the state of the BPL.

214. On the 13th August 1979 the Medicines Inspectors' report arrived at BPL (although I was absent at the time). At the same time I received a response from Dr. Holgate (document no 907) in which he sympathised and indeed agreed with some of my comments, and stated (by way of reassurance) that formal discussions of the reports (presumably those of the Inspectors) and the forwarding of final recommendations had already been accelerated and that (leaving aside political considerations) there seemed to be support for the idea that Stop-Gap should proceed. That said, the last sentence of paragraph 2 reads:-

> "In addition, a great deal can be done without high expenditure in addition to Stop-Gap".

215. The main report is a fairly detailed document, but the essence of it perhaps captured in the conclusions and recommendations of the Medicines Division which were sent by Mr. Firstbrook under cover of his letter of the 10th September 1979 (document no. 918) to Mr. Harley at DOH. As he mentions in that letter, the main report was considered by the Inspection Action Group of the Medicines Division, and their conclusions and recommendations were set out in the appendix enclosed with his letter (and it was these that Dr. Harris obviously had knowledge of and which so prompted his comments referred to above). Immediately prior to that letter, Mr. Dutton of DOH had obviously sent to me a draft of his memorandum on the subject of improving manufacturing conditions at BPL (document no. 917) for initial comments before he finalised the document. It followed a meeting we had the day before which was concerned with the short

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term measures necessary as a consequence of the Medicines Inspectors' report. It would appear that at the time we were still working on the basis of the draft report which had been circulated in August. Paragraph 2 of the note concerns itself with the staffing problems which were certainly the cause of a number of the criticisms levelled by the Medicines Inspectors. There were a number of detailed points made in the draft, but suffice to say, that it is a fair summary of what I said at the time.

216. As is indicated in the last paragraph of Mr. Dutton's memorandum, I thought it probable in the light of the comments which I had received from Mr. Dutton and others at the DOH, that no immediate attempt to increase the output of the Laboratory would be made. In these circumstances, our efforts directed towards dealing with the Inspectors' recommendations much depended upon the amount of money we were provided with for this purpose.

217. I think the essence of the Inspectors' findings is best summarised in the appendix to Mr. Firstbrook's letter of the 10th September 1979. Paragraph 7 of this states:-

> "If this were a commercial operation, we would have no hesitation in recommending that manufacture should cease until a facility was up-graded to a minimum acceptable level."

218. Notwithstanding this, there is a statement in paragraph 8 to the effect that the products produced at BPL were essential to the health and well being of the nation, and that alternative sources of supply were severely restricted. In these circumstances, production could continue at Elstree provided certain aspects/ standards of production and control were improved immediately, and plans were formulated to deal with other improvements immediately with a view to their

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very early implementation. Strictly speaking, this paragraph was not correct, since many of the products we manufactured (and particularly Factor VIII concentrate) could have been obtained from commercial sources. It is not correct to say that these sources of supply were severely restricted. I would add that deficient though the facility was by the standards which the Medicines Inspectorate (properly) applied, one should, notwithstanding, bear in mind that some aspects of our facility compared favourably with some that were licensed by the Federal Authorities in the USA.

219. As will be seen from paragraph 9, there was an embargo on increasing production (paragraph (a)). With regard to the manufacture of freeze-dried plasma which is referred to in paragraph (b), I personally was very pleased to be able to stop manufacturing this. The additional comment at paragraph 12 is interesting, in that the Inspectors recommended that the Stop-Gap proposals should be proceeded with as quickly as possible to provide additional cold storage space, warehousing, goods received and despatched, containing, washing and preparation, but only if such development could be incorporated into a new manufacturing facility. However, the Inspectors' commented that in proceeding with Stop-Gap, there should be no increase in production which they characterised as already "over loaded and seriously deficient in standards." They went on to comment that they did not see the need to develop a green field site for the new manufacturing facility (although in the event this is of course what happened).

220. The JMC met on the 12th September 1979 (document no. 922). The minutes record at paragraph 3 that Stop-Gap had been halted and go on to record that there was considerable discussion of the Medicines Inspectors' report but no firm decision was taken in the light of it. I cannot remember the detail of this discussion but I have very little doubt that I would have been pressing for a continuation of Stop-Gap as I had done in correspondence and in the papers

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which I had prepared. Under paragraph 6 "Any Other Business", there is reference to the concern which I was expressing at this time about my liability as the Director of BPL in relation to the Medicines Act if an adverse event were caused by BPL products. I recall that despite the matter being referred to the DOH Solicitors and my taking advice from the Solicitors for NWT, no one could give me a clear answer as to the extent of my responsibilities.

221. Mr. Dutton, in a handwritten memorandum to me on the 12th September 1979 (document no. 923) proposed the establishment of a Working Group to discuss the implications and implementation of the Medicines Inspectors' recommendations as set out in their report. The purpose was for the Working Group to prepare a paper for submission to the JMC. The idea was to produce a report within about four weeks. Apart from myself, the other members of the Working Group were from the DOH. I replied on the 13th September 1979 (document no. 924) objecting to the limited terms of reference of the Working Group and its composition. As to the former, I felt it was necessary to take a far more definitive and far reaching view (I had in mind keeping Stop-Gap and the phased redevelopment of BPL alive - not just a make do and mend to the Medicines Inspectors' report). As to the latter, I thought it essential that we look at the steps to be taken in relation to BPL in the context of the National Blood Transfusion Service and that, as such, the Working Group should include the Consultant Adviser to the DOH and someone (I suggested Dr. Gunson) to represent the Regional Transfusion Centres' interests. I also suggested that the Scientific and Technical Committee should be represented on the Group and that Mr. Smart should perform this role. My requests were turned down.

222. In my letter of the 14th September 1979 addressed to Mr. Flint of the Medicines Division (document no. 925), I formally responded to the Medicines Inspectors' report indicating that, following lengthy discussions with the

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Inspectors during the course of their visit, I had, in the main, reached agreement with them on the majority of the matters on which they had reported with the consequence that I generally accepted their report. I enclosed a list of detailed comments but, as can be seen, this was not a long one.

223. I prepared a report on the 19th September 1979 entitled "Future Preparation of Plasma Protein Factions by NBTS: a Re-assessment of Requirements" (document no. 928). This paper was prompted by the need, as I saw it, to ensure that we did not attempt to resolve the problems faced by the BPL without regard to those which were faced by the Regional Transfusion Centres who were providing our raw materials. The DOH would have received my paper and I feel fairly sure that, at the time I wrote it, I was also preparing myself for another attempt to lift the hold on Stop-Gap. As will be seen on page 6, I advocated, in the absence of any mention of the National Blood Transfusion Service and the Royal Commission Report, that there should be some entity which took responsibility for the service - perhaps a Special Health Authority. Ironically, some ten years later, in the first report for the United Kingdom National Blood Transfusion Service Directorate (set up in the autumn of 1978 by Order of the Secretary of State) they proposed Special Health Authority status for the body to run the NBTS.

224. My letter to Mr. Dutton of DOH on the 21st September 1979 (document no. 929) obviously enclosed a copy of my paper and I explained my purpose in producing it was to have it tabled at the next Scientific and Technical Committee meeting. I also asked that the document be put before Dr. Tovey's Ad Hoc Group dealing with Trends and future production requirements. The Group (which is considered in greater detail in Appendix 2) was composed of the Consultant Adviser, departmental members, the Director of BPL and Regional Transfusion Directors who were Chairmen of the NBTS Super-regional Groups. It operated

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during the tenure of Dr. G.H. Tovey's advisory role in blood transfusion (i.e. as Consultant Adviser in Blood Transfusion to the DOH. By virtue of its ad-hoc nature, it was not a well-defined Group.

225. On the 26th September 1979 (document no. 933), an ad hoc group of the Regional Transfusion Directors met to consider the implications for the Regional Transfusion Centres of meeting the requirements of the Trends Working Party. As will be seen from the second paragraph of the minutes of the meeting, there was no universal acceptance by those present of the proposition that blood products should be distributed by BPL to Transfusion Centres proportionately to plasma supplied by them to BPL. This is hardly surprising, since there were some Regions and Centres providing very little plasma when compared to others. As I remarked in the course of the meeting, we had noted that plasma supplies were beginning to tail off in many Regions. The reaction of the Transfusion Directors was that this was not a result of a shortage of donors but was genuinely due to a shortage of money needed to maintain the level of plasma supplied.

226. The Scientific and Technical Committee also met on the 26th September 1979 chaired by Professor Mollison. I was present at that meeting. As will be seen from paragraph 5 of the Minutes (document no. 935), there was discussion of the way forward in the light of the Medicines Inspectors' report, and the Medicines Division's conclusions and recommendations. One thing was fairly obvious from the comments made by the DOH representatives. Beyond the amounts already budgeted for the Stop-Gap programme, there was no certainty of any additional monies being found and no commitment to proceed with the full scale rebuilding of BPL which was, of course, the next phase after the implementation of Stop-Gap. I pointed out (see the top of page 3 of the minutes) that the money which was available at that time to finance Stop-Gap would do little more than pay for the improved cleanliness which was seen as a first

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priority but which was only one of the improvements immediately necessary to satisfy the Medicines Inspectorate. On the back of this, I once again reiterated my concerns about my own position as Director and touched upon the fact that I was receiving legal advice.

227. It will be seen that Mr. Harley's position paper STC(79)7 (document no. 934(d)) was tabled. It is a particularly interesting document which provides an overview of the various considerations which were then exercising the minds of the DOH Officials.

228. Under the heading "Other Considerations", there is reference in paragraph 13(a) to investigations which were then underway to determine whether the PFC in Edinburgh should be utilised to assist in the fractionation of English plasma. Paragraphs 13(c) and (d) are also interesting. Paragraph (c) is a reference to the continuing and increasing demand for Factor VIII concentrate, and the reality that clinicians were increasingly prescribing it without regard to the costs involved. Paragraph (d) touches on the relative economic merits of investing in increased production against paying increased disability pensions for haemophiliacs (i.e. on the assumption that by not treating them properly, they would be unable to lead normal lives and would become qualified for disability pensions which might not be required if they received sufficient treatment to allow them to lead normal lives).

229. Dr. Dunnill, who was very much an advocate for the Scottish PFC (and indeed had been involved in the development of the equipment installed at PFC which was intended to provide for continuous production), raised, at page 4 of the minutes, the question of the absence of PFC representatives on the Scientific and Technical Committee. I remained concerned about the claims made of PFC by Mr. Watt. Mr. Smart suggested that to clear the path for a decision to redevelop

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BPL, the claims for PFC be tested. Mr Watt and Mr Cash for PFC were required to agree to a trial of fractionation. I deal with this in more detail below.

230. In October 1979, Professor Mollison as Chairman of the Scientific and Technical Committee produced a draft of a paper which he had undertaken to prepare commenting on the implications for the National Blood Transfusion Service of an adverse report on BPL (document no. 938). The draft in my papers was fairly comprehensively amended by various people but I believe it subsequently went to Ministers. The reasons for the Committee rejecting the idea of abandoning production at BPL are set out in paragraph 4. In essence, these were:-

(a) it was more economic to continue producing blood products from unpaid donors when compared with the alternative of buying plasma and plasma fractions from commercial sources;

(b) that voluntary donors might be unhappy if they learned that their blood was being processed alongside that of paid donors and then being sold; and

(c) - "Plasma from paid donors is known to be more likely to transmit disease (particularly hepatitis) than is plasma from volunteer donors."

231. In the event, for reasons I describe in more detail below, I think that this last point is an over simplification and probably not correct so far as hepatitis NANB is concerned. It was most probably true of HIV.

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232. My paper on the National Blood Transfusion Service (document no. 928) was sent to Dr. Harris of the DOH under cover of my letter of the 22nd October 1979 (document no. 944). As will be seen from the letter itself, the inter-relationship between the budgeting and forecast exercise I had recently been engaged in and the uncertainty about the future of BPL which affected this exercise, were compounded by the lack of central management of the Blood Transfusion Service: if we were to up-grade the BPL facility to provide much greater quantities of blood products, we had to have an assured supply of the basic raw material - plasma. This itself required a coherent planning mechanism within the National Blood Transfusion Service which appeared to be singularly absent at that stage. The letter was acknowledged in Dr. Harris' absence, but I do not recall receiving any substantive reply from him subsequently.

233. The response of the DOH to the Medicines Division following the publication of their report on BPL was made in November and, much to my surprise, was made without having first been shown to me.

234. A special meeting of members of the Scientific and Technical Committee was held on the 14th November 1979 (document no. 955). There was further discussion of Stop-Gap but, in addition, the extra items which would be necessary to keep the facility operating as well as the steps which should be taken to keep the phased redevelopment proposals alive. The conclusion reached was that I, together with members of the Scientific and Technical Committee, should produce two or three alternative sets of plans for the redevelopment of BPL with broad costings, and that these should be presented to the Scientific and Technical Committee for further consideration.

235. On the 4th December 1979, there was an ad hoc meeting of the Regional Transfusion Directors held at Sheffield (document no. 965) which I attended. I

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used the opportunity to emphasise the importance which I attached to the pro rata system or something akin to it, so there was a positive incentive for Regions to increase plasma production. At the same time I urged that thought be given to rationalising plasma production by perhaps concentrating it on four or five Centres where there might be extensive use of plasmapheresis to assist in this regard.

236. The JMC met on the 19th December 1979 (document no. 971) and several familiar topics came up. First, estimates were produced for tackling the worst defects identified by the Medicines Division (see paragraph 4 of the minutes), and these produced a figure of £800,000 for the financial year 1980/81. The question of my responsibility in the light of the Medicines Inspectors' report was also raised again (paragraph 5), and it was agreed that I should have further discussions with the DOH Solicitors about my position. They had already advised me that they could give me no precise legal opinion because the law on the subject was complex but the idea of an indemnity which was discussed at the meeting was not subsequently endorsed.

237. As paragraph 9 of the minutes show, there was further discussion about the pro rata scheme but no real conclusions were reached. I was instructed, together with Dr. Tovey of DOH, to prepare a paper for the next JMC meeting which would examine the case for pro rata distribution.

238. Looking back on the year, the Medicines Inspectors' report threatened the future of BPL; by the end of the year it had resulted in postponement of Stop-Gap without any decision regarding the long term redevelopment of BPL. The production at BPL, in the facility condemned by the Medicines Inspectorate, was about at its peak (in the region of 15m. iu of Factor VIII concentrate per annum), and the Inspectorate had stopped any increase above this level.

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239. The future of BPL was again discussed at a meeting of the Scientific and Technical Committee held on the 23rd January 1980 (document no 982). The DOH had prepared a paper entitled "The Future of the Blood Products Laboratory Elstree" (STC(80)1) **[P11, can a copy be obtained?]** which was tabled at the meeting. It contained Ministers' views on what was to be done with regard to BPL. In effect, the decision was to make some further investment in BPL sufficient to up-grade it but not to the full extent required by the Medicines Division. There is an indication that since the paper had been prepared, there had been further discussions on the up-grading required at BPL and that Mr. Harley of DOH would be able to confirm if there was to be a substantial measure of up-grading. The main point in the second paragraph on page 2 is that Ministers had decided to defer the eventual decision on building a new Laboratory within the NHS until the other possibilities had been investigated. These included offering the Laboratory to the private sector. As will be seen from the last paragraph on page 2, there is mention of co-operative ventures with industry. I pointed out that it was necessary to ensure that the Minister, Dr. Gerrard Vaughan, appreciated the inter-dependence between the Laboratory and the Regional Transfusion Centres. In summary, the measures proposed fell somewhere short of Stop-Gap and of course did not include any commitment to redevelop BPL. Since I saw Stop-Gap merely as a stage in the comprehensive redevelopment of BPL, I was disappointed. I urged that consideration of the phased redevelopment of BPL should continue and not be deferred pending discussion with industry. I sought a firm policy statement from the DOH on the planning work for the redevelopment of BPL.

240. It was suggested that STC(80)1 should be reworded to avoid the difficulty of the Ministers' decision being construed as leaving a large gap between what

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was done and what the Medicines Division recommended should be done. The essential work necessary to meet the requirements of the Medicines Inspectors was also discussed.

241. An ad hoc meeting of the Regional Transfusion Directors was held on the same day and considered the organisation of the National Blood Transfusion Service. I attended the meeting. Dr. Jenkins reiterated his view that there was now a need for some central organisation to take control of the National Blood Transfusion Service and for a totally new method of financing to be devised. It was agreed that the voluntary unpaid donor must remain as the cornerstone of the National Blood Transfusion Service but, that there might be a need for Centres specifically concerned with plasmapheresis.

242. In my letter of the 29th January 1989 (document no. 986) to Mr. Dutton of the DOH, I sought once again to lobby hard for a policy decision with regard to the commencement of work on the redevelopment of BPL.

243. On the 7th February 1980 (document no. 989), Mr. Dutton of DOH wrote formally approving expenditure on most of the items mentioned in a letter from me of the 24th January **[this appears to be an important letter which we do not have]**. This approval was to be short lived following the intervention of the Health Minister, Dr. Vaughan, which I describe in greater detail below.

244. The subject of the re-organisation of the National Blood Transfusion Service was raised again at an ad hoc meeting of Regional Transfusion Directors which took place on the 15th February. In addition, DOH now supported the idea of a pro rata distribution of product, and had produced a paper (JMCCL(80)1 **[can a copy by obtained? P12]**) on the subject. The author of this was

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Mr. Dutton. The document sought the JMC's views on the introduction of pro rata and was considered and agreed by those attending the meeting.

245. The JMC met on the 20th February (minutes document no 998) and at this meeting Mr. Dutton's memorandum was considered. Dr. Tovey reported that Regional Transfusion Directors accepted the scheme but that Regional Medical Officers and Regional Transfusion Directors would require about 12 months notice of the introduction of a new scheme. Dr. Tovey undertook to explain the plans for a revised scheme (to take account of the requirements of certain areas with high concentrations of haemophiliacs) to Regional Transfusion Directors followed by the preparation of a paper for Regional Medical Officers and Regional Scientific Officers.

246. The future of BPL was also discussed by the JMC. Professor Mollison stated that the Scientific and Technical Committee had received a report of the Minsters' decisions on the actions which needed to be taken following the Medicines Inspectors' report, but they were left with the general feeling that the implications of letting industry become involved in the processing of voluntary donated plasma may not have been adequately explained, in particular as to the effect of a commercial partnership on the volunteer donor system.

247. Dr. Harris stated that the submission to the Ministers had emphasised the gravity of the situation at BPL and that the Scientific and Technical Committee's paper (STC(79)15) - (document no. 938), "Implications for the NBTS of Adverse Report on BPL Elstree by the Inspectors of the Medicines Division" had been brought to their attention. Faced with the constraints on funds, Ministers had to decide what action was practicable and necessary in light of the Medicines Divisions' requirements and, as so often happened in the industrial situation, a uitable compromise would have to be reached between the practical and the ideal.

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248. Dr. Harris noted that the short term measures needed to improve the conditions at BPL which Ministers agreed should be undertaken, were now in hand but meanwhile Ministers had asked that all options, including commercial participation, should be investigated. Ministers wished to have a progress report every two months.

249. Dr. Harris assured me that the Secretary of State and the DOH assumed product liability for BPL subject only to the normal responsibilities of professional staff for their actions. It was noted that the Medicines Division had a continuing responsibility to monitor the situation at BPL and would undertake a re-inspection shortly. They were also available to give whatever advice was necessary on the remedial measures to be undertaken.

250. It is apparent from the minutes of the meeting that the DOH anticipated that there would be £750,000 available for capital refurbishment at BPL in 1980/81, and that this was intended to deal with "Stop-Gap" and several other projects. I felt it necessary to point out at the time that the cost of even relatively short term development of the Laboratory would be in the order of £2m. to £2½m. over two to three years. Of course at this stage we had no commitment beyond the 1980/81 financial year. Following the Minister's visit to BPL, on which I comment below, even this inadequate sum of £750,000 was made subject to further reduction.

251. On the 12th March (document no. 1009), Mr. Smart wrote to me on the subject of the minutes of the Scientific and Technical Committee meeting which had considered the Ministerial Policy statement regarding BPL, and the costs involved in implementing the recommendations made by the Medicines Inspectorate. Mr. Smart was really trying to smooth over the problems which

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arose in the course of that meeting about the less than complete response that the Ministerial Policy statement appeared to make in relation to the problems thrown up by the Medicines Inspectorate.

252. Shortly afterwards, on the 21st March, the Minister of State for Health, Dr. Gerrard Vaughan, paid a visit to BPL. A minute was prepared by the DOH recording the events of that day (document no. 1015). As a specific comment, I would point out that whilst it is recorded in paragraph 6 that the Union, ASTMS, had not seen a copy of the Medicines Division report, this in fact was incorrect. My own impression at the end of the visit was that having heard the views from the staff and from management regarding BPL being commercially run (all expressed reservations about this), the Minister was convinced of the need to up-grade BPL in the short term and redevelop it thereafter. However, the Minister decided to reduce available funds which were already inadequate for the task of satisfactorily up-grading BPL in the short term, on the understanding that a decision would be taken about long term redevelopment. No actual commitment was made to the latter.

253. The Scientific and Technical Committee met again on the 23rd April 1980 (minutes - document no. 1023 (including correction by document no. 924)). I attended this meeting. Paragraph 4 is a very brief (and in retrospect perhaps somewhat optimistic) record of the Minister's visit to BPL in March, but paragraph 5 on page 3 of the minutes contained what, at the time, was something of a bombshell as far as I was concerned. The minutes record Dr. Harris making the following comments:-

> "Ministers recognised that there were difficulties at the BPL which needed to be resolved and they and the Department would accept responsibilities for these deficiencies. However, Medicines Divisions'

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requirements for improvements had to be considered in the light of the present financial situation, and the Department had accordingly agreed a package of measures which had been approved by the STC. Ministers were now asking that these measures be re-examined to see if there might be scope for further savings. Ministers were anxious that the Public Accounts Committee should be satisfied that the cost of the short term improvement at BPL was justified in view of the fact that the Laboratory was to be rebuilt. Dr. Harris agreed that the requirements of the Medicines Act could not be fully met except by complete rebuilding, but Ministers had nevertheless decided that BPL should continue to make blood products."

In summary, the Minister had said that it was agreed:-

(i) that the voluntary blood-donor system should be maintained;

(ii) that co-ordination between BPL and the Regional Transfusion Centres should be improved;

(iii) that the existing Laboratory should be kept going whilst its future was being considered;

(iv) that the BPL should be re-built either as an entirely NHS concern or in partnership with a British (and not a foreign) company and that the possibility of making such a partnership attractive to a British firm should be explored urgently; and

(v) that expenditure on up-grading should be reviewed and minimised pending a decision on the laboratory's future."

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254. To me the implications were clear enough. We had already, prior to the Minister's visit, been promised a sum of money which was inadequate to meet the very modest targets of Stop-Gap, which sum of money was to be spent in a somewhat piecemeal fashion with one eye on the Medicines Inspectors' requirements.

255. Now it seemed that the Minister was saying that even this sum was to be reduced. The Stop-Gap programme originally envisaged was intended to improve the existing BPL facilities and enable us to make reasonable increases in our production output pending a major redevelopment of the BPL. The Medicines Inspectorate had effectively put a cap on any increases in production and had set a series of (not unreasonable) requirements for BPL. Since it appeared that we would not be allowed to pursue Stop-Gap as originally perceived, (which would have taken care of most of the Inspectors' concerns), future manufacturing requirements would be more compromised by lack of resources, than envisaged even before the Minister's visit.

256. Mr. Smart, at page 2, noted that there was no British company with fractionation expertise. Certain companies could take on the task for the NHS but they might not be keen to do so because:-

- the capital investment required would be high (up to £25 million plus equipment);

- the companies preferred to undertake projects which had good potential for overseas sales;

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- industry might not find the BPL site attractive nor the fact that their industrial staff might be working with BPL staff who had different terms and conditions of service;

- industry would be worried that another administration might not be as favourably disposed to industrial participation.

257. A meeting was arranged by the DOH for the 29th April to consider the short-term up-grading of the BPL (minutes - document no. 1028). In addition to Dr. Harris, Mr. Wormald (Under-Secretary) was present at the meeting. From the first page of the minutes it is evident that the Minister had not committed himself to the provision of a new Blood Products Laboratory. It was clear that even when he did, no one imagined that it would take less than about six years to replace BPL in its existing form. Notwithstanding this, my view was that insufficient money was being spent even by way of temporary expedient to ensure the standards were improved sufficiently to satisfy the Medicines Inspectorate's immediate requirements, much less achieve the aims and objects of the original Stop-Gap proposals. As will be seen on page 2 of the minutes there was considerable discussion of Stop-Gap. The fact was that the original costings were now out of date and that decisions needed to be taken quickly if we were to try and increase production. Stop-Gap originally envisaged an increase from 15m. iu to 30m. iu a year which was still well short of any reasonable estimate of what was required for self-sufficiency. Mr. Wormald's minuted contribution is perhaps illuminating:-

> "Mr. Wormald expressed concern that the way in which the cost of up-grading appeared to be escalating in view of the Minister's firmly expressed view that very little should be spent on the BPL. It might be difficult to persuade him that all that Dr. Lane thought was necessary did

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not represent some over provision if it was firmly decided to build a totally new laboratory. Dr. Harris thought that rather than compromise the up-grading, the Minister should be persuaded of the advantage of providing the full facilities associated with a production level of 30 million international units of Factor VIII, and the introduction of the single donor pack."

258. At the conclusion of the Minutes there is reference to my producing a final schedule of requirements with capital and revenue costs shown separately. This was intended to be an update of Stop-Gap sufficient at least to meet the requirements of the Medicines Division. Dr. Walford prepared a paper entitled "Measures considered by the Department to be critical for the short-term operation of the BPL" for this meeting (document no. 1027). The paper concluded that approximately £600,000 spread over two years would be required together with extra revenue of £150,000. I had prepared a response to Dr. Walford's paper (document no. 1038) setting out the historical background to Stop-Gap, the remedial programme approved by the DOH and the JMC and my own views on the short-term upgrading of BPL.

259. My response to the above meeting was to write, on the 1st May, to Dr. Harris (document no. 1029). I asked that the contents of my letter be made known to the Minister, since I was fairly sure he misunderstood the position with regard to interim requirements if the laboratory was to function properly whilst (as we were at that stage having to assume) BPL was rebuilt.

260. I said:-

"BPL has had no growth since 1977 and is deteriorating as a result; yet the clinical demand is growing at a rate which could be projected as

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doubling requirements in the next five year period from 1977. Unless BPL meets some of this extra need in the NHS during the next five years, the cost of imported blood products will be in excess of £30 million on two products alone at today's prices."

In conclusion I said that:-

"Manufacturing requirements at BPL during this interim period must be decoupled from considerations relating to a new laboratory. BPL will need to continue to work at a stated output with maximum safety and cost effectiveness up to the day it is closed prior to handover to new premises. The Laboratory's requirements are dependent upon its production targets and not the reverse. A controlled expansion means limited budgetary increases but the Laboratory pays for itself at present and there is no reason why, with proper management, it should not continue to do so during this interim period."

261. On the 22nd May (document no. 1037), I wrote to Mr. Harley at DOH enclosing revised costings of Stop-Gap which I had been asked to prepare at the meeting on the 29th April. This was not the "Stop-Gap" of old since, as my letter indicates, I had tried to keep to the Minister's imperative that expenditure should be limited to matters of absolute necessity. In order to distinguish the programme of work to which this related from the original Stop-Gap programme, we redesignated the programme as MARP01 ("Medicines Act Rehabilitation Programme").

262. It had been decided to establish a Protein Fractionation Technology Working Party to be chaired by Dr. Dunnill to advise on the technology that might be used for any new fractionation facility and on the 22nd May Mr. Dutton

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of DOH wrote to me (document no. 1039) enclosing the revised terms of reference.

263. There was a meeting on 11th June 1980 to discuss further the question of expenditure on the up-grading of BPL. This meeting was, I believe, held at the DOH and as will be seen from the notes (document no. 1042) appeared to result in still more pruning. It has to be borne in mind that the original Stop-Gap planned expenditure of some £2 to £2½ million (at 1978 prices) had become first, £750,000 to be spent in 1980/81 then £600,000 and now I was asked to provide a list of what I would have invested if I were given only £500,000. I advised most strongly against such a course and did not wish to accept any responsibility for the outcome of reducing expenditure to this level. I can only liken the situation to one where you are told you may purchase a motor car and subsequently informed that you only be allowed a sum of money which is materially less than the purchase price and should decide which bits of the car you would like to buy. Those at the meeting were quite insistent that I sat down and straight away prepared the list of how I would spend £500,000 if given it, and the list I produced with the costings alongside may be seen in the notes of the meeting.

264. On the 18th June I was present at an ad hoc meeting of the Regional Transfusion Directors (document no 1048) at which it was noted that the Director of the PFC Liberton had indicated that he was in a position to fractionate any plasma that the Birmingham Regional Transfusion Centre might care to send to him. The Regional Transfusion Directors agreed that the aim should be to see that PFC was in a position to fractionate all the Birmingham Regional Transfusion Centres' and for that matter other regions' plasma. Mr. Dutton of DOH undertook to speak to the Scottish Home and Health Department to ensure that any offer from PFC was made formally through the correct channels between Departments.

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265. On the same day, the Scientific and Technical Committee met (minutes document 1046). Mr. Harley of the DOH stated, at page 2, that there were three options which could be put to Ministers in respect of the redevelopment of BPL. These were:-

- the existing budget allocation (approximately £773,000) which would allow minimum safety standards to be implemented but would not allow an increase in production;

- a reduction in the existing allocation which could result in a serious shortfall in safety standards and no increase in production;

- the budget could be increased as suggested in my revised budget estimate (document no. 1037) which would provide greater safety standards coupled with a doubling of production.

266. My revised budget of course still had quite a number of the elements of the original Stop-Gap programme in it, but I would point out that it pre-supposed a continuation of the programme over two years or so and preliminary estimates of costs of some £1.3m. In the event, expenditure reached approximately £2.6m. As will be seen from the minutes, the Chairman's view was that the Committee should support my revised budget and I argued strongly that anything less than this would really fall short of what was necessary to keep BPL operating safely.

267. The whole situation remained, however, at a standstill as my letter to Mr. Smart on the 18th June shows (document no. 1050). The DOH were meant to be sounding out industry with regard to participation in the production of blood

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products (Mr. Smart was actually involved in this exercise), but otherwise we were effectively sitting and waiting for major decisions to be taken.

268. On the 19th June 1980 (document no. 1053), Dr. Dunnill wrote to the members of the Protein Fractionation Technology Working Party setting out the various matters for discussion at a meeting which he had arranged for the 2nd July. He planned that the first meeting would be to discuss the various subjects he identified and in doing so, provide some indication of what the practical options were. He proposed that a second meeting should take place in late September by which time he hoped the Working Party would be in a position to construct a brief for the Scientific and Technical Committee on the whole subject.

269. At about this time, Mr. Vallet and Dr. Harvey both produced papers on fractionation technology (document nos. 1055 and 1056 respectively).

270. The Protein Fractionation Technology Working Party met on 2nd/3rd July **[we appear to have no minutes for this meeting]**, and on the 4th July, Dr. Dunnill wrote to the Health Minister, Dr. Gerrard Vaughan, reporting on the Working Party's deliberations (document no. 1063). I am not aware that anything happened as a consequence of his letter, but it is interesting to see him making several points which I was in agreement with at the time and one which I was not.

271. First, Dr. Dunnill sought to stress that the expenditure required to maintain production at Elstree pending the building of a new facility (which for the purpose of his letter he took as given) was not to be regarded as somehow transitional wasted expenditure, but rather an integral part of the development of the new production facility. I had been advocating this for a little while but, as I have indicated above, I expressed concern from time to time that this point did not appear to be accepted by the DOH.

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272. Secondly, he regretted the fact that, for purely policy reasons (quangos being out of favour at the time), no Special Health Authority was to be created to manage the overall affairs of fractionation of human plasma. He said in particular:-

> "I am advocating coherent professional management of advance production facilities and their sophisticated feed stock supplies in place of occasional management by hard pressed and dedicated people who are nevertheless amateurs in several key respects."

273. Thirdly, Dr. Dunnill makes a case for closer collaboration between England and Scotland. Throughout this period I was unconvinced that Scotland had the ability to assist England to any great extent despite what I regarded as excessive claims made from time to time by Mr. Watt. Dr. Dunnill, as I have mentioned, was involved in developing some of the equipment used at PFC Liberton and therefore sympathetic to the continued Scottish involvement and participation through PFC. As his letter makes clear, he was sensitive to the fact that this was certainly not an opinion I shared.

274. The JMC met on the 9th July 1980 and in paragraph 5 of the minutes (document no 1067) it will be seen that Mr. Harley of the DOH was in the final stages of preparing a submission to Ministers on the short-term redevelopment of the Laboratory, and that he indicated that the most favoured option was that which I had been advocating which involved expenditure of some £1.3m. over the next two financial years. As I have indicated, this retained only some elements of the original Stop-Gap proposals, in view of the severe financial controls being exercised. For example, the new proposal did not provide for a Microbiology Laboratory or new changing facilities for production staff.

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275. On the 18th July 1980, Dr. Dunnill wrote to me (document no. 1068) enclosing a copy of his letter to the Minister on which I have commented above. As will be apparent from the first paragraph of his letter, some of his comments were the consequence of views which I and others had expressed during the first meeting of the Protein Fractionation Technology Working Party. In the second paragraph of his letter, he pursues his wish for closer links between England and Scotland. He knew that proposing the participation of Mr. Watt in the Working Party was likely to cause some difficulties as far as I was concerned (and, for that matter, some others,) but his perseverance eventually resulted in Mr. Watt joining the Working Party.

276. At some stage right at the beginning of August 1980, the Minister appears to have given approval for the revised Stop-Gap scheme which became known as MARP01. Mr. Harley of the DOH formally reported on the Minister's' decision at the meeting of the Finance Sub-Committee of the JMC (notes-document no 1076) which took place on the 13th August 1980 and confirmed that it had been agreed there should be capital expenditure of £1.3m. for short-term improvements over the financial years 1980/81 and 1981/82. There is also reference to additional revenue expenditure of £100,000 being authorised for 1981/82 directed towards increasing staff numbers. I made the point during the course of the meeting (and this is minuted), that this was only part of the problem. In order to attract staff, we had to make sure that the future of the Laboratory was settled and the uncertainty regarding its major redevelopment was bound to harm recruitment.

277. At about the start of September 1980, I received under cover of a note from Dr. Rizza and Miss Spooner (document no. 1090) the 1979 Haemophilia Centres' Annual Returns which were to be discussed at the forthcoming annual

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meeting of the UK Haemophilia Centre Directors. Table 1 showed that usage of commercial Factor VIII concentrate had reached 24.7m. iu as against NHS Factor VIII concentrate of 14.6m. iu during 1979. Cryoprecipitate was dramatically falling in usage and contributed only 9.2m. iu giving a grand total of 48.5 iu consumption during the year. Fig.1 graphically shows the increase in use of commercial Factor VIII.

278. On 12th September 1980, Dr. Dunnill wrote to members of the Protein Fractionation Technology Working Party indicating that there was to be a further meeting on the 23rd and 24th September 1980 and that the main priority was to prepare a report for Ministers.

279. On 16th September 1980, I prepared a document entitled "Plasma Fractionation Working Party" (document no. 1095) in which I specifically tackled the problem of plasma supply. I believe this was prepared for the forthcoming meeting of the Working Party. I addressed the question of the supply of FFP when any new plant at BPL was commissioned. The conclusion I drew from the review was that there would be a shortfall unless steps were taken reasonably quickly to increase the supply of FFP. As I mentioned above, we were eventually obliged to manufacture a product of greater purity in order for it to withstand heat treatment, and this affected the assessments of the amount of FFP required as set out in this paper and others produced at around the same time.

280. At the meeting of the Scientific and Technical Committee which took place on the 17th September 1980 (document no. 1101), there was once again reference in paragraph 7 of the Minutes to the Minister's approval of the capital expenditure of £1.3m. for the next two financial years and concurrent increase in revenue expenditure. It was stated, however:-

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"NW Thames RHA had agreed to take on project management of the up-grading work, although the precise arrangements had yet to be formalised."

281. In the event, for reasons which may be understandable but which gave rise to a further frustrating period of delay, NWT refused to take over the management of the project until their capital works personnel had re-checked the building estimate. Their view (not unreasonably) was that since they had not been consulted about these figures and had made no contribution to their formulation, they had a vested interest in checking them before becoming the responsible client body on behalf of the DOH.

282. At paragraph 14 of the minutes, there is reference to Mr. Harley of the DOH reporting to the meeting, that Ministers had agreed to replace the existing Central Committee for the National Blood Transfusion Service with an Advisory Committee. It is noted in the minutes that the existing Central Committee for the National Blood Transfusion Service had not met since 1978! It seems a little surprising that over this critical period, the Committee charged with advising the DOH on the National Blood Transfusion Service had not met for some two years.

283. Following the meeting of the Protein Fractionation Technology Working Party at the end of September 1980 **[we do not have the minutes]**, Dr. Dunnill wrote to me on the 9th October (document no. 1111). In his letter, Dr. Dunnill said that he believed the new production unit should be smaller than that required to process 400,000 litres of FFP per year. He went on to comment on the manifest differences between Liberton and Elstree at that time. As I mentioned above, he was somewhat predisposed towards Liberton although, in this particular letter, he characterises himself as holding the middle ground. This letter caused me to reply (document no. **not found**). He did not seemingly understand that the

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reality was that the DOH would only commit major capital expenditure on one occasion and that a phased building programme was improbable.

284. The JMC met on the 22nd October 1980 (document no. 1120) and we discussed (see paragraph 7 of the minutes) the short-term redevelopment which was now designated MARP01. As I have mentioned above, NWT had insisted on looking over the figures which had originally been produced and this paragraph records the fact that they were concerned that the expenditure, spread over two years, and possibly into a third, would not be assured from Finance Division. After discussion this assurance was eventually given by DOH. As to the possible disposal of BPL (the DOH had made no decision to keep BPL within the NHS which in turn meant no decision had been taken with regard to the long term redevelopment of BPL), it was recorded at paragraph 17 of the minutes that only Beecham Pharmaceutical appeared to be showing any interest in redeveloping BPL. I was not privy to any DOH discussions with Beecham.

285. In December 1980 the first meeting of the new Advisory Committee on the National Blood Transfusion Service took place (document no. 1137). The terms of reference of the Committee were marginally narrower than the terms of reference for the old Committee which had not met for two years, but nothing turns on this. It is clear from paragraph 6 of the minutes that by now Ministers had apparently decided against collaboration with private industry in the long term redevelopment of BPL. A press release and a Parliamentary Question answered by the Minister for Health on the 26th November were tabled evidencing this, but I am not sure that I had seen any other documentation before this. As indicated, the DOH were now considering how a new fractionation facility might be funded and management arrangements made for it. As will be seen, there was reference to self-sufficiency in blood and blood products (paragraphs 8 and 9 of the minutes) but nothing of any great moment is referred to under this heading.

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Plasmapheresis as a way of increasing supplies of FFP was touched upon as was (in paragraph 10) the question of improving the yield of Factor VIII by varying the anticoagulant. So far as demand was concerned, paragraph 12 of the minutes read:-

> "The Committee was given broad details of Factor VIII usage and production 1973-1979. This showed a continuing rise in demand which was expected to grow to 90m. iu in England and Wales by the mid-1980's. This substantial rise was due to a number of factors including longer life expectancy of haemophiliacs, the provision of home therapy and the trend towards the use of Factor VIII in prophylaxis. The Committee agreed that an accurate assessment of demand was essential to the planning of fractionating facilities, and Dr. Tovey was invited to convene an informal meeting between RTD Divisional Chairmen, the representatives of Directors of Haemophilia Centres and to report back to the Advisory Committee. In the light of this it might prove necessary for RMO's and RTD's to investigate discussions with clinicians regarding the level of usage of Factor VIII within Regions."

286. Pro rata distribution was touched on in paragraph 15 of the minutes and it was proposed that pro rata should be introduced as from 1st April 1981. Two of the papers which were available at the meeting merit comment. The first is AC(80)1 (document no. 1138) which summarises the structure of the Blood Transfusion Service in the United Kingdom as it was at the end of 1980. It also sets out (paragraph 13) by way of comparison, the old Committee's terms of reference. On the third and fourth pages, there are a series of questions which it was felt the Committee might usefully advise upon. Under the heading (iii) "Plasma Fractionation" there was a query as to whether uniform standards for specification of products made by BPL and PFC should be adopted. The answer

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to this was no. The national policies on finished product requirements differed between England and Scotland: this was reflected in their respective finished product specifications and the approach adopted by BPL has been towards developing higher potency and purer fractions always taking into consideration the impact of this policy on process yields. Certainly in the earlier years of Factor VIII production commercial manufacturers in the United States were giving priority to developing a purer product (not necessarily at the time with heat treatment in mind), albeit that this led to sacrifices in terms of yield. The price of the product simply reflected this and there appears to be no shortage of customers.

287. Also of interest is paper AC(80)3 prepared by Dr. G. Tovey (by then Consultant Adviser to the DOH) (document no. 1139) on the subject of the supply of plasma to BPL. This makes clear the need amongst the Regions to set targets and to increase production of FFP in anticipation of the doubling of the production capacity of BPL from 15m. iu per annum to 30m. iu by 1982. This demonstrates that any increase in BPL capacity had to go in tandem with decisive efforts on the part of Regional Transfusion Centres to produce enough FFP.

288. The year came to a close with Mr. Harley of the DOH writing to me on the 22nd December 1981 (document no. 1151) enclosing copies of two follow up reports from the Medicines Inspectorate which covered their visits on the 26th November and the 9th December. Essentially these were concerned with points of detail which required attention but are not particularly relevant to the present proceedings, save that in the second paragraph on the last page of the Medicines Inspectors' second report, there was a comment to the effect that it was apparent that the Laboratory was not being effectively managed and that there had been little, if any, improvement since the initial inspection. Regrettably this was indeed true. We needed key experienced staff to manage the facility and we

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could only offer them the public sector terms and conditions agreed by the Whitley Councils and these were not sufficient to attract suitably qualified applicants. We had three attempts at recruiting a pharmaceutical Factory Manager. We eventually recruited Gilbert Mallory who has subsequently been replaced by Dr. Snape who was trained at BPL. We also had four attempts before securing an Engineering and Maintenance Manager. The person eventually recruited is now responsible for capital projects and an operational engineering manager is still required.

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289. There were several events during the course of the year which are relevant to the issue of self-sufficiency. The usage of Factor VIII in all its forms but, in particular, concentrate was still climbing rapidly as the figures for 1980 (which became available during the course of 1981) clearly showed. We had at last received the go ahead for MARP01 and it commenced during the course of the year with the target of completing that work by the autumn of 1982.

290. Armed with the results of the Protein Fractionation Technology Working Party review, there was tentative movement in the direction of the redevelopment of BPL and the commissioning of a feasibility study by Matthew Hall Norcain Engineering Limited ("Matthew Hall"). There was no binding commitment at any stage during the year to the redevelopment of BPL, and it remained to be shown whether PFC Liberton had sufficient capacity and adopted working conditions to share the fractionation capacity of the United Kingdom with BPL. A trial of 24 hour continuous fractionation was run towards the end of 1981 at PFC Liberton which ultimately proved unsuccessful and ultimately lead to the expressed view by SHHD that the redevelopment plans for BPL should not take Scottish requirements into consideration.

291. The future role of PFC Liberton was raised by Mr. Meakins of the School of Pharmacy and Pharmacology at the University of Bath who wrote to the Times on the 2nd January 1981 (document no. 1159). This followed a course at the University of Bath at which Mr. Watt had made a presentation setting out his view on PFC's potential. Mr. Meakins suggested that the insufficiency of blood products in the United Kingdom was "largely self imposed by bureaucracy" and went on to say:-

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"Blood processing is carried out for the National Blood Transfusion Service (of England and Wales) at the Elstree plant, whilst the Scottish National Blood Transfusion Service has its own Laboratory in Edinburgh. The output from Elstree is limited by the plant and process which are largely outmoded and inefficient by modern standards. In contrast production in Scotland is limited by the blood supply; the plant at Edinburgh is seriously under utilised, working at less than one third of its current capacity. On more than one occasion a Director of a Regional Transfusion unit, south of the border, has stated that blood collection could be doubled if only Elstree could process it. Because the Health Departments for England and Wales and Scotland are independent, blood is not sent north across the border.

"In my view this state of affairs is nothing less than scandalous in the current deficiency situation which is disadvantageous to both patients and the tax payer."

292. This was incorrect. PFC Liberton's equipment was designed for continuous operation and one stage in a multi-stage process had a potential capacity of an estimated 6,000 litres per week. This capacity as was shown in the above mentioned trial, was not matched by similar capacity in other stages which both preceded and followed: likewise the stage in question required 24 hour manning - a situation never agreed or accepted by the work-force. When, during the course of 1981, there was a detailed comparison of the BPL and PFC products, my impression, to the extent that we could get to the truth of the matter, was that the PFC products were of a lower specification. The trial which subsequently took place clearly showed that without substantial investment in building new facilities and installing additional plant and equipment up and down

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stream of the central processing plant and equipment, PFC Liberton could not operate to the stated capacity.

293. I should mention that Dr. Meakins' letter also misrepresents the position with regard to plasma supply at the time. During this period, [1981-1985] there was no major imbalance between plasma supply and BPL/PFL's ability to fractionate plasma produced in England and Wales. Obviously any unprogrammed significant increase in plasma supply would have overwhelmed BPL/PFL, but as later events show, the co-ordination of increase in plasma supply and commitment to redevelop BPL both proved difficult to achieve. At the time in question there was no material surplus of plasma which, for want of fractionation capacity, was being wasted and therefore no immediate role for PFC Liberton to play, since they would merely be taking plasma which BPL/PFL needed.

294. Dr. E. Harris replied to Mr. Meakins' letter through the Times (document no. 1166) on 7th January 1981, and pointed out that the question of co-ordinating the facilities at BPL with those of PFC was one which had been receiving urgent attention, and it was clearly something which was in the mind of the DOH at the time, albeit that I was not privy to their thinking.

295. At the start of February 1981 in a letter dated 2nd February (document no. 1186) Mr. Collins of NWT wrote to me giving me express authority to proceed to tender for MARP01.

296. On the 4th February 1981, I prepared a paper entitled "Blood Products Laboratory: Summary of performance in September 1979" (document no. 1188) which coincided with the first round of discussions with the Medicines Division. In the summary on page 2, I said:-

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"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 the situation only removed by re-development of the Laboratory. The sense of urgency is evident."

The summary covered the deficiencies in the buildings and staff as I saw them at the time. I referred to:-

- MARP01
- the equipment including services employed at BPL
- shortcomings of the Technical Services Section
- the "vacuum" in which I had been working since taking up my appointment as Director
- the long term management requirements for BPL and the need for an Executive Management body.

In effect, the document was a critique of BPL over the relevant period and a review of all the factors which had contributed to create problems, set in the context of the Medicines Inspectorate's report.

297. The long term development of BPL was considered at the 10th meeting of the JMC which was held on the 6th February 1981 (document no. 1198). It was reported that Ministers had instructed officials to begin work on planning and designing a new BPL. Mr. Armour of NWT thought that NWT might be willing to take on the task of Project Management providing that certain conditions on accountability, control and methodology were agreed. NWT were against the idea of employing a commercial project management firm.

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298. On the 12th February 1981, Mr. Godfrey of DOH circulated a discussion paper for the next meeting of the Advisory Committee on the National Blood Transfusion Service (document no. 1200) in which he examined the question of whether Factor VIII supplies should be held by Regional Transfusion Centres. The paper touches on usage and says:-

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

299. The second meeting of the Advisory Committee on the National Blood Transfusion Service took place on the 23rd February 1981 (document no. 1217) and the first matter which was discussed was the problem of increasing the supply of plasma. We had already seen a copy of the paper circulated on 4th February 1981 (document no 1190) together with a summary of current and possible future supplies of plasma to the BPL. It is clear from the minute that the increase in plasma required over the next two years by BPL was to a level which would enable BPL to produce 600 iu of Factor VIII per 1,000 population (30m. iu per annum). This may be contrasted with my estimates of what would ultimately be needed. Dr. Harris explained that planning work on the redevelopment of BPL was to begin, and it seemed possible that NWT might take on the project management. He added that it was thought that the new Laboratory might be completed in five years time (circa 1986/7). The DOH put forward possible arrangements for the pro-rata distribution of blood products for consideration by the Advisory Committee. I stated that the United Kingdom was self-sufficient in Factor IX (this has consistently been the case over the years). The Advisory

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Committee agreed that there was therefore no need to operate a pro rata system for this product.

300. Dr. Gunson tabled a paper (AC(81)8 - document no. ? **[Can we get a copy? [P16]]**) at the meeting, which considered the role of plasmapheresis in helping to attain self-sufficiency in Factor VIII production in England, Wales and Northern Ireland. On the assumption that the target for Factor VIII would (ultimately) be 90/110m. iu and assuming this would require a total input of 490,000 litres of plasma, Dr. Gunson calculated that 207,000 litres of FFP could be collected by normal donation and 283,000 litres by plasmapheresis. He envisaged that 55-60,000 active plasmapheresis donors would be required per annum. Equally, if the target requirement for Factor VIII was 135m. iu per annum, requiring a total plasma volume of 720,000 litres, on the assumption that 207,000 litres would be obtained from whole blood collection, then 513,000 litres would be needed through plasmapheresis. The general consensus was that it was vital to consider the role of plasmapheresis in harvesting supplies of plasma. It was agreed that a Working Party should be set up under Dr. Gunson's chairmanship, with Dr. Tovey and Dr. Walford among its members, and that it should have the following terms of reference:-

> "To advise on supplies of plasma for self-sufficiency in blood products in England and Wales."

301. It was established as the "Working Party to Advise on Plasma Supplies for Self-Sufficiency in Blood Products".

302. On 27th February, Dr. Dunnill prepared his Chairman's comments on the Protein Fractionation Technology Working Party report (document no. 1223). In

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many ways the paper is a summary of the report but there were some partisan comments by Dr. Dunnill regarding PFC Liberton on page 1:-

> "1. There is uncertainty about the scale of operation required due to the lack of data on UK requirements and 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).
>
> "2. Multi-shift operation with substantial automation would almost certainly be adopted by an industrial management as a means to reduce capital cost. It would be hampered here by administrative difficulties and by manpower problems in the Elstree region. In this respect, other sites might be preferable, (emphasis added) but removal would cause considerable difficulties in the interim period.
>
> "3. Maximum utilisation of plant could be achieved by continuous thawing of plasma and continuous large-scale fractionation. This option is limited by the lack of experience of truly continuous operation, by the absence of process engineering staff at Elstree, and by the lack of coherent management of Scottish and English facilities. (In the opinion of the Chairman, the immediate institution of coherent management and transfer of staff as appropriate, would be a means to resolve these problems)."

303. In these various comments, one glimpses Dr. Dunnill's sympathies. Whilst automation had been brought into the plant at Liberton (a plant designed in theory for continuous operation), the Laboratory was, nevertheless plagued by manpower problems and the refusal to work shifts. Reference in the third

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paragraph to "coherent management", was an unrealistic proposition: the real problems lay in the terms and conditions imposed by the Union, and the structure within the NHS itself.

304. In the Protein Fractionation Technology Working Party's report, the need was identified as a requirement to fractionate some 450,000 litres of plasma a year to meet the projected demand of 90m. iu for Factor VIII per annum. Plasma supply is dealt with in appendix 7 on page 24 and reference is made to the single donation bag, and the fact that the first regional trial of 6,000 single donations of plasma was then under way.

305. There was a further inspection of BPL on the 5th and 6th March 1981 by Mr. Ayling and Mr. Flint of the Medicines Inspectorate (their report is document no. 1236). The inspection covered general conditions of the processing areas and standards of housekeeping, and concluded that:-

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

In the final paragraph it is said:-

> "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."

There were two further recommendations:-

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"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 counter-productive 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."

306. On 9th March 1981, I wrote to Dr. Harris (document no. 1237) 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 concluded my letter:-

"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."

307. On the 20th March 1981, the JMC met (document no. 1245) and amongst the various matters discussed, was the appointment of key personnel and the long term development of the Central Laboratories. Mr. Armour reported that NWT could accept the task of Project Management for the BPL, provided that agreement could be reached on arrangements for accountability and control. Of interest are ASTM's views on the long term management as set out in document JMCCL(81)13 (document no. 1247). They agreed with my view that BPL/PFL should be constituted as a Special Health Authority with an executive committee on board responsible directly to the DOH.

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308. On the 23rd April 1981, there was a meeting between representatives of the Haemophilia Centres and the Blood Transfusion Service Directors, the main points of which are summarised in the document prepared by Dr. Walford dated the 14th May 1981 (document no. 1281). The purpose of the meeting had been to consider the foreseeable requirements for blood products containing coagulation factors used in the treatment of haemophilia, relative to the Minister's aim for self-sufficiency. Use of Factor VIII in 1979 totalled 52m. iu. It was believed that by the mid-1980's, some 80-100m. iu of Factor VIII would be required. It was felt that 150m. iu 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 100m. iu."

309. So far as Factor IX was concerned, no significant increases in usage were envisaged for the mid-1980's. There was now general agreement between the DOH, NBTS and users regarding the forecast requirements for coagulation concentrates - this was not the case during the previous decade.

310. As a slight digression, it can be seen that in May (see DOH letters dated 18th May 1981 - document nos. 1283 and 1284) formal inspections by the Medicines Inspectorate of the Regional Transfusion Centres were only just beginning. I should also mention that at this time PFL had not yet been inspected.

311. The Scientific and Technical Committee met on the 10th June 1981 (see document no. 1304) and amongst other matters, there was reference on page 2 of the minutes to the trials which were being proposed with regard to shift working at PFC Liberton. These trials were planned to take place in October 1981. Their relevance to BPL was stated to be in the context of assessing a target capacity

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figure for the redeveloped BPL. That is to say, to establish what PFC could contribute and the reduction in the capacity of a redeveloped BPL which could be achieved in consequence. The re-organisation of PFL at Oxford was also discussed. I was aiming for a division of functions between PFL and BPL. I was thinking ahead to the time when we could use PFL to direct its resources at new products and process development leaving BPL to manufacture the end product. I was well aware that funds of the extent made available to BPL would not be available to PFL.

312. On the 11th June 1981 the DOH circulated paper AC(81)11 (document no. 1307) for discussion at the 3rd meeting of the Advisory Committee on the National Blood Transfusion Service which was due to take place on the 22nd June 1981. AC(81)11 was the preliminary report of the Working Party to Advise on Plasma Supplies for Self-sufficiency in Blood Products dated June 1981. The Working Party noted that:-

- it had been determined that 100m. iu Factor VIII concentrate was a reasonable estimate for clinical requirements in England & Wales by the mid-1980's

- consideration of various types of Factor VIII concentrates had led to the conclusion that intermediate Factor VIII concentrate was a 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

- an estimated 500,000 kg of plasma are required to meet the requirements for Factor VIII concentrate

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- it would be possible to obtain 200,000 kg of plasma from whole blood donations

- it would be possible to collect the remaining 300,000 kg of plasma by increasing whole blood collection or by introducing plasmapheresis

- the option of plasmapheresis had advantages over the procurement of plasma entirely from whole blood donations in that the wastage of red cells was avoided, and donor panel size could be reduced because of the increased frequency of attendance of plasmapheresis donors

- it would be difficult to have a national programme based on frozen cryoprecipitate because:-

(i) high yield was not always attained in large scale production;

(ii) lack of confidence in the Factor VIII content led to over-ordering and waste;

(iii) there was a significant incidence of adverse reactions due to the presence of residual plasma;

(iv) the product was not convenient to store, transport and infuse, particularly for home or self-therapy;

(v) there were difficulties in ensuring adequate quality assurance and control.

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313. On the 16th June 1981 (document no. 1313) I wrote to Dr. Gunson with my comments on AC(81)11. I anticipated reaching the situation where not enough plasma was available because of lack of money 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."

314. On the 22nd June 1981 (document no. 1318) the Advisory Committee on the National Blood Transfusion Service met. It was noted that although there might seem to be disadvantages in not providing a wider range of Factor VIII preparations, these would be outweighed by the fact that commercial concentrates (with their attendant risks i.e. of hepatitis) need no longer be purchased and that if the redeveloped BPL were to produce the required quantity of Factor VIII, it might become necessary to insist on clinicians using the BPL product except where it was absolutely essential to use a particular commercial substitute. Dr. Harris of the DOH commented that although self sufficiency was a desirable goal, it would be necessary to balance the cost of collecting plasma against the

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value of products especially at the level after which the plasma might be needed solely to meet the demand for Factor VIII. The Advisory Committee discounted the possibility of buying in plasma from abroad.

315. On 23rd and 24th June 1981, the Medicines Inspectorate carried out an inspection of PFL at Oxford. Mr. Ayling prepared the report which followed (document no. 1354). PFL came out of the inspection quite well, but the report noted:-

"(a) PFL produced all the Factor IX required by the UK then produced Factor VIII from plasma supplied by Oxford and the Wessex Regional Transfusion Centres.

(b) PFL exercised no direct control over the plasma supplied which was its main raw material. Reliance was placed on dialogue between BPL and Regional Transfusion Directors."

The report concluded that:-

"(i) PFL were staffed by people of a high academic standard;

(ii) PFL suffered from poor basic design and layout and had not been brought up to modern standards;

(iii) the present facility did not meet the necessary standards of good manufacturing practice that would be required of a commercial operation, and if licensable products were to be produced, a detailed schedule of up-grading had to be agreed in the immediate future."

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316. PFL was a small compact Laboratory (employing 23 people and never more than 28 people) and as the Inspectors found, staffed to a high level of competence. It was easier to recruit staff there than it was at 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. PFL was always perceived as something of a development unit whereas Elstree's role was very much that of a straight forward production unit from the mid-1970's onwards. For these various reasons, whilst the Medicines Inspectorate had criticisms, they were not as serious as they were in relation to BPL.

317. On the 24th August 1981 (document no. 1363) the Policy Steering Group which had been formed to assist in relation to the redevelopment of BPL, met for the first time. One of the documents circulated prior to the meeting was a DOH note on financial provision for redevelopment (PSG(81/3) (document no. 1362(a)). The estimated cost of redevelopment was £17m. based on 1978 prices. In 1978, I had estimated expenditure to comprise the following; £10m. on building; £5m. on plant and £5m. allocated between revenue consequentials and small equipment. This estimate was based on refurbishment and extension of existing buildings and not on a green field site development.

318. The DOH had picked up on those figures and two years later were suggesting that the cost of the plant was unlikely to be less than £17m. (the original 1978 cost less the revenue element).

319. It was reported (on page 2 of the minutes of the first meeting of the Policy Steering Group) that the potential for PFC Liberton to fractionate a proportion of English plasma had not yet been determined. It had been decided

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not to use a processing system requiring 24 hour shift work in any redeveloped BPL facility. It was recognised on page 3 that spare capacity to process plasma must be built into the BPL in its redeveloped form. As well as an increase in the level of plasma supplied by RHA's, I was hoping for a 20% improvement in yield from FFP over the next two years. It was a 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 supplies. The role of the PFC Liberton is mentioned again on page 6, and this reference marks the slight shift in thinking: Dr. Walford suggested that it might prove uneconomical to send plasma to Liberton to fractionate.

320. A meeting of representatives of the Haemophilia Directors, the Blood Transfusion Service Directors and the DOH (minutes - document no. 1378) took place on the 15th September 1981, and was chaired by Dr. Tovey, Consultant Adviser to the DOH. The concept of retaining the clinicians' right to choose their products, is brought out once again on page 2 of the minutes. The current purchasing systems varied as between 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 re-considered 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.

321. In a manuscript note to me dated the 23rd September 1981 (document no. 1384), Dr. Smith refers to the fact that during 1981, the combined fractionation capacity of BPL and PFL ran at 150,000 kg of plasma per annum, and that during the same year the laboratories produced some 20m. iu of Factor VIII.

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322. At the 4th meeting of the Advisory Committee on the National Blood Transfusion Service which took place on the 28th September 1981 (document no. 1387). Dr. Tovey ducked the issue of keeping Regional Transfusion Directors informed of commercial purchases made by Haemophilia Centre Directors. There was clearly no way all 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. As I had mentioned previously, this question of control over Factor VIII concentrate was a perennial theme. We supplied NHS Factor VIII concentrate to Regional Transfusion Centres for onward transmission to Haemophilia Centres. The Haemophilia Centres controlled their own purchases of commercial Factor VIII which was not supplied via the Regional Transfusion Centres and were protective of their position in this regard. On the question of plasma supply, as a result of the most recent meeting of the Haemophilia Centre Directors, it had been decided that target plasma supply required to achieve self-sufficiency could be reduced to 435,000 kg from 500,000 kg based on a presumed process yield greater than 250 iu per kg. The quantity of plasma to be made available in fact changed once heat treatment became a requirement because earlier yield assumptions were invalidated. On page 3, it is clear that Mr. Harley of the DOH again hinted that PFC Liberton might be jointly meeting the UK's needs for blood products with any redeveloped BPL. "Further discussions" would be needed between the DOH and the Scottish Home and Health Department.

323. Another matter for discussion was the future role of the Working Party on Plasma Supplies for Self-Sufficiency in Blood Products. Its important role in terms of increasing plasma supplies was recognised. However, it was noted that the Working Party was merely an advisory body with no executive powers. This is a little ironic when one examines the issues relevant at the time.

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324. On the 2nd October 1981, Mr. Godfrey of the DOH prepared an action list (document no. 1391) following the meeting of the Policy Steering Group referred to above. Mr. Smart was the Chairman of the Policy Steering Group. I discussed the problems associated with PFC Liberton and the claims made for it with him, and he had suggested that we should again try to resolve the extent of PFC's role by a trial of fractionation. (Given the claims for PFC capacity it is surprising that the proposed trial was not actively undertaken and that so much delay in implementation actually occurred). As a prelude to any further review, both BPL and PFC were to provide product specifications. It will also be seen from Mr Godfrey's action list that a feasibility study with regard to the redevelopment of BPL was to be approved by the JMC.

325. On or about the 5th October 1981, I wrote to various contractors identified by the DOH, inviting them to tender for proposals for a feasibility study for the redevelopment of BPL. Following the responses received, further discussions over the telephone and in meetings took place, and a decision was taken by the Policy Steering Group to instruct Matthew Hall to carry out the feasibility study. Approval was given by the JMC.

326. In a letter by Mr. Watt to the Scottish Home and Health Department dated 14th October 1981 (document no. 1397), he set out certain data in relation to PFC Liberton products which was part of the exercise instituted by the DOH to ascertain the role which PFC Liberton might be able to play in the provision of blood products. PFC Liberton did not in the course of time produce all the relevant data. In particular under the heading "Factor VIII Concentrate", Mr. Watt states that the specifications of the product being issued from PFC were in a state of change.

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327. With regard to what is said on the second page of the letter under the heading "Stable Plasma Protein Solution" I should perhaps clear up one point which arises from Mr. 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 BPL produced Plasma Protein Fraction ("PPF") which is a purer product than SPPS by pharmacopoeial definitions.

328. 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.

329. On the 19th October 1981, the Policy Steering Committee met again and the action list arising from that meeting (document no. 1405) 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.

330. It can also be seen from the minutes of the Policy Steering Group meeting of 19th October 1981 (document no. 1404) that in the context of the discussion about the proposed trial of PFC Liberton, they had not been receptive to the idea that we send observers (an idea which originated with me).

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331. On 23rd October 1981, I wrote to Matthew Hall to confirm that they had been selected to prepare and submit a feasibility study for the redevelopment of BPL and, at the same time, wrote to Mr. G. Collins at NWT to advise him that the JMC had approved his acting as Project Manager for the redevelopment.

332. Mr. Godfrey of the DOH sent under cover of his letter of the 2nd November 1981 (document no. 1416) what I believe was the final form of documentation setting out the product data from both BPL and PFC which was to be used for comparative purposes in conjunction with the trial at PFC Liberton. In his note of 5th November 1981 (document no. 1417) Mr. Vallet deals with the matter that I have mentioned above, i.e. the deliberate misdescription of the UK albumin produced, and points out that the misuse of the nomenclature is somewhat surprising, given that Mr. Watt had for many years been on the Blood Products Panel of the Pharmacopoeia Europa.

333. On the 24th November 1981 there was a meeting of the Scientific and Technical Committee and amongst the various matters discussed, the minutes (document no. 1436) record that the shift working experiment had been carried out at PFC Liberton, (although the report on the exercise was not available until January 1982). The plasma used was BPL outdated plasma supplied to PFC some time previously. The PFC trial related only to an evaluation of continuous production of SPPS: Factor VIII production was not included and therefore outdated plasma could be used. Mr. Wesley, head of the Large Fractionation Department at Elstree, supervised the PFC shift work experiment. Dr. Dunnill felt that certain benefits would be derived from the shift work exercise:-

"1. An indication as to whether PFC could handle more plasma;

2. The advantages or disadvantages of a continuous operation system."

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334. The PFC trial was considered at the meeting of the Policy Steering Group that took place on the 18th December 1981 (document no. 1447). Paragraphs 6, 7 and 8 deal with the trial. Mr. S. Hibbert reported that PFC was capable of 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 effective than BPL, but also that PFC hoped it would eventually service the northern English Region. Mr. Hibert said that 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 the equipment could function on such a basis. I expressed reservations regarding the experiment in that the study had concentrated on one stage only of what was a complete production process. It was all very well fractionating plasma on a continuous basis, but the facilities both up and down stream had also to be capable of handling the raw product and end product from the continuous manufacturing process. The experiment at PFC Liberton was inconclusive (as paragraph 7 of the minutes show), and the commitment of the SHHD to PFC Liberton would be critical to the mode of its future use. Meanwhile, as the minute shows, the discussion of the redevelopment of BPL was continuing with a feasibility study being further reviewed.

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335. Mr. D. Wesley's report on the PFC Liberton trial became available around the turn of the year, and on the 5th January 1982, I sent David Smart a copy. (document no. 1458). It seemed to me that the report supported my concerns about PFC Liberton's ability to assist England and Wales in the production of Factor VIII, since the trial was unrepresentative of what would happen in practice. The product produced on a continuous basis during the experiment was SPPS prepared from time-expired plasma and not Factor VIII or other blood products prepared from FFP. By concentrating production on this one product, the experiment gave at best a distorted picture of PFC's ability. My own feeling was that the experiment was inconclusive. In his report, David Wesley noted that:-

- the CSVM (continuous small volume mixing) system which lay at the heart of the PFC fractionation plant, was capable of continuous operation for periods of at least 120 hours, and that there was no reason to believe that the system would not be operated permanently for such periods with 48 hour breaks at weekends for maintenance, etc.;

- there was no data to indicate how purity of yield of the product was affected by truly continuous CSVM fractionation;

- with the available bulk fractionation equipment, continuous fractionation would prevent the production of immunoglobulins and salt-poor albumin;

- during the feasibility exercise, Factor VIII production was limited to the normal quantity. No evidence was available from the exercise to

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suggest what increase could be made to such production by the fractionation of a large volume of FFP;

- with the exception of quarantine storage through to inspection and despatch, all support sections appeared to have capacity to handle the product from 1,000 litres of time expired plasma per day;

- storage space throughout PFC was at a premium and increased production would probably place an even greater strain on an already overloaded system.

336. David Wesley's report was also useful in that it contained a description of the continuous fractionation process which PFC Liberton employed and which they called CSVM. As can be seen from the report, it was necessary if continuous operation were to be introduced, to reach a special agreement with the Trade Unions to work on a shift basis. There were considerable reservations expressed at the time and later as to whether or not the Trade Unions would indeed be prepared to work on a shift basis or at least one which made economic sense. On the 5th January 1982, I also sent a copy of the report to Mr. Godfrey at the DOH.

337. On the 8th January 1982, I took the opportunity to write to Dr. Harris of DOH in his capacity as Chairman of the JMCommittee (see document no. 1461) and, as can be seen from my letter, I advised him that the combined output of BPL and PFL of Factor VIII for 1981 came to 22m. iu (up from approximately 15m. iu in the year before). Given the problems which we had faced during the course of 1981 and, in particular, the interim building programme and the need to comply with the Medicines Inspectorate requirements, I felt that performance had been extremely good. The level of production had really increased to the point

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where there was no spare capacity remaining although, of course, the interim up-grading programme was due to be completed towards the end of 1982 by which time the capacity would reach 30m. iu per annum at BPL.

338. There followed a very important letter written by the SHHD to the DOH dated the 11th January 1982 (document no. 1462) which, concluded that PFC would not be considered in the future planning of self-sufficiency in England and Wales.

339. The letter begins with the suggestion that PFC could make a substantial contribution towards processing English plasma, but this positive statement then becomes submerged beneath a series of very serious caveats which collectively qualify the letter to such an extent that subsequently no further consideration was given to PFC Liberton assisting in the fractionation of English and Welsh plasma. The letter repays reading in full, but the essential qualifications were:-

(a) the need to negotiate terms with the relevant Trade Unions through the Whitley Council machinery to operate on a shift work basis (something which would almost certainly have had quite substantial cost implications);

(b) the need to invest some £6m. to £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

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uncertainty which pervades the letter, gives the impression that this too 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.

340. In summary, it was clear that without substantial changes in working practices, an investment of some £6m. to £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), PFC Liberton would be in a position to fractionate sufficient amounts of English plasma but at a cost which no one could predict.

341. The 5th meeting of the Policy Steering Group was held on the 1st March 1982. As will be seen from paragraph 4 of the minutes (document no. 1485), Mr. Godfrey of the DOH reported an approach which had been made by the DOH to Regional Health Authorities enquiring about their ability and willingness to increase plasma supplies. RHA's 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 the same pattern, it would be necessary to build up in stages towards a target figure for self-sufficiency.

342. At paragraph 6 of the minutes, there is a record of Mr. Harley's report to the meeting on the letter received from SHHD following the PFC Liberton "experiment". He said that PFC Liberton would not be able to fractionate any

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substantial quantity of English plasma without the introduction of a three shift working system. Mr. Harley had asked the DOH 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 with SHHD 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 JMC to proceed on the assumption that for planning purposes, 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 do not think that the shift working system was the sole obstacle to increasing capacity. This is borne out by a paper which the DOH personnel later produced for the Minister (to which I contributed) 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 economic wisdom of this course of action.

343. As the minutes also record, there was a discussion of the feasibility study prepared by Matthew Hall (and paragraph 9 records the fact that the Policy Steering Group would invite Matthew Hall to prepare "at their own expense" estimates for three possible levels of production). The feasibility study estimated a cost for the new plant which was in excess of the Treasury's budget estimates and Matthew Hall were asked to cost three levels of production at 435, 325 and 250 tonnes of plasma per year.

344. On 20th April 1982, I finalised the annual report for BPL and PFL for the period 1981/1982 (document no. 1500). I noted in the report:-

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- input of FFP had increased for the first time in 5 years

- all input FFP was fractionated to Factor VIII with only minimal losses and output of intermediate Factor VIII concentrate and other main products increased accordingly. In particular, Factor VIII output was up by 30% and Factor IX output was up by 38%.

- the Laboratory and staff progressively accommodated the philosophy and practical implications of Good Manufacturing Practice and other regulatory requirements. The major design faults remained and continued to exert a real compromising effect on laboratory performance and product safety, and the need for an early target date for completion of the new BPL process factory could not be under stated.

- the laboratory was approaching capacity or above capacity in all main stream activities.

- the interim refurbishment only allowed improved product safety and production volume to a limited degree.

345. I also noted that over the next two years the programme to increase Regional plasma supply could realise between 150 and 200 tonnes of FFP for fractionation. I was concerned, as the annual report makes clear, that the greater the success in promoting increases in plasma supply from the Regions, the greater the risk of an imbalance arising as between supply and our ability to fractionate it.

346. Paragraph (iii) on page 11 of the report refers to a number of visits during the year to BPL for Regional Transfusion staff and the programme on

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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 Plaintiffs' suggestion that there was a lack of dialogue between BPL and the Transfusion Centres although, as will be seen, the frequent meetings of the Regional Transfusion Directors at which a representative of BPL was invariably present, along with representatives of the DOH and, on occasions, the Haemophilia Centre Directors really give the lie to this allegation.

347. On the 31st March 1982, the Advisory Committee on the National Blood Transfusion Service met and, as will be seen from the minutes (see document no 1495), there was a discussion of the progress in formulating arrangements for fractionating plasma from Northern Ireland at PFC Liberton. The logistics of transport were in the process of being ironed out, and it was hoped to begin operations by the end of April 1982 (operations subsequently began and at the 6th meeting of the Advisory Committee held on the 15th September, it was reported that batches of plasma from Northern Ireland had been satisfactorily processed at PFC Liberton) (see document no. 1551). There was 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 up-graded BPL now had capacity to process all available FFP.

348. On the 7th May 1982, Dr. Harris, Deputy Chief Medical Officer of the DOH, wrote to the BPL/PFL (ASTMS) Secretary (document no. 1506) referring to the substantial increases in the laboratories' output (with Factor VIII up by 30% and Factor IX by 38%) and congratulated the staff on the performance during the financial year 1981/82. The letter is evidence that we were doing our best (within the resources available) to respond to the need for more Factor VIII and Factor IX.

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349. On the 13th May 1982 I wrote to all Regional Transfusion Directors in England and Wales (document no. 1509) alerting them to the fact that for the period of about three months commencing in June 1982, there would be a restriction on the supply of Factor VIII. I sent with my letter a note setting out the quantities of Factor VIII which we anticipated producing during June 1982 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 full commission so there would be no overall loss of Factor VIII over this period.

350. On the 18th May 1982, Mr. Godfrey of the DOH 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. He also enclosed a Parliamentary Question announcing the establishment of a Special Health Authority to manage the Central Blood Laboratories (see document nos. 1511, 1511(a), 1511(b)). Confirmation of the decision is also to be found at paragraph 9 of the minutes of the 13th meeting of the Scientific and Technical Committee (document no. 1521) held on the 21st June at which Mr. Harley of the DOH reported that Ministers had agreed to the establishment of the Special Health Authority and were being consulted on the Authority's name and constitution. It also records that Mr. Smart had accepted the invitation to be the Authority's first Chairman and that it was hoped that the new Authority would come into being on the 1st November 1982 - in the event it was the 1st December 1982.

351. At the JMC Policy Steering Group meeting on the 23rd June 1982 (document no. 1523), it was agreed that Mr. Angilley, from the DOH, in conjunction with myself, should prepare a detailed financial appraisal of the various options for the redevelopment of BPL for submission to the Treasury. In the meantime the DOH were to prepare a paper for the Minister explaining all the

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various options, pointing out the revenue savings on 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. This was in the context of a decision by the Group that there were sufficient financial benefits flowing from the building of a laboratory which had the capacity to process 435,000 kg of FFP to justify the higher level of capital expenditure.

352. On the 28th June 1982 (see document no. 1524), I wrote to the DOH advising them that we had concluded that the MARP01 reconstruction had reached the 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 Regional Transfusion Centres to expect).

353. At the end of July 1982, the joint memorandum which Mr. Angilley and myself were charged with producing was completed (see document no. 1536). I contributed quite considerably to this paper. It should be noted that in paragraph 3 the memorandum 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 on a larger scale than originally intended. The conclusion (see paragraph 28) was the recommendation to build a 400 tonne laboratory at a cost which was then budgeted at £21.1m. spread over the years 1982/3 to 1985/6. The uncertainty with regard to plasma supply was reviewed in paragraph 30, together with the need to ensure that, at the same time as BPL was being redeveloped, there was an increase in the supply of raw material for fractionation.

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354. In about mid-August 1982, we received the Haemophilia Centre Directors' Annual Returns for 1981 (see document no. 1542). Total Factor VIII consumption during 1981 came to 65.7m. iu. Of this consumption, 35.5m. iu came from commercial Factor VIII concentrate, and 22.4m. iu from the NHS equivalent. Cryoprecipitate by this stage amounted to only 7.7m. iu. In percentage terms, commercial Factor VIII concentrate represented 54% of the Factor VIII units used by Haemophilia Centres during 1981. The trend in fig.1 of the Haemophilia Centre Directors' Annual Returns, shows commercial concentrate purchases beginning to level off as BPL produced more Factor VIII during the course of 1981.

355. At the beginning of September 1982, there is reference in the minutes of the meeting of the Central Advisory Committee for the National Blood Transfusion Service which was held on the 2nd September (document no. 1543), that plasmapheresis was undergoing a trial at the Bradford Regional Transfusion Centre. This was part of the wider trial which led to the increasing use of plasmapheresis with consequential improvements in the amount of plasma available for fractionation.

356. At the 15th meeting of the JMC held on the 5th October 1982 (document no 1561) , I was able to report (at paragraph 3) that the work on the final stage of MARP01 was due for completion by the end of the financial year (i.e. by March 1983). Mr. Collins estimated that the programme would be completed approximately four weeks behind schedule. At the time 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 as management contractors for the redevelopment (see paragraph 12). It was recorded that after careful study of the range of options, the Group had recommended that BPL

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should be redeveloped on the 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 the it would receive. It was also recorded that approval was awaited from the DOH Ministers and the Treasury.

357. On the 11th November 1982 a press release was made by the DOH (document no. 1568) announcing the formation of the Central Blood Laboratories Authority and the release also gives information regarding the membership of the Authority which, as I have indicated above, was to be chaired by Mr. D. Smart.

358. The first meeting of the CBLA (albeit an informal meeting) took place on 3rd December 1982 (see minutes - document no. 1574) but the meeting was preceded by a letter from the Minister (Norman Fowler) to Mr. D. Smart dated the 17th November (document no. 1569) in which the Minister set out his views on the functions to be performed by the CBLA. In this regard, the annex to the letter is also relevant in that it sets out the main tasks of BPL and PFL. A letter written on the 30th November by Mr. Illingworth of the DOH to the Secretary of the CBLA (document no. 1570) enclosed directions by the Secretary of State for the CBLA setting out the requirements for exercising the building and engineering functions of the Authority. The delegated limit for building and engineering works was £150,000.

359. However, in the papers for the CBLA meeting on the 3rd December 1982 which were attached to the agenda (document no. 1573) it was made clear in relation to the agenda item dealing with the redevelopment of BPL, that after consideration of an investment appraisal prepared by DOH with the assistance of the former JMC's Policy Steering Group, and following advice on the supply of plasma from the Advisory Committee on the National Blood Transfusion Service,

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DOH Ministers and the Treasury had agreed that BPL should be redeveloped at a size:-

(a) capable of making England and Wales self-sufficient in blood products (i.e. an annual through put of 400,000 kg of fresh frozen plasma), and

(b) capable of extracting all therapeutic products from the plasma, those products surplus to NHS requirements to be sold to the pharmaceutical industry.

360. Based on the feasibility study commissioned by the Policy Steering Group, the papers record that a sum of £21.1m. (at November 1981 prices) would be allocated to the CBLA for the project. It was stressed that this represented the budget cost limit and was intended to cover all aspects of the redevelopment programme including necessary site clearance, etc., and that no sum was to be added for contingencies. In the event, the project cost was £58m. although in the course of its execution, there were additional changes in its scope. The CBLA were advised that the Treasury had also agreed that the project should be "fast tracked" using a management contractor, and the DOH required the Authority as a matter of urgency:-

(a) to produce an estimate of the spread of expenditure, in particular the level of expenditure likely to be incurred in 1982/3; and

(b) proposals for managing the project.

361. The meeting of the CBLA on the 3rd December 1982 was, as the minutes make clear, very much a general introduction to the members who were meeting

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for the first time. Dr. Harris of DOH briefly summarised the history of the inception of the CBLA, and I gave details of the history of the BPL and PFL. I distributed copies of what became known as the "Black Book" (document no. 2126) which gave comprehensive details regarding BPL and PFL, their product ranges, staffing, financing and the technical aspects of their operations (e.g. the fractionation process).

362. On the 13th December 1982, Mr. Lillywhite of the DOH wrote to CBLA (document no. 1575) enclosing directions on financial management and control of expenditure for the CBLA, and confirmed that the delegated limit for capital expenditure was £150,000 which would be reviewed from time to time.

363. Thus the year closed with CBLA in the management driving seat, and with DOH/Treasury approval for the redevelopment of BPL on the basis of a capacity which it was generally agreed amongst all the interested parties, would be enough to achieve self-sufficiency.

364. As originally conceived, it was not expected that the redeveloped BPL would be available to produce Factor VIII before 1985/6 (in the event it was commissioned in 1987/1988). By this time, HIV transmission in coagulation products had been effectively controlled.

365. It can be seen, therefore, that the CBLA was established too late to have any influence over the primary definitions of self-sufficiency, and the subsequent delay in completion of the redevelopment (1986-1988) is of no relevance to the chronology as set out above.

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1983

366. For the reasons I have indicated above, the events of the next three years up to the point where testing for HIV antibody and heat treatment combined to eradicate the risk of HIV in Factor VIII and Factor IX concentrates, cannot be regarded as having more than background relevance so far as the issue of self-sufficiency is concerned. We were embarked on the planning and realisation of the new BPL facility and, in tandem, were looking at ways of increasing the supply of FFP in line with the intended capacity of the new facility. At the time, it was anticipated that the new facility would be commissioned in or about December 1985. Finally, R&D was in place to achieve inactivation of hepatitis virus (primarily Non-A Non-B) in Factor VIII and Factor IX concentrates.

367. Certainly supplies of FFP were gradually increasing. One of the papers produced for the meeting of the Advisory Committee on the National Blood Transfusion Service which took place on the 10th January 1983 (AC(83)8) (document no. 1590) shows that supplies for 1981 amounted to 109,000 kg and in 1982 this had risen to 127,000 kg. Although there was a suggestion at about this time that supplies of FFP were reaching a level where BPL no longer had the capacity to fractionate all the FFP which was available, this was not correct. My letter of 17th January 1983 (document no. 1594) addressed to Dr. Wagstaff who was the Director of the Regional Transfusion Centre at Sheffield, followed up on criticism which was levelled at BPL at the 187th Regional Transfusion Directors' meeting which took place on the 14th January 1983 (document no. 1593). In particular I dealt with the suggestion that plasma supplies were being improved through the introduction of optimal additive solutions ("SAG M"). Red blood cells re-suspended in SAG M form a product suitable for clinical use having an extended shelf life of up to 35 days. It was alleged that this increase in plasma

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supply was not being matched by increased product from BPL - this was not the case and I felt it necessary to put the record straight.

368. The document which is attached to my letter is an extract from the Blood Preservation Working Party documentation which was discussed at the meeting on the 14th January 1983 and contained several suggestions which were not true. (The constitution of the Blood Preservation Working Party is described in Appendix 2; it was a Sub-Committee of the Regional Transfusion Directors' meeting, concerned primarily with the production of frozen blood). 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 became necessary to design a larger bag to take the extra volume of plasma resulting from the introduction of the use of SAG.M. This anticoagulant additive allowed Transfusion Centres to increase recovered plasma volume per donation from approximately 200 ml to approximately 280 ml. As far as yield was concerned, the comments in the note 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 a Working Party advocating continued use of the 5 litre pack. On top of all this, some of the members of the Working Party were in favour of SAG.M whilst others were not. I replied that the Working Party's criticisms of BPL were unfounded. I circulated figures at the meeting on the 14th January 1983 which confirmed that BPL had in fact managed to make a substantial increase in Factor VIII productivity. I supported the SAG.M programme and confirmed that a major research commitment towards improved Factor VIII yields existed at BPL.

369. I continued to do what I could to encourage increases in FFP production in anticipation of the new BPL facility. On 25th May 1983, I prepared a document entitled "Budget - Function Relationships - Blood Products Laboratory,

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PESC Estimates related to BPL Manufacturing Requirements", (document no. 1638). This document was developed for a talk which was given to the Transfusion Service at a Travenol annual symposium. The paper and its supporting documentation was intended to show the future demands for plasma to service the new BPL plant which, at the time, we anticipated would be commissioned in December 1985, and would have a capacity to fractionate 450 tonnes of FFP per annum.

370. The minutes of the Advisory Committee on the National Blood Transfusion Service meeting which took place on the 17th October 1983 (document no. 1689), contain reference to the redevelopment of BPL which was, at the time, on schedule and also contained a statement that the project costs were "fully in hand". The meeting was chaired by Dr. Harris, the Deputy Chief Medical Officer of the DOH. Subject to what I say below, this was, at the time, broadly a correct description of the situation with regard to the new BPL facility, but of course the timetable subsequently lengthened and the costs increased. There was discussion (see particularly paragraphs 16 to 19 of the minutes) of the need to dramatically increase the supply of FFP if self-sufficiency were to be achieved. I explained at the meeting that we had mounted a campaign to make the Regional Health Authorities fully aware of BPL and the long term benefits to the Authorities of increased plasma procurement, in line with the findings of the earlier investment appraisal: DOH representatives said that they would discuss with the CBLA what assistance might be given by the DOH in reaching RTO's (Regional Teams of Officers). In fact this assistance was never forthcoming. Interestingly, it will be seen that supplies of FFP to BPL in the first six months of 1983 amounted to 73,704 kg showing that, on an annualised basis, FFP supplies were showing a reasonable increase over the previous year where the total had been 127,000 kg.

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371. On the 11th November 1983 (document no. 1694), I wrote to the DOH addressing the statement contained in the minutes of the Advisory Committee on the National Blood Transfusion meeting referred to above, to the effect that redevelopment of BPL was on schedule and the 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 the CBLA and the DOH, project costs were under control with a regular report being made to the DOH. 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 manufacture, and the second being that no doubt the Chairman of the CBLA would be discussing the BPL redevelopment with Ministers at their meeting in November.

372. During the course of the CBLA meeting which took place on the 23rd November 1983 (document no. 1697), there was some discussion of the consequences of the short period of shut down which we underwent during 1982 as part of the MARP.01 up-grade. The reference is to be found at paragraph 92.3 of the minutes which 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 Factor VIII short-fall could be made good during the next year."

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373. As stated earlier, the shortfall in Factor VIII caused by the temporary shutdown of facilities the previous year was in due course made up. The problems with the Factor IX process were coincidental. **[Dr Lane: What problems were these? P16].**

374. Two documents were produced by me during the course of 1983 which were designed to try and increase awareness of the need to improve the supply of FFP.

375. The first of these was a paper I prepared entitled "Plasma Supply-National Blood Transfusion Service" (document no. 1704) which is designated RTD(83)(7) (which was discussed at the 188th RTD meeting on 18 May 1983 minutes document no. 1637). The paper was intended to bring together a number of threads (the information regarding BPL's development, likely future capacity and requirements for plasma) to inform Regional Transfusion Centre Directors what was required for the future. As can be seen from page 10 of the paper, the development of national projections was the subject of a further document prepared by Mr. N. Pettet which drew to the attention of Regional Transfusion Directors the idea of a five year plan aimed at supplying the projected plasma needs of BPL. I would draw attention particularly to fig.3 which shows what was required in terms of FFP to supply a maximum input of 440 tonnes using a mixture of recovered plasma, SAG.M plasma, and plasmapheresis.

376. The other document prepared in 1983 for the Travenol symposium for the National Blood Transfusion Service dealt with the value of SAG.M systems in the provision of plasma products (document no 1705). Again, the idea was to inform the Transfusion Service of the advantages of using SAG.M which, if accepted by clinicians, would have a major impact on the plasma procured by NBTS for supply to BPL.

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377. Looking back on 1983 from 1984 (see the Haemophilia Centre Directors' Annual Returns for 1983 dated 31.7.84. - document no. 1810(a)), it will be seen that by the 31st December 1983 there were 4,745 registered haemophilia A patients in the United Kingdom. The annual returns showed that the total amount of Factor VIII used in 1983 was 71,008,000 iu. However, some Haemophilia Centres had not sent in returns for 1983 and therefore the total usage was estimated to be about 76m. iu. It was noted that:-

- the amount of NHS Factor VIII concentrate used had increased to 30,018,000 iu.

- the amount of commercial Factor VIII concentrate had decreased to 36,217,000 iu.

- the amount of cryoprecipitate used had decreased to 4,722,000 iu.

- the average amount of Factor VIII used for the treatment of haemophilia A patients remained at nearly 33,000 iu per year and more than half of the Factor VIII used was used for home treatment.

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1984

378. In my report to CBLA dated the 16th January 1984, I noted that the annual Factor VIII output at BPL had increased to 30m. iu and that Regional Transfusion Centres had increased the input of FFP to 150,000 kg per annum (document no. 1716).

379. My lengthy report on BPL covered the period April 1982 to April 1983, and from April 1983 to December 1983. The report itself was produced to coincide with the end of CBLA's first year of management. The summary to the report is set out on pages 2 and 3. Reference is made to the expenditure of £2.5m. on modernisation and extension of the existing buildings (MARP.01). As indicated above, the Minister had allocated £1.3m. for refurbishment. I had said from the outset that somewhere in the region of £2.5m. at the then prevailing prices was required to do the minimum job. I referred to the development of the new production building for which site work had commenced at Elstree in April 1983, and said that it would cost in excess of £21m.

380. The 10th meeting of the CBLA took place on 25th January 1984 (document no. 1722). Mr. Watt was no longer the Director of PFC Liberton. The Scottish Blood Transfusion Service had reported to Mr. Smart that a recurring surplus of Factor VIII was forecast and that their surplus stocks could be made available to BPL for distribution in England and Wales. In fact Scotland made available one lot of Factor VIII comprising some 2m. iu, which we subsequently distributed.

381. On the 8th March, Dr. Kernoff sent me a copy of a draft of a paper he was to present at the Haemophilia Society Residential Seminar on the 10th March (document no. 1737). The paper, entitled "Blood Products and their Problems"

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touches upon 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 cites, on a couple of occasions, the Scottish experience by way of comparison: he said that Scotland was not dependant on imported commercial plasma products and that its administrative system gave rise to fewer problems. However, as I have indicated above, the Scottish Blood Transfusion Service and the PFC were, relatively speaking, more generously financed than BPL and the Regional Transfusion Centres in England and Wales and, of course, the scale of the undertaking in Scotland was smaller and, I would submit, more easily administered.

382. At the 11th meeting of the CBLA which took place on the 28th March 1984 (document no. 1756), Dr. Harris' comments at the bottom of page 2 in relation to plasma supply are characteristic of the shambles which existed at that time. Nothing else of any real note arose from the meeting with the possible exception of the fact that Mr. Norman Fowler, MP had laid the foundation stone of the new factory at BPL on the 23rd March 1984. Matthew Hall projected at that time factory commissioning in 2 years.

383. At the 9th meeting of the Advisory Committee on the National Blood Transfusion Service which was held on the 10th April 1984 (minutes - document no 1761), it was noted that, due to resource constraints within Regions, Regional Transfusion Directors were less optimistic of attaining their targets towards increasing the supply of plasma to BPL to a self-sufficiency level, than they were in mid-1983. To an extent, this and the work which followed demonstrated that

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it was no small feat to increase the supply of FFP to the level where there was sufficient to service the new facility at BPL.

384. The possibility of a contribution of Factor VIII by the Scottish National Blood Transfusion Service was again touched upon in a letter from Mr. Perry to Mr. Pettet of BPL on the 8th June (document no. 1776). The first proposal on the part of the Scots was to supply a total of between 7m. and 9m. iu to BPL for distribution in England and Wales. It was stressed that a "regular supply commitment" could not be made.

385. However, Mr. Perry's letter (he was the acting Director of the PFC in Edinburgh at the time) of 7th September 1984 (document no. 1808) confirmed that only 2,123,500 iu 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 we should not plan on any additional quantities being available.

386. My circular letter to Regional Transfusion Directors of the 3rd August 1984 (document no. 1795) deals, inter alia, with arrangements for an "up-date" meeting to be held at BPL on the 18th September 1984. As the timetable and agenda make clear (document no. 1816), the plan was to show those attending around the new factory which was of course in the process of construction, and to discuss various matters of common interest but, of particular relevance to the present litigation, plasma procurement and supply, plasmapheresis trials (then underway) and the supply of Scottish Factor VIII. In addition, the BPL development was a general topic of discussion. Again, this evidences the dialogue which we sought to promote at various times with the Regional Transfusion Directors. The Scottish Factor VIII was to be made available in September/

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October and was to form an addition to the normal pro rata allocation to Regional Transfusion Centres.

387. The CBLA met again on the 26th September 1984 (document no. 1822) and the redevelopment work was proceeding at that point to the extent that there were concerns regarding the levelling off (or so it seemed at the time) of the supply of FFP. It is interesting to note Dr. Gunson's comment (paragraph 69.2) that the requirement for Factor VIII was, by that time, in excess of 100m. iu per year.

388. In October 1984, Mr. Perry wrote to BPL (document no. 1826) 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 1984 (document no. 1838) confirming that just as we would not wish to send out batches of our own product which failed our quality control test, we would really have to take the same line in relation to Scottish product.

389. By the end of 1984, it was clear that implementation of self-sufficiency would be affected by the requirements of maintaining product safety. We were, of course, planning and preparing for a facility which would, on the figures we then had available to us, achieve self-sufficiency when the facility itself was commissioned. We were at the same time working towards appropriate increases in the supply of FFP. However, by October/November 1984, we were committed to heat treating our intermediate product and well advanced in the development

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of the new 8Y and 9A products. The heat treatment of our intermediate Factor VIII (as described below), produced losses of product due to denaturation and during the initial stages of the production of 8Y we experienced a drop in yield which had implications for the supply of Factor VIII unless plasma supply was increased. (Subsequently the expected improvement in 8Y yield has enabled the early targets for Factor VIII supply and plasma processed, to be met).

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1985

390. Plasma supply was considered during the course of the meeting of the CBLA which took place on the 1st February 1985 (document no. 1932). By this stage, Dr. Harris, the Deputy Chief Medical Officer, was no longer a member of the Authority. There is reference in the minutes 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 the consequential requirement to ensure that plasma supply was adjusted accordingly. Dr. Gunson was encouraging the use of plasmapheresis, and, as the minutes make clear, for the appropriate level of central funding for its more widespread application. Of course plasmapheresis had by this time become well established as a procedure and the matter of sufficient funding was of primary importance.

391. On the 5th February 1985, in a Written Answer (document no. 1945-extract from Hansard) Mr. Kenneth Clarke stated that the new BPL was scheduled for completion in January 1986, and that it was intended to provide the capacity to meet the forecast demand on the NHS in England and Wales for Factor VIII. However, he too noted that the heat treatment process reduced the product yield, and that the consequences of this on the timetable for achieving self-sufficiency were being examined.

392. That said, self-sufficiency was beginning to drop away as an issue. As will be seen from a letter which I wrote to Dr. Collins of the Regional Transfusion Centre in Newcastle on the 12th April 1985 (document no. 2048), (acknowledging receipt of the agenda for the forthcoming meeting of the Regional Transfusion Directors to be held on the 17th April 1985), 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.

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393. In the event, plasma supply was discussed at the 18th meeting of the CBLA held on the 22nd May 1985 (document no. 2093). Dr. Gunson reported that a meeting had been held to consider data received by the DOH from Regional Transfusion Centres on projected volumes of plasma to be supplied over the next four years. The meeting noted there was a principal shortfall from four Regions. **[The minutes of the relevant meeting are said to be attached as an appendix but they are not].**

394. In July 1985, BPL issued an information sheet to Haemophilia Centre Directors and Regional Transfusion Directors in England and Wales on the subject of the new product 8Y which noted that until the new BPL production unit was completed, output of 8Y would meet about one third of the current demand for Factor VIII concentrate (document no. 2149).

395. Also, in July 1985, I prepared a paper entitled "Evaluation of MARP.01 Programme and other Capital Expenditure Projects between 1981 and 1983" (document no. 2148). This paper designated CBLA85/39, shows that the final cost of MARP.01 project at 1985 prices, amounted to £3.038m. which may be compared with the original £1.3m authorised by the Minister. The value of the product which this investment produced we calculated to be £12.257m. so it was clearly money well spent.

396. Over this period, the slippage in the building programme for the new BPL facility was increasing. On the 8th October 1985, there was a meeting of the Regional Transfusion Directors at BPL (document no. 2188) at which it was suggested that the new factory was reasonably close to commissioning. So close, in fact, that the documentation for this was being prepared. In reality, as we subsequently found out, the situation was quite different. We were certainly

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encouraged by Matthew Hall in the belief that commissioning was likely to take place about three months later than originally planned. However, in fact, the slippage was much greater than we then realised 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 achieve.

397. In November 1985 at the 11th meeting of the Advisory Committee on the National Blood Transfusion Service held on the 6th November (document no. 2202), I again reported on progress on the BPL redevelopment project and stated that commissioning would be gradual. I expressed concern about maintaining a quarantine supply of plasma. Mr. Williams of the DOH 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 DOH 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 DOH were playing a rather more direct role than historically had been the case in encouraging increases in supply to keep BPL functioning.

398. The Annual Return prepared for the Haemophilia Centre Directors' meeting that took place on the 21st October 1985 were forwarded to us on the 12th November (document no. 2204(a)). The number of patients diagnosed by this stage had risen to 4,918 haemophilia A patients as at 31st December 1984. It was recorded that the amount of NHS concentrate used by Centres had increased and the amount of commercial Factor VIII decreased, and that for the first time since 1974, more NHS concentrate than commercial concentrate was used. This really reflected the MARP.01 up-grading with the consequent effect on output. As can be seen, the average consumption of Factor VIII approximated to 34,000 iu per patient per annum.

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1986 AND BEYOND

399. I refer to Dr T. Snape's Statement for a description of the commissioning of BPL, the eventual cost and a note on current output.

SUMMARY OF SELF-SUFFICIENCY CLAIMS AND CBLA REBUTTAL

400. Turning to the particulars of negligence and/or breach of statutory duty by the CBLA in relation to the issue of self-sufficiency in the Blood Transfusion Service, it may be helpful to summarise the points which emerge from what I have said above, and relate these to the particular claims raised on pages 105 and 106 of the Re-Amended Main Statement of Claim.

401. (95(a)) Failed to Administer the BPL properly

This allegation is so general as to be impossible to respond to sensibly. Obviously it is a proposition which CBLA would not agree with.

402. (95(b)) Failed, after its creation on 1st December 1982, to set in place with urgency, alternatively diligence, a proper policy of development and improvement

At the time CBLA took over responsibility for BPL/PFL and BGRL, the decision with regard to the future redevelopment of BPL had, to all intents and purposes, been taken and CBLA were charged with the responsibility for carrying through the redevelopment. In common with all major capital projects, the decision as to whether or not to sanction the project lay with the DOH. The programme for the redevelopment of BPL as originally planned would have resulted in the new facility being commissioned by December 1985 at the earliest. For the reasons I have touched on above, this would have been too late to have had any beneficial effect, so far as the risk of HIV infection in haemophiliacs was concerned. There

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is no doubt that subsequently the programme for the redevelopment slipped and the costs escalated. We have just reached the point where it can be said that England and Wales are self-sufficient in NHS Factor VIII concentrate. If one means by this that we can supply clinicians with all the NHS Factor VIII they request, some still use commercial products and, I suspect, always will. However, in my view none of these points are relevant and even if the delays and cost escalation in relation to the new BPL facility could be said to be relevant, a detailed review of the history of the redevelopment of BPL would, I believe, reveal there was no negligence on the part of CBLA in relation to their involvement in the project. During the period from December 1982 until the end of 1985, it can be seen from what I have said above, that we were endeavouring to maximise production of Factor VIII. By the time CBLA took over responsibility for BPL, the MARP.01 up-grading was all but complete, and the facility which we then had was running at the maximum capacity achievable, given the available facilities and the amount of FFP which Regional Transfusion Centres were able to send to us. As a generalisation, I think it is correct to say that throughout this period (and despite the odd ill informed comment to the contrary), we were generally ahead of the supply of FFP from Regional Transfusion Centres in terms of our capacity to fractionate. Within the obvious constraint that we did not control the Regional Transfusion Centres and, in particular, certainly did not control their funding we did our best, I believe, to encourage Regional Transfusion Centres to maximise their contribution of FFP by:-

(i) introducing a pro rata system of distributing Factor VIII concentrate which rewarded increases in FFP production;

(ii) encouraging the change from 5 litre bags to single donation bags;

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(iii) (prior to CBLA taking over), encouraging clinicians to use concentrated red cells releasing more plasma for fractionation;

(iv) promoting more extensive use of plasmapheresis;

(v) encouraging the wider use of SAG.M as a way of increasing the plasma which could be taken from each donation and

(vi) introduced a highly effective test for hepatitis screening of donors.

403. **(95(c)) Failed, from 1982 to co-operate with the RHA's sufficiently or at all in providing a National Blood Transfusion Service sufficient for BPL's needs**

The first point to make is of course that CBLA is not responsible for providing a National Blood Transfusion Service. The Service is essentially provided under the auspices of the Regional Health Authorities. They are responsible for providing the funding for the service out of their own budgets which in turn are dictated by the amount of funding they receive from the DOH. I think it is difficult to look at the period after 1982 in isolation. It will be clear from what I have said above, that from 1978 onwards our involvement at all stages in efforts to encourage Transfusion Centres to increase their supply of FFP, was extensive. Of course we had no control over the funds which were necessary if methods such as plasmapheresis were to be more widely employed, but to the extent possible, we advised the DOH, Regional Transfusion Centre Directors and (as appropriate), Haemophilia Centre Directors as to what BPL would require by way of FFP supplies, and how we thought the required increases could be achieved. We could not force Regional Health Authorities to implement our recommendations and the DOH showed their procedural reluctance to intervene and direct that Regional Health Authorities allocate a certain proportion of their funds on specified Transfusion Centre activities. From 1982 onwards, our efforts were particularly

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directed towards increasing production to a level where FFP was sufficient to supply the new BPL facility and, in turn, make England and Wales self-sufficient in Factor VIII concentrate. As in the past, a BPL representative (usually myself) attended the important Regional Transfusion Centre Directors' meetings, Haemophilia Centre Directors' meetings, together with Working Party meetings which were relevant to plasma supply, and assisted in the identification of the quantities of plasma required at any particular time, as well as producing statistics on plasma supply for Regional Transfusion Centres. The Transfusion Service was also represented by Dr. Gunson who was a member of the CBLA and attended the Authority's meetings. As will be seen, by the end of 1985 the DOH was actively involved in monitoring FFP production against targets, but once again, one has to bear in mind that from 1982 to 1985 (after which Factor VIII concentrate products whether commercial or NHS were rendered safe by testing/heat treatment), the capacity of BPL to fractionate plasma in its old facility was, at most times, in balance with the quantity of FFP Regional Transfusion Centres found themselves able to supply.

404. <u>(95(d)) Failed, from 1982, either properly or at all to assess future needs for Factor VIII</u>

I think it is fair to say that by the time the CBLA was established and took over the management of BPL, the future needs for Factor VIII had been accurately estimated and formed the key to the planned redevelopment of BPL. It may be said with the benefit of hindsight, that the estimates were marginally high, but I do not see that the Plaintiffs have any ground for criticism on this score. Moreover, it must be remembered that the estimates were not prepared by the CBLA nor, for that matter, were they prepared in any sort of vacuum. The estimate on which the rebuilding of BPL was based, was the result of considerable discussion between all interested parties but, in particular, the Haemophilia Centre Directors who probably had most to contribute in this regard and whose approach

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to clinical treatment would have most influence over the quantities of Factor VIII consumed.

405. (95(e)) Failed, from 1982 or such later time as may be justified on the evidence of trial, either properly or at all to set itself targets, alternatively reasonable targets, and to communicate and co-ordinate such targets both for the future production of Factor VIII and for the collection of plasma to and with the Health Authorities

This is really a repetition of 400 and 401.

406. (95(f)) Failed, from 1982 or such later time as may be justified on the evidence of trial, to achieve such targets

I think the only target that really matters here is the target which was set as part of the MARP.01 up-grade. Within the financial and regulatory constraints imposed on us by the DOH and the Medicines Inspectorate respectively, the target of an annual production equivalent to 30m. iu of Factor VIII was the best that could be set, and of course this all pre-dated the CBLA's involvement with BPL. By the time the CBLA took over, MARP.01 was substantially complete, and maximum production from the facility achieved. It was not until the commissioning of the new facility that substantial increases above this general level of production became possible. As originally planned, phased increases would not have been possible before December 1985 (too late to assist haemophiliacs in relation to the HIV problem), and the fact that these increases were not achieved until several years later than planned is not, in the context of this litigation, relevant.

407. (95(g)) Failed, from 1982 or such later time as may be justified on the evidence of trial, to advise the Department of Health and the Health Authorities

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to use the spare production capacity in Scotland to eliminate or reduce the Welsh and English need to import commercial Factor VIII concentrate

Again, this issue had been run to ground shortly before CBLA took over BPL. From the period I first joined BPL up to 1982, BPL had been haunted by the spectre of PFC Liberton and the grandiose claims made for it by those responsible for its administration (who were hardly independent). I think it is clear from the material to which I have referred above, that the trial carried out at PFC Liberton with the intention of determining what its spare capacity might amount to was, at best, inconclusive and it resulted in the SHHD making it clear to the DOH that PFC Liberton was not in a position to assist without substantial expansion of its facilities which would take a considerable period of time to achieve, a considerable amount of money and, moreover, require a radical alteration to existing working practices. By the time CBLA took over, the die was cast and the DOH were determined that BPL should be redeveloped on a scale which would achieve self-sufficiency without any contribution from Scotland. The assistance which Scotland was able to provide came in the form of a "once and for all" contribution of some 2m. iu of Scottish Factor VIII which was promptly distributed to Regional Transfusion Centres. Despite suggestions that more might be available, it was not forthcoming. The belief that there was any significant spare capacity immediately available for fractionating English and Welsh plasma at PFC Liberton was, I believe, a myth. However, quite apart from this, there was no major imbalance at any time between 1982 and 1985 (after which the issue became irrelevant) between the supply of FFP from English and Welsh Regional Transfusion Centres and our requirement to fractionate it.

408. (95(h)) Failed, from 1982 or such later time as may be justified on the evidence of trial, to advise the Department of Health and the Health Authorities to use plasmapheresis to boost the yield of plasma from volunteer donors in

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England and Wales so as to eliminate or reduce the need to import commercial Factor VIII concentrate

Again, I think that the facts as outlined above show that we took all reasonable opportunities to advise both the DOH and the Health Authorities as to how FFP production might be maximised. This included the increased use of plasmapheresis, but this required additional investment and we were in no position to provide the funding or to force the DOH or the Regional Health Authorities to do so. The advice to all concerned with regard to boosting FFP supplies pre-dates 1982 by some years, but continued after CBLA took over responsibility for BPL.

409. (95(h)A) They failed, from 1982, to approach commercial products manufacturers to fractionate plasma from volunteer donors in England and Wales, and/or they failed to advise the Department of Health and the Health Authorities to do this

Again this allegation assumes an excess of FFP which BPL/PFL were unable to fractionate. Of course had RHA's and the DOH injected substantial funding into the NBTS, there was a possibility that the FFP supply might have outstripped our capacity to fractionate it, but this was not the case at least from December 1982 to December 1985.

410. (95(i)) Being responsible for the redevelopment of the BPL from 1982, failed to achieve self-sufficiency by 1989, or such later time as may be revealed by the evidence at trial

For the reasons I have touched on above, self-sufficiency, if it has any relevance at all as far as CBLA is concerned, ceased to be relevant by the end of 1985 when heat treated products (NHS and commercial) made from tested plasma, were available in quantities sufficient to satisfy haemophilia patients' requirements for treatment.

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HEPATITIS RISK AND/OR RISK OF OTHER VIRAL INFECTIONS

411. At this point it is appropriate to depart from the order in which the Plaintiffs' allegations against the CBLA are set out in the MSC. The allegations summarised at pages 105 to 113 of the MSC concentrate on issues relating to the manufacture of non heat treated concentrates, heat treatment and the screening of donors and testing for HIV and are listed before those contentions which arise under the general heading of hepatitis risk and/or risk of other viral infections. However, a better understanding of the issues comes from a discussion of the impact of the hepatitis risk on the production process and the need to introduce virus inactivation.

412. Accordingly, I intend to deal first with hepatitis and then HIV. In the case of the former, it is necessary to look back several years prior to the point at which the CBLA became responsible for BPL/PFL. The problem presented by HIV was resolved within the procedures being adopted to produce clotting factors free of hepatitis viruses. This stage of the development coincides more closely with the period during which the CBLA has been responsible for BPL/PFL.

413. I set out below a general description of hepatitis in its various forms. As far as Factor VIII and Factor IX are concerned, we need only consider hepatitis B and hepatitis Non-A Non-B, although the latter may actually embrace more than one strain of hepatitis virus. Whilst a test has recently been developed for one such strain (known as hepatitis C or HCV), it is still appropriate to talk in terms of hepatitis Non-A Non-B rather than hepatitis C for this reason.

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Types of Hepatitis

414. Hepatitis presents in acute, sub-acute and chronic forms. With hepatitis B and C the acute form may be severe and fulminant resulting in death. Sub-acute and chronic hepatitis may be life-shortening in haemophiliacs although the records of fatalities indicate hepatitis as a cause of death in only a minority of the total recorded deaths. By way of illustration, a paper reprinted from the British Medical Journal, 19 March 1983 by C.R. Rizza and Rosemary J.D. Spooner records the causes of death in patients with haemophilia A and haemophilia B over the period 1976-1980 (see miniprint table Vm on page 8 of document no.). Cerebral haemorrhage was the commonest cause of death in haemophilia A patients, accounting for 26 of the 89 deaths. Hepatitis was recorded as the cause of death in one patient with haemophilia A and one with haemophilia B (although the type of hepatitis is not specified). The longer expected survival of haemophiliac patients introduces a higher clinical significance to the chronic disorder. On page 5 of the same paper, median life expectancy was 69.1 years for severely affected haemophiliacs, as compared with 72.8 for normal males. (The paper notes, however, that these figures should be trated with caution: the numbers in the calculations were relatively small and it was possible that deaths may not all be reported to haemophilia centre directors).

Hepatitis A:

415. This is sometimes called acute infectious hepatitis. Its transmission is not customarily considered as a transfusion transmitted form of hepatitis although there are published reports of rare associated cases in patient recipients of blood. The viral infection is through the enteral (intestinal) route usually from faecal contamination of water or food. The infection is often sub-clinical i.e. it is without symptoms, particularly the young: otherwise symptoms may be mild and

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associated with abdominal discomfort. Treatment is symptomatic. The duration of infectivity of the patient is uncertain but is probably from 7 to 14 days before to seven days after the onset of jaundice. Treatment in the majority of cases is symptomatic. The prognosis is good and patients make a satisfactory recovery associated with immunity against further infection.

Hepatitis B:

416. This is also called serum hepatitis. It has an incubation period which may be up to six months, but is commonly 10 to 16 weeks after infection. It is transmitted parenterally and sexually and at birth in the case of the infected mother. Therefore it is transmitted by transfusion of infected blood and blood products manufactured from such blood, or by the use of contaminated syringes or needles. It is therefore a disease associated with parenteral addiction. Hepatitis B is a serious disease. It carries published mortality rates between 2% and 5% and after the acute infection may be associated with the development of chronic liver disease and association with the hepatitis D (delta) virus and an associated increase in hepato-cellular carcinoma. Recovery from the disease is most frequently associated with development of immunity although a small percentage of patients retain carrier status (approximately 0.1% in the UK but up to 5% in Asiatics) and are capable of transmitting the disease by any of the above routes.

417. The presence of hepatitis B infection may be associated with a number of viral markers. At the onset of infection the patient's serum may be found to contain actual virions or virus particles known as core particles (Dane particles) associated with core particles are various amounts of surface antigen (and abbreviated as HBsAg). In the majority of patients the early immune response follows the viraemia and may demonstrate all or some of the following features: the presence of antibody to the core antigen; to e-antigen which is core

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associated; and against HBsAg. It is generally considered that the absence of antigen and the presence of antibody to HBsAg reflects recovery from infection and non infective status.

418. The Transfusion Service and blood product manufacturers test all donors/donations/plasma pools/finished products for HBsAg by an approved third generation test. Tests used by the Transfusion Service and BPL/PFL since the start of the 1970's are described in Appendix 7.

Hepatitis Non-A Non-B:

419. This expression is thought to include a group of viruses which may be transmitted by both enteral and parenteral routes. Within this group the recently described hepatitis E virus is transmitted in a similar manner to hepatitis A and is a reported cause of epidemic hepatitis particularly in Asian countries. Although not yet visualised, a virus now described as hepatitis C (HCV) has been defined through its presumed genomic structure: this virus probably accounts for greater than 70% of parenterally transmitted Non-A Non-B (HCV) infection associated with the transfusion of blood and blood products. Most recent published information suggests the presence of hepatitis C antibody in the normal population of 0.5% to 2% but levels up to 6% to 10% in high risk groups e.g. addicts.

420. The result of initial infection is most frequently sub-clinical. However, there may be a mild acute illness associated with abdominal discomfort and slight jaundice and in rare cases a fulminant hepatitis similar to that of hepatitis B, may result in death. The more significant feature of HCV infection is the progression in a percentage of patients (possibly up to 50%) of sub-acute and chronic forms of hepatitis which may be life shortening.

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421. Following the reduction in transmission of hepatitis B as a result of effective donor screening during the 1970's and early 1980's, Non-A Non-B hepatitis emerged as the dominant form of transfusion associated hepatitis. The true rate of transmission following blood transfusion in the UK has yet to be reliably determined. However, blood products prepared from large plasma pools have accounted for viral infection in most treated haemophiliacs. Factor VIII prepared from commercially collected donor plasma had an early association with HCV transmission because it caused an acute clinical condition in many patients. However, the use of liver function tests (alanine aminotranspherase "ALT") in all haemophiliacs had shown by the early 1980's that virus transmission occurred with Factor VIII prepared from voluntary donor blood sources, although these products did not produce an acute illness in more than a small percentage of patients. Most recent information indicates an order of magnitude more virus donors in the commercial donor population than in the voluntary donor population, thus accounting for a higher viral load in plasma pools and finished products with the possible resultant increase in overt acute infection.

422. Clinical, epidemiological and experimental studies in laboratories, have indicated that Non-A Non-B hepatitis may be caused by two and possibly more than two infectious agents. Clinical evidence is based on the observation of multiple attacks of hepatitis in individual patients. Epidemiologically, short incubation (2 to 5 weeks) and long incubation (5 to 10 weeks or longer) forms of Non-A Non-B hepatitis have been described. The incubation period, however, does not appear to be a reliable index for differentiating between the two Non-A Non-B types of hepatitis, and the differences in the incubation period may represent differences in viral dose or patients' susceptibility to infection.

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OVERVIEW

423. The problem of the transmission of hepatitis B to haemophiliacs treated with concentrate manufactured from pools of plasma which included infected donations, was certainly one which was appreciated throughout the 1970's. That said, it was not a condition which resulted, save in relatively few cases (as I have mentioned above), in fatalities amongst those infected with the virus. The likely outcome of infection in haemophiliacs was the development of antibodies to the hepatitis B virus providing immunity against repeat infection. Although, as I describe below, the problem of hepatitis B transmission through blood products gave rise to a consideration of manufacturing products from small pools of plasma, there were, in the case of hepatitis B, a number of reasons why this approach was not adopted.

424. First, Regional Transfusion Centres tested the source of plasma supplied to BPL and PFL for the manufacture of blood products (and BPL/PFL also carried out their own tests) for the hepatitis B antigen using tests of increasing sensitivity as these became available.

425. Second, the level of usage of product amongst severe haemophiliacs in particular was such that, by the end of the 1970's, those who had received treatment had at one time or another become infected with hepatitis B and had, in the vast majority of cases, satisfactorily recovered with the consequence that they were immune from further infection.

426. Third, by the early 1980's, a vaccine was developed which enabled clinicians to vaccinate new patients against hepatitis B before treating them with concentrates, thus providing additional protection to that afforded by the

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screening of plasma donations. However, for the reasons described below, it was not generally available until 1984.

427. The approach to the control of transmission of hepatitis B was through the effective screening of blood donations and latterly through active immunisation of recipients at risk. The incidence of hepatitis B transmission was substantially reduced by these approaches, thereby indicating their efficacy. The problem with Non-A Non-B hepatitis and later HIV, represented different challenges, for reasons which are considered below.

428. From 1975 onwards increasing control of hepatitis B infection in haemophiliacs revealed patients suffering from a form of hepatitis which, due to the absence of detectable known viral markers, was defined Non-A Non-B. It is now known that the acute infection in many patients was sub-clinical (or asymptomatic) and at the time in question went un-noticed.

429. Further research revealed that at least one, (and probably two) viral strains were responsible for the disorder labelled Non-A Non-B hepatitis.

430. This research also showed that the long term effects of Non-A Non-B hepatitis were far more serious than had at first been appreciated. Fatalities were rare, but the infection clearly resulted in sub-acute or chronic liver disease. The difficulty in detecting hepatitis Non-A Non-B was due to the absence of marker tests available at the time. In fact, it is only in 1990 that a test for one Non-A Non-B virus (HCV) has been licensed. Even in the case of hepatitis C, the virus has not been visualised although its genome has been described and the marker test relies on antibodies to recombinant fragments.

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431. Because of the difficulties referred to above, fractionators began to consider ways of inactivating the Non-A Non-B hepatitis virus in the production process. This work was underway at the time when it was accepted that a new virus, HIV, might be present in plasma pools and be transmissible in finished products. In the absence of early information on HIV it had to be assumed that the virus inactivation process being devised for Non-A Non-B hepatitis would be equally applicable to the virus associated with AIDS cases.

432. The Plaintiffs' claim pre-supposes that heat treatment was something which should have been embraced to deal with "hepatitis" and other unspecified viruses much earlier than in fact was the case. However, hepatitis B, for the reasons given above, was controlled by donor screening and patient immunisation and only when it became apparent that Non-A Non-B hepatitis could carry serious long-term sequelae was it necessary to give consideration to a virus inactivation process that did not compromise the safety or efficacy of the products in question. In respect of Non-A Non-B hepatitis, further thought was given to using small plasma pools to supply products to haemophiliacs who needed only occasional treatment. In a trial of small pool product this procedure alone failed to prevent Non-A Non-B hepatitis transmission.

433. Against this background, heat treatment, along with other methods of virus inactivation, had to be reviewed and researched. However, it must be understood that fractionators must exercise care when making changes to their processes. Any change in the manufacturing process can lead to changes in the product itself which may deprive it of some or all of its effectiveness or give rise to the possibility of adverse reactions, side effects, etc. Significant process variations require that full clinical evaluation of the product confirms product safety and efficacy in line with regulatory requirements.

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434. Without due clinical evaluation, clinicians are unlikely to use a new or modified product. In relation to NHS heat treated concentrate when it became available for trial in 1984, even with preliminary knowledge of HIV there were clear differences in clinical opinion concerning its use; the balance of judgement lay between the unproven efficacy of the heat treatment process in virus inactivation on the one hand and potential protein denaturation and increased immunogenicity on the other hand.

435. Prior to a chronological review of the developments in relation to hepatitis B, hepatitis Non-A Non-B and then HIV, the risk benefit analysis by patients and their clinicians applicable to the use of Factor VIII and Factor IX concentrates and the impact of HIV on this analysis, must be reviewed. Hepatitis B proved fatal in relatively few cases and was an ever reducing risk through the 1970's for the reasons given above. Although hepatitis B and Non-A Non-B infection was universally recognised during the 1970's and even when the longer term sequelae of Non-A Non-B hepatitis became apparent, the steady significant increase in patient demand for Factors VIII and IX from any source indicated that the benefit to patients from control of bleeding exceeded the perceived risk or discomfort from hepatitis infection. By 1980 haemophiliacs could look forward to normalisation of their lives in terms of usefulness, quality and longevity. The intervention of HIV infection dramatically changed the balance: the product which saved life, itself assumed the trappings of a death sentence. An invidious choice.

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HEPATITIS B AND HEPATITIS NON-A NON-B 1973 TO 1985: THE DETAIL

1973

436. An early seminal work is an article prepared by Dr. Rosemary Biggs and entitled "Jaundice and Antibodies directed against Factors VIII and IX in patients treated for Haemophilia or Christmas Disease in the United Kingdom" (written in 1973 and published in the British Journal of Haematology in 1974) (document no. 89). It is perhaps a good starting point in any chronological review of the subject of hepatitis. The article was the consequence of a decision taken in 1967 by the Haemophilia Centre Directors to carry out a study of hepatitis in relation to patients they treated. The period covered by the study was 1969 to 1971.

437. There are perhaps two points to note in relation to the article. First, one has to be particularly careful about the implications to be drawn from the results. The paper was published too early to provide a foundation for reliable conclusions with regard to Factor VIII concentrate and its role in transmitting the hepatitis B virus. The use of concentrates was only just beginning at the time; hepatitis Non-A Non-B had yet to clearly emerge, and the results were based on overt signs of hepatitis (i.e. jaundice) amongst patients which is not a reliable yardstick to adopt in estimating the actual incidence of Hepatitis B or Non-A Non-B infection. The summary of the findings of the study recorded that the incidence of jaundice in all patients, for the three year period of the study, was 3.48%, and the average annual incidence of episodes of jaundice among patients treated in each year was 1.83% of patients treated. It was said that the use of freeze dried concentrate (in comparison to cryoprecipitate) did not cause a dangerous increase in episodes of jaundice, but again I would point out that concentrate usage was at a low level.

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438. Screening of donors for the hepatitis B antigen had begun at Regional Transfusion Centres. Appendix 7 to my statement sets out details of the various tests used at BPL/PFL and Regional Transfusion Centres from 1970 to date. However, the level of sensitivity of the early tests would not exclude all hepatitis B from entering the fractionation pools. Dr. Biggs acknowledged this in the article at page 314:-

> "Since then, the screening of all donors for hepatitis B antigen has been instituted and the incidence of samples grossly contaminated with hepatitis B virus is now certainly less. Screening, however, is unlikely to remove all infected samples because more than one virus is involved [my underlining], and because the screening method is not sufficiently sensitive to detect all samples infected with the hepatitis B virus."

439. It is interesting to note that Dr. Biggs states that more than one virus was involved.

440. It will be seen that at page 318, Dr. Biggs considers the effective pool size. For the purpose of her consideration, she assumed the incidence of infection with hepatitis B to be 1 in 800 donations. However, for the reasons I have given above, her conclusion that patients receiving Factor VIII concentrate as opposed to cryoprecipitate, showed no dangerous increase in episodes of jaundice, has to be treated with some caution. At this time a severely affected patient receiving cryoprecipitate or concentrate derived from small plasma pools would be exposed to similar numbers of plasma donations and therefore risk of viral infection.

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1974

441. Hepatitis was one of the topics discussed by the Haemophilia Centre Directors at their meeting in Oxford on the 1st November 1974. It is apparent from the minutes (see page 4 - document no. 162) that Dr. Biggs had results for 1973, and that these showed the incidence of jaundice amongst patients treated during 1973 to be 2.43%. For the reasons already given, I do not think any particular conclusions can be drawn from these figures.

442. At page 5 of the minutes Dr. Craske of the PHLS reported on an epidemic of hepatitis A and B in haemophiliac patients in Bournemouth, and Dr. Rizza referred to the fact that since January 1974, there had been 11 episodes of hepatitis in Oxford patients, 9 of whom had received commercial concentrates, but all of whom had also had NHS concentrate with the consequence that it was not easy to identify the material which had caused the jaundice. From the minutes there was obviously a discussion of the problems arising from the use of therapeutic materials which might be contaminated with various hepatitis viruses, and Professor Stuart expressed the view that material identified as containing hepatitis B antigen need not be withdrawn from use, since this material could be given to patients known to have hepatitis B antibody or to have had hepatitis. It should be noted that Dr. Biggs said (fairly), that it was not yet proved that the commercial Factor VIII was much more dangerous from the point of view of causing hepatitis than other preparations, and that she hoped that this material would not get an unnecessarily bad name. It was in fact clinically invaluable while the NHS supply was so limited. Dr. Craske agreeing with this, said that he felt that NHS concentrate was likely to be safer when that was available.

443. As we see later on, whilst the strong impression emerged over the next few years that US commercial concentrates were less safe than their NHS

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counterparts, this was incorrect so far as the incidence of transmission of Non-A Non-B hepatitis was concerned. Screening for the hepatitis B antigen was routinely used both in the United States and in the UK with the consequence that, by about 1980, clinicians were really only concerned, in the majority of cases, with hepatitis Non-A Non-B. Hepatitis Non-A Non-B transmitted by US commercial concentrate was more clinically evident in patients treated with it compared with patients receiving NHS Factor VIII and IX. Eventually studies revealed that the rate of hepatitis Non-A Non-B infection from the use of US and UK concentrates was probably the same (somewhere close to 100%) and, moreover, the long term effects of either "type" of hepatitis Non-A Non-B were likely to be similar.

444. Also during 1974, Dr. Biggs produced a paper entitled "The Incidence of Jaundice and Antibodies in Patients in the United Kingdom" (document no. 172). The paper reviewed a six year period during which patients treated at Haemophilia Centres increased from 1,046 to 2,450. The estimate was that the probable number of patients in the country was somewhere in the region of 3,000. By way of comparison, the figure in 1990 is believed to be about 5,500.

445. Under the heading "The Types of Virus Known to occur in Plasma" Dr. Biggs refers to a recent review which suggested that there might be hepatitis viruses other than type B in a high proportion of hepatitis cases (80%). In paragraph 2, Dr. Biggs refers to the same review and to the contention contained in it that commercial donor blood may be as much as ten times as likely to contain what is now known as hepatitis Non-A Non-B, (now known to be close to current estimates) and also reference to the fact that pooling of the plasma from many donations would increase the probability of an infected sample being included in the pool whether made from volunteer or paid donor blood.

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446. At this stage the data which might have supported the contention that commercial Factor VIII concentrate was more likely to communicate hepatitis was too limited for firm conclusions to be drawn from it as far as hepatitis B infection was concerned. Dr. Biggs indicated that every effort should be made to increase the supply of intermediate potency concentrate made from UK plasma, based on the above belief.

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1975

447. In an article entitled "An Outbreak of Hepatitis Associated with Intravenous Injection of Factor VIII Concentrate" published on the 2nd August 1975 in the Lancet (document no. 277), Dr. Craske reported on an outbreak of jaundice associated with the use of commercial freeze dried Factor VIII concentrate at the Bournemouth Haemophilia Centre between April and June 1974 (referred to above). There appear to have been 20 patients who were regularly seen and treated, and 9 of these contracted hepatitis; 4 with hepatitis B, 7 with "Non-B" and inclusive of 2 patients who contracted both terms. 18 were receiving commercial Factor VIII concentrate at the time. It can also be seen (page 2) that some of those infected developed jaundice, whilst others did not. Jaundice is more common with hepatitis B, than it is with hepatitis NANB. On page 4 under the heading "Discussion", Dr. Craske put forward his theory that pool size might be critical in Factor VIII concentrate. The perceived added risks of large donor pools were not quantified on the basis of the evidence then available (or I would submit in view of the prevalence of Non-A Non-B virus in donors in pool sizes greater than 100 litres in commercial and NHS concentrate, as tests later established).

448. On page 5 (the third paragraph from the end), Dr. Craske states:-

> "What is required is a freeze-dried Factor VIII concentrate prepared from volunteer donors in the UK prepared according to an approved protocol of testing. A small quantity is available, but it is likely that some reliance will have to be placed on commercial sources for some time to come."

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449. In September 1975, Dr. Craske put forward proposals for a prospective study of the relationship of HBsAb test results in haemophiliacs to the risk of contracting hepatitis B after infusion with Factor VIII concentrate Hemofil (document no. 241). The proposal followed outbreaks of hepatitis B (including the one at Bournemouth) caused by commercial Factor VIII concentrate. At the same time Dr. Peter Kirk (based at Lord Mayor Treloar College, a school for haemophiliac boys at Alton in Hampshire) put forward a protocol (document no 242) for a prospective study in hepatitis in haemophilia associated with the use of Factor VIII concentrates. As Dr. Craske indicates in his paper, this prospective study was one in which he and Dr. Kirk were co-operating. Dr. Kirk notes in the protocol that despite increased sensitivity in hepatitis B testing, there was still a substantial failure to prevent post transfusion hepatitis. The following hypotheses were put forward:-

- that testing methods were still not sensitive enough;
- that other known viral agents were responsible, e.g. hepatitis A, EB (Epstein Barr) virus, cytomegalovirus;
- that other, as yet unknown viruses, caused a significant amount of post-transfusion hepatitis.

The first and third possibilities were indeed, we now know, correct.

450. Dr. Kirk also noted that treatment with Factor VIII concentrates exposed the patient to a much greater risk of contracting transfusion hepatitis, because the fractionated product was processed from donor pools. Furthermore, commercial Factor VIII concentrates were made from large pools of some 2,000 to 6,000 litres of plasma from paid donors. 6000 litres of plasma represents 10-12,000 donations. BPL's pools at the time were in the region of approximately 200 litres. Dr. Kirk quotes Dr. Prince (who was based at the New York Blood

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Centre) who had suggested in an article in 1975, that recipients of all commercial blood had a ten-fold higher risk of developing Non-A Non-B post-transfusion hepatitis than recipients of all volunteer donor blood.

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1976

451. The year does not appear to have been a particularly eventful one. There was correspondence between Dr. Craske and Dr. Maycock (Dr. Craske's letter to Dr. Maycock of 19th October 1976, Dr. Maycock's reply of the 29th October and Dr. Craske's to Dr. Maycock of the 17th December (documents 402, 407 and 454 respectively) on an idea which Dr. Craske was promoting for extending the study which was already underway regarding the incidence of hepatitis arising from the use of Hemofil to a study which included NHS Factor VIII. He suggested this because it was becoming apparent to him that there was a fairly constant incidence of hepatitis occurring after transfusion of both English Factor VIII and other commercial preparations. Dr. Maycock agreed with the idea that the extension of the study was dependent upon the consent of the Haemophilia Centre Directors.

452. From January 1976 a new commercial RIA test was introduced at BPL which tested for the Hepatitis B antigen. PFL's products were tested at BPL using the RIA test. The test was more sensitive than the RPH tests which were then currently in use at Regional Transfusion Centres and offered, as a consequence, additional protection to those being treated with NHS commercial Factor VIII concentrate from contracting Hepatitis B (see the report entitled "Blood Products Laboratory - Report to the Advisory Sub-Committee on the Blood Products and Blood Group Reference Laboratory of the Central Committee of the National Blood Transfusion Service - 1976") (document no. 366).

453. In December 1976 Dr. Smith of PFL produced a document entitled "Comparison of cryoprecipitate and intermediate purity concentrate for the treatment of haemophilia" (document no 464). In general terms the paper discusses the benefit of purity at a time when the future use of cryoprecipitate

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was subject to considerable discussion. In my view Dr. Smith's paper is a clear statement of common sense backed up by fact. The paper comments that cryoprecipitate cannot compete with concentrate in safety, reliability or convenience for the patient and throws doubt on the validity of claims that it was cheaper or more economical in its use of plasma resources. Dr. Smith's paper limits its scope to the consideration of the relative merits of cryoprecipitate and concentrate for self administration and brief outpatient treatment at Haemophilia Centres: it is generally conceded that surgical cases are accorded priority for higher potency concentrate. The paper embarks on a comparison of the two products under various paragraph headings. Paragraph 5 is entitled "Hepatitis Risk". Dr. Smith comments that although concentrates made from large pools of plasma carry a greater risk of transmitting Hepatitis B than cryoprecipitate, the increased risks could be minimised by careful allocation of batches to patients.

454. When Dr. Smith's paper was written cryoprecipitate use was at its zenith but its use was being questioned. There was no doubt that, for the majority of clinicians and patients, concentrates were the treatment of choice and consumption of the commercial products was growing rapidly.

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1977

455. The year saw Dr. Craske pursuing his proposals for a wider study of the incidence of hepatitis arising from treatment with concentrates and on the 13th January 1977 at a meeting of the Haemophilia Centre Directors (document no. 486) he presented a written report to the meeting and outlined the findings to date.

456. Dr. Craske's survey later published under the title "Haemophilia Associated Hepatitis - 1974-75 in the United Kingdom a Retrospective Survey" (document no. 578) may be viewed as something of a state of the art document at that time. In the survey, Dr. Craske observed two types of hepatitis:-

- A short incubation Non-B hepatitis (only cases with symptoms and signs compatible with a diagnosis of hepatitis were included); and

- Hepatitis B

457. The survey concluded that the first introduction of Hemofil as Factor VIII replacement in the UK was associated with an overall incidence of 17.7% of transfusion hepatitis. Before the introduction of commercial Factor VIII concentrate, the incidence was about 1.8%. Dr. Kirk who was co-author of the paper noted that the hepatitis survey showed that all the cases of clinical hepatitis (hepatitis B) and almost all the cases of asymptomatic hepatitis (Non-A Non-B hepatitis) were confined to the patients restricted to commercial concentrates.

458. His study was, at this time, concentrating on hepatitis in patients treated with Hemofil. He reported that 371 patients receiving Hemofil had been followed up. Only one death was possibly attributable to Hepatitis B. Dr. Craske

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indicated that he would like to continue with his study over the next two years. The review recognised that more than one type of hepatitis was at work and it is interesting to note that Dr. Craske was asked to clarify how he distinguished between Hepatitis B and Non-B types and replied that he looked at each individual case. In relation to Dr. Craske's extended study the revised minutes record:-

> "This continued study would include a follow up of patients who had had Hemofil associated hepatitis to study the incidence of chronic sequelae, and a comparison of jaundice associated with NHS Factor VIII and commercial products".

459. Dr. Craske followed this up with a letter to Dr. Maycock on the 28th January 1977 (document no 495) explaining that his idea was to compare Hemofil, Kryobulin, Scottish and NHS Factor VIII as regards the incidence of hepatitis after infusion with these various concentrates. He explained that he had obtained the provisional consent of the Newcastle, Manchester and Alton Haemophilia Centres to participate in the study of selected batches of the Elstree product. He enclosed a draft protocol and sought Dr. Maycock's comments. A reply to his letter was sent by Dr Maycock on the 22nd February 1977 (document no. 507) setting out various detailed comments on the protocol.

460. Dr. Rizza wrote to Dr. Maycock on the 17th February 1977 (document no. 505) explaining that, at the meeting of the Haemophilia Centre Directors on the 13th January, the question of setting up Working Parties to tackle certain problems in the field of haemophilia management and research was raised. Dr. Rizza explained that the general feeling of the meeting seemed to be that Working Parties, provided these were limited in numbers, might prove useful but that probably only three or four Working Parties should be set up in the first

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instance. He enclosed a suggested list of Working Parties which included a Working Party to study the incidence of hepatitis in haemophilia. This appeared as the first item in the list which otherwise contained a total of seven suggested topics for Working Parties to tackle. Dr. Maycock's response to Dr. Rizza dated 28th February 1977 (document no 509) is quite interesting. Having been invited to list the Working Parties in order of priority Dr. Maycock placed the Hepatitis Working Party last in his order of priorities:-

> "I put this last because the sensitivity of tests used to screen donors is now very good (a third generation test is obligatory in USA and recommended in UK - here we rarely make anything obligatory nor, as is sometimes unkindly said about the German attitude to things, do we say "anything which is not obligatory, is forbidden".) All products in UK and USA are tested by RIA. Among the other reasons for putting the subject last is that any worthwhile survey, now, of hepatitis is going to be very expensive, in man hours (needed for follow up, interviewing, correspondence), in laboratory tests (e.g. liver function tests, the value of which in subclinical cases is often debatable, unless several different tests are done at fairly close intervals and all other causes of positive results in such tests are considered and eliminated; hepatitis tests should also be mentioned here) and lastly, it is now suggested in the States that most cases of hepatitis in patients given blood products are neither Hepatitis A nor Hepatitis B. I think it would be worth waiting till the Non-A Non-B disease is confirmed and defined.
>
> "I imagine most Centres routinely test their registered patients for HBsAg and anti-HBs. If it could be arranged without great expense for all registered patients at a given number of centres to be tested for antigen and antibody by agreed simple but sensitive tests, some information of

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value might be gathered. One would have to decide whether one was going to test certain categories of patient (e.g. a group based on severity) or take in all registered patients. But such an exercise could quickly fan out into a big affair unless kept under tight control.

"Craske is planning a survey to compare in certain Centres the numbers of cases of hepatitis after certain different preparations of concentrate. Perhaps he should be encouraged to constitute himself as a Working Party and the proposal should be left at that.

"If a cheap reliable test for A and anti-A hepatitis became available and one were found which would distinguish the so called Non-A Non-B hepatitis, then I think this question should be re-examined.

"I think it is possible that hepatitis may have attracted undeserved attention".

461. The third generation test which Dr. Maycock refers to is in fact radio-immunoassay or RIA. At the time, it was in use at BPL but not at Regional Transfusion Centres where the less sensitive RPH test was still in use. He proposed that any study should wait until Non-A Non-B disease was confirmed and defined. In fact only one of the so called hepatitis Non-A Non-B viruses has, to date, been so confirmed and described and this is some 12 years after Dr. Maycock's letter.

462. On the 1st April 1977 Dr. Kirk wrote to Dr. McGrath at the National Institute of Biological Standards and Control ("NIBSC") (document no 520) referring to the hepatitis survey which at that time had been going for some 19 months and indicated that all the cases of clinical hepatitis and almost all the

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cases of asymptomatic hepatitis were confined to patients restricted to commercial concentrate. He said there were no significant differences between the cases restricted to Hemofil and Kryobulin.

463. On the 7th April 1977 Dr. Craske sent to Dr. Maycock (document no 522) the final version of the protocol for the study of jaundice after transfusion of Elstree Factor VIII concentrate.

464. It was in September 1977 that Dr. Craske and Dr. Kirk published their retrospective survey paper on which I have commented in some detail above. As I have said the paper was something of a landmark and led to an extended comparative study of cryoprecipitate, NHS and Scottish products which at the time Dr. Craske was still in the process of setting up. In essence the findings of the study were that commercial product transmitted hepatitis B to haemophiliacs. In the conclusions set out on page 8 of the document (document no. 578) the survey shows that the introduction of freeze-dried commercial Factor VIII prepared from large plasma pools obtained by plasmapheresis from paid donors for the treatment of UK haemophiliacs resulted in an incidence of hepatitis of 17.7% as mentioned above.

465. As I have mentioned elsewhere, although this survey did not extend to include results obtained from patients treated with, inter alia, NHS Factor VIII concentrate, this early work supported what I believe was in fact the case i.e. that US commercial concentrate was more likely to be infected with hepatitis B having regard to the fact that the plasma from which it was manufactured was obtained from paid donors. The social status of these donors was such that they were more at risk of contracting Hepatitis B than volunteer donors although even in the UK there was a higher incidence of virus carriers in the main metropolitan areas. A non-reactive result with the most sensitive hepatitis B test

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will not exclude all infectious plasma. Therefore, an intrinsically higher incidence of hepatitis B carrier donors in the total donor population places an added risk of infection into large plasma pools.

466. Notwithstanding Dr. Maycock's coolness towards the idea, the Haemophilia Directors set up a Hepatitis Working Party in May 1977 and we see the earliest documentary evidence of its work in CBLA's possession, in Appendix C to the papers distributed for the Haemophilia Centre Directors' meeting on the 24th October (document no. 611(c)). Appendix C is entitled "Haemophilia Directors Hepatitis Working Party Hepatitis Associated Commercial Factor VIII 1976". As the paper makes clear it deals with the continuation of the study of Hemofil begun in 1974 and, in particular, with the decision to study the incidence of hepatitis after infusions of Kryobulin in 1976 and to compare this with the incidence due to Hemofil. Much of the material is common to the paper which Dr. Craske and Dr. Kirk published and (which I refer to above) and again one sees, at the bottom of page 2, the reference to Non-B hepatitis and to there possibly being two types of such hepatitis. It was felt that the two virus types had epidemiological incidences which varied between the United States and the United Kingdom. For example one patient had NHS associated Non-B hepatitis in 1973 followed by Hemofil associated Non-B hepatitis in 1974. This supports the comment I made earlier, i.e. that the Non-A Non-B hepatitis virus(es) seemed to be different as between the virus(es) transmitted by US commercial concentrate and by NHS concentrate. The US variant made itself more apparent in the patient but ultimately the long term effects of both forms of Non-A Non-B hepatitis were found to be the same. The study of hepatitis in NHS concentrate had not yet been started by Dr. Craske at this stage.

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467. It will be seen that quite a lot of the paper is devoted to Non-B hepatitis. The conclusions were that it was essential to continue the studies with the object of answering the following questions:-

"(i) The effect of the RIA screening for HBsAg of the plasma donations used to prepare plasma pools on the incidence of commercial Factor VIII hepatitis B.

(ii) The number of types and incidence of Non-B hepatitis.

(iii) The incidence of sequelae after acute hepatitis".

468. The further projects proposed at the time were:-

"(i) A study of hepatitis after NHS concentrate....

(ii) A retrospective study of the records of past years at Oxford to study the incidence of multiple attacks of hepatitis.

(iii) The compilation of a register of carriers of HBsAg...."

469. From my part in Appendix A1 to my paper, which was produced in September 1977 for the Advisory Sub-Committee covering the year ending July 1977, (document no. 594) I suggested, on page 3, that RIA testing for HBsAg should be promoted for all donor units in Regional Transfusion Centres. I alluded to the fact that although RIA testing was carried out by BPL, 5 litre pooling of plasma by Regional Transfusion Centres meant that a positive plasma in a 5 litre pool implicated some 25 to 30 other donations. In addition, the dilution effect of

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5 litres on a single donation might invalidate even the more sensitive BPL RIA test. These were the reasons why I advocated a move to a single donation pack.

470. Dr. Craske's letter to Dr. Maycock of the 22nd November 1977 (document no. 620) indicates the difficulty he was having in obtaining information from Haemophilia Centre Directors. He suggested that someone from BPL might sit on the Haemophilia Centre Directors' Hepatitis Working Party. Dr. Maycock agreed that BPL should be represented (see his letter of the 25th November document no. 623).

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1978

471. 1978 was a busy period in terms of our attempts to obtain a commitment from the DOH to upgrade BPL in the short term and re-develop it in the medium term. My paper "Stop-Gap provision for plasma fractionation at BPL" which I prepared in January 1978 (document no. 641) and was considered at a meeting between the DOH and BPL on the 18th January (document no. 644) touched on the testing of plasma for hepatitis B.

472. I noted that the control of HBsAg transmission in plasma fractions depended upon a constant surveillance of the whole human plasma so that antigen-positive material was excluded from processing. At the time various assays were available which varied by several orders of magnitude in their sensitivity of detection of antigen (see Appendix 7 which summarises the tests). Even so the most sensitive test (radio-immunoassay) did not exclude the possibility of hepatitis transmission but it did provide the highest level of confidence in the safety of a plasma fraction which was then currently available.

473. FFP was being tested for HBsAg by RIA at BPL unless this test had already been done at a Regional Transfusion Centre (at the time for example the Regional Transfusion Centre in North London was using an RIA test for "new" donors). I noted in the paper at page 2 that:-

> "Before use at BPL, all FFP must be tested to exclude HBsAg by the most sensitive test available - at present RIA, thus to cope with plasma supplied as single FFP donations, these will have to be tested either at RTCs or at BPL on arrival. General policy at present does not advocate the extension of RIA for HBsAg into all fourteen RTCs, a policy generally based on cost of RIA per test using commercial reagents: donor selection

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coupled with a second generation test for HBsAg may provide an adequate cost-effective scrutiny of donors at the Regional level.

This appraisal of Regional requirement is not adequate for BPL.

(i) Large plasma pools (i.e. 2000 single donations or more) are involved [at **BPL**] in production of Factor VIII and would form the basis for cryoprecipitate supernatant as a freeze-dried plasma substitute). The importance of excluding HBsAg from a single donation in a large plasma pool is obvious.

(ii) The highest available level of sensitivity of HBsAg testing should be used for plasma processed into large pool products (RIA testing of source plasma is a production requirement in the USA). While such a level of testing could be advocated as being desirable on all FFP donations prepared at RTCs costs are a deciding factor: equivalent considerations would not apply to RIA testing of FFP donations at BPL for reasons detailed below."

474. At the time I was advocating centralised testing at BPL using the RIA test but instead of using a commercial test with the associated costs of use instead, our own test developed in collaboration with the Middlesex Hospital (Dr. Dane), the North London RTC and ourselves.

475. I attended the discussion at the DOH on 18th January 1978 together with Dr. Maycock and met Dr. Waiter, Mr. Dutton and Mr. Cleaseby of the DOH. As can be seen from paragraph 1 of the notes of the meeting I had calculated that the cost of a commercially produced RIA test was between 30p. and 90p. per test according to the volume of testing performed. In contrast I estimated that an

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RIA test developed as a collaborative venture as indicated above would cost between 10p. and 15p. per test. I again stressed the importance of a testing regime over which we had control. This was the idea behind my advocating that BPL should carry out the testing which is noted in paragraph 2:-

> "In response to the suggestion that implementation of RIA testing of all FFP at BPL would lead to some units being tested twice by the same method, at additional cost to the NHS, Dr. Lane said that he could not accept any testing over which he did not have direct control as being in line with his policy of achieving maximum safety standards at BPL. The recommendations in the Second Report of the Advisory Group on Testing for the Presence of Hepatitis B Surface Antigen and its antibody which advocated RPH as the most desirable screening test, were aimed at RTCs and did not apply in the different conditions at BPL, where a single contaminated unit of plasma could render unfit for processing an entire pool of 3000 donations. He thought that legislative requirements for RIA testing by producers would be introduced in due course, in line with practice in other countries".

I proposed:-

- A programme for developing the RIA test in the UK to avoid the need to use costly commercial RIA tests **[this proposal is not noted in the document]**

- Double testing of plasma by RIA at Regional Transfusion Centres and BPL could be avoided if collaborative arrangements for testing at Regional Transfusion Centres by BPL accredited methods could

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be established. In a sense this was the alternative to BPL carrying out the testing centrally and was eventually the solution adopted.

476. At about the same time Dr. Craske was pressing on with his proposals for an expanded study and on the 8th February (document no. 657) produced a paper entitled "Haemophilia Centre Directors' Hepatitis Working Party - study of the incidence of chronic sequelae of Factor VIII associated B and Non-B hepatitis."

477. On 30th January 1978, Dr. Craske had written to Dr. Maycock (document no. 654) indicating that he was having discussions with the Medicines Commission and the DOH with a view to getting a research grant to study the incidence of hepatitis associated with all brands of Factor VIII over the next three years. On 20th February (document no. 662) Dr. Maycock responded to this letter stating that he was in general agreement with the proposal to study the incidence of hepatitis and suggesting, if this was not already intended, that the study might extend to subicteric cases (that is to say cases where the hepatitis does not manifest itself through jaundice). Dr. Maycock touches on the Hemofil study and in this context makes a somewhat unfortunate comment in the third paragraph of his letter:-

"Too close investigation of these patients might suggest to any who were found to have chronic hepatic sequelae that they have been negligently treated originally and that a claim for compensation might be in order. If this aspect has not been considered I think it should be, if only to dismiss it. I believe concentrate is becoming progressively safer, both here and in other countries, so that it may be undesirable to be seen to be giving emphasis to this complication of the use of the earlier batches of "Hemofil", the use of which was attended by considerable publicity. What is going to be gained? It is known that an attack of post-

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transfusion hepatitis associated with HBsAg may entail chronic hepatic damage."

478. In his reply on 13th April 1978 (document no. 684) Dr. Craske, not surprisingly, disagreed with Dr. Maycock's views. He said:-

"I discussed this with several Haemophilia Centre Directors, and they are all of the opinion that what is required is an accurate assessment of the chance of any patient acquiring chronic hepatitis from these products. This information could then be taken into account in deciding which patient should be treated. There is no doubt that for many patients these products represent a major advance in treatment. Therefore, in my view, it is important to study any possible hazards which might be associated with their use, and to devise methods of eliminating them."

479. Dr. Craske's application for funds for the proposed study was in fact sent on 19 April 1978 by the DOH to Dr. Maycock who was asked to act as a referee in respect of Dr. Craske's application. (document no. 686).

480. On the 2nd May 1978, Dr. Maycock commented on Dr. Craske's application (document no. 698) but, subject to his comments, made it clear that he supported the proposal and, in a letter dated 31st July (document no. 751) the DOH indicated that the proposal had their conditional support having being reviewed by the Small Grant Committee and having obtained views "from a wide basis of consultation".

481. By December I was advocating (as can be seen at page 6 of a paper I prepared for the DOH entitled "Increased Provision of Fresh Frozen Plasma ("FFP") (document no. 822) that:-

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"All single donations should be tested at RTCs by RIA and the single units sent to BPL for processing. This is the best safeguard for Factor VIII, Factor IX and I preparation and is in accordance with FDA requirements in the USA".

482. In 1978 in the absence of established evidence that NHS Factor VIII transmitted HCV with a high order of incidence of chronic aggressive hepatitis, the logical drive was to increase output of NHS Factor VIII from U.K. plamsa since this appeared to carry less risk and to make sure that hepatitis B testing efficiency was optimised in the NBTS.

483. It is also clear from the material in 1978 that there was a better understanding of Non-A Non-B hepatitis. This can be seen from an undated document in the form of a report prepared by Dr. Craske which summarises the work of the Haemophilia Centre Directors' Hepatitis Working Party - 1978 (document no. not found). The report dealt with the incidence of hepatitis since the introduction of Hemofil and considered the incidence of multiple attacks of hepatitis indicating the existence of two types of Non-B hepatitis.

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1979

484. Dr. Craske pressed on with his work during the course of the year and in the early part of the year wrote to me (22nd February - document no. 844) enclosing a document which set out the criteria for attempting to relate different batches of Factor VIII concentrate to cases of hepatitis reported from Haemophilia Centres.

485. On the 14th May 1979, Dr. Drummond-Ellis of BPL produced a memorandum for me (document no. 876) in which he summarised cases of hepatitis associated with Elstree Factor VIII concentrate and commented that there was no strong evidence of infectivity of any batch of Oxford Factor VIII or IX. The report shows there were two batches (of Elstree Factor VIII) with strong evidence of infectivity, one with equivocal evidence of infectivity and 51 with unsubstantiated association with infectivity. The two batches with strong evidence of infectivity provided a historical indication that hepatitis B virus could be present in plasma pools.

486. Possibly the most interesting document which was produced during the year was the report of the Haemophilia Centre Directors' Hepatitis Working Party 1979 (document no. 957(b)) which was amongst the papers for the 10th meeting of the UK Haemophilia Centre Directors held on the 20th and 21st November. The report (page 2) makes use of the nomenclature Non-A Non-B in place of Non-B, symptomless hepatitis and other expressions previously used where the hepatitis did not appear to be hepatitis B. It commented that the prevalence of hepatitis in 1978 and 1979 had been at about the same level as that observed in 1976-7. However, there had been an increase in the proportion of cases of Non-A Non-B hepatitis reported in patients with mild coagulation defects receiving concentrate for the first time to cover operations. The observed increase in mild

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haemophiliacs contracting hepatitis was, said the report, probably due to the fact that most severe haemophiliacs had already been exposed to viruses present in all brands of concentrate and were therefore immune to re-infection. There was, said the report, evidence to suggest that the contamination rate with hepatitis B virus may have dropped. I am sure this was due to the improved screening. The report goes on to say at page 3:-

> "Since September 1975, a considerable number of batches of NHS **[and ?]** commercial concentrate associated with cases of hepatitis B have been screened in Dr. Dane's laboratory in London and all have proved negative for HBsAg although (RIA) techniques have since improved in sensitivity. However, cases of hepatitis B are still regularly reported and most severe haemophiliacs are immune to hepatitis B".

487. Although there are some comments in relation to numbers of patients diagnosed as having Non-A Non-B hepatitis I think that at this stage such figures have to be treated with some caution. Testing and diagnostic techniques were still to some extent unreliable. The report indicates there were no fatalities due to acute hepatitis during the period and refers at page 7 to the possibility that there may be two types of Non-A Non-B hepatitis:-

> "The observations recorded in the 1978 report were described in a letter published in The Lancet (Craske, Spooner et al (1978) Lancet ii 1051). Observations made since then have given additional evidence for the existence of two types of N/A N/B hepatitis causing short incubation illness in haemophiliacs on Factor VIII therapy. One is probably related to commercial concentrate originating from the USA and the other to NHS Factor VIII and Kryobulin".

488. Under the heading "Prevention of virus infection" at page 8 there is reference to a hepatitis B vaccine:-

> "As indicated in the 1978 report, one vaccine is at present undergoing trials in the USA, and preliminary results should be available in the Summer of 1980. We are due to have further discussions with persons involved in this trial to see whether such a vaccine would be of value in haemophiliacs. There are, however, considerable difficulties to be overcome before this can be considered."

489. With regard to Non-A Non-B hepatitis the report goes on to state:-

> "Collaborative experiments with the Bureau of Biologics in Washington are about to start. Similar experiments are being undertaken in collaboration with Professor Arie Zuckerman of the Department of Microbiology of the London School of Hygiene and Tropical Medicine. One group at the Communicable Disease Centre Atlanta Georgia has published results suggesting that the N/A N/B hepatitis associated with haemophilia is due to a small round virus (Bradley, Cook et al (1979) J Med Virol 3 253-269). This work remains to be confirmed.

490. At the first meeting of the Blood Transfusion Research Committee on the 17th December 1979 (document no. 970), Dr. Jenkins commented, that the transmission of Non-A Non-B hepatitis was still a problem with Factor VIII concentrates.

491. The year ended with my commenting at the meeting of the JMC held on the 19th December that BPL should be free to charge Regional Transfusion Centres for the provision of the BPL RIA test for hepatitis B which had up to

that point been provided free to Regional Health Authorities on a trial basis (introduction of this test is considered in greater detail later in my proof). I proposed charging, to generate the revenue to cover the cost of preparation of the BPL RIA test, but it was intended that the test should be cheaper than equivalent commercial tests.

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492. In contrast with the previous year there was a lot of activity during 1980 with regard to hepatitis.

493. As requested by the JMC I provided for the DOH a full costing of the supply of RIA test kits comparing commercial tests with estimates of the cost of the BPL test (my letter to the DOH - Mr. Brechin is dated 7th January 1980, document no. 975). I would reiterate that at the time BPL and PFL were both using an RIA test (our own) during the course of producing Factor VIII and Factor IX but most of the Regional Transfusion Centres were still using the reverse passive haemaglutination (RPH) test.

494. On the 21st January 1980, Dr. Jones of the University Hospital of Wales wrote to me (document no. 980) stating that he had some evidence which might suggest that Non-A Non-B hepatitis was as common amongst haemophiliacs on cryoprecipitate as those given freeze-dried Factor VIII concentrate. Although Dr. Jones states that the data he relied upon would be published shortly, I am not aware of its subsequent publication.

495. BPL's RIA test came up for consideration at the fourth meeting of the Scientific and Technical Committee held on the 23rd January 1980 (minutes-document no 982). I outlined at page 4 my proposals for making the test available to the Health Service at a cost below that which Centres were then paying for commercial tests and the Committee recommended that the DOH should finance the development of the test at BPL and, if necessary, invite regions to pay for it.

496. The Scientific and Technical Committee's recommendation was noted at the 6th meeting of the JMC held on the 20th February. Also on the 20th February 1980 was the 6th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party (document no. 997), Dr. Craske reported that the first report to the DOH on the research project started in September 1978 had been submitted in October 1979 and copies had been circulated to members of the Working Party. The aim was to analyse the cases of hepatitis reported to Oxford for the years 1977 to 1979 inclusive. Preliminary analysis of the figures was available for 1977 and treatment returns for 1977 and 1978 were presented at the meeting:-

> "One surprising outcome had been that at least 33% of patients treated in 1977 and 1978 received only one product". It was agreed that more information was needed on the risk to patients of developing chronic Non-A Non-B hepatitis by prospectively following patients first exposed to concentrate or other products e.g. mild haemophiliacs undergoing non-emergency surgery. It was agreed, in relation to Non-A Non-B hepatitis, that answers were needed to the following questions:-
>
> "(i) The incidence of post transfusion hepatitis both overt and symptomless, especially Non-A Non-B following first exposure to treatment with Factor VIII and IX concentrates particularly if there is any difference between different products. (Commercial, NHS concentrate and cryoprecipitate).
>
> "(ii) What is the chance that symptomless or overt Non-A Non-B hepatitis may become chronic and lead to chronic active hepatitis or cirrhosis. This would include the natural history of the disease

and whether re-exposure or immunosuppressive drugs such as steroids pre-disposed to recrudescence of the disease.

"(iii)Is there any risk of spread of Non-A Non-B hepatitis to close household contacts or spouses of the affected patients."

497. With regard to the hepatitis B vaccine Dr. Craske reported at paragraph 6 to the meeting that he had met with Dr. Reichle, Associate Medical Director in Europe of Merck, Sharp & Doehme, regarding the possibility of carrying out a trial of hepatitis B vaccine in British haemophiliacs.

498. This vaccine, (which eventually became available in 1984) together with more recently developed products, is now routinely available to vaccinate all previously untreated haemophiliacs before they receive Factor VIII or Factor IX treatment.

499. Although BPL had been represented (by Dr. Drummond-Ellis) on the Haemophilia Centre Directors' Hepatitis Working Party, I wrote to Dr. Craske on the 1st April saying that I would like to represent BPL personally on the Working Party as hepatitis was clearly going to be a major problem area for some years to come. I mentioned that we should be thinking in terms of encouraging the UK to develop its own hepatitis Non-A Non-B test. Dr. Craske replied on the 22nd April confirming that I could join the Working Party.

500. On the 7th July 1980 there was a further meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party **[we only appear to have the agenda - document no. 1064]**. The Agenda features chronic hepatitis resulting from hepatitis Non-A Non-B. As a result of studies carried out by Dr. Craske and others, clinicians now know that hepatitis Non-A Non-B was responsible for sub-

acute and chronic hepatitis in a significant percentage of cases. This is a condition which took time to establish itself and its "gestation" period was roughly comparable to the period during which Factor VIII concentrate began to be used more widely. The clinical concern now evident concerning Non-A Non-B hepatitis became the catalyst for BPL to direct research into viral inactivation.

501. In the latter part of 1980 I consulted with senior staff of BPL on procedures available for inactivation of Non-A Non-B hepatitis virus. The directive carried major resource implications for R&D which at the time were fully disposed to improving Factor VIII product and production yield.

502. In August 1980 Professor Zuckerman prepared a paper (document no 1085) entitled "Transmission of Hepatitis Viruses by Plasma and Blood Clotting Factors". "The Risk of Commercial Donors". This paper appears to have been prepared at about the same time as a number of other papers for the Protein Fractionation Technology Working Party and it is possible that the document was either prepared for the Working Party or was amongst the documents which the Working Party considered. Professor Zuckerman noted:-

- That hepatitis A was not transmitted by blood and blood products.

- That the pooling of a large number of units of plasma for the preparation of plasma derivatives increased the risk of contaminating the pool with an infectious unit.

- That the WHO Expert Committee on Viral Hepatitis had noted that many studies had shown that paid donors constitute a particularly high risk group for transmitting hepatitis, and that every effort

should be made to introduce an entirely voluntary blood donor system.

- That there was an urgent need for specific laboratory tests for markers of infection with the viruses of N/A N/B hepatitis.

[Dr. Lane has agreed to find out if we can obtain any material generated by the WHO Expert Committee on Viral Hepatitis? P17]

503. The 7th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party was held on the 3rd September 1980 (document no. 1088); Dr. Smith from PFL attended in my place. At the meeting the minutes show that Dr. Craske reported on the preliminary data from the hepatitis surveillance project for the years 1977-79. The conclusions up to that point were:-

"(i) Non-B hepatitis antibodies at the same level as 1974-5 for Hemofil and Kryobulin and similar figures are available for other US concentrates. Apparent variations in the incidence of hepatitis B were most likely to be associated with changes in the use of different products e.g. the incidence in cases of hepatitis B and non-B associated with Armour Factor VIII were associated with an increase of 300 patients treated with this product from 1977-79.

"(ii) Hepatitis B. Despite screening of donations for HBsAg this continued at a low level. Survey of hepatitis B antibodies in Oxford haemophiliacs had shown a high correlation with exposure to Factor VIII concentrate with a positive blood test for anti-HBs.

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"(iii) Chronic hepatitis B is not a major cause of chronic liver disease in British haemophiliacs, as only 3/124 patients studied were carriers of HBsAg.

"(iv) Hepatitis B is associated with a low risk of secondary infections in household contact of haemophiliacs.

"(v) There is no evidence of overt secondary Non-A Non-B hepatitis in household contacts of British haemophiliacs who contract Factor VIII associated Non-A Non-B hepatitis."

504. It was stated that the most common association of Non-A Non-B hepatitis was a first transfusion of Factor VIII, particularly US commercial Factor VIII.

505. Dr. Craske circulated data that suggested that NHS Factor VIII made at Oxford might be associated with a lower risk of Non-A Non-B hepatitis than batches of Elstree Factor VIII (i.e. Elstree) or commercial Factor VIII. It was stated that Oxford Factor VIII had a pool size of 500 donations whereas Elstree Factor VIII had a pool size of 3,500 donations. Dr. Craske proposed a prospective study of the incidence of acute and chronic hepatitis in haemophiliacs as a result of first exposure to Factor VIII concentrate or cryoprecipitate. It was also noted that it would not be possible to undertake an evaluation of the hepatitis B vaccine for at least another year due to problems with obtaining trial certificates for the UK. Dr. Smith produced a short memorandum following his attendance at the meeting (document no. 1089) dated 4th September. There is reference in the third paragraph to Dr. Craske asking whether BPL had measured anti-HBsAg in Factor VIII which he thought might have some protective effect. The note states that he might propose to BPL that they look at some series of batches

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including those suspected of producing hepatitis B in 1978. **[Dr Lane will locate Dr. Tedder's paper: Dr Tedder found some information suggesting that antibody had been found in preparations transmitting hepatitis B [P18]]**

506. The subject of the BPL RIA test came up again at the Scientific and Technical Committee meeting which took place on the 17th September 1980 (document no. 1101). I advised members that the BPL radioimmunoassay test was in routine use at Elstree and at some Regional Transfusion Centres. There was increasing interest in the test and other RTCs had indicated a willingness to pay the cost - approximately 3p. to 4p. a test by that time - for the BPL RIA test. Evaluation reports had encouraged us to proceed with the development of the test for general supply purposes, but Burroughs Wellcome had now claimed that BPL would be engaging in unfair trading practice and that this would be prejudicial to their own RIA test. This had resulted in uncertainty over the future development and supply of the test. Dr. Walford from the DOH explained that a strong case for supporting the BPL test had been presented to the Department but consideration of the need for private industry to demonstrate a healthy home market in order to inspire interest and confidence in its product abroad had significantly influenced the decision to review production and supply of the BPL test. This decision had been taken at the highest level. Members were strongly opposed to the idea of medical considerations being disregarded in favour of what seemed political ones and the meeting considered the position as it was in relation to the BPL RIA test in more detail. The following points were noted:-

"(i) BPL had sufficient raw material available to permit production of reagents for 200 million RIA tests in the future".

"(ii) BPL's yearly output [of **therapeutic products**] is equivalent to a financial costing of £40-45 million, and therefore for all practical

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purposes it should be possible to consider BPL as an established industry. It was suggested that this point should be put before Ministers for consideration.

"(iii) Regions would not simply be able to select the BPL RIA test as a "best buy", because departmental involvement with North West Thames Regional Health Authority in respect of the Blood Product Laboratory means that decisions taken centrally would influence the supply situation of the test.

"(iv) Although the PHLS has, in the past, enjoyed freedom in the practice of giving reagents away, free of cost, this would probably not continue to be the case in respect of diagnostic products and no parallel can therefore be properly drawn when considering the BPL RIA tests.

"(v) Burroughs Wellcome had been offered the opportunity to develop the RIA test some 7-10 years ago, but did not respond to the offer. BPL undertook the activity and has successfully overcome all the difficulties and problems encountered during the developments of the test. BPL had established a test now in use and it was unfair that its test should be suspended in favour of BW.

"(vi) It was a matter of concern that suppression of the BPL test would in the event of any subsequent failure of the BW venture, result in total dependence on the Ausria test; and that a loss of NHS expertise would mean that the future of the test would lie completely in the hands of industry. The Committee was unanimous in expressing strong disapproval of, and great concern about, the

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decision to place an "injunction" on Dr. Lane - (BPL) preventing the development and future supply of the BPL RIA test for use in the NHS".

507. BPL serological reagents for the RIA test were obtained as a gift from G.D. Searle.

508. The "Ausria" test referred to was the US supplied commercial test which, until BPL developed their own test, we were obliged to use and which had also been in use at certain Regional Transfusion Centres. Eventually after considerable vacillation, we were allowed to supply RIA tests to Regional Transfusion Centres notwithstanding the considerable pressure which I believe was brought to bear by Burroughs Wellcome on the DOH.

509. The minutes [not in this copy] are also interesting because they make reference to a DOH decision, in the light of numerous requests to the Department for advice on diverse problems regarding viral hepatitis B and Non-A Non-B - to set up a body to be called the Hepatitis Advisory Group which was to meet for the first time in October 1980. The DOH envisaged that the main Committee would depend on a sub-committee to advise it on technical aspects of tests for viral hepatitis. The terms of reference of the Hepatitis Advisory Group were "to provide medical advice to the Chief Medical Officers of the Health Departments of the United Kingdom on all aspects of communicable hepatitis". I became a member of the Hepatitis Advisory Group.

510. On the subject of pool size, which became something of a focus of attention in the coming months, I sent a memorandum to Dr. Smith on the 29th September (document no. 1103) indicating that I could see no reason why the limit

on donations per batch of product should not be lifted to enable 900-1,000kg of some types of plasma to be processed. I mentioned:-

> "In connection with the risk of transmission of hepatitis, I am sure that once one has exceeded the 100-200kg pool size, one has already exceeded any possibility of small pool protection. I have discussed this with John Craske recently and he agrees exactly on this point."

511. The conclusion was based on the belief that the Non-A Non-B virus carrier rate in donors approximated to 1%, and that 100kg of plasma would comprise inputs from a minimum of 200 donors.

512. From a fractionator's point of view, it is, in any event, necessary to pool plasma to manufacture concentrate and there are several reasons why large pools are preferable to small ones from a manufacturing standpoint. The most obvious is the economy of scale which this brings to the production process. Second, very small pools do not provide enough product for severe haemophiliacs who would very quickly exhaust Factor VIII or Factor IX concentrate produced in such a way, requiring product from another pool thereby defeating the object of a small pool approach. Thirdly, the administrative aspects of establishing and running small pools on any scale would be quite disproportionate to the amount of product such methods could produce. Fourthly, large pools have the effect of producing a more standardised (and more predictable) product in terms of quality. By way of explanation of this point, we found enormous variations in the Factor VIII content of plasma provided to us by different Regional Transfusion Centres and the pooling process itself eliminated these peaks and troughs which would otherwise have complicated the manufacturing process.

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513. At Appendix 11 I list the correspondence, product labels and decisions relating to pool size of Factors VIII and IX during the relevant period.

514. The 11th meeting of the UK Haemophilia Centre Directors was held on the 30th September 1980 (document no. 1105) and Dr. Smith attended in my place at the meeting. Dr. Craske as Chairman of the Hepatitis Working Party reported on the Party's activities and presented a short written report (document no. 1104) chiefly comprising statistics gathered during the previous year. It was noted that the hepatitis B vaccine was still unlicensed for use in the United Kingdom but was under trial in the United States. The minutes state at page 9:-

> "The Working Party planned to continue with the National Surveillance for hepatitis and symptomless cases of hepatitis were being studied in detail at the Royal Free and at Oxford. Large pool concentrates appeared to give a higher risk of hepatitis than small pooled concentrates and Dr. Craske felt that increased usage of small pooled concentrates would help to reduce the incidence of hepatitis in the haemophilic population. First time exposure to large pooled Factor VIII concentrate resulted in many cases of hepatitis, especially in Von Willebrand's disease patients. Professor Bloom wondered whether cryoprecipitate would be a better product to use for mild haemophiliacs and Von Willebrand's disease but pointed out that there was a problem over the amount of Factor VIII in these materials. Dr. Craske agreed and he said that 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. Screening procedures used for donors of plasma used to make 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".

515. Dr. Smith sent me a memorandum on the meeting on the 15th October 1980 (document no. 1116). With regard to the Hepatitis Working Party report he commented:-

"Dr. Craske presented his report (attached). Although tables three and four do not really show it, he interpreted small differences in the incidence of Non-B hepatitis from BPL concentrate, PFL concentrate and cryoprecipitate to support the use of small plasma pools. Tables 3, 4 and 5 appear to me to offer ammunition against importation of US plasma or its product, but objections can be made to any of these comparisons on such grounds as (a) we do not know if all products are being used in the same way (b) most haemophiliacs show signs of having been exposed to hepatitis B at some time and (c) UK patients may get a lot of Non-B hepatitis from US products, but they may already have been exposed to UK type Non-B from UK products. I would have thought that one attack is better than two."

516. The formal announcement of the establishment of the Hepatitis Advisory Group can be seen from document JMCCL(80)5 in October 1980 (document no. 1118).

517. In November 1980, Dr. Smith wrote to Dr. Craske (17th November- document no. 1130) picking up on the comment on pool sizes which appeared in the minutes of the Haemophilia Centre Directors' Hepatitis Working Party meeting on 3rd September, the minutes of which Dr. Smith had obviously only recently received. He said:-

"I feel I must comment on item (c). Although for the last few years the typical pool size for Oxford batches was of the order of 500 donations, the stated limit has been 3,500 donations and on occasions batches up to about 1,500 donations have been released. PFL have responded to an increased demand for Factor VIII concentrate and introduction of Wessex plasma by producing larger batches, and during 1980 it has become quite common to pool products of at least 1,500 donations; the economy of product and effort is quite significant. I am sorry if I did not make this absolutely clear at the Oxford or Glasgow meetings....."

I am by no means convinced that the most recent data show a significant gradient in infectivity from cryoprecipitate through Oxford concentrate to BPL concentrate and I fear that current pooling policy will make it even more difficult to discern differences."

518. Dr. Craske replied on the 12th December 1980 (document no. 1146). He thought that it would be a good idea to explore the possibility of a correlation of batch sizes of Oxford Factor VIII in the presence, or absence, of abnormal liver function tests in recipients of these batches (i.e. whether they had hepatitis Non-A Non-B or not as a consequence of being treated with smaller pool batches). A little later, as I describe below, the so called small pool trial which started rather promisingly ended with the conclusion that small pools offered no real protection to those treated with the concentrate derived from them against hepatitis Non-A Non-B.

519. At the 8th meeting of the Haemophilia Centre Directors' Hepatitis Working Party held on 15th December 1980 (document no. 1148) the results of the

three year surveillance of UK Haemophilia Centres was presented. The results showed that:-

- The cumulative attack rate of all types of hepatitis was still about 5% per year.

- A few cases of hepatitis B still occurred.

- There was firm evidence that transfusion of commercial Factor VIII concentrate was associated with a four to ten times higher risk of overt Non-A Non-B hepatitis.

520. Dr. Craske noted that:-

"There is as yet no firm evidence about the relative risk of symptomless hepatitis associated with different products.

- There might be a lower risk of transfusion hepatitis associated with batches of NHS Oxford Factor VIII concentrate compared with NHS Elstree Factor VIII concentrate.

- It was proposed that a research application to carry out a prospective study of acute and chronic hepatitis associated with the use of different brands of Factor VIII and IX concentrate at Oxford would be submitted to the DOH."

521. Dr. Kernoff said that the experience of the Royal Free Hospital was that nearly every batch of commercial Factor VIII concentrate was contaminated with Non-A Non-B hepatitis viruses.

522. It is important to note that Dr. Craske, in talking about the higher percentage risk associated with commercial Factor VIII concentrate is talking about overt hepatitis (most of it Non-A Non-B by this time). As I have previously said, commercial concentrate produced more overt, and therefore apparently more aggressive Non-A Non-B hepatitis (ie icteric). In contrast, UK concentrate gave recipients asymptomatic Non-A Non-B hepatitis detectable only by tests for liver dysfunction.

523. Over the next few years the clinical diagnosis of Non-A Non-B hepatitis increased in haemophiliacs treated with concentrate (of whatever source) and experience showed an incidence of infection close to 100% in susceptible patients. The observation applied equally to concentrates made from 100 litre pools and the larger BPL pools of 1,000 plus litres. Although undated, Dr. Craske's second project report to the DOH on the epidemiology and chronic sequelae of Factor VIII and IX associated hepatitis in the UK was produced some time after September 1980. Dr. Craske comments on page 5 that 85% to 90% of the patients with severe Factor VIII or Factor IX deficiency had antibodies to hepatitis B virus and were therefore immune from infection. He goes on to say (on page 6) that:-

> "It is the opinion of the Working Party that the risk of acquiring non-B hepatitis (overt or symptomless) after first transfusions of Factor VIII concentrate (NHS Elstree or US commercial) is 90-100% patient transfused".

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524. During the latter part of 1980 a decision had finally been made to allow BPL to market its RIA test alongside (and in competition with) the Burroughs-Wellcome test. At the 8th meeting of the Scientific and Technical Committee held on the 3rd December 1980 (document no. 1187) it was noted that the DHSS had agreed that, with effect from 1st March 1981 or earlier, (depending on whether the Burroughs-Wellcome test and equipment were ready), BPL would be allowed to market its RIA test to Regional Transfusion Centres at a cost of 20p. per test.

525. This issue was picked up again at the 10th meeting of the JMC held on the 6th February 1981 (document no 1198) and Dr. Walford of the DOH confirmed what had been announced back in December to the Scientific and Technical Committee. However, at the second meeting of the Advisory Committee on the National Blood Transfusion Service held on 23rd February 1981 (document no. 1217) many members felt that it was wrong to levy a charge of 20p for BPL's RIA test when the actual cost could well be less than this (and indeed it was). I believe its introduction at all Regional Transfusion Centres was delayed by non-essential commercial considerations.

526. In February an article was published in Medical Laboratory Sciences by Angela Dike of the Blood Transfusion Centre at the John Radcliffe Hospital Oxford, entitled "Post-transfusion hepatitis B transmitted by HBsAg negative blood containing anti-HBs" (document no 1220). The author noted:-

- Hepatitis B surface antigen testing had reduced but not abolished the incidence of post-transfusion hepatitis B.

- Cases had been reported of post-transfusion Hepatitis B where donors were HBsAg negative by RIA.

- At the Oxford Regional Transfusion Centre all donations had been tested for HBsAg by RIA since February 1979.

- Of approximately 110,000 donations negative by RIA only 1 donor had been shown to be a transmitter of hepatitis B infection and this did not at present seem to be sufficient justification for screening all donor blood for hepatitis B core antibody.

527. The article provides evidence of the diminution in incidence of hepatitis B but in the same month on 13th February 1981 (document no. 1207), I circulated a memorandum concerning the availability of DOH funds for research and development for appropriate and supported projects. A proposal dated 27th February (document no. 1221) was prepared with the project title:-

"The development of methods for the production of coagulation factor concentrates with reduced risk of hepatitis transmission" .

528. The first paragraph in the proposal reads:-

"Recent improvements in methods for the detection of hepatitis B surface antigen (HBsAg) have dramatically reduced the incidence of hepatitis B in patients receiving Factor VIII and Factor IX concentrates (Craske 1980). This change has also highlighted the importance of Non-A Non-B hepatitis as an undesirable side-effect of transfusion of blood and blood products. Although there is some evidence that the risk of transmitting Non-A Non-B hepatitis is greater for imported blood products (Craske 1980), the

incidence of Non-A Non-B hepatitis following infusion of NHS concentrates is still a cause for concern."

The proposal concludes:

"The significance of a product demonstrably free of hepatitis risk cannot be ignored and it is essential that BPL/PFL be well placed to take advantage of such developments. Since this particular development work involves the handling of large quantities of plasma known to be infective, a choice of a location for the work is important. Clearly the work would have to be sited outside the regular production area".

529. The proposal was one of those which were reviewed at the 9th meeting of the Scientific and Technical Committee which took place on the 4th March 1981 (document no. 1229). The project is listed along with five others at paragraph 12 in the minutes and it will be seen from paragraph 13 that during the course of discussion it was pointed out that there were risks attached to some of the projects (hepatitis in particular was singled out) and that not many institutions were in a position to provide appropriate working conditions. I alluded to the possibility of using the old Lister laboratories if converted for research and development and said that a quantity surveyor had been asked to look at the cost of converting the buildings. The meeting agreed that I should formally forward my proposals for research with details of their likely cost. Where appropriate the DOH could then approach the office of the Chief Scientist to consider funding. No additional capital was forthcoming.

530. An article appeared in March 1981 in Medical Laboratory Sciences entitled "Hepatitis of the Non-A Non-B type following blood transfusion in the North London Region" (document no 1231). The authors were a Dr. Barbara and

Dr. Briggs. The paper sets out the results of studies of the incidence of post-transfusion hepatitis of the Non-A Non-B variety in the regions served by the North London Blood Transfusion Centre. The paper reports that in an American survey 90% of post-transfusion hepatitis cases were of the Non-A Non-B type. It also commented that there seemed to be a higher incidence of post-transfusion hepatitis generally in the USA than in the UK. The paper also touches on the types of tests used at the Centre between 1970 and 1980. The earliest test in use up to 1972 appears to have been immunodiffusion. In 1972 EIOP was introduced (electro-immuno-osmophoresis); towards the end of 1973 the RPHA test was introduced (reverse passive haemaglutination) and at about the same time RIA (radioimmunoassay testing) for certain cases.

531. Also in March an article of mine was published in the Medical Laboratory Sciences entitled "Hepatitis B surface antigen testing: The Blood Products Laboratory Radioimmunoassay (BPL/RIA) system" (document no 1240). The purpose of the article was to bring to everyone's attention the fact that we had developed, in-house, a radioimmunoassay kit for the detection of hepatitis B surface antigen which was inexpensive and had a sensitivity at least equal to that of the best commercial preparations.

532. In the introduction I said:-

> "During the last decade the English National Blood Transfusion Service (NBTS) has introduced hepatitis testing in a heterogeneous manner. By 1978 most centres were using haemaglutination (HA) for the detection of hepatitis B surface antigen (HBsAg), either in a conventional manner or with an in-house modification of a commercial kit: only three centres were using radioimmunoassay (RIA). In the North London Blood Transfusion Centre (NLBTC) it was shown that in general terms 1 in 600

positive reactions accrued when testing new blood donors, whilst with regular donors the incidence lengthened to 1 in 12,000 or more. Using RIA on the regular donors was not expected to turn up a positive test missed by haemaglutination more than, perhaps once in 5 to 10 years. In other centres the sensitivity of haemaglutination varied considerably as judged from data collected at the Blood Products Laboratory (BPL) after testing 51 pools of donor plasma.

"The pooling of plasma has always caused concern at the BPL since the single plasma donation negative by HA at the 20ng/ml level would probably be missed by RIA when pooled with 25 other donations. Without doubt, HBsAg has been missed in the past for this reason, and positive donations incorporated into pools for fractionation.

"Reference to pooling for fractionation is mainly in connection with Factor VIII but Factor IX and immunoglobulin preparations (prepared by methods alternative to existing cold-ethanol fractionation) 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 5,000 donations (1,000kg) from the normal blood donor programme the need for sensitive surveillance of hepatitis markers is obvious.

"With the decision to discontinue pooling of plasma in the Regional Transfusion Centres the opportunity presented itself to test all plasma donations by RIA, and particularly those to be used for coagulation factor production. Initially an RIA test was to be performed at the BPL on each single donation, but it was considered that if a more sensitive test was to be employed then the recipient of the cellular elements of

blood donation should benefit equally with the recipients of plasma products from the added assurance provided by the extra sensitivity of RIA over HA. In 1978 one practical matter was contrary to this approach: the high cost of conversion to commercial RIA throughout the NBTS. The BPL then decided to prepare its own RIA test, to be available (if desired) for general distribution throughout the NBTS."

533. The removal of viruses from blood products was an item on the agenda for the second meeting of the Working Party on Post-Transfusion Hepatitis to be held on the 25th June 1981 (minutes - document no. 1325 (incomplete)). At the meeting Professor Zuckerman presented a report on the identification of agents carrying Non-A Non-B hepatitis. He noted that there was evidence of two types of Non-A Non-B hepatitis associated with the transfusion of blood and blood products. One type, with a short incubation period (7-70 days) was usually associated with 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 in the minutes are missing from the file: <u>important</u> we need paragraph 4.3 "removal of viruses from blood products" [P20]]**. I was present for the meeting of the Working Party by invitation and was again present at the meeting of the Blood Transfusion Research Committee which was held on the same day (I was a member of this Committee) (document no. 1326) which also touched on hepatitis. As the minutes show (from bottom of page 2) Dr. Gunson outlined the role of the Hepatitis Working Party and noted:-

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

534. It was agreed that there was at present:-

> "No need to screen potential blood donors for Non-A Non-B hepatitis **[by ALT or by hepatitis B care antibody i.e. surrogate]** but the production of a vaccine would be awaited with interest...."

535. In retrospect this now looks rather an odd comment. At the time the virus(es) had not been identified (and in a sense this still remains the case). Today there is still no vaccine available and the HCV test developed for one of the Non-A Non-B hepatitis viruses (hepatitis C) is only just becoming commercially available.

536. On the 30th June 1981 Dr. Craske sent me a paper (document no 1330) entitled "Reducing the risk of hepatitis B associated with antihaemophilic factor and Factor IX complex". In the first paragraph of the abstract, the presence of anti-HBs (antibody to the hepatitis B surface antigen) in antihaemophilic factor (in other words Factor VIII) was 100% in 1979. This was a reflection of pool size. It reflected that the incidence of hepatitis B immunity in the donor population varies, but it is higher than the virus carrier rate (with Hepatitis A in certain metropolitan areas, e.g. Glasgow, the antibody incidence is more than 60% in adults). 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). A large excess antibody to hepatitis B surface antigen (anti-HBs) when added to Factor IX has been shown to completely neutralise infectious HBV. Recent data ... indicate that anti-HBs is normally present in many AHF and Factor IX lots".

The presence of anti-HBs does not assist in the prediction of the occurrence of Non-A Non-B infectivity. (The donor incidence of HCV antibody is 0.5 to 1.0%).

537. In August 1981 the Medical Research Council reported on the incidence of Non-A Non-B hepatitis in the United Kingdom (document no. 1350). The report is not confined to the incidence of hepatitis following treatment with blood or blood products. Amongst the cases in the study 3% of cases of Non-A Non-B hepatitis died between 3 to 5 weeks after the onset of illness. This contrasted to the number of deaths attributable to hepatitis A which was 0.5% of those infected. The report concluded that further study of the relationship of Non-A Non-B hepatitis to blood and blood product related disease and chronic hepatitis was required.

538. The Medical Research Council report did not study the chronic morbidity (or chronic sequelae) of the disease: it merely studied the acute episode. Plasma samples had been collected for the study and it was planned to do a prospective study of Non-A Non-B hepatitis virus contained in blood, to evaluate the results of the study already undertaken. The Medical Research Council, however, lost the blood samples and a repeat study was considered too expensive.

539. Also in August Messrs. Gabra Crawford & Mitchell in a letter (document no 1355) to the British Medical Journal entitled "Post-transfusion hepatitis" advocated the use of small pool products such as dried cryoprecipitate whenever possible until such time as a reliable test for the markers of Non-A Non-B hepatitis became available. This suggestion however was right outside mainstream opinion.

540. At the UK Haemophilia Centre Directors' Hepatitis Working Party meeting held on 11th September 1981 (document no. 1369), Dr. Craske presented some

preliminary data as a result of the four year surveillance of Factor VIII and Factor IX associated hepatitis. He noted:-

- The cumulative attack rate had stabilised at 5% per annum.

- Three infectious agents were involved; hepatitis B and two types of Non-A Non-B hepatitis.

- Hepatitis B still occurred, but at a reduced level.

- There had so far been no evidence of any change in the risk of contracting Non-A Non-B hepatitis after first exposure to Factor VIII or Factor IX concentrate.

- There was evidence that US commercial Factor VIII had a 4-20 times greater incidence of symptomatic Non-A Non-B hepatitis in patients treated with one product in any treatment year compared with NHS concentrate.

It should be noted however that NHS Non-A Non-B hepatitis was asymptomatic.

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

542. Dr. Craske prepared a further paper in October 1981 entitled "Haemophilia Centre Directors' Hepatitis Working Party Report for the year 1980/81" (document no 1396) which it is useful to review. The report noted that:-

- 283 episodes of hepatitis had been reported of which 197 were Non-B hepatitis and were therefore probably Non-A Non-B. In effect diagnosis was to a large extent by exclusion i.e. if the patient tested negative for hepatitis B but still had the signs of hepatitis infection then the likelihood was that the patient was suffering from hepatitis Non-A Non-B.

- There was a 4-20 times higher incidence of overt Non-A Non-B hepatitis associated with US commercial concentrate compared with NHS concentrate.

- 70-80% of cases of Non-A Non-B hepatitis were associated with the first dose of concentrate that the patient received and that most patients treated with any batch of concentrate would be immune to Non-A Non-B hepatitis since batches of concentrate of any brand were contaminated with one or more sero types of these agents.

- Hepatitis B was still present at a low level but donor screening appeared to have eliminated any difference between commercial and NHS concentrate in this respect.

- Merck, Sharpe & Doehme had approached the Working Party with a view to carrying out a trial of their hepatitis B vaccine in the UK and that discussions were proceeding with a view to carrying out a limited trial.

543. For the reasons I have indicated above i.e. the more symptomatic nature of the US type of Non-A Non-B hepatitis, it was misleading to draw any conclusions from the statement that US commercial concentrate appeared to have a 4-20 times higher incidence of overt Non-A Non-B hepatitis. This was true but the NHS concentrate appeared to contain a different type of Non-A Non-B hepatitis the long term effects of which were identical to its American counterparts. The state of any immune protection conferred on a patient following infection by NANB hepatitis from US or NHS concentrate remained unknown, although current research based on HCV virus already suggests that more than 1 serotype is likely to exist, as is cross-reacting serological behaviour. Research on the genomic structure of HCV within research Centres and research Centres has already identified differences in structure which may represent simple mutant variability within one virus type or may be so significant as to define a major variant or different virus strain (e.g. HTLVI and HTLVII). The immune response to closely related viruses or to major variant types may show common structural which will be represented as cross-reacting antibodies. However, the status of immune protection in patients with NANB hepatitis remains unconfirmed.

544. The delay which occurred in relation to the introduction of the hepatitis B vaccine was in fact due to the emergence of HIV. Donors supplying the hepatitis B infected plasma, which sourced the virus or vaccine preparation, were also in a high risk donor category for HIV and AIDS. There was concern that the vaccine prepared from their blood might be contaminated with HIV. Subsequently, this was shown not to be so, but intercurrent investigations on safety brought about a delay in vaccine use.

545. With regard to the tables which appear immediately behind Dr. Craske's paper I would only reiterate that until a proper awareness of the extent of sub-clinical Non-A Non-B hepatitis emerged, interpretation of the data would be misleading.

546. At the Scientific and Technical Committee meeting which took place on the 24th November (document no. 1436), Dr. Smith of BPL gave a short address on the subject of inactivation of hepatitis in BPL products which is summarised in Annex A. From Annex A, Dr. Smith noted that the risk of hepatitis might also be diminished by:-

- More specific and sensitive screening of blood donations intended for fractionation.

- Limiting the size of plasma pools for recovery of certain products.

- Neutralisation or absorbtion of virus with an excess of hepatitis antibody.

- Vaccination of recipients.

- The selective removal of viruses during fractionation, e.g. by precipitation with PEG.

- Inactivation of virus e.g. with B propiolactone or by heating in the presence of reagents preserving the biological activities of plasma proteins.

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547. I comment further on Dr Smith's comments in the section of my proof dealing with heat-treatment, below.

548. During the year (unfortunately the document is undated) Dr. McClelland, Regional Transfusion Director Edinburgh prepared a preliminary draft of proposals for a prospective study of post-transfusion hepatitis in the UK which, I recollect, was produced as part of a discussion between Dr. McClelland and the MRC with regard to funding research in this area. I do not believe that the research as set out in the proposals was ultimately funded.

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549. In January Dr. Smith sent a memorandum (document no 1463) to me seeking consent to increase the pool size for Factors VIII and IX to the equivalent of 7,500 donations per pool, intending to make optimum use of our freeze-drying plant and the manufacturing process. Consent was given and PFL and BPL labels and quality control documentation suitably altered.

550. On the 5th March (document no. 1486), I wrote to Dr. Wagstaff at the Regional Transfusion Centre in Sheffield following up on the suggestion put to him 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 question of post-transfusion hepatitis and to have, as part of their brief, the compilation of statistics regarding hepatitis Non-A Non-B infection in the United Kingdom. In my reply to what was actually a circular letter to Regional Transfusion Directors in England and Wales on the part of Dr. Wagstaff, I supported the idea of a combined Working Party, particularly in the light of the anticipated demise of the MRC Post-Transfusion Hepatitis Committee which, at the 3rd meeting of the MRC Blood Transfusion Research Committee held on the 8th March, was disbanded (document no. 1488). The composition of the Working Party was agreed by the Regional Transfusion Directors at the 185th meeting held on the 10th May which I attended. I was one of those asked to become a member of the new Working Party.

551. By this time, as I noted in the Annual Report dated 20th April covering the period 1981/82 for BPL and PFL (document no. 1500), RIA tests developed by BPL had been produced and supplied to all UK Transfusion Centres. I noted, at page 5, that 35,711 routine tests for HBsAg had been carried out on plasma pools and products at BPL with 16 positive results. Of the 16 positive tests, 14 samples

which proved positive came from plasma which had been supplied in 5 litre bags, supporting the proposals for their phasing out. A positive test in a 5 litre pool reflected poor mixing of contents and/or a technical failure at the RTC to exclude a strong positive donation.

552. Mr. Ayling, of the Medicines Inspectorate, in his report on his visit to BPL on the 10th June (document no. 1516) noted that two batches of products had been rejected for hepatitis B. He commented that the test on the plasma donation carried out by the Regional Transfusion Centre (an RPHA test at the time) had failed to detect HBsAg but that RPHA had now been replaced by the more sensitive RIA test. Further, the sample from the 5 litre plasma pack did not test positive at BPL, but the index donation was diluted 1 in 25 in the 5 litre pool. Mr. Ayling questioned the usefulness of such sample testing and felt that this was yet another reason for speeding up the introduction of the single donor pack. There were further incidents where plasma with HBsAg was detected at BPL having previously been tested and passed at Regional Transfusion Centres: visits to Regional Transfusion Centres made by BPL staff examined ways in which the assurance of plasma RIA testing at Regional Transfusion Centres could be improved. (See for example the report on Dr. Snape's visit to Liverpool Regional Transfusion Centre on the 13th July (document no. 1529) and the report on the visit to the Sheffield Regional Transfusion Centre dated 19th August (document no. 1540)).

553. By the end of August the Hepatitis Working Party had not met for some six months. Dr. Craske had written to me on the 3rd August (document no. 1537) indicating that he had deliberately not called a meeting since last year because there was little further fresh information which required consideration. However, he proposed calling a meeting of the Working Party to briefly review the results of recent surveys and to consider any proposals for further work. He

commented that the study of hepatitis B vaccine in Oxford was about to start but the prospective study of Factor VIII and Factor IX hepatitis had been refused a grant by the MRC earlier in the year. He mentioned that he had managed to carry on with a feasibility study at Oxford using funds from the local Haemophilia Society and a grant from commercial sources.

554. He went on to say that, at present, he was approaching Action Research for the Crippled Child to see whether it would be possible to get a grant so that the full project could be started some time during the following year. He proposed that the meeting of the Hepatitis Working Party would be held on the 13th September, after the Haemophilia Centre Directors' meeting on the same day.

555. At the meeting of the Haemophilia Centre Directors on 13th September 1982 (see the minutes - document no. 1549), Dr. Craske alluded, at page 10, to the fact that a preliminary study of hepatitis in mildly affected or seldom treated haemophiliac patients in Oxford had provided interesting data and the results of this study were currently being prepared for publication. He suggested that the advantage of the hepatitis-reduced risk products which might soon be available (he had in mind the heat treated commercial products just emerging at this time) should be evaluated along similar lines to the study which had been conducted in Oxford on the seldom-treated patients. He confirmed that the hepatitis B vaccine had been licensed in the United Kingdom in May 1982. The DHSS had decided not to purchase any vaccine centrally owing to the high cost and each region had to find the funds from existing budgets to purchase supplies. The vaccine would be available at the end of September and the DHSS had drawn up a list of priority patients who should be offered the vaccine. A trial was to be conducted in Oxford.

556. Interestingly we see in the minutes, also at page 10, an early reference to Acquired Immune Deficiency Syndrome. The Haemophilia Reference Centre Directors had asked Dr. Craske to look into the report from the United States that this syndrome, whilst mainly found in homosexuals, had apparently affected three haemophiliacs. The minutes record:-

> "It appeared that there was a remote possibility that commercial blood products had been involved".

557. It was confirmed that the Working Party was considering the implications of the reports from the USA. I deal with the chronology of the AIDS problem in greater detail below.

558. At the Haemophilia Centre Directors' Hepatitis Working Party's meeting later in the day (13th September 1982) (see the minutes - document no. 1548), Dr. Craske gave more detail on the study being carried out at Oxford. He said that 32 patients had been enroled in the study, and 28 of these had been followed for a period of at least 6 months. They were all patients with mild coagulation defects who had less than two infusions of Factor VIII or Factor IX concentrate during the previous year. Nine out of nine patients treated with one batch of concentrate who had no previous transfusions of Factor VIII or Factor 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 pool sizes of the batches of NHS concentrate administered varied between 1,436 to 2,504 plasma donations. The work implied that there was more than a 90% chance of contracting Non-A Non-B hepatitis after first treatment with NHS or US commercial Factor VIII concentrate. No cases of hepatitis B had occurred.

559. Here we see the foundation for the conclusion (later confirmed) that US and UK Factor VIII and Factor IX concentrates were equally infective so far as hepatitis Non-A Non-B was concerned, the only variation between the two being that NHS concentrates resulted mainly in asymptomatic infection.

560. The minutes also record, at page 5, under the heading "Acquired Immune Deficiency Syndrome (AIDS)":-

> "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 here one of the earliest references to AIDS.

561. On the 17th September 1982 Dr. Craske wrote to Dr. Gunson (document no. 1552) regarding the forthcoming meeting of the NBTS Working Party on Post-transfusion Hepatitis to take place on the 27th September 1982. Aside from attempting to define 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 he said might have implications for the Blood Transfusion Service.

562. As can be seen from the minutes of the meeting on the 27th September 1982 (document no. 1555) (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 could be applied to other infections where applicable. In short therefore, despite the name of the Working Party, there was an agreement that it would keep AIDS under review.

563. At about the same time a draft paper was circulated 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 (document no 1557). The paper essentially identifies the complexity of the investigation into Non-A Non-B hepatitis virus and in particular the problems raised by the absence of any specific marker for the virus.

564. Small pool production, whilst not featuring to any great extent in discussions at around this time, was raised by Dr. Smith of BPL on the 27th October 1982 in a paper which he prepared entitled "Strategy for small-pool cryoprecipitate production in new BPL" (document no. 1562). 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 Non-A Non-B. 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...."

565. Some facilities for small pool production were planned in the re-development of BPL but the space allocated for them was not utilised since, by

the time the new facility was commissioned, heat treated high purity 8Y had replaced the small pool option.

566. On the 16th October 1982 Dr. Craske wrote to me (document no. 1564) reporting that he thought it likely there would be sufficient patients enroled to make the trial observation for the incidence of hepatitis Non-A Non-B 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 small pools of plasma from plasmapheresis donors. This became known as the Oxford small pool experiment.

567. The last document to make specific reference to in this year is the "Third annual report on project number J/S240/78/S - preliminary results" which was a document produced by Dr. Craske (document no. 1587). Its precise date is unclear but it covers the period from 1st January 1980 to 1st January 1982. It is in fact the third report by Dr. Craske on the DOH sponsored research study into the epidemiology and chronic sequelae of Factor VIII and IX associated hepatitis in the UK. The report noted that table 6 of the second report (published in 1980) suggested that hepatitis Non-A Non-B associated with NHS Factor VIII had a considerably lower attack rate than that associated with commercial Factor VIII. Dr. Craske stated that preliminary results of a prospective survey had failed to confirm this (he was referring to the Oxford survey) and that it was possible that the previously reported lower attack rate associated with NHS concentrate might be due in part to the fact that a higher proportion of Non-A Non-B hepatitis cases associated with NHS Factor VIII might be sub-clinical compared to those associated with US commercial concentrates. The preliminary results suggested that there was a 90% chance of contracting Non-A Non-B hepatitis when first infused with either NHS or commercial concentrates.

568. Again we see confirmation that hepatitis Non-A Non-B occurred with equal frequency after infusion of US or NHS concentrates.

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1983

569. Concentrating on developments with regard to hepatitis one may perhaps get a somewhat false impression of the level of activity during the year. In truth the issue of Non-A Non-B hepatitis and what was to be done to our products to deal with it expeditiously, was merged with the HIV issue giving impetus to both ourselves and commercial fractionators in connection with research into virus inactivation.

570. Dr. McClelland's outline proposal for a prospective study of Non-A Non-B hepatitis associated with the transfusion of blood products (document no 1596) was circulated at the second meeting of the UK Working Party on Transfusion Associated Hepatitis held on the 18th January 1983. However, by the time the third meeting of the Working Party was held on the 20th April 1983 (document no. 1628) it was noted that no source of funding had been found for the proposal.

571. At the same meeting Dr. Craske reported on the hepatitis surveillance in 30 Oxford haemophiliacs and repeated his finding that of the 9 patients who had not previously received concentrate, all 9 developed Non-A Non-B hepatitis.

572. In a paper which was more directed towards AIDS than hepatitis ("AIDS, progress with heat treatment of human plasma products" 26th July 1983 document no. 1659). I commented that the severity of hepatitis Non-A Non-B in haemophiliacs might result from impaired immune responsiveness in these patients brought about by repeated infusions of protein concentrates. This had motivated plasma fractionation organisations to re-examine means whereby hepatitis virus could be inactivated in large pool concentrates without intercurrent denaturation (damage) to the proteins themselves. At the 12th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party held on the 14th September 1983

(document no 1667) Dr. Craske said that Non-A Non-B hepatitis followed treatment with NHS or commercial concentrates in all susceptible patients.

573. In the same minutes it is reported at page 2 that there were two cases of the AIDS syndrome in haemophilia A patients treated with commercial Factor VIII concentrate in the UK. This was the first Working Party documentation of AIDS in haemophiliacs in the UK. There is also reference to the implications for the hepatitis B vaccine which, as I have explained above, was believed might carry a risk of AIDS virus transmission.

574. The minutes of the CBLA Working Group on AIDS in relation to Blood Transfusion held on the 14th October 1983 (document no. 1684) contained reference to the "small pool" experiment which we had embarked upon at Oxford. At paragraph 3.2.1. of the minutes there is reference to my having outlined investigations with respect to the infectivity of Non-A Non-B hepatitis with the use of pools of plasma containing donations obtained by plasmapheresis. I commented that the preliminary results were encouraging. 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 transmitting hepatitis Non-A Non-B to the recipient. However, whilst the experiment began well, its progress was disappointing since attempts to minimise infectivity by using small pools on these patients were unsuccessful. 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 (plasmapheresis) 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 of blood products".

However with HIV and unlike NANBH the accreditation of the plasmapheresis donor would depend on a plasma marker as well as a donor history examination.

575. The Oxford small pool experiment is considered further below, and in greater detail in Dr. Smith's statement, to which I refer.

576. Dr. Craske presented a report on the work of the UK Haemophilia Centre Directors' Hepatitis Working Party to the 14th meeting of the Haemophilia Centre Directors which was held on the 17th October 1983 (see document no. 1691(a)). The report noted:-

- That the prospective study at Oxford showed that the risk of contracting NANB hepatitis was 100% on first exposure, whether NHS or commercial Factor VIII was used.

- That a protocol had been drawn up for the evaluation of the infectivity of heat treated Factor VIII since no (specific marker) tests for NANB hepatitis were available. The results of the study were actually published in the British Medical Journal on the 10th December (document no. 1698). The abstract quoted below confirms the 100% incidence but also touches on the high proportion of patients who might experience long term effects as a result of hepatitis Non-A Non-B infection:-

- 30 patients who had not previously received treatment with Factor VIII concentrate or who had been treated only infrequently with

Factor VIII concentrate were studied after a transfusion of Factor VIII. Tests of liver function were performed frequently. Four patients had evidence of chronic liver disease before transfusion. In 17 of the remaining 26 patients serum transaminase activities became raised and 10 patients developed jaundice. All of the nine patients who had not previously received Factor VIII transfusion developed Non-A Non-B hepatitis. 4 out of 12 patients followed up for a year had persisting abnormalities of liver function.

577. The pattern of illness suggested that more than one serotype of Non-A Non-B hepatitis virus may be transmitted by Factor VIII concentrate prepared by the National Health Service from volunteer donors in the United Kingdom.

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1984

578. These thoughts may be found in a memorandum from Dr. Smith to myself dated 3rd January 1984 (document no. 1712) in which Dr. Smith repeated that it was now common-place that virtually all patients receiving either commercial or NHS Factor VIII or IX for the first time would contract overt or sub-clinical infection with Non-A Non-B hepatitis. Although the incubation period and severity might differ, long term sequelae were equally feared. I also noted in my report to the CBLA dated 16th January 1984 (document no. 1716) that NHS Factor VIII and Factor IX concentrates continued to transmit hepatitis Non-A Non-B to susceptible patients (usually those receiving large pool concentrates for the first time).

579. At the third meeting of the Central Committee for Research and Development in Blood Transfusion which was held on the 28th February 1984 (see document no. 1732) I reported, at paragraph 4.2, on the Oxford small pool experiment which was being undertaken with Dr. Rizza on the use of Factor VIII which had been prepared from pools of plasma which had been obtained from the panel of plasmapheresis donors at Leeds. I commented that encouraging initial results had been obtained with 18 patients where the short-incubation Non-A Non-B hepatitis appeared to be absent whereas with Factor VIII obtained from plasma from randomly collected donations the attack rate was 100%. The implications for plasma supply of these results were confirmed and noted, and the need for Factor VIII derived from similar plasma obtained from other parts of the country was recognised.

580. On the 15th May 1984 in a document entitled "Patients who have received special batches of Factor VIII, updated 15.05.84" (document no 1769) further results were given confirming a significant incidence of transmission of short-

incubation Non-A Non-B hepatitis, but less than the predicted 100% incidence rate with large plasma pool product. In a letter dated 22nd June 1984 addressed to Dr. Delamore of the Department of Clinical Haematology at the Royal Infirmary in Manchester (document no 1783) Dr. Smith of BPL referred to the small pool experiment:-

> "The interim results from an Oxford Haemophilia Centre study of untreated concentrate from small panels (300-1200 donors) of regular Haemonetics (i.e. plasmapheresis) donors, mainly from Bradford, suggest that the infectivity of these batches for NANBH is already significantly diminished. One batch given to two patients did not appear to transmit hepatitis and two other batches have given less than the expected 90-100% attack rate. Batch performance is however, too variable to allow the Oxford experience to be seen as a control for the batches to be used in the proposed trial."

581. Reference to the "proposed trial" is to a proposal to heat treat residual product from implicated batches for clinical assessment using the existing database as the control.

582. Updated results were prepared on the 4th September 1984 (document no. 1805) of the special small pool batches prepared, it appeared that the initial favourable results suggesting non-transmission were in fact exceptional, and that a small pool approach to fractionation based on 100 litre pools was not an assured method of proceeding with planning for large scale fractionation.

583. In a paper entitled "Incidence of hepatitis in patients with congenital coagulation defects treated by UK Haemophilia Centres during 1980-83" (document no. 1810(d)), Drs. Craske and Spooner included some interesting statistics. The

document itself was one of a number of appendices to the annual Haemophilia Centre Directors' reports. In table 1, 258 patients, amounting to approximately 5.6% of those treated, developed acute hepatitis and by far the highest proportion of cases of hepatitis were of the Non-A Non-B variety.

584. On the 8th November 1984 Dr. Kernoff wrote to me (document no 1843) 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% incidence of transmission of Non-A Non-B hepatitis infection irrespective of the source of product. In the summary, the paper states:-

> "After a first exposure to Factor VIII concentrates, 9/9 British patients treated with US 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; one also contracting prolonged incubation hepatitis B."

585. As can be seen there is a reference to the apparent severity of infection with US commercial concentrate as compared with NHS concentrate.

586. In his memorandum to Dr. Harvey on the 12th November 1984 (document no. 1846) entitled "Options for heat treatment of coagulation factor concentrates" Dr. Smith reviewed the "intermediate" specific activity 8CRV made from restricted plasmapheresis pools. He observed that there was evidence of a reduction in transmission of Non-A Non-B hepatitis from about 100% to 50-60% in a pattern

suggesting that only one or two carrier donors may infect a pool of about 1000 donations. Dr. Smith noted however that the potential product from this method of manufacture was about 1m. iu per year. In this regard he was reflecting the difficulties of organising manufacture on a small pool basis which meant that this form of production could only really be used for patients requiring infrequent treatment.

587. The year closed with the publication of an article in the Lancet on the 22nd December 1984 entitled "Blood Transfusion, Haemophilia and AIDS" (document no. 1889). This is something of a landmark article and repays reading in full. However, aside from AIDS there is reference to the fact that in the UK unheated large pool concentrates, even those prepared from voluntary donations, had transmitted Non-A Non-B hepatitis and, in addition, that the first generation of commercially prepared heated concentrates had similarly transmitted the disease. (This latter point is touched on in rather more detail below).

588. By the start of 1984 experience of heat treatment as a virus inactivation procedure was gained with 8CRV at PFL. This product had been infused into three patients without untoward clinical effect and follow-up had not shown elevation of alanine aminotranspherase (ALT) levels indicative of NANB hepatitis transmission. These results were encouraging and attention was turned to application of this heat treatment procedure to the main production batches of intermediate concentrate (HL) manufactured at BPL. In November 1984 it was realised that HL would not tolerate heat treatment to the same extent as 8CRV, probably because of its higher content of fibrinogen. Heat treatment of HL resulted in variable and significant loss of Factor VIII activity in the finished product and the method was considered materially unsuitable for application to the main production process. Since by mid-1984 R&D had successfully prepared a high purity Factor VIII concentrate code-named "8Y" which had been shown by

November to tolerate extreme heat in the dry state without significant loss of potency, a decision was taken to halt further development on product formulation of HL to make it heat resistant, but to direct all resources behind acceleration of 8Y for earliest clinical evaluation and issue for clinical use.

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1985

589. From the stand point of product safety so far as hepatitis was concerned, 1985 saw accelerated development of heat treated high purity Factor 8Y with heat treatment of the intermediate concentrate HL as a stop-gap measure to provide the NHS with a safe product pending the issue of 8Y. After February 1st 1985 only heat treated Factor VIII concentrate was released by BPL. From April 1st 1985 initial issues of heat treated 8Y became available and only 8Y was issued after August of 1985. Heat treated Factor IX was issued by October 1985. Since their introduction there has been no confirmed report of hepatitis virus transmission or transmission of HIV from Factor 8Y or Factor 9A concentrates. After 5 years' clinical use the level of assurance of safety has developed to a credible level.

590. At a meeting of the Haemophilia Centre Directors' Hepatitis Working Party held on the 6th February 1985 (we do not have the minutes of the meeting, merely indirect evidence in the form of Dr. Snape's memorandum to me dated 7th February - document no. 1956), Dr. Preston presented strong evidence based on paired liver biopsy results with a time interval of five years between biopsies, of progression of haemophiliacs to increasingly severe forms of liver disease arguably attributable to repeated exposure to Non-A Non-B hepatitis virus. This concept of superinfection has not been confirmed. The data in question was to be presented at the Annual Meeting of the Haemophilia Centre Directors.

591. The progress and success of RIA testing at Regional Transfusion Centres is touched on in a paper prepared by Dr. Combridge and Dr. Barbara in March 1985 entitled "Effect of Screening of Serum Donations for HBsAg at English Regional Transfusion Centres by Immunoradiometric Assay" and is included in Appendix [7].

592. Dr. Combridge outlined the history of testing thus:-

> "Since 1970, pooled plasma received at BPL from these Centres (i.e. the Blood Transfusion 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-electro-osmophoresis (a first generation test) replaced by reverse passive haemaglutination techniques (RPHA) (second generation test). Since 1979, however, all incoming plasma pools had been screened by a third generation immunoradiometric test".

593. Table 1 in the paper shows the chronology of usage of the first, second and third generation tests by both 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 had dropped to zero by 1984 when both the Regional Transfusion Centres and BPL were all using the same RIA test. The third 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 the second generation tests at the Regional Transfusion Centres, largely solved the problem of hepatitis B.

594. The Haemophilia Centre Directors' annual returns for 1984 were provided to those attending the UK Haemophilia Centre Directors' meeting on the 21st October 1985 and forwarded to us on the 12th November (document no. 2204(a)). One of the papers included with the returns (Appendix D(i)) (document no 2204(c)) was the UK Haemophilia Centre Directors' Hepatitis Working Party report 1984/85. The report noted:-

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- Heat-treated Factor VIII products came into general use in the UK in 1985.

- Limited information available from trials of these products indicated that Travenol dry-heated concentrate showed little or no reduction in associated cases of hepatitis and that Profilate "wet" heat-treated products had passed on hepatitis Non-A Non-B in one of the first batches to be used in the test.

- A recent report from Sheffield on the follow up of patients with chronic liver disease with repeated liver biopsy showed that the previous reports of relatively benign sequelae from acute Non-A Non-B hepatitis might have significantly underestimated the risk of serious chronic liver disease resulting from infection with hepatitis Non-A Non-B.

595. This report by Dr. Craske confirmed the serious long-term sequelae of hepatitis NANB infection in patients studied over more than a 5 year period. The morbidity of NANB hepatitis more than justified attempts by the industry to achieve comprehensive viral inactivation in coagulation products.

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SUMMARY OF "HEPATITIS" CLAIMS AND CBLA'S REBUTTAL

596. If one pauses at this stage to look at the allegations grouped under the heading "Hepatitis Risk and/or Risk of other Viral Infections" as contained in the MSC at page 111, I think it is worth making some preliminary comments (although it will be necessary to return to these allegations once HIV and heat treatment have been reviewed).

597. (95(aa)) Failed from 1982 to appreciate sufficiently or at all:

(i) The risk of infection with hepatitis and/or other viruses to which haemophiliacs were exposed by treatment with Factor VIII and Factor IX concentrate;

(ii) The serious and potentially fatal nature of hepatitis and/or other viral infections;

(iii) That the risk of infection with hepatitis and/or other viruses was substantially higher for haemophiliacs treated with commercial concentrate

As with other claims the CBLA became responsible for BPL with effect from 1st December 1982. By this time, as I have indicated above, hepatitis B was, to all intents and purposes, controlled through the introduction of RIA testing both at BPL/PFL and Regional Transfusion Centres. The results of the various surveys carried out revealed that by the start of the 1980's hepatitis B transmission to Factor VIII and Factor IX had decreased to very low levels in patients at risk.

598. Accordingly, it was necessary so far as CBLA were concerned to concentrate on the management and control of Non-A Non-B transmission. By the time CBLA became responsible for BPL/PFL it had been established, through the work of Dr. Craske and others, that hepatitis Non-A Non-B was a serious and widespread problem and, by 1983, that its transmission rate was similar in NHS and commercial concentrate albeit that the US variety appeared to cause a more serious acute clinical disorder. By the time CBLA became responsible for BPL and PFL we were giving consideration to methods available for virus inactivation which would assure the safety and efficacy of the product. CBLA supported this ongoing programme of work in two main respects: first, to develop a more highly purified Factor VIII preparation which would, secondly, accommodate virus inactivation procedures without undue loss of potency, efficacy or yield. This research was well underway by the time it became necessary to include HIV in the list of target viruses.

599. Although it is statistically impracticable to exclude transmission of hepatitis B infection since it had not been reported following introduction of heat treated Factors 8Y and 9A, it is probable that hepatitis B is inactivated under the applied conditions, but the input of virus into plasma pools must now be infrequent.

600. There are no other serious clinical disorders of viral origin associated with the use of coagulation products which might therefore be shown to have been rendered non-infective by heat treatment.

601. (95(ab)) Failed from 1982 or such later time as may be justified on the evidence at trial to take any or any sufficient steps to remove, alternatively, reduce that risk by:

(i) Eliminating or reducing the need to use imported (non-heat-treated) commercial Factor VIII concentrate.

(ii) Heat treating both Factor VIII and Factor IX concentrate.

(iii) Reducing pool sizes of donated blood for home-produced product; alternatively requiring and/or advising such reduction to be made.

The first paragraph is merely a repetition of the self sufficiency arguments dealt with above and the second paragraph we deal with in more detail after reviewing the history of heat treatment.

602. As to the third paragraph, I mentioned the small pool experiments undertaken at Oxford. These demonstrated that small pool concentrates offered only limited assurance of safety from transmission of NANB hepatitis. In that it is now known that for hepatitis C, donors have a carrier rate of 0.5 to 1% then on average 1 to 2 donations of infected plasma would be present in each pool greater than 100 litres. Similarly, although the incidence of HIV in the donor community is much lower, one infected donation in a small pool, by reason of its limited dilution, might carry an increased risk of infecting finished product. To achieve self-sufficiency, the logistics of small-pool fractionation, the reduction in efficacy of process and of consistency in quality, argued against the small pool approach. The answer is to have a successful heat inactivation procedure applicable to product from any size of plasma pool.

603. In short, small pools offered no guarantee of protection, would be quickly exhausted by the severe haemophiliacs most of whom are the Plaintiffs in the present proceedings and, given what was know about hepatitis Non-A Non-B

in the early 1980's would not have justified the re-organisation necessary to change production to exclusively small pool. By the time the realities of AIDS were apparent to all, most severe haemophiliacs had, I would submit, already become infected with HIV in any event and the solution in the form of heat treated Factor VIII and IX was just around the corner.

(iii) THE AIDS RISK

OVERVIEW

604. As I have mentioned above, the early description of AIDS in the UK (or what we now know as HIV infection), marginally preceded the establishment of the CBLA. In the United States, the problem of AIDS was developing towards the end of the 1970's and in about the summer of 1981 early reports were made of opportunistic infections and Kaposi's sarcoma (KS) in predominantly homosexual men. The Centers for Disease Control (CDC) based in Atlanta, Georgia in the United States, received these initial reports and in or about June 1981 a description of an associated group of symptoms and signs was given collective definition as acquired immune deficiency syndrome (AIDS). At the time, AIDS appeared to be confined to the United States and certain Haitian people. The cause of the syndrome reported to the CDC (by about August/September 1982) was still a matter for speculation when it became known in the United States that three cases of Pneumocystis Carinii pneumonia (PCP) had been reported amongst haemophiliacs giving strong support to the view that AIDS might be a virus-associated and could therefore be blood borne. Evidence to support the viral theory was actively sought but considerable uncertainty about the true aetiology of AIDS remained for some time.

605. Medical and scientific literature published early details of AIDS and reports of infection amongst three US haemophiliacs and this information was immediately received in the UK (the earliest documentary evidence of this is September 1982).

606. The end of 1982 saw those interested in the treatment of haemophilia, starting to obtain information from the United States and a rapidly growing

interest in AIDS during 1983 evidenced, inter alia, by the establishment of various working parties. The first tentative identification of the virus thought to be the cause of AIDS was made in 1983 and confirmed in 1984 as described in more detail below. Throughout this period, the working parties and individuals who were charged with or had taken on responsibility for considering the implications of AIDS, monitored the progress of work in the United States and elsewhere. News that the virus was heat labile, that is to say could be inactivated through heat treatment, came in about September 1984.

607. As I describe in greater detail below, BPL/PFL work on viral inactivation began in or about December 1982, and has continued throughout. As with the commercial manufacturers, the rationale for starting this work was the growing concern over hepatitis Non-A Non-B. The rate of this research and development was regulated by (a) available resources for research and development and (b) the fact that we were seeking to inactivate an unidentified virus which up to that time had not diminished the demand for, or rate of growth, in the use of product. By 1984 the HIV virus had been identified and was shown to be extremely heat labile, and at PFL 8CRV had already been successfully heat-treated and product made available for clinical evaluation. We were also at an advanced stage in the development of new "high purity" Factor VIII, designated 8Y, which by October 1984 was shown to tolerate heat treatment in the freeze dried state at a level which exceeded any other heat treatment programme then extant world-wide. As an interim measure, however, we planned to heat existing intermediate purity concentrates (8CRV and HL) to a level which (a) they would tolerate and (b) which would inactivate HIV (according to existing published literature) but probably not the NANB hepatitis virus. These heat treated intermediate concentrates were available from February 1 1985 until August of that year when they were replaced by 8Y.

608. Batches of 8Y were evaluated in March 1985, and routinely issued after April 1 1985. Heat treated Factor IX concentrate was issued from October 1985 (the delay in issue of heated Factor IX concentrate was due to the need for detailed assessment of safety of the product following heat treatment).

609. The next section of my statement looks at the chronology of our knowledge regarding AIDS, and I then deal with our work on viral inactivation against the background of both hepatitis Non-A Non-B and HIV before covering the history of the introduction of screening for HIV in England and Wales.

1982

610. The earliest reference to AIDS in CBLA's documentation is September 1982. The minutes of the UK Haemophilia Centre Directors' Hepatitis Working Party meeting held on the 13th September (document no. 1548) , contained a reference to AIDS. I attended this meeting. The reference is to be found in paragraph 5 on page 5 of the minutes under the heading "Acquired Immune Deficiency Syndrome (AIDS)":-

> "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."

611. The issue of AIDS was raised, for the first time, at the meeting of the Haemophilia Centre Directors held earlier on the same day (see agenda and minutes - document nos. 1549).

612. Reference to AIDS appears on page 10 of the minutes which record 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 included 3 haemophiliacs. There was "a remote possibility that commercial blood products had been involved." The basis of the information was an article in the Journal of the American Medical Association on which I comment below.

613. On the 24th September an article was published in the Journal of the American Medical Association entitled "Acquired Immunodeficiency Syndrome Cause(s) still Elusive" (document no 1554) which would have been routinely available to all scientific staff at BPL/PFL.

614. The article is a very useful one in that it is partly retrospective and traces the history of AIDS from its early manifestations in about June 1981 up to the time the article was written. There are several relevant passages which it is worth quoting from the article, although this should be read in full. The article begins:-

> "More than a year after the first reports of opportunistic infections and Kaposi's sarcoma (KS) amongst homosexual men and intravenous (IV) drug abusers, the Medical Committee still is baffled by the alarming number of cases of acquired immunodeficiency syndrome (AIDS)."

In the third paragraph of the article, it is stated:-

> "The recent addition of 3 haemophiliacs and 36 Haitian immigrants to the growing list of about 600 cases of patients with no previous history of underlying immunosuppressive illness or therapy has further confounded the search for the cause or causes of AIDS."

615. Alongside this particular paragraph in my copy of the article there is a marginal note "plus 2" and some additional wording which is unclear. This is not in my handwriting, but as will be seen later, 3 cases became 5 very shortly thereafter, and I imagine the article was updated by someone with the marginal note as a consequence.

616. At the bottom of the first page, the article continues:-

"The 3 cases of P Carinii pneumonia among haemophiliacs are alarming to some since they suggest 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."

617. It will be seen from reading the article that there was much uncertainty at that time as to the cause of AIDS. This is reflected later in the article at page 1426:-

"Most researchers agree that a combination of factors may contribute to AIDS, which can then manifest as opportunistic infection or KS. The life-style of some male homosexuals - exposure to a variety of sexually transmitted diseases through multiple partners, chronic antigenic stimulation by sperm semen or microbial infections, and use of immunosuppressive recreational drugs - probably contributes etiologic factors, although none of these factors is restricted to the homosexual population.

But if life-style is the key, the question still remains: why has AIDS also occurred in heterosexual men (84 so far), women (32 cases so far) mostly heterosexual Haitians and haemophiliacs."

618. In summary, therefore, as at September 1982, there was a growing body of knowledge about the extent and nature of secondary infection in AIDS patients but little information as to a primary infectious aetiology. We see an early implication for the blood supply as a source of transmissible infection.

619. On the 17th September 1982, Dr. Craske had written to Dr. Gunson (document no. 1552) regarding the forthcoming meeting of the National Blood Transfusion Service Working Party on Transfusion Associated Hepatitis due to take place on the 27th September 1982, suggesting 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 AIDS, the epidemiology of which might have implications for the Blood Transfusion Service. I have mentioned this point in the section dealing with Hepatitis, above. At the meeting (minutes - document no 1555), however, the decision was against widening the brief of the Working Party:-

> "The brief was not widened to include other specified infections; however, experience gained in dealing with co-ordination of reports, etc., of transfusion - associated hepatitis, could be applied to other infections where applicable. This also applied to "acquired immunodeficiencies."

620. On the 11th November 1982, Dr. Craske circulated a letter enclosing information on AIDS (document no. 1567). In the letter he said:-

> "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 Center, Atlanta, Georgia. He telephoned me last week. The latest information is that there are 5 haemophiliacs who have been identified with this syndrome, 2 of whom recently died. All these cases

are without the usual association of homosexual practices, drug addition or treatment with immunosuppressive drugs, which are factors which have been found in other patients acquiring opportunistic infections.

"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."

621. In the accompanying paper under the heading "Aetiology", Dr. Craske states:-

"Several theories have been advanced. It seems likely that this is a "new" syndrome.

"(1) The effect of drugs such as Amyl Nitrate taken by homosexuals to heighten sexual experience. This is not a factor as the disease has been described in patients who do not use the drug.

"(2) The immunosuppressive effect of cytomegalovirus (CMV) infection which has been suggested as a cause of KS. This seems unlikely, as CMV infection is rarely the primary cause of profound immunosuppression such as is described here, though a lesser degree

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can be demonstrated in patients with CMV associated infectious mononucleosis, etc.

"(3) The association with sexual promiscuity, intravenous drug abuse and possibly the transfusion of commercial blood concentrates, together with evidence of clustering and prodromal phase, suggest an infectious agent with a similar epidemiology to that of hepatitis B, possibly specific for the human T cell population. The presence of this syndrome in Haitian immigrants to the USA suggests that this agent may have spread from one previously unidentified ecological niche, perhaps situated in the tropics.

"If (3) is the most likely cause, then it seems possible such an agent might be present in plasma of hepatitis B carriers used to prepare hepatitis B vaccines."

622. Here we see some evidence of the concern which I mentioned above in relation to the hepatitis B vaccine and its potential to transmit HIV. More important for present purposes, we see one of the earliest documents recognising the possible risk of AIDS for haemophiliacs in general, through treatment with Factor VIII. Interestingly the document which Dr. Craske enclosed with his letter also contains a statement to the effect that the Communicable Disease Surveillance Centre in the UK had 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.

623. On the 22nd December 1982, Dr. Craske wrote to me (document no. 1583) in the context of a proposed meeting of the Hepatitis Working Party in January 1983, and enclosed a copy of a paper he had prepared for the MRC Hepatitis

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Vaccine Group which described early information about AIDS in the USA. He said that the latest information from the CDC in Atlanta was that 8 cases had occurred in haemophilia A patients. All these were patients with severe coagulation defects requiring regular treatment with Factor VIII. He said:-

> "We have, as yet, no information about whether any brand or batch of concentrate is implicated. In addition, 2 cases have occurred in non-haemophiliac patients which may be related to whole blood transfusions between a year and 18 months prior to the onset of the syndrome."

624. The enclosures with his letter were a document which summarised the various clinical disorders which were associated with AIDS, and a copy of the document he enclosed with his earlier letter of 11th November which is not materially different from the document I comment on above.

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625. As the minutes of the UK Working Party on Transfusion Associated Hepatitis meeting which took place on the 18th January 1983 (document no. 1598) make clear, Dr. Craske summarised the position as it currently stood in relation to AIDS (see paragraph 8 of the minutes). I was in attendance. Dr. Craske said that he would be studying the effects of American Factor VIII on UK recipients and would be examining immunological markers, but the field was currently very confused. This is a reference to the very early tests which we used on a surrogate basis to try and identify HIV. In effect, such tests look for viruses associated with common epidemiological pathways e.g. various forms of hepatitis, sexually transmitted infections and HIV were commonly represented in high risk groups such as active homosexuals, but could be expected in other groups such as prostitutes and drug addicts. Therefore, exclusion of hepatitis markers could be considered a likely means of coincidentally defining individuals at risk of HIV infection, thus HBcAb (hepatitis B core antibody) would be a surrogate marker for HIV.

626. At the 11th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party which took place on the 19th January 1983 (document no. 1599), there was further discussion of AIDS. At page 3, Dr. Craske reviewed developments in the field since the last Working Party meeting. At Dr. Kernoff's suggestion, he said that he had written to Dr. Dale Lawrence at the Communicable Diseases Center, Atlanta, Georgia, who was the co-ordinator of the surveillance of AIDS cases in haemophilia A patients in the USA. Dr Craske reported that:-

> "So far 10 cases of AIDS had occurred in haemophilia A patients. They had none of the predisposing causes such as heroin addiction, promiscuous

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homosexuality, or treatment with immunosuppressive drugs, and had occurred in areas of the USA where cases had not been found before. All except one patient were patients with severe coagulation defects on regular Factor VIII therapy. The youngest was aged 7 years, both Pneumocystis carinii and Kaposi's sarcoma had been found in this group of whom 5 had since died. It seemed possible that Factor VIII or other blood products administered to these patients might be implicated.

"The CDC AIDS task force were working on the hypothesis that an infective agent was involved, possibly a virus specific for human T-cells in the same way that E.B. virus was specific for human B-lymphocytes. Further support for this hypothesis had come from the report of 3 cases associated with whole blood or platelet transfusions. Two were in 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 20's from New York. However, further investigations of these donors was not at present possible owing to medico-legal problems. The third case was that of a 20 month old boy from California who had been transfused with blood platelets at birth for Rh haemolytic disease of the new born. Fourteen months later he developed an AIDS-like syndrome with an auto-immune type thrombocytopenia. One of the donors of a unit of platelets was a young homosexual who subsequently developed classical AIDS and died in 1982. Incubation periods of the cases was between 6 months and 2 years."

627. Dr. Craske reported further that the Americans were keen for UK Haemophilia Centre Directors to collaborate in the reporting of cases of AIDS possibly associated with transfusions of US commercial Factor VIII. No cases had so far been found in haemophilia B patients. Dr. Craske reported that he had

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been sent the detailed protocols of the National Haemophilia Foundation survey by the Americans. The Working Party it was suggested should consider the kind of survey which should be undertaken in the UK. He suggested that a retrospective survey might be conducted where Haemophilia Centre Directors were asked to report patients suspected to have the clinical features of AIDS-like disease. There was a comment about the fact that recent publications had suggested that patients treated with freeze-dried concentrate had depressed immunity in any event, although the degree of depression was not so profound as was the case with the classical AIDS syndrome. The matter was left on the basis that Dr. Craske would draw up a form for reporting of AIDS cases and consider what further information was needed in relation to a retrospective study.

628. The question of AIDS came up for the first time within the CBLA at the Authority's meeting on the 23rd March 1983 (document no. 1620). The minute shows (paragraph 40.3) that Professor Bloom (then a member of the Authority) suggested that the Authority should discuss the acquired immune deficiency syndrome at a future meeting. He explained what the syndrome was and the reasons for his concerns about it. Dr. Gunson stated that the subject would be discussed at the next meeting of the Council of Europe's Committee on Blood Transfusion in May, which he was due to attend, and in these circumstances it was agreed that he would report on this to the Authority in June and that Dr. Harris of the DOH would supply information on meetings between the DHSS and the US authorities.

629. The following day (24th March 1983) I sent a memorandum on the subject of AIDS to Mr. Mallory of BPL (document no 1621) copying in, inter alia, Dr. Smith and Dr. Snape. This followed on Professor Bloom's comments at the meeting on the 23rd March 1983 on the problems that were becoming associated with blood transfusion and blood product administration, with the increasing

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incidence of reported AIDS cases which, at that stage, were gaining momentum in the United States on a monthly basis. I commented that the high mortality in reported cases was a cause for concern, and was a primary factor behind what was described as the American over-reaction to the problem. At that stage the aetiological factor or factors remained unknown. I recorded that Professor Bloom would continue to keep the Authority informed and that Dr. Gunson would be attending the Council of Europe meeting and would report back to the Authority.

630. I went on to say that in the meantime, patients potentially at risk in the United Kingdom (notably haemophiliacs) were evidently concerned and resistance against the use of imported American coagulation factor concentrates was becoming apparent. This concern was being expressed to the haemophilic clinicians by their patients. I observed that equally there was a likelihood that a return to cryoprecipitate as a desirable form of treatment might become irresistible, whether logical or not.

631. I said:-

> "It is necessary for this Laboratory to develop a policy, which may only be implemented on a short-term basis, which will allow for the presentation of a large proportion of NHS Factor VIII as cryoprecipitate. Staff will be aware that many Regional Transfusion Centres have not made wet cryoprecipitate for some time and would now be both out of practice and in some cases without the facilities to recommence large-scale production. The implications for BPL source material are very real.
>
> "A meeting involving those circulated with this memorandum should be set up at the earliest convenient opportunity to discuss the strategical alternatives at BPL for manufacturing small pool freeze-dried

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cryoprecipitate to off-set the requirement for manufacturing at BTS level. Considerable adjustments to resources would be envisaged and taken account of. Equally, a (temporary) fractionation programme commencing with cryoprecipitate supernatant from the BTCS's should also be taken into consideration. The implications concerning Factor IX production will need to be examined and the potential benefits of pasteurisation of Factor IX given some priority."

632. The reference to pasteurisation reflects the stage we were at with our viral inactivation research work being carried out at the time (see below). My memorandum was written against the background of an expectation on my part 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 preferred method of treatment until the cause of AIDS was properly diagnosed and preventative measures put in place. This would clearly have important effects on BPL as far as our source material was concerned, i.e. plasma would be used to manufacture cryoprecipitate at the Regional Transfusion Centres and not sent to us for fractionating. It seemed to me that against this background we needed to be thinking in terms of converting to the production of small pool freeze-dried cryoprecipitate to assist Blood Transfusion Centres where they were out of practice or otherwise ill equipped to revert to cryoprecipitate manufacture. Neither BPL nor PFL had ever produced cryoprecipitate for transfusion.

633. In the event, the anticipated pressure for a switch to the use of cryoprecipitate as a temporary expedient never happened. It was a matter for the haemophilia clinicians (and to an extent the Licensing Authority if it thought US concentrate unsafe) to direct this change. The factilities at BPL/PFL have thus never been used for the production of small pool cryoprecipitate.

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634. The meeting which my memorandum foreshadowed, took place on the 18th April 1983 (see meeting notes dated 21st April 1983 - document no. 1625). The notes of the meeting were prepared by Norman Pettet. As is clear from the first page, there were a number of uncertainties at the time. There was 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 concentrate and a reduction in risk from AIDS. Dr. Smith said that there was, at the time, little firm knowledge on how effective heat treatment was on the hepatitis Non-A Non-B virus or, for that matter, AIDS, nor the effect of heat treatment on yield. There were several considerations which had to be borne in mind and these were listed at paragraphs 1 to 4 on the second page of the note:-

"(1) Do the UK haemophiliacs perceive the threat as serious as do the USA?

"(2) Is large pool material worse than small pool? - very little evidence in this area.

"(3) What would be the effect if BPL only able to produce one half of the UK requirement for FVIII, if heat treated yields were much lower than those seen currently for normal material.

"(4) The arguments for Non-A Non-B and AIDS were separate and different with respect to risk, e.g. the risk of Non-A/Non-B was seen in low and medium users, whereas AIDS would be of greater risk to heavy users."

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635. This impact of AIDS on heavy users was the logical result of uncertainty at the time of the incidence of viral infection in the donor community. Were this substantially less than for NANB hepatitis (as has been subsequently shown), then transmission would automatically be likely in frequent users of large quantities of Factor VIII.

636. Of particular importance was paragraph (3). We were conscious that heat treatment would almost certainly carry with it a penalty in terms of yield, further reducing our ability to supply product to the NHS.

637. On the third page of the minutes, it will be seen that there was a discussion about the wisdom of moving to small pool (i.e. small volume pools) and or small panel (i.e. large volume pools with fewer donors) as a means of producing Factor VIII and Factor IX, and the general feeling of those attending 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 directions from the haemophilia clinicians and DOH before we could react to produce what was needed.

638. At the third meeting of the UK Working Party on Transfusion Associated Hepatitis which took place on the 20th April 1983 (document no. 1628), it was noted that Dr. Gunson would be attending the Council of Europe meeting on AIDS and blood transfusion in May. Dr. Craske reported that there were no cases of AIDS in UK haemophiliacs, though there were 6 likely cases in UK homosexuals. It was also noted that because of AIDS, the uptake of cryoprecipitate would probably rise in the UK and that this would mean a drop in the supply of plasma to BPL.

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639. Our conclusion was to "wait and see" with regard to AIDS and is reflected in the note which I prepared for the CBLA dated the 22nd April 1983 entitled "Acquired Immune Deficiency Syndrome (AIDS)" (document no. 1627). I referred to the meeting which took place on the 18th April to review the Laboratory policy and said that the current position in the UK was that the disorder was limited to some 14 cases in known active homosexuals. There was, at that time, no evidence of AIDS in haemophiliacs. Haemophilia Directors had been alerted to maintain heightened levels of clinical surveillance for the disorder. I said:-

> "The production policy at BPL will adopt a "wait and see" basis with continued manufacture of Factor VIII concentrate and with continued attention to research and development programmes designed to inactivate transmissible viruses by heat pasteurisation and other methods. The potential of the Laboratory to manufacture small pool freeze-dried cryoprecipitate in significant amounts as an alternative to large pool intermediate Factor VIII concentrate, has been ruled out on logistic production considerations."

640. The "logistic production considerations" I was referring to, related to the equipment at the laboratory. Our facilities were geared towards production of concentrates from large pools. A shift to small pool production would have required a monumental turn-around. I continued:-

> "Whilst the situation in the UK appears to be under control, it is recognised that a first genuine report of AIDS in a haemophiliac could well bring about a sudden and significant general request for single unit wet cryoprecipitate for a large number of haemophiliacs. Whether this demand could be suppressed is unknown, but it would seriously reduce the

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efficiency of the current plasma procurement programme to satisfy BPL targets for Factor VIII concentrate. An elaborate programme of pooled capture under sterile conditions of regional cryoprecipitate supernatant would have to be introduced to provide starting material for Factor IX, immunoglobulin and albumin products."

641. I concluded by saying:-

"The possible impact of AIDS and the high incidence of Non-A Non-B hepatitis has caused the Director to review the current level of resources set aside for virus inactivation, and further proposals will be put to the Authority if it is felt that expansion of this programme is needed."

642. Whilst it was appreciated that special requirements for haemophiliac care/ products might require acute attention, BPL was required to preserve a reliable supply of source material for fractionation of Factor IX, immunoglobulin and albumin, all of which are life-saving products. Cryoprecipitate supernatant would necessarily form that source material, should RTC's elect or be required to revert from FFP collection to single unit cyroprecipitate manufacture. The review of resources for virus inactivation work raised unaccepted demands at that time.

643. Also in April 1983 a summary of the work of the Regional Transfusion Directors' Committee Working Party on Transfusion Associated Hepatitis dated 28th April 1983 (document no. 1633) was produced. 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 the use of cryoprecipitate. To date, there have been no

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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 product."

644. This reflects the general view at the time, i.e. that there was still insufficient information on which to make informed decisions on the AIDS problem. From the CBLA's standpoint, we were, of course, pressing on with our virus inactivation programme which had begun life as our response to the problem of hepatitis Non-A Non-B. The intervention of AIDS did not deflect us from this course, since we were already working on a programme which would simultaneously resolve the problem of HIV and NANB hepatitis, information gathering on the cause and progress of AIDS was the only relevant and appropriate activity.

645. Since BPL has never determined the clinical choice of products used by haemophilia clinicians, BPL continued to prepare intermediate purity concentrates of Factor VIII and to develop a high purity heated concentrate in the absence of an alternative directive from either the market or from the DOH and the regulatory authority. BPL therefore determined its R&D and production policies and procedures as described above.

646. At the Regional Transfusion Directors' meeting that took place on the 18th May 1983 (document no. 1637), AIDS was on the agenda and it can be seen from paragraph 10 that Dr. Walford reported on the DOH meeting which had taken place, and stated the position of the Department on the issue. I was not personally involved with DOH meetings on this subject, and I cannot recall the substance of Dr. Walford's report this length of time after the event. It would appear from the minutes that at that stage, Dr. Gunson, on behalf of the

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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.

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

648. The subject came up again at the meeting of the Central Committee for Research and Development in Blood Transfusion which took place on the 21st June 1983. Dr. Gunson chaired the meeting and Professor Bloom was also in attendance (he was both a member of the CBLA and one of the Haemophilia Centre Directors). Dr. McClelland attended (he was from the Scottish Transfusion Service) and Dr. Stuart from Wellcome was also present. The minutes (document no 1645) record the discussion on the subject of AIDS at paragraph 4/83. As recorded in the minutes, it appeared by this stage that it was known 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

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considering how to cope with the problem, and the DOH were putting out a circular asking "high risk" donors not to give blood, but of course this relied upon the integrity of the donor. The problem at this point was that insufficient was known about AIDS to arrive at any concrete conclusions. The Chairman asked those attending (which included myself) whether they felt that sufficient research was being done into AIDS or whether an ad hoc group should be formed to consider the problem and possible courses of action. Dr. Frazer suggested that since the Haemophilia Centres and Dr. Tedder's group at the Middlesex Hospital were already carrying out research, the Blood Transfusion Service should initiate some work in the donor field. It was agreed that the Chairman (Dr. Gunson), Dr. Bell, Dr. Frazer and Dr. McClelland should arrange for the formation of an ad hoc group to consider the problem and report back at the next meeting.

649. During 1983 scientific information gathering and initiation of research was multi-focal within the UK for the reason that particular areas of the problem emerged through the haemophilia service, the Blood Transfusion Service, fractionation services, hospital clinicians receiving AIDS patients and the virological institutes in leading hospitals. Sharing of information and co-ordination occurred automatically since many key individuals occupied positions on more than one group and the role of the DOH and MRC was secured through observers and led ultimately to the MRC taking a lead role in the British response to problems with the HIV infection.

650. Digressing for a moment to the subject of heat treatment, I should mention that the likelihood of a lymphotrophic virus had been identified in the Spring of 1983 (see article by Montagnie Science, 20th May 1983), and whilst inactivation through the use of heat treatment could not be validated on this virus it was a compelling reason for continuing with our programme of virus inactivation which, in a memorandum from Dr. Smith to Mrs Winkelman dated 23rd

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June 1983 (document no. 1648) was given "A1" priority. I would add that the programme had already been accorded high priority.

651. On the 26th July 1983, I prepared a memorandum entitled "AIDS-Progress of Heat Treatment of Human Plasma Products" (document no. 1659). I believe this paper was prepared for the CBLA.

652. In my memorandum, I stated that the severity of Non-A Non-B hepatitis in haemophiliacs probably associated with the co-existent impaired immune responsiveness of these patients had motivated plasma fractionation organisations to examine means whereby the hepatitis virus could be inactivated in large pool concentrates. In this regard, my reference to impaired immune responsiveness is not, in fact, to AIDS but to the general depressed level of immune responsiveness which was a particular feature of severe haemophiliacs exposed to heavy treatment with concentrates.

653. Under the heading "AIDS" on the second page, I recorded the view current at that time, that the AIDS syndrome was likely to include in its aetiology an infective virus, and the possible phenomenon of reactivation of an existing virus in individuals concerned. In short, although a virus was described, the mechanism by which it worked was unclear. AIDS virus, like hepatitis viruses, might be partially or completely inactivated by heat treatment. The reasons are set out under the heading "Means of heat treatment of blood products". Pasteurisation, common to the production of albumin was as yet unsuitable for coagulation products. Dry heat treatment was the first obvious method available to manufacturers. Initial claims made for some commercial products were invalidated but the technique was potentially the quickest way to a safer product. As is apparent from the third page of my note, we were

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necessarily concerned about yield and were endeavouring to find an effective heat treatment which did not carry an unacceptable reduction in yield.

654. At the 12th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party held on the 14th September 1983 (document no 1667), there were several references to AIDS.

655. At the bottom of the first page of the minutes it is noted that:-

> "In discussion, it became apparent that there was still considerable concern about the possible transmission of an infection related to 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."

656. Of major significance, is a reference in the second paragraph on page 2 of the minutes to the fact that 2 cases of AIDS syndrome had been reported in haemophilia A patients treated with commercial Factor VIII concentrate in the UK. This was the first documentary evidence of the arrival of AIDS amongst haemophiliacs in the UK. There is a further reference to the implications for hepatitis B vaccine which, as I have explained above, might have carried the AIDS virus.

657. The Regional Transfusion Directors met on the 22nd September 1983 (document no. 1672), and as can be seen from paragraph 3(a) of the minutes,

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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 when donors were contacted; some were being handed to donors when they attended at Centres and others were simply being left at donor sessions for donors to pick up. The DOH were preparing a further supply of leaflets.

658. At the fourth meeting of the UK Working Party on Transfusion Associated Hepatitis held on the 27th September 1983 (document no 1676), Dr. Craske summarised the current position with regard to AIDS. He reported that in the USA there had been 18 Factor VIII related cases, although others were being investigated. Approximately 20 blood transfusion associated cases are under review. In the UK, he said that there had been a very low number (20) of AIDS cases and these seemed to be mainly "imported" from the US. He mentioned that 2 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 HIV.

659. On page 4 under the heading "Non Specific Test for AIDS", there was some discussion of surrogate tests which might be employed but no firm conclusion was reached. Two possible surrogate tests were mentioned - the TPHA (syphilis) test and the anti-HBc test. Additionally, there were reports from Japan of the value of the beta microglobulin test. The Regional Blood Transfusion Services in the UK considered surrogate testing to be inconclusive in use, and had anticipated that following a description of the virus, a marker test specific to the virus would be developed in due course.

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660. There was a report on Dr. Gunson's attendance at the Council of Europe AIDS meeting. The recommendations set out at paragraph 4.3 of the minutes on page 4 were fairly straight forward. They were to aim for national self-sufficiency in blood and blood products, and 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. It was recognised that this might pose problems in the UK where the exclusion of product for batch quality control procedures resulted in disproportionately greater loss of product for issue when batches were small. Another possibility, that of using accredited donors in relation to patients with "low immunity" (e.g. babies) or "infrequent users" (e.g. mild haemophiliacs undergoing surgery) was also suggested. The last point emerging from the Council of Europe meeting was a recommendation that information on AIDS should be provided to all donors so that high risk donors could exclude themselves. It was also suggested that physicians and selected recipients should be informed of the potential hazards of haemotherapy so that blood (or its products) was not given unnecessarily.

661. There may have been scope for limiting or avoiding the use of concentrates. For example, a mild haemophiliac might be treated with cryoprecipitate or simply have the operation he was due to undergo postponed whilst the AIDS risk existed. It was probable is that by this stage severe haemophiliacs who had over recent years been treated with large quantities of Factor VIII, much of it from commercial sources, were already infected with HIV.

662. A meeting of the MRC Working Party on AIDS took place on the 10th October 1983 (the Minutes are document no. 1679). This particular group had just begun its work at about this time. There were no representatives of the Transfusion Centres or any member of BPL sitting on the Working Party, but the DOH were represented and in fact I recollect that it was a DOH initiative to

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establish the Working Party in the first place. The Working Party were to review scientific knowledge and research on AIDS in the UK and abroad, and to encourage contact and co-operation between research workers in this field. Lastly, they were to advise the MRC on the current state of knowledge in the field and on topics for research. As is apparent from paragraph 3(a) of the minutes entitled "Clinical", there was difficulty in establishing a marker or markers which could identify an individual as a sufferer:-

> "It was noted that AIDS provided a good example of a problem arising in clinical medicine which was posing many new and unexpected questions of basic science. The overall clinical picture of AIDS was a very specific and severe form of immunodeficiency with a range of presenting disorders extending from Kaposi's sarcoma to multiple opportunistic infection. The broad resemblance to the congenital immunodeficiency SCID [sub-acute combined immunodeficiency] was noted. The manifestations were noted to vary according to both host and environmental factors. The pattern emerging in early UK cases seemed different in some respects from the American experience, and the gastrointestinal problems were noted as a particularly important area for research. The laboratory markers for disease were well established for AIDS itself, but their relevance in screening and in a possible precursor state was not established. The problems of definition and interpretation of these so called precursor syndromes were outlined by several members. The special features arising in relation to haemophilia were discussed, and the possibility of identifying the role of imported Factor VIII concentrate used for UK patients was outlined. There followed discussion on the varying and considerable period of incubation (1 to 4 years) and the possible relationship between the size of inoculum of the proposed agent and the length of latency. The possibility that AIDS as currently defined was the

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tip of an iceberg in terms of a range of clinical or sub-clinical responses to infection with a putative AIDS agent was mentioned; it was recognised that the existence of milder forms would be hard to establish without a marker for such an agent."

663. As can be seen under the heading "Aetiology" there was still doubt as to whether HIV was a totally new virus. That there is mention of retroviruses (HIV turned out to belong to this group of viruses), and reference also to HTLV which was the original description given to the HIV virus as it was identified in the United States (LAV was the term used by the French). As can be seen from paragraph 7, the DOH were effectively identified as having a liaison role between national and international groups. There were three specific grant applications for investigative and research work in the area of AIDS and these were reviewed as paragraph 9 of the minutes shows.

664. On the 14th October 1983, the first meeting of the CBLA Central Committee for Research and Development in Blood Transfusion Working Group on AIDS took place (the Minutes are document no. 1684). Dr. Gunson invited me to put forward two suggested members for this Group in July (his letter of 14th July 1983 - document no. 1653), and I replied on 18th July 1983 (document no. 1656) suggesting Drs. Mortimor and Tedder. It was noted that a few days earlier the MRC Working Party 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 he might usefully form a link between the two bodies.

665. In paragraph 3 of the minutes, there is reference to the leaflet "AIDS and how it concerns Blood Donors" (document no. 1684(a)) and to the distribution of this by Regional Transfusion Centres. Co-ordination was lacking with regard

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to circulation of the leaflet. Some leaflets were sent out to donors with a card/letter, other donors merely received them at donor sessions. I expressed the view that a professional marketing/advertising group would be able to give advice on getting the information to the public in a more effective manner.

666. As can be seen from paragraph 3.1.2 of the minutes, 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.

667. At paragraph 3.2.1 of the minutes, there is reference to the use of small donor plasma pools, 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 offering some protection against the transmission of hepatitis Non-A Non-B. However, whilst the experiment started well, as I explained above, it finished rather badly. 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."

668. Although the prevalence of HIV in the donor community was not known at this time, it was likely to be far less than NANB hepatitis virus. The use of smaller pool product was thought to offer some theoretical advantage to infrequent users of product, although the affect would be negated in heavy users.

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669. The Advisory Committee on the National Blood Transfusion Service met on the 17th October 1983. The meeting was chaired by Dr. Harris, the DCMO at the DOH. At the beginning of paragraph 27 of the minutes (document no. 1689) 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 1983 the Committee had set up the Working Group on AIDS and that the discussions in this Working Group had centred on two main topics:-

(i) the use of surrogate tests, and

(ii) 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 surrogate tests (e.g. HBcAb) had been shown in the USA to give positive results with greater frequency in AIDS patients. There were limited studies being undertaken to assess the incidence of HBcAb in donors and a survey was to be carried out at two transfusion centres in Bristol and North London, which did not directly involve the CBLA.

670. The second meeting of the Central Committee for Research and Development in Blood Transfusion took place on the 7th November 1983 and considered the matters discussed by the Working Group at its meeting on the 14th October 1983. Paragraph 11 of the minutes (document no. 1692) refers to the Working Group and to action taken by the DOH in respect of community health councils (to assist in the advice to high risk groups). At paragraph 11.2.2 it is stated that the Committee welcomed the action taken with respect to the investigation of the use of surrogate tests and the Committee looked forward to

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Dr. McClelland's report. [See para. 675. **Dr. Lane will look to see if he can find the paper**].

671. At the 9th meeting of the CBLA held on the 23rd November 1983 (minutes document no. 1697), it was noted that the Chairman of the MRC Working Party on AIDS had welcomed co-operation with the CBLA Working Group on AIDS, and it had been agreed that the minutes of the two Committee meetings should be exchanged. It was also noted that Dr. Gunson would be invited to meetings of the MRC Committee at times when his expertise would be valuable.

672. In December, a letter was sent by the Director of the Center for Disease Control, Atlanta (CDC) to Dr. Watt at PFC (letter dated 14th December- document no. 1700) referring to his participation in the World Health Organisation meeting on acquired immunodeficiency syndrome. BPL were not represented. The letter encloses a draft of a paper (document no. 1701) which attempts to assess the situation in the world as at December 1983. The paper itself is of general interest.

673. Looking back on the year, we see that a virus was confirmed as the aetiological factor of AIDS and that it was transmitted, inter alia, by blood and blood products and the first two cases of infection amongst UK haemophilia sufferers were reported. We proceeded with our viral inactivation programme concentrating on heat treatment, but apart from leaflet distribution encouraging self exclusion in the case of donors from high risk categories, the approach adopted by most was "wait and see" until such time as further information became available.

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674. Our work on efforts to reduce transmission of viral diseases was referred to in the lengthy report dated 16th January which I prepared on BPL covering the period April 1982 to December 1983 (document no. 1716). On page 39, I mentioned HIV. I drew attention to the fact that Factors VIII and IX continued to transmit Non-A Non-B Hepatitis to susceptible patients (believed to be those receiving largepool concentrates for the first time), and I added:-

> "There is considerable interest in the possible transmission of acquired immune deficiency syndrome through intravenous concentrates".

The report makes reference to the fact that conditions had been established for heating concentrate in the dry state.

675. At a meeting of the Regional Transfusion Directors which took place on the 25th January 1984 (document no. 1723), Dr. Wagstaff reported that no offence had been caused to donors regarding the introduction of the AIDS leaflet at donor sessions. Aside from this, no other discussion of AIDS is recorded.

676. Also in January 1984, the CBLA Working Group on AIDS held its second meeting on the 27th (document no. 1725) and considered the use of surrogate tests to identify high risk donors. The meeting was chaired by Dr. Gunson and I was one of those present. The meeting covered a number of issues. First, Dr. McClelland appears to have circulated a discussion paper to members which outlined proposals with regard to surrogate testing. It would appear from the minutes that Dr. McClelland was proposing anti-HBc screening as a possible candidate for a surrogate test, and that there should be a trial of this. Consideration was given to his views which covered the following points:-

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"(a) The significance of non-specific screening tests applied to a donor population;

(b) Consequences of donor screening for non-specific markers possibly related to AIDS (including several options open to Regional Transfusion Directors);

(c) Further investigation of donors already known to be anti-HBc positive;

(d) Evaluation of non-specific tests which could be applied to the donor populations;

(e) Implication for supply of Hepatitis B Immune Globulin.

677. There was discussion of a possible trial of anti-HBc screening in addition to the routine screening for HBsAG at Bristol and the matter was left on the basis that a protocol for a prospective study, to include probable costs, co-ordinated by Dr. Wallington, a consultant in the Bristol Transfusion Service should be drawn up prior to the next meeting of the Central Committee for Research and Development in Blood Transfusion. A recommendation would then be put forward to the CBLA at its meeting in March. As I have explained above, the presence of antibody was indicative of past infection and the development of immunity which did not exclude potential infectivity.

678. The meeting also touched on the question of the use of small donor pool concentrate. I referred to the plasma collections obtained from the Blood Transfusion Service in Leeds and Bradford commencing two years earlier, and

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confirmed this had provided the first opportunity to look at material obtained from pools with a lower than usual donor input. I was referring here to the Oxford small pool experiments and I commented that Dr. Rizza (at Oxford) was currently looking at this product. I said that the first pool of Factor VIII involving 1,000 donors had been exhausted and the second and third batches involving 300 donors were now being used. I said that there was a possibility that 4 or 5 small select donor pools might be available from BPL by the end of the year.

679. The Minutes also record that Dr. McClelland attended the World Health Organisation Meeting on AIDS in Geneva in November 1983 and that a document he obtained there which represented an assessment of the then situation in the world would be circulated to Working Group Members for information. The paper is document no 1728 which I have referred to above. **[Paper not included with 1728 note says "At Elstree"]**.

680. The minutes of the meeting of the MRC Working Party on AIDS which took place on the 10th October 1983 were made available and Dr. Tedder reported that the MRC Working Party had held a subsequent meeting on 20th December 1983 and that much of the business had been taken up with what the MRC Working Party would entail. Dr. Tedder is recorded as expressing some concern that the MRC Working Party had not given much time to the subject of blood transfusion in their discussion. It was noted that the only relevant issue they had touched upon was whether or not any patients who had contracted AIDS had previously given a blood donation.

681. The minutes record that Dr. Tedder reviewed some of the most recent studies in progress with regard to what was then described as the HTLV virus

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studies and that he commented on certain implications, but I cannot now recall the detail of this.

682. On 28th February 1985 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 present (minutes - document no 1732). There was a report on the second meeting of the Working Group on AIDS which I have referred to above. 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 test proposed would be for Hepatitis B Core antibody (anti-HBc). At this point, HTLV antibody tests had been developed but were only under preliminary evaluation. Later on in the year HIV antibody tests appeared for wider evaluation, rendering future requirements for surrogate testing obsolete. At this time, Dr. Wallington was still planning an investigation based on the screening of 50,000 blood donor samples for anti-HBc at the North London and Bristol Regional Transfusion Centres. It was recorded in the minutes that recent experience had shown that this would produce 500 positive results; both the positive donors and an equal number of controls would be traced and interviewed by medical staff. On the samples from both positives and controls, further laboratory investigations would be carried out, viz TPHA and HTLV antibody, along with other assumed markers.

683. Plasma from donations positive only for surrogates would be separated and stored frozen for use only for investigations but the red cells would be transfused since there was no indication at that time that they were unsafe. With respect to suppliers of plasma for anti-HBs immunoglobulin, fractionators would decide the significance of the anti-HBc result in the context of surrogacy. It was subsequently shown not to be significant.

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684. Dr. Thomas, Consultant from NIBSC, pointed out that the proposed study, although initiated by a consideration of the AIDS problem in blood donors did not in itself constitute a study into AIDS. Nevertheless, he considered that it was an important investigation in its own right. Members of the Committee agreed that the proposals should be written in the form of a grant application to the MRC but Dr. Gibson from the Medical Researc Council commented that the MRC was in the position of having to turn down acceptable projects on AIDS because funds were over stretched. However, a study such as the one proposed might be appropriate for funding under the Health Services Research. Dr. Wallington undertook in collaboration with his colleagues to put forward a formal grant application and the Committee requested that these proposals receive support from the CBLA and the DHSS which could be communicated to the MRC.

685. I commented on the study which was being undertaken at Oxford by Dr. Rizza on the use of Factor VIII prepared from small pools of plasma obtained from the panel of plasmapheresis donors at Leeds. I referred to the encouraging initial results which had been obtained with 18 patients where short incubation Non-A Non-B Hepatitis appeared to be absent in contrast to Factor VIII obtained from plasma randomly collected where the attack rate was 100%. The minutes cross refer to the MRC Working Party on AIDS and there was also a report on a meeting with Commercial Manufacturers. Dr. Thomas, from NIBSC, reported on the discussion which had taken place with Commercial Manufacturers about the implications of AIDS. It was generally agreed that an effective scheme was required in the UK indicating where an AIDS patient had contributed to a plasma pool. It was noted that PHLS had recently informed myself of one such case, although the procedure was an informal one. The meeting resulted in a procedure being set up whereby notification of AIDS and later HIV infectivity to the PHLS

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was made available to the relevant Regional Transfusion Centre. If the Transfusion Service were involved, they informed BPL.

686. During March 1984, a document was produced by the Advisory Committee of the NBTS (AC(84)3 - document no. 1746) setting out comments on the first six months' experience of distribution of the AIDS leaflet. The document appears to have been produced for the Advisory Committee on the National Blood Transfusion Service. The document records returns from the 14 Regions giving details of their distribution methods, donor response and any other comment. Clearly there was no homogenous procedure to develop communication with donors and potential donors. By way of illustration South London, the largest Region, distributed a very small number of leaflets in comparison with some of the smaller Regions.

687. It was in April 1984 that the subject of a system for reporting AIDS diagnosis surfaced as a subject again, and Dr. Gunson prepared a note entitled "Surveillance of AIDS in relation to Blood Transfusion" (document no. 1759) which recorded the result of a meeting between Dr. Gunson and Dr. Galbraith, Director of the Communicable Disease Surveillance Centre ("CDSC") and Dr. McEvoy also of the CDSC on 4th April. The CDSC is the reporting centre for the PHLS, based at its headquarters in Colindale. The proposed system provided for the CDSC to inform the appropriate Regional Transfusion Director when a patient was found to be infected with HIV or was diagnosed as having clinical AIDS; if the patient admitted to donating blood, contact would be made by telephone.

688. Thereafter the procedure was as follows:-

> "1.1 Investigation will be undertaken to find out whether the person is registered as a donor.

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1.2 If the answer is No, CDSC will be informed.

1.3 If the answer is Yes, further action will be:-

1.3.1 Trace the fate of blood donations, with respect to all products, given during the previous FIVE years.

1.3.2 If plasma has been sent to BPL for fractionation, Dr. R.S. Lane will be informed as soon as possible.

1.3.3 The appropriate hospitals will be asked to identify the patients who received the blood products, provide any information they have on the subsequent progress of the patients and name the patient's family doctors.

1.3.4 Subsequent to consultation with the Defence Organisations a communication will be sent to the family doctor informing him of the circumstances and a copy of the letter sent to the CDSC who will carry out any further follow-up.

1.3.5 CDSC should be kept informed of progress."

689. CDSC were also to inform the appropriate Regional Transfusion Director when a patient was diagnosed with AIDS who stated that he/she had received a transfusion of blood and/or blood products. Thereafter, the procedure was, inter alia:-

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"2.1 If the patient has received blood products derived from pool plasma which may involve a large number of donors, Dr. McEvoy will discuss with the RTD the practicalities of follow-up within the resources available. If the patient is a haemophiliac, Dr. J. Craske, Consultant Virologist, PHLS, Manchester, will also be involved. If the patient has received NHS product derived from pool plasma, Dr. R.S. Lane will be informed."

690. BPL is able to trace all donors involved in plasma pools used for the production of all products. This is independent of pool size. In fact, the Basingstoke incident showed that all patients who received product could also be located without difficulty even with a normal batch size.

691. The note went on to describe what should happen in the case where the patient had received blood products which had been prepared and issued from the RTC (e.g. cryoprecipitate). Prior to this time, there had been no obvious liaison arrangement whereby an AIDS diagnosis could be reported to the PHLS and/or by the PHLS to the National Blood Transfusion Service. The Transfusion Service and the Central Laboratories were circulated with the procedure, and the procedure was implemented.

692. The Advisory Committee on the National Blood Transfusion Service met on the 10th April 1984 and the Minutes (document no. 1761) contained a reference to AIDS:-

"10. Dr. Smithies reported that by the end of March 1984, 40 cases had been reported to the Communicable Disease Surveillance Centre (CDSC), Colindale of whom 22 had died. 33 of those reported were homosexual and 2 were haemophiliacs. The six months trial period

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of the leaflet "AIDS and How it Concerns Blood Donors" was now complete and the survey of RTD's showed little adverse comment. DHSS now proposed to prepare, in consultation with RTD's, a revised version of the leaflet for submission to Ministers. Dr. Rogers suggested that RTD's should adopt a more aggressive approach to discourage donors from high risk groups from giving blood. The Committee recommended that although the method of distribution during the trial period had been left to the discretion of RTD's, Ministers should now consider the issue of the revised leaflet with donor call-up cards in all Regions.

11. Dr. Gunson explained that he had discussed with Dr. Galbraith of CDSC the possibilities of following up patients who may be blood donors and would be presenting proposed guidelines to RTDs.

12. Dr. Harris assured the meeting that DHSS was in close liaison with the MRC, CBLA and HEC [Health Education Council] on the subject of AIDS. The latter organisation were themselves considering the production of an AIDS leaflet for distribution through STD clinics."

693. During this period, liaison between the DOH and the CBLA was through the existing Committee structure. There were regular meetings of the CBLA at which Dr. Harris, Dr. Smithies, Dr. Gunson and myself were present. Members of the DOH were also present at meetings of Regional Transfusion Directors and meetings of the National Blood Transfusion Service, at which the DOH had observers from the medical and administrative wings.

694. The Regional Transfusion Directors 191st meeting took place on the 11th April 1984 and, as the minutes show (document no. 1762), effectively the same

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ground was covered as in the meeting on the 10th April. On 17th April 1984 (document no. 1763) Dr. Wallington wrote to Mr. Smart as Chairman of the CBLA enclosing a copy of the application he had put together for financial support from the MRC for a research project aimed at evaluating surrogate tests for antibody to hepatitis B core antigen (anti HBc) as a screen to exclude blood donors who presented a high risk of transmitting AIDS. In his proposal under the heading "Purpose of proposed investigation", Dr. Wallington states that the causative agent of AIDS was unknown. However a number of surrogate markers were found commonly in AIDS cases and people belonging to groups where the risk of developing AIDS was high. He states that Anti HBc were the commonest surrogate marker. 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."

695. Under the next heading, Dr. Wallington attempts to identify those high risk groups whose life style exposed them to special risk. He adds that although the cause of AIDS was unknown, its epidemiology suggested strongly that an infectious agent was responsible.

696. In the event, the proposal did not receive financial support and was quickly overtaken by the confirmation in the spring of 1984 that AIDS was caused by a virus. Identification of that virus led to consequential rapid development of tests to detect the antibody to the virus.

697. On the 19th April, Dr. Gunson sent me some interesting news briefs reproduced from the American Association of Blood Banks ("AABB"). The news briefs are dated April 1984 (document no. 1764). The Americans were conducting

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a similar review of the use of anti-HBc testing as a surrogate marker at the same time. However, opinions were divided: Aaron Kellner of the New York Blood Center said:-

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

698. This is an interesting comment to be made as late as April 1984. On the second page of the piece under the heading "AIDS up-date", 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% and a corresponding 30% increase in cryoprecipitate use. However, at the same time, it was reported from the USA that AIDS had developed in a haemophiliac who had been treated only with cryoprecipitate.

699. In some European countries where the haemophiliac patients were treated with mainly cryoprecipitate, there is a low incidence of HIV seroconversion, for example, Belgium and the Netherlands. The reason why there is such a low rate of HIV in Belgium is because their policy restricted manufacture of concentrate and cryoprecipitate to plasma sourced from Belgian donors. Similarly in the Netherlands, HIV infection was limited to 24% in severe haemophiliacs consequent upon the same restrictions being observed in the selection and use of plasma from volunteer, unremunerated donors. An equivalent parallel is seen in the U.K. with the low expression of HIV infection in the recipients of Factor IX made wholly from U.K. volunteer donor plasma.

700. At the 12th meeting of the CBLA on the 23rd May (the Minutes are document no. 1772), Dr. Gunson made reference at page 3 to the grant application to the MRC:-

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"Dr. Gunson confirmed that a grant application to carry out a study involving blood donors, investigating the usefulness of performing non-specific tests had been submitted to the MRC, and a decision was now awaited. He said, however, that this had now somewhat been overtaken by events. It seemed most likely that an HTLV virus was the causative agent of AIDS. It was noted that as a result of the latest developments, Dr. Gunson and Dr. Wallington were subsequently preparing a paper modifying proposals in regard to the grant application.

"Dr. Gunson referred to a letter dated 21st May 1984 which he had received from Dr. D.A.J. Tyrell, Chairman of the MRC Working Party on AIDS, outlining its willingness to assist the CBLA in looking for antibodies against the "AIDS agent". It was agreed that such collaboration would be advantageous and a positive response should be forwarded to Dr. Tyrell."

701. I am not certain what became of the paper referred to above. It may have come to nothing, as a specific marker was shortly to be identified.

702. The minutes are also of interest because they make reference to trials of BPL heat treated Factor VIII. Dr. Gunson reported that together with myself, he was attempting with Haemophilia Centre Directors in Manchester, Liverpool and Newcastle and with regard to heat treated product to set up a trial which it was hoped to commence by late summer. Agreement of the protocol for the trial was delayed by Directors' concerns that heat treatment might have undesirable effects on the protein constituents of the concentrates. In fact, the protocol was not agreed before events with viral inactivation overtook this preliminary study and work focused on heat treatment of all product for routine use and specifically on

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development of 8Y. The protocol was finally agreed and used for evaluation of 8Y (elsewhere in my proof reference is made to the successful use of heat treated PFL 8CRV in a study in 3 patients during 1984 at the Middlesex and London Hospitals).

703. AIDS got a brief mention at the 192nd meeting of the Regional Transfusion Directors held on the 11th July 1984. (The Minutes are document no. 1790). Dr. Gunson reported that he had approached the Medical Defence Union. They advised that it was an adequate precaution if a patient had been given "at risk" blood to inform the patient's general practitioner in confidence. Remarkably, apart from this and a passing reference to the new AIDS leaflet which was in the course of being drafted and on which DOH were receiving comments from various interested parties, there were no other references to AIDS at the meeting.

704. At the 13th meeting of the CBLA on the 18th July 1984 under the heading "Any Other Business" the minutes record (document no. 1792):-

> "The Director of BPL informed members that he had received information from Dr. Tedder, Middlesex Hospital, about work currently being carried out as a result of the identification of the HTLV virus as the causative agent of AIDS. It was noted that financial assistance had been sought from the Authority by Dr. Tedder for the purchase of equipment to assist in antigen and antibody marker testing, and to see whether there would be a requirement to test all blood donors in the North London area. The specification of the equipment, which would cost between £5,000 and £10,000 would be made by Dr. Tedder within the next week. It was agreed that the Authority should finance the purchase of this equipment."

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The equipment was purchased as specified.

705. On the 31st August 1984, Dr. Harris the Chief Medical Officer of the DOH wrote to myself and others (document no. 1801), inviting my participation in a meeting to take place in October to consider the implications of two recent developments in relation to AIDS. These were the recent isolation of the HTLV III and LAV virus(es) (it was still a little unclear at that time whether these were in fact just different names for the same virus) which appeared to be closely related to AIDS and the development in the UK of a radioimmunoassay technique for the detection of the HTLV III antibody. The 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 DOH Medical Division dealing with scientific services. I subsequently attended the meeting which did not in fact take place until November 1984.

706. In a paper produced on the 9th September 1984 for the forthcoming meeting of the Haemophilia Centre Directors due to take place on the 27th September, Dr. Craske endeavoured to calculate the patients potentially at risk as a consequence of the two reported cases of HIV in haemophiliacs which were, at this stage, known about. The document is entitled "Current situation regarding AIDS" and was Appendix E to the paper circulated with the agenda for the meeting on the 27th September 1984 (document no. 1810(f)). The conclusion was that the total number of patients "at risk" came to some 600, although the whole exercise should be treated with some caution. Nevertheless, it does demonstrate the potential complexity involved in trying to trace potentially infected batches "down the line" to the patients.

707. Interestingly, an article appeared in the Lancet on 29th September 1984 entitled "Recovery and Inactivation of Infectious Retro-viruses Added to

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Factor VIII Concentrates" by Levy et al (document no. 1824) a summary of which read as follows:-

> "The ability of an infectious retroviruses to withstand the procedures used for Factor VIII concentrate was investigated. Mouse retroviruses added to human plasma survived at these procedures and remained infectious in lyophilised samples of Factor VIII. Lyophilised material had to be heated at 68°c. for several hours before substantial quantities of infectious virus became inactivated. These findings support the possible role of retroviruses in AIDS, and indicate that Factor VIII concentrates must be heated to inactivate these infectious viruses."

708. HIV was shown to be a retrovirus and in the autumn of 1984 (see Dr. Smith's statement) final confirmation came from the US that HIV was heat labile which promoted the existing approach to development of a heat treated Factor VIII concentrate.

709. In October, an update on AIDS was published in the American Morbidity and Mortality Weekly Review for the 20th October 1984 (document no. 1835). This is an important document. The report which is entitled "Update: Acquired Immunodeficiency Syndrome (AIDS) in Persons with Haemophilia", states the number of haemophilia cases where AIDS had been reported. The review shows the marked increase in the number of cases of AIDS in haemophiliacs from 1982 onwards:-

> "Reports of haemophilia - associated acquired immunodeficiency syndrome (AIDS) in the United States were first published in July 1982. Since then, the number of US patients with underlying coagulation disorders who develop AIDS has increased each year. In 1981, one US case was

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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 one 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. To physicians treating patients with haemophilia, they recommend that:-

(1) cryoprecipitate be used in Factor VIII deficient new born infants

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and children under four years of age and in newly identified patients never treated with Factor VIII concentrate;

(2) fresh frozen plasma be used in Factor IX - deficient patients in the same categories; and

(3) desmopressin (DDAV) 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 a coagulation factor concentrate, should strongly consider changing to heat-treated products with the understanding that protection against AIDS is yet to be proven." They also recommend that all elective surgical procedures for haemophilia patients be evaluated with respect to possible changes 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)."

710. The 10th meeting of the Advisory Committee on the National Blood Transfusion Service took place on the 8th November 1984 (document no. 1841). I attended this meeting. AC(84)13 gives details of the formation of the Advisory

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Committee on the National Blood Transfusion Service Working Group on AIDS and sets out the composition of the Group (document no. 1840(f)). 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 representatives from the Scottish Home and Health Department and the Scottish National Blood Transfusion Service in addition to three representatives from the DOH. The terms of reference were:-

> "to consider the implications for the National Blood Transfusion Service of testing blood donations for antibody to HTLV III and to report"

In essence, the Working Group was to look at the whole question of testing for HIV. Dr. Harris the DCMO at the DOH had written to me in August inviting my participation in the Working Group which eventually met, for the first time, in November.

711. Under the heading "AIDS cases reported by CDSC" in the minutes, there is reference to Dr. Smithies reporting that by the end of October 1984, 88 cases and 37 deaths had been reported to the CDSC. Of these, 75% were homosexuals, and 3 were haemophiliacs but none were associated with blood transfusion. 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. The meeting also touched on the question of testing for HIV and I deal with this in more detail in the section of my Proof dealing with screening and testing, below.

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712. Of course at this stage we were pressing ahead with our heat treatment programme, notwithstanding that there was no clear proof that heat treatment would inactivate the HIV virus. Given all the uncertainties which still existed at that time, it was a calculated risk to hope that heat treatment would inactivate HIV along with (we hoped) hepatitis NANB which had really been our target at the outset of the heat treatment programme.

713. It is interesting to note in the minutes of the fourth meeting of the Central Committee for Research and Development in Blood Transfusion held on the 9th November 1984, Dr. Tedder reported at paragraph 8.2 under the heading "Developments with respect to AIDS" (document no. 1845), that the causative agent of AIDS was now known to be a retrovirus which was called HTLV III. Again, as might be expected given the positive identification of the HIV virus a few months earlier, much of the ensuing discussion was given over to the subject of testing for HIV which I deal with in greater detail below. It was, however, noted that a batch of Factor VIII concentrate in Scotland which had been fractionated in November 1983 was found to transmit HTLV III by August 1984, and that the virus attack rate for this product looked like being as high as 80%. Although there was still no test for HTLV III in August 1984, some of the Scottish patients already started to show signs of ARC which led to the conclusion that the Factor VIII concentrate fractionated in November 1983 transmitted HTLV III. The remainder of the product had been withdrawn but the salutary effect of this dreadful problem which Scotland experienced with just one batch of Factor VIII was considerable.

714. The EEC workshop on AIDS held at the Institut Pasteur in Paris between 20th and 22nd November 1984, provided some interesting data on AIDS (document no. 1854) reported the distribution of AIDS cases in Europe at that time and refers to the fact that some 6,000 cases had been notified in the USA. This

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compared with some 559 in Europe, 88 of which were in the UK. It was recorded that 3 haemophiliacs had developed clinical AIDS. It will be noted on page 3 of the report under the heading "Sero - Epidemiology" that there is a reference to the work at the PHLS Virus Reference Laboratory and by the Middlesex Hospital/ Chester Beatty Group which suggested that in the UK, approximately 10% of homosexuals with multiple partners and 20-30% of most promiscuous homosexuals were anti HTLV III positive. 30% of haemophiliacs overall but an estimated 70% to 80% of those receiving regular doses of commercial Factor VIII were also HTLV III positive.

715. This demonstrates that by the time of the EEC Report in the autumn of 1984, most of the severe haemophiliacs who because of the severity of their condition, had been receiving regular treatments of commercial Factor VIII, had seroconverted.

716. On the 21st November 1984, the CDSC produced what may be regarded as another landmark document entitled "Acquired Immunodeficiency Syndrome Surveillance in the United Kingdom September 1981 to November 1984" (document no. 1855). Although the document repays 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 a donor who had subsequently developed AIDS and that red cells and whole blood from that donated had been given to two patients, and the plasma had been used to produce Factor VIII concentrate subsequently received by over 391 patients with haemophilia. At this stage, there were still only 3 haemophiliacs who had developed full blown AIDS although, I suspect, there were already a number of cases where AIDS was in the process of developing but had not yet been confirmed.

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717. Looking back at 1984, one can see that the year began with continuing uncertainty as to the causative agent of AIDS but that, in the spring, this was positively identified as a virus originally called HTLV III or LAV, and that heat treatment was potentially the answer so far as blood products were concerned. This resulted in our pressing forward with our heat treatment programme as fast as practicable and by making arrangements to produce all heat treated product (replacing non-heat treated product) through the autumn of 1984. From the start of 1985, some non-heat treated product was available but only on specific request from an informed clinician. With the identification of the HIV virus, attention very quickly turned to the question of testing and this is particularly apparent from the various meetings which took place during the second half of 1984, and which are dealt with in greater detail below.

718. The documentation in 1985 reveals that, aside from the introduction of heat treated product (which I have also dealt with below), most of the discussion of AIDS centred upon the development and then the introduction of a test in the UK and, this being the case, it is perhaps best at this juncture to review the position with regard to the testing for HIV beginning with the developments during 1984 (before considering the Plaintiffs' allegations in the MSC under the heading "AIDS risk").

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IV. SCREENING OF DONORS AND TESTING FOR HIV

OVERVIEW

719. I think it is important to bear in mind the chronology of events in relation to AIDS when considering the subject of screening tests. First, it was not until the Spring of 1983 that the first tentative identification of the cause of AIDS as a virus was made, with confirmed identification in the Spring of 1984. A specific test for this virus was dependant on knowledge of viral structure and isolation of the virus in culture. The first commercially available US tests were licensed in or about March 1985, but were considered unsatisfactory in the UK because of the false positivity rate. The UK was developing a test based on a method which was known to minimise false positive reactions. This test was available for routine use in the National Blood Transfusion Service by October 1985.

720. In relation to BPL/PFL the introduction of HIV testing of donors by the Transfusion Service (including the possibility of surrogate testing) is reviewed below.

721. By the time commercial tests were available in February 1985, BPL/PFL had ceased to release any non-heat treated Factor VIII concentrate. Subsequent follow-up of heat-treated product confirmed the manufacturing aim of full viral inactivation of HIV in the product. This was true of the limited study of heat treated intermediate concentrate HL and 8CRV and was never in doubt for 8Y and 9A in due course.

722. With regard to surrogate testing, this was only operationally viable as a testing procedure on donors carried out by the Blood Transfusion Service at the

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time of donation. For example, the presence of HBc antibody in pools is not a reason to withdraw a pool or its product, whereas HBc antibody in a donor may result in further investigation of the donor for specific markers or for a relevant social history of higher risk which would exclude the donor from further participation.

723. As with hepatitis B, Blood Transfusion Service policy was to test for viral markers at the Regional Blood Transfusion Centres before FFP was sent to BPL for fractionation. This enabled rapid identification of an infected donor and ensured that the benefits of testing blood were shared by the recipients of both cellular and plasma based products. A separate programme of testing plasma has always raised the question of creating dual standards of safety for recipients of cellular versus plasma products.

724. Our own testing for HIV at BPL/PFL was introduced in December 1985 on **[Dr. Lane please insert exact date [p33]]**. This was [?] weeks after the introduction of testing at Regional Transfusion Centres. The test is applied both to the plasma and end product at BPL (similar marker tests on the plasma start pool and finished products are used), and at the National Institute of Biological Standards and Control (NIBSC). Test procedures on finished product may reflect the lack of antibody (immunoglobulin) in the product. **[Dr. Lane is to check whether there is a recorded antibody positive test on the finished product e.g. for batch HL3186 [P28]]**.

725. Antibody testing gives information on the history of infection, but is not an index of infectivity since some antibodies imply recovery from infection. With HIV and some other viruses, viraemia may co-exist with the presence of antibody but the implication for infectivity is not necessarily a direct one. With HIV it is expected that markers for actual viral antigens will become routinely available in

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the future. Tests are now being evaluated, mainly for research use, which depend on the identification of viral RNA. These supplemental tests have value in a confirmatory role for marginal results by the routine antibody test.

726. The above overview deals in the main with Factor VIII. Heat treatment of Factor IX required additional testing to exclude activation of the clotting potential (thrombogenicity) of the product. This additional safety requirement delayed release of the product until October 1985. In the meantime, NHS Factor IX was available for use subject to clinicians' choice. Approximately one third of product used during this time was imported heat treated Factor IX; in other words two thirds of clinicians chose to continue treatment with NHS Factor IX throughout.

727. I will now describe the development of the screening of donors and testing for HIV by reference to the relevant documentation during the period 1983 to 1985.

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1983

728. In 1983, epidemiological evidence alone pointed to a possible infective aetiology for AIDS.

729. On the 19th January 1983 at the 11th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party (document no. 1599), Dr. Craske reported on information which he had just received from the Communicable Disease Center in Atlanta, Georgia. At that date, ten cases of AIDS had occurred in haemophilia A patients in the United States (there were of course none at this stage in the UK). The first indications as to the cause of AIDS were beginning to emerge as can be seen from the minutes at page 3:-

> "The CDC AIDS taskforce were working on the hypothesis that an infective agent was involved, possibly a virus specific for human T-cells in the same way that E.B. virus was specific for human B-lymphocytes."

730. It will be seen, however, that the situation was very unclear and that there is no reference in the US or, for that matter, in the UK to developing surrogate tests given the considerable uncertainties which then prevailed.

731. On the 18th April 1983 we held an internal meeting at BPL to consider how best to deal with the problem of AIDS as it was then perceived. The note of that meeting prepared by Norman Pettet dated 21st April (document no. 1625) is important. Of course at that stage it was still not possible to think in terms of a test for AIDS, whether surrogate or specific, and so our chief concern as Norman Pettet's note makes clear, was to consider how best to respond in terms of our own production approach. Our heat treatment research was at an early stage at this time, and so consideration was given to the question of pool size.

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Of course this discussion was also taking place in advance of the Oxford small pool experiment and therefore in the absence of knowledge as to the effectiveness of small pool arrangements so far as hepatitis NANB was concerned (and by implication HIV). The situation is probably well summarised by the following quotation from page 2 the note:-

> "The Director asked the meeting to consider a situation where AIDS was established in the UK and that some haemophiliacs had evidence of an altered immune state (AIDS related or not) - what is the ability of BPL to respond to a request to make small pool material, or that only any heat-treated product was required by Haemophilia Directors.
>
> "The general feeling was that a response to these requests would be difficult."

It was noted that US plasma was of two main types:

1. recovered plasma pools (made up from large (i.e. up to 50,000 donors) numbers of donors' routine blood donations);

2. source plasma pools (made up from smaller representative donor panels using plasma collected by plasmapheresis).

In the UK only large donor recovered plasma pools were used, i.e. there was still no major use of small donor panel plasmapheresis plasma, and plans were in progress to increase plasma collection primarily by the use of recovered SAG(M) with secondary use of plasmapheresis.

The note continued:-

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"It will be difficult to change the philosophy, once major progress had been achieved in the SAG(M) programme. In addition, the use of small panel accredited donors would be very expensive.

"Mr. Vallet suggested that if the present risk of using a large pool was small, the effect of an expensive screening programme of donors would have to be large to reduce this present risk by any significant extent.

"The answer to the AIDS question was therefore to consider what was feasible and what was not. Thus, if BPL was to be involved in the preparation of small pool concentrates, free of AIDS, there would have to be an extensive pool of accredited donors (or at least a high follow up procedure for donors)."

Later in the note it is recorded:-

"The Director asked Dr. Smith whether BPL should promote the collection of small pool material into a working programme, e.g. by the use of increased Leeds Haemonetics (currently 100kg/week).

"Dr. Smith felt that Dr. Robinson (Leeds) would be unwilling (for reasons associated with the present programme) or unable to provide significant increases in Haemonetics plasma.

"Dr. Smith suggested that the meeting differentiate between small pool (i.e. small volume pools) and small panel (i.e. large volume pools with few donors), and ask whether BPL should not be making small <u>panel</u> F VIII and F IX in additional to normal concentrate. If the answer was yes, a

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careful costing exercise would need to be carried out. The general feeling of the meeting was that BPL should go for both small panel and heat treated products.

"The overriding concern was that in trying to provide full UK demand with a secure product, BPL may end up not being able to supply the demand.

"The Director also asked whether the current problems posed by AIDS could be used to obtain financial support for more work in this area.

"Several views were expressed - notably the lack of space and staff, and the doubts on which programme of direction to follow. The overriding view was one of wait and see."

732. Looking forward from this point, we carried out some research in relation to hepatitis Non-A Non-B through the Oxford small pool experiments which are covered elsewhere and referred to in the above quotation (which refers to the Leeds Haemonetics material which was in fact the material used for the Oxford small pool experiment). We now know that the experiment was not successful and how successful it would have been in relation to HIV is a matter of speculation. In the event, the whole approach of BPL/PFL was directed towards producing concentrate from large pools. It would have been a tremendous upheaval not just for BPL/PFL but also for Regional Transfusion Centres to take an about turn and attempt to establish a small pool system at a time when simply not enough was known about the causative agent of AIDS to form any considered view as to whether such an approach would, in any event, be successful. We were starting our work on heat treatment taking our lead from published scientific literature (so far as it existed) and our efforts were concentrated on

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this programme over the next year and a half. It became our chosen solution to the AIDS problem. Small pool fractionation was not adopted by the US industry. The chosen procedure amongst most fractionators was to opt for virus inactivation.

733. The first sign of AIDS amongst haemophilia patients was reported at the 12th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party meeting on the 14th September 1983 (document no. 1667). Two cases of AIDS in haemophilia A patients were reported and, at about the same time, the first AIDS leaflets were issued.

734. The MRC Working Party on AIDS met on the 10th October 1983 (document no. 1679). It reviewed the whole issue and in relation to testing, the following quotation from the minutes at paragraph 3(a), is relevant:-

> "It was noted that AIDS provided a good example of a problem arising in clinical medicine which was posing many new and unexpected questions of basic science. The overall clinical picture of AIDS was a very specific and severe form of immunodeficiency with a range of presenting disorders extending from Kaposi's sarcoma to multiple opportunistic infections. The broad resemblance to the congenital immunodeficiency SCID [sub-acute combined immuno-deficiency] was noted. The manifestations were noted to vary according to both host and environmental factors. The pattern emerging in early UK cases, seemed different in some respects from the American experience, and the gastrointestinal problems were noted as a particularly important area for research. The laboratory markers for disease were well established for AIDS itself, but their relevance in screening and in a possible precursor state was not yet established. The

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problems of definition and interpretation of these so called precursor syndromes were outlined by several members."

735. "Laboratory Markers" are confirmatory markers of the secondary infection e.g. presence of pneumocystis Carinii pneumonia.

736. The possible use of surrogate tests was discussed at the CBLA Working Group on AIDS in Relation to Blood Transfusion meeting that took place on the 14th October (document no. 1685). The following appears in the minutes:-

"The use of surrogate tests

"It was generally agreed that if investigation into surrogate tests was to be carried out, it would be preferable to investigate the use of anti-HBc screening rather than TPHA.

"With respect to anti-HBc screening, the Working Group learnt that in the Bristol region, 10,000 donor blood samples had been screened for anti-HBc and 75 positives were found (incidence 0.75%) whilst in north London the incidence was 2.6% after screening 25,000 donor blood samples. The latter screening was still in progress and the results of 5,000 tests will be available in the near future.

"It was apparent that regional variations of anti-HBc positives may be considerable and a discussion took place on the possibilities of a pilot study. One area of concern was with respect to the follow up of the donors and the ethical considerations involved.

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"It was agreed that Dr. B. McClelland would collate the information that had already been obtained on anti-HBc screening and Drs. Fraser and Tedder agreed the results of their studies would be made available in confidence to the Working Group.

"Having considered the value of the available data, Dr. McClelland would submit outline proposals for a prospective study in time for the next meeting early in 1984.

"The Chairman stressed that economical considerations could not be ignored if it was concluded that an additional test for screening blood donors was proposed. It was noted that a monoclonal reagent was available, and this may help reduce the cost of the testing.

"It was agreed that other surrogate tests such as detection of alpha a-thymosin, alpha interferon and beta 2 microglobulin were not suitable yet for large-scale screening, but they may be of value in a study for examining blood samples of anti-HBc positives."

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1984

737. One of the earliest meetings in 1984 was that of the CBLA Working Group on AIDS in Relation to Blood Transfusion, whose second meeting took place on the 27th January 1984, and considered the use of surrogate tests (document no. 1725). The minutes record that Dr. McClelland circulated to members a discussion paper, a copy of which I do not hold, outlining proposals for further action that could be taken in relation to donors found to be anti-HBc positive. Consideration was given to the views of Dr. McClelland and following discussion of the then current anti-HBc screening in Bristol, Dr. Gunson raised questions as to whether it would be valuable if a study included interviews with donors and whether or not permission was needed to carry out further laboratory tests. The minutes continue:-

> "Arguments for and against informing donors prior to carrying out the tests were put forward and it was agreed that any proposed study should at the present time be confined to laboratory investigations only, and the question of approaches to donors be deferred until a clearer picture of the problems had been defined. If studies involving additional tests to the ones currently being carried out in Bristol and Edgware were carried out, the question of resources would need to be considered and therefore the CBLA through the Central Committee for R&D would have to make a decision on the viability of this. It was also felt that an approach to the MRC might be appropriate.
>
> "It was subsequently agreed that a protocol for the prospective study to include the probable cost involved, co-ordinated by Dr. Wallington, should be drawn up prior to the next meeting of the Central Committee for R&D in Blood Transfusion. A recommendation would then be put forward to

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the CBLA at its meeting in March. The problem of what use to make of the donations for clinical use could be resolved in this study, since the contents of the donation would be required for investigation."

738. With regard to small pool material, the minutes also contain reference to the discussion which took place on this subject:-

"Use of small donor pool material

"Dr. Lane referred to plasma collections obtained from BTS at Leeds and Bradford commencing two years ago which, because it was rapidly frozen, contained some batches with a high yield of Factor VIII, and confirmed that it was the first opportunity to look at the use of material obtained from pools with a lower than usual donor input. It was noted that Dr. Rizza was currently looking at this product.

"Dr. Lane confirmed that a first pool of Factor VIII involving 1,000 donors had been exhausted and second and third batches, involving 300 donors, were now being used. He commented finally on the possibility that 4 or 5 small select donor pools may be available from BPL by the end of the year."

739. We can see, therefore, that at this point the idea of surrogate testing was being considered by Dr. McClelland (Consultant in charge of Edinburgh BTC) and was to be carried forward by Dr. Wallington (Consultant at Bristol). This work was a personal initiative on their part. The reference to the small pool work is to the Oxford experiment. Although it would have been impractical to completely alter the method of manufacture of concentrates, the experiment was, nevertheless, taking place with the consequence that we would have the benefit of the results from the experiment to make an informed decision as to the route

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to follow in the future. Of course a number of circumstances combined to render the small pool idea redundant by the end of the year, not least the lack of success of the experiment.

740. Surrogate testing came up again at the meeting of the CBLA Central Committee for Research and Development in Blood Transfusion on the 28th February (document no. 1732). It was reported that at the second meeting of the AIDS Working Group, it had been agreed that Drs. Wallington, Tedder and McClelland would consult Dr. Contreras and Dr. Fraser (Directors of North London and Bristol Regional Transfusion Centres respectively), to consider putting forward proposals for a study, involving blood donors, to investigate the practicality and usefulness of performing non-specific tests which had given a significant number of positive results in the majority of patients suffering from AIDS. At the meeting, Dr. Wallington presented proposals which were discussed by the Committee. They are perhaps best summarised in the quotation from his subsequent MRC grant proposal (document no. 1763) set out below.

741. Dr. Wallington explains the basis for the surrogate tests he proposes:-

> "How might screening be approached? The analogy between the putative AIDS agent and hepatitis B is more than illustrative. Persons within high risk groups show evidence of infection with this virus and other agents with similar modes of infectivity. Screening tests for these infections might be used to detect them. A number of other abnormalities indicators of disorder within the immune system, have also been described in these person which might prove useful as screening tests. None of these tests are specific for AIDS and their value will only be established by trial in blood donors. To be useful, they must meet certain criteria:- they must identify at risk donors without excessive loss of donations due

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to positives in donors not at risk, technically they must fit into transfusion practice not leading to the loss of donations through unacceptable delays.

"Screening for hepatitis B is well established. In addition to tests for HBsAg, well tried tests for antibody to core antigen (anti HBc) are available and indicate past as well as present infection.

"Pilot studies of screening for anti-HBc in two Regional Transfusion Centres show that it is possible to screen large numbers of blood donations within the limitations imposed by Transfusion practice. A small number of donors (0.5 - 2%) have positive results. Results reported from the Centers for Disease Control, Atlanta, show a very high prevalence of this antibody in AIDS patients (84.2%), patients with probable AIDS (78.1%) and asymptomatic homosexuals/bi-sexuals (80.3%). Studies in London record a lower but substantial incidence (45%) of homosexual men having anti-HBc and/or anti-HBs. AIDS patients show marked disorder of B-lymphocyte function with increased spontaneous immunoglobulin production. This may be why they commonly display high titres of antibody to past infections, a finding helpful to screening. For these reasons, we have chosen to evaluate screening for anti-HBc in the detection of blood donors at risk of transmitting AIDS. The significance of positive results will be investigated by interviewing these donors and matched controls in order to establish whether or not they belong to at risk groups. Further tests will be performed on these samples with the object of increasing discrimination for at risk donors through clustering of positives.

"These other tests have been chosen on the following basis:-

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"Serum immunoglobulins: IgG, IgA, IgM. These are commonly raised in AIDS where B-lymphocyte dysfunction is well described. They are easily measured in the serum sample routinely available from blood donors.

"Circulating immune complexes. Raised concentrations of circulating immunoglobulins as detected by Staph A and Clq based tests are common in AIDS patients (65%), and at risk homosexuals/bi-sexuals (83%). They can be measured in the serum sample routinely available from blood donors.

"B-2-microglobulin. This serum protein, possibly a product of leucocyte turnover, is raised in AIDS patients (69.3%) and at risk homosexuals/bi-sexuals (21%). It can be measured in the serum sample routinely available from blood donors.

"Interferon Alpha. Increased titres of interferon alpha as measured by biological assay have been reported in AIDS patients. Recently an immunoassay based on a monoclonal antibody to interferon has been described. This can be applied to the serum sample routinely available from blood donors.

"Treponema Pallidum Haemaglutination (TPHA). This test is used routinely for screening in some Transfusion Centres. It has value to the study as further evidence of past exposure to venerally transmitted infection one of the risks associated with AIDS.

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"Antibody to human T-Cell Leukaemia Virus (HTLV). HTLV is an agent especially attractive as the cause of AIDS as it is a retrovirus showing tropism for T-helper phenotype cells, the population of immunocytes depleted in established AIDS. 25% of a series of male homosexual AIDS patients had antibody to HTLV whilst it was present in only one of 81 matched controls. This does not suggest high utility as a screen for high risk status. This test is included in our protocol as providing information of potential value to epidemiological studies in other risk areas.

"Lymphocyte numbers will be measured when positive donors and controls are followed up. Suitable samples are not available at routine donations. 33% of symptom free homosexuals were found to be lymphopenic in a recent series in London."

742. The above is supported by a series of cross-references to research papers, etc.

743. The minutes of the CBLA Central Committee for Research and Development meeting on 28th February record at the bottom of page 3:-

"The plan of investigation was based on the screening of 50,000 blood donor samples for anti-HBc at the N London and Bristol RTC's. Recent experience has shown that this will produce 500 positive results; both the positive donors and an equal number of controls will be traced and interviewed by medical staff. On the samples from both positives and controls, further laboratory investigations will be carried out, viz; TPHA, Alpha-interferon, circulating immune complexes, beta-2 microglobulin, immunoglobulin and HTLV antibody."

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744. Dr. Wallington undertook in collaboration with his colleagues, to put forward a formal grant application covering the proposed research, and the Committee requested that the proposals receive support from the CBLA and the DOH and that this should be communicated to the MRC (the source of funds). The proposal did indeed receive support from the CBLA and I believe the DOH, but was quickly overtaken by the work on tests directed to the identification of the HIV antibody which was clearly preferable to a surrogate test.

745. We see Dr. Wallington's application for a grant went forward on the 12th April but very shortly thereafter at the 12th meeting of the CBLA held on the 23rd May, (document no 1772) Dr. Gunson stated that Dr. Wallington's research application had been overtaken by events and it now seemed likely that human T-cell lymphotropic virus (HTLV) was the causative agent of AIDS.

746. The first scientific paper to describe the AIDS virus (by L. Montagnier et al) was published on 20th May 1983. The paper opens with the statement:-

> "A retrovirus belonging to the family of recently discovered human T-cell leukaemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS)...."

This document is referred to in paragraph (aw) of Appendix 6 to the MSC.

747. The full details of Gallo's research were printed in Science on 4th May 1984. The paper is entitled "Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV III) from Patients with AIDS and at Risk for AIDS", which is

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referred to in paragraph (bv) of Appendix 6 to the MSC. It was reported in The Lancet on 12th May 1984 that AIDS was probably caused by the HIV virus. The article is entitled "The cause of AIDS?" and is referred to in paragraph (br) in Appendix 6 to the MSC.

748. On the 21st May, Dr. Tyrrell the Chairman of the MRC Working Party on AIDS wrote to Dr. Gunson (document no. 1773) as follows:-

> "When we were in contact earlier, you indicated that you would like to be in touch over research on AIDS. I must say that at that time I felt there was nothing which could be regarded as particularly likely to help you in your special needs for controlling the transmission of the "AIDS agent". You will no doubt have read the papers by Montagnier in the Lancet and the recent clutch by Gallo in "Science"; although the evidence is obviously not in, I think these probably refer to the same or closely related agents and that it or they are a key factor in the production of AIDS. You will realise that these rapid technical advances will mean that it will now be possible to look for antibodies against the "AIDS agent" by a simple routine ELISA test and that this is most likely to be positive in just those people whom you would like to detect "the pre-AIDS" subject. It therefore seems to me that the MRC Committee could be most helpful to you by facilitating your getting hold of this technology and setting up a study in the blood transfusion situation. We already have plans to look for retroviruses and their antibodies in cases of the disease and high risk individuals.
>
> "I have no wish to force myself or the Committee on you, and if you wish to organise everything and feel you have no need for help, I shall not mind at all. However, I did wish you to know what my scientific

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opinion was and that I would be happy to try and assist if such assistance were acceptable to you."

749. This letter was written against the background of the confirmed identification of the virus which was thought to be the cause of AIDS which, as the letter shows, was the result of publications in the scientific press by Montagnier and Gallo. Although their viruses were differently named, they were in fact the same. (Montagnier's virus was LAV and Gallo's virus was HTLV III).

750. As I have mentioned previously, Dr. Harris wrote to me (and others) on the 31st August (document no 1801) proposing the establishment of the Advisory Committee on the National Blood Transfusion Service - Working Group on AIDS. In his letter he said that with the recent isolation of agents HTLV III and LAV which appeared to be closely related to AIDS and the development in the UK of a radioimmunoassay technique of the detection of antibody to HTLV III, it was necessary for a group of experts to consider the implications of this for the National Blood Transfusion Service. I was invited to join the Working Party which was to be chaired by Michael Abrams, Head of the DOH Medical Division. The reference to a radioimmunoassay technique for the detection of antibody to HTLV III was to work being done at the Middlesex Hospital to apply their established procedure for RIA to the detection of HTLV antibody and to the fact that this technology was subsequently transferred to Wellcome and technically exploited by them (but not until 1985).

751. In the Lancet on the 1st September, (document no. 1803) a paper was published entitled "Prevalence of Antibody to Human T-Lymphotropic Virus Type III in AIDS and AIDS-Risk Patients in Britain". This was the result of research by a number of medical scientists including Drs. Craske and Barbara at PHLS and North London BTC respectively. The summary of the article reads as follows:-

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"2,000 persons in the UK were examined serologically for antibodies to human T-lymphotropic virus type III (HTLV III). Sera reacting in a membrane immunofluorescence assay (IFA) to HTLV III were also positive when tested against cells infected with lymphadenopathy virus (LAV1), and cross-absorption tests indicated that these retroviruses are probably identical. A competitive radioimmunoassay (RIA), which was wholly concordant with IFA, was used to screen the sera. 30/31 patients with the acquired immunodeficiency syndrome (AIDS) were sero positive, as were 89% patients with persistent generalised lymphadenopathy (PGL), 17% symptomless homosexual men, 34% haemophiliacs receiving pooled clotting factors, and 1.5% intravenous drug abusers. None of more than 1,000 unselected blood donors was sero positive. These data confirmed the close association between HTLV III and AIDS and PGL, and show that infection with HTLV III is also prevalent in the populations in whom these syndromes are most likely to develop. However, it would be unwise to presume that AIDS will necessarily develop in sero positive subjects."

752. After identification of a virus and a cell culture system in which it could be propagated, it became possible to test for antibody to viral markers expressed on the surface membrane of the cultured cells. Bound antibody is identified by the use of a fluorescent chemical marker attached to the antibody. The test is performed using microscopic methods. It is therefore a slide assay and is standard immunological procedure. The development of a means to culture the virus also provided a way of developing viral protein markers which could be used to identify the presence of related antibody in the plasma of affected people. Here, the antibody is identified by an attached radio-isotope label instead of a fluorescent chemical marker. Again, the radioimmunoassay is routine technology and its application, for example, had been established in the BPL/RIA test for

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hepatitis B and was likewise applied by the Middlesex Hospital Virology Department to the screening of HIV antibody. Both tests were dependent upon culture and isolation of the identified virus.

753. It is interesting to note that out of the 184 haemophiliacs who were part of the test (the patients were drawn from the Middlesex, St. Mary's and St. Stephens Hospitals), 63 (34%) were shown to be sero positive by then.

754. Replying to Dr. Harris' letter regarding the Advisory Committee on the National Blood Transfusion Service Working Group on AIDS on the 5th September, I indicated my willingness to join the Working Party.

755. In September, Dr. Craske prepared an update on AIDS (AGH(84)9 (document no. 1820) for the Advisory Group on Hepatitis. The figures which he quoted in that update were from the same source as the figures published in the Lancet. However, it is worth quoting a part of his paper which demonstrates the position as it was then understood and has particular relevance in relation to the tests which were being utilised at that time:-

> "The most significant development in the last 6 months has been the isolation and characterisation of the human T-cell lymphotropic virus (LAV) by Montagnier in Paris, and Gallo et al (HTLV - III) at NIH in the USA. The French virus, originally named LAV or lymphocytic associated virus, has been shown to be serologically identical to the American virus by several groups of workers. This virus is the most serious candidate so far found for aetiological agent of AIDS.
>
> "The evidence in favour of this association can be summarised as follows:-

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(i) The isolation of LAV and HTLV - III strains in France and the USA from T-cell lymphocytes by co-cultivation techniques from cases of AIDS and the AIDS related complex.

"(ii) Serological studies based on indirect ELISA, Western Blot, competitive RIA and immunofluorescent techniques show a high prevalence of antibody to HTLV III and LAV in patients with AIDS and the AIDS related complex, and also in symptomless patients known to be at a high risk of contracting AIDS compared with control."

Later in the paper he says:-

"The significance of a positive test for HTLV III antibody in the absence of any symptoms or signs of AIDS, remains to be determined. The association of the virus with AIDS remains unproved but it is the most likely candidate."

756. The ELISA test is an alternative to RIA in which the radio-isotope marker is replaced by a colour marker generated through an enzyme bound to the antibody. Western Blot is a confirmatory technique based on a preliminary separation of viral proteins which are then screened with an antibody carrying an appropriate marker (the other tests mentioned are described above).

757. At the meeting of the Advisory Group on Hepatitis which took place on the 9th October (document no. 1830), Dr. Craske presented his update on AIDS and in the course of this, explained that a reliable immunoassay procedure had been developed at the Middlesex Hospital Medical School. This was the earliest major RIA development test in the UK. Dr. Smithies of the DOH said that a new

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AIDS leaflet was to be published shortly which would advise that practising homosexuals should not donate, and I took the opportunity to say that the development of heat treatment should result in a reduced risk (referring here to BPL's work in this regard).

758. On the 12th October, I wrote (document no. 1833) to Dr. Harris at DOH as follows:-

> "Further to our telephone conversation, I attach, for your attention, a copy of page 77 from Plasma Forum 84, the official vehicle of the American Blood Resources Association. In the introductory paragraph, you will see that it is reported that the German government has introduced strict new requirements for plasma importers, and it is interesting to note that ABRA sees this as threatening from a commercial point of view. In fact ABRA is quite pleased to respond to the German government's stricter requirements, since Germany has the available money to pay the higher price that the industry wants.
>
> "I repeat the view I made by telephone that the UK should be adopting a similar strict approach to specification of imported labile blood products from all commercial organisations, and a recent discussion on the subject at the Advisory Group on Hepatitis, leads me to believe that my views are widely supported.
>
> "Our own position in this country is not static and we are actively planning dried heat treatment of all our Factor VIII on the empirical basis that it has a satisfactory process efficacy for inactivation of HTLV III.

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"I hope we can have an opportunity to talk about this and other matters on plasma supply soon after your return from abroad."

759. By way of explanation of the above, I should explain that Germany imported US source plasma for fractionation. Germany wanted to improve the specification for plasma and plasma products. I was advocating a review of our specification for products imported into England and Wales. I was not advocating a ban of those products.

760. At the 10th meeting of the Advisory Committee on the National Blood Transfusion Service held on the 8th November (document no. 1841), the meeting noted that the AIDS Working Group which Dr. Harris was setting up was to meet on the 27th November, and the following reference appears at page 3 in relation to testing:-

"AIDS - HTLV III Testing

"11. Dr. Smithies advised that the Middlesex Hospital and the Chester Beatty Laboratory were testing for HTLV III antibody using a radioimmunoassay method. The survey of 1,000 NBTS donors had revealed no infection, but it was hoped to undertake a larger survey to confirm findings. Pilot screening at an RTC was one of the points to be considered by the Working Group on the 27th November. Dr. Cash advised that in the USA the individual's permission was necessary before screening could be carried out; there were many implications for donor morale.

"12. Dr. Lane asked for an update on both the Gallo and British isolate availability and was advised by Dr. Smithies that the USA had been

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> approached for permission to use the Gallo isolate in the UK; some progress had been made on the British isolate but the position would be clearer by 27th November. Dr. Gunson advised that five American companies were licensed to use the Gallo isolate to develop tests."

761. The British isolate was an isolate from a virus from a British sufferer with AIDS. It was used to develop the source of viral protein antigen for the Wellcome test.

762. On the 8th November Dr. Harris, recently returned from an official visit to China and Hong Kong wrote to me (document no. 1842) in response to my letter of the 12th October. He said:-

> "The points you have made in your letter will be among those which I expect the AIDS Advisory Group to discuss at their meeting on the 27th November. 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 HTLV III 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 the 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."

763. I must say that this was a very unusual letter to receive given that we were so advanced with our heat treatment work (which Dr. Harris was well

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aware of because he was a member of the CBLA). It must be remembered that heat treatment was instituted to tackle the NANB hepatitis problem for which no test existed. Heat treated Factor VIII was available many months ahead of first a licensed HIV screening test being available and second the planned introduction of the chosen test for donor screening by the NBTS.

764. On the 9th November 1984 the fourth meeting of the CBLA Central Committee for Research and Development in Blood Transfusion took place (document no. 1845) and I attended the meeting. With regard to AIDS, Dr. Tedder reported that the causative agent of AIDS was known to be a retrovirus designated HTLV III, and testing for the virus was then discussed both in relation to the USA and the UK, and it was noted that Dr. R. Weiss was working with a British isolate although this was not as reactive at present as the material currently being used in the USA. Dr. Weiss worked at the Chester Beatty Institute as a virologist.

765. Dr. Tedder expressed the opinion that Porton, Unilever or Wellcome Diagnostics were the only firms in the UK with the capacity to be involved in this work. It was reported that five USA companies were currently licensed to develop a test. At that time, it was anticipated that the test kits would be available for sale by the end of the year but this subsequently proved to be optimistic:-

> "It was noted that the presumptive prevalence of an infective agent with positive antibody tests was very high, although the overall numbers of positive tests in the population appeared to be very low. In answer to a question raised by Dr. Thomas in relation to what advice should be offered to the Director, BPL, Dr. Tedder expressed the opinion that blood

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products should be withdrawn if a constituent unit of plasma was from a donor known to be anti-HTLV III positive."

766. The Working Group on AIDS established by Dr. Harris met on the 27th November 1984. I do not have a copy of the minutes of this meeting. There were oral reports on AIDS cases in the UK; tests for HTLV III antibody; prevalence of HTLV III antibody; haemophilia and HTLV III antibody. A paper was submitted (WGA(84)2) (document no. 1860(b)) on arrangements for collecting and testing of blood donations in the NBTS. This contained some references to testing as follows:-

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"1. Background

It is necessary to consider the best way to protect our supply of blood and blood products in view of the increasing prevalence of the acquired immune deficiency syndrome (AIDS) and the AIDS related syndrome (ARC) which it is known can be transmitted by infected blood donors to recipients. At present there is limited availability of a UK devised radioimmunoassay test for HTLV III antibody. It is expected that commercial test kits for screening for HTLV III antibody will be available from the USA early in the new year. The Group's views are sought on the need to apply a screening test to blood or plasma donations, what the consequences of testing would involve and, if initially the test will have only limited availability, what should be the priority for testing."

"3. Screening for HTLV III antibody

A radioimmunoassay for HTLV III antibody has been developed in the UK and the paper by Cheinsong - Popov et al Lancet 1984 September 1st, describes the test and the prevalence of the antibody found in 2,000 persons. A thousand blood donors tested were all negative for antibody to HTLV III, whereas it was present in patients with AIDS and high risk groups. The test has been used subsequently in a limited manner. It has not yet been possible to scale up the production of the test reagent to any degree because the original isolate used to develop the test was acquired from Dr. Gallo in the USA, on the basis of an exchange between scientific workers in the same field. As is well known, five USA drug and biotechnology companies have been awarded licences by the US government which gave them access to HTLV III

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from Gallo's original isolate for commercial development. Tests developed by the US companies for HTLV III antibody which could be used for screening blood donations are expected to be available early in 1985. DHSS has just received a reply to its representations to the US Health Authorities to authorise the use of the Gallo isolate more widely in the UK. A British isolate of the retrovirus HTLV III is now available, and it is expected that a radioimmunoassay test using this material will be developed further details will be available at the meeting.

"It seems probable that first test reagents will only be available on a restricted basis. If so, consideration will need to be given as to how best to use the tests in the NBTS.

"Relevant factors include:-

(a) Whether there is a case for preferential testing, i.e. all whole blood donations or plasmapheresis donations or donations for cryoprecipitate.

(b) Whether those centres collecting donations in areas with increased prevalence of high risk groups need to institute testing before others."

767. HTLV III antibody screening came up again at the combined meeting of the Haemophilia Reference Centre Directors, Blood Transfusion Service Advisors and plasma fractionation staff at BPL on the 10th December which was a meeting called at my initiative, to advise those concerned of the progress with regard to the supply of NHS heat treated Factor VIII and to obtain directions from all

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concerned. (Notes of the Meeting are document no. 1874). The meeting was to cover the question of the type of concentrate to be recommended in general and specific recommendations (if advisable) in relation to mild patients, Von Willebrand's patients, infants and children, "virgin" patients, home treatment, prophylaxis, elective surgery, inhibitors and Factor IX. With regard to testing, the questions were: should all patients be tested? Should patients be informed of results? Should spouses be tested? Should contraceptive advice be given? These points emerged in the aide memoire tabled by Professor Bloom who chaired the meeting.

768. With regard to HTLV III antibody screening, the notes record the following:-

> "Dr. Tedder reviewed the current situation by saying that the Gallo cell line was available for investigation although the USA had made the isolates difficult to obtain. The British isolate required an organisation to handle the bulk of the virus culture: Porton (PHLS) and Wellcome are the only ones so far interested. There are problems in obtaining the antigen. Dr. Tedder's test uses a cruder antigen.
>
> "Several problems remained in getting the test into the NBTS:
>
> (1) cost of the kit?
>
> (2) the extra staff required to run the test?
>
> (3) advice to donors found to be HTLV III positive?
>
> (4) how soon can the test be introduced?

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

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

"In summary, testing was likely to be recommended for patients and contacts in addition to the 2,500 haemophiliacs who would require regular testing, (the testing of contacts for haemophiliacs alone would be of the order of 10,000).

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

"(ii) Availability of Tests

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

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

"Some discussion took place on which organisation would be best placed to organise the testing, and whether DHSS financial support would be forthcoming. Dr. Lane (BPL) suggested that if resources were available,

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BPL would play a part co-ordinating the endeavour. Dr. Smithies advised that she would take all these points back to the DHSS for consideration.

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

"(iii) Blood Donor Testing

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

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

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

"(iv) Significance of HTLV III Antibody Test

"Dr. Taylor outlined the significance of HTLV III from a virologist view point.

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"(a) The presence of antibody may be a suggestion of developing AIDS, but not necessarily so.

"(b) There could well be advantages in being able to remove the antibody positive donors from the donor pool.

"(c) It is likely that to be HTLV III antibody positive suggests previous exposure to the antigen. Virus can be isolated from many antibody positive persons so that one must assume that many of them are infective. In haemophiliacs the presence of antibody is probably the result of infection rather than passive transfer of concentrate. There may be a period of viraemia preceding seroconversion.

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

"Dr. Ludlam confirmed that in Scotland some patients who previously antibody + VE [positive] are now - VE [negative]. Does this suggest passive transfer of antibody?

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

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

769. We see here the DOH effectively being held responsible for determining the future course of testing. On behalf of BPL, I offered to assist with development and distribution of an HIV antibody test along the lines of a test established earlier for HBsAg.

770. It is interesting to note that elsewhere in the minutes, Dr. Kernoff commented that some 70% of haemophiliacs were HIV positive remarking (somewhat curiously) in this context that, in these circumstances, it might be considered irrelevant if one did or did not tell the individual the results of the testing. Dr. Kernoff was probably using one of the commercial tests under evaluation.

771. In the issue of the Lancet covering the period December 22nd to 29th, there appeared another landmark article entitled "Blood Transfusion, Haemophilia and AIDS " (document no. 1889) which noted in the second paragraph that:-

"- the main immediate spin-off from the virological advances reported in 1984 would be the large-scale development of antibody tests to exclude donors who were HTLV III antibody positive."

772. There had been 52 haemophilia-associated cases reported in the USA but only 3 in the UK. These were of course cases of clinical AIDS, while infection with HTLV III would be even more prevalent amongst the haemophilia population by this stage, remembering that the period of development of AIDS following infection had not been defined. The article states that 32% of healthy

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haemophiliacs were found to be antibody positive in the UK compared with 72% in the USA. Dr. Kernoff's higher incidence of infection in UK haemophiliacs (see above) would reflect the generally greater severity of diseases therefore greater level of treatment in patients attending the Reference Unit managed by Dr. Kernoff at the Royal Free Hospital.

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773. In a document prepared in December 1984 and circulated in January 1985 by Professor Bloom and Dr. Rizza, Haemophilia Centre Directors were given advice on HIV related matters (document no. 1902). The document is entitled "Haemophilia Centre Directors' Organisation - AIDS Advisory Document". The document notes that tests for HTLV III antibody were available for haemophiliacs via Dr. Mortimer at PHLS in Colindale, and Dr. Tedder at the Middlesex Hospital Medical School. It was recommended that patients should be tested. With regard to donors, the advisory document notes:-

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

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

774. With regard to treatment, the note recommends the use of heat treated NHS Factor VIII or heat treated US commercial Factor VIII. For haemophilia B (Christmas Disease) patients, FFP is suggested for mild sufferers and the same for "virgin" patients. In the case of severe and moderate Christmas Disease patients previously exposed to Factor IX concentrate, the continued use of NHS Factor IX is recommended. There was in fact an incomplete departure from the use of Factor IX. Commercial Factor IX (which I believe was heat treated) accounted for 1/3 of use. It was, however, generally thought that continued use of NHS non heat treated Factor IX was to be advocated, because of potential problems of thrombogenicity. Also, it was not yet known whether heat treatment worked.

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775. The 194th Regional Transfusion Directors' meeting held on the 23rd January (document no. 1920) cross-referred to the meeting of the AIDS Working Party in November 1984. The minutes state:-

> "It was felt by RTD's in attendance that this was an unproductive meeting, there being as yet no new leaflet, no finance and no positive move towards full donor screening."

776. I think this is probably a fair characterisation of that meeting. The meeting of the AIDS Working Party in November 1984 was the last one I attended. On that occasion, I had a disagreement with the Chairman, Dr. Abrams, about the HTLV III (as it then was) test. I said that I thought the introduction of the test should be accelerated. My manuscript note at the bottom of the last page of the briefing document designated WGA/84/2 (document no. 1860(b)) tabled at the meeting on the 27th November 1984, reads:-

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

This note refers to a point I raised about having the necessary financial resources to make a test for HIV antibody, along the lines of the hepatitis B test which had been in existence for some years at BPL, which produced the response from Dr. Abrams that if we were short of money, it was due to an overspend on the re-building programme of BPL at that time. I took great exception at the time to this unsolicited comment and I wrote to Mr. Smart on the 28th November 1984 (document no. 1863) recording my objection to the remarks made by Dr. Abrams of the DOH during the course of the meeting. Suffice it to say that the meeting was not particularly effective. The question of

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what tests were to be developed and introduced and how they were to be applied was largely a financial one, for which the DOH was responsible for clear guidance on policy, subject to advice from experts.

777. At paragraph 7 on page 4 of the minutes of the RTD meeting under the heading "AIDS", there is a record of the discussion which took place on that subject. Dr. Gunson gave information regarding the publication of a new leaflet which was then due to come out on the 1st February 1985. Dr. Contreras was asked to report on the status of HTLV III testing but, as yet, there was no date for the availability of a test for a pilot study. There was reference to the anti-core test proposed to be evaluated at Edgware on stored samples. This was to assess the value of hepatitis B core antibody as a surrogate marker, in a Region where the incidence of viral carriers reflected the metropolitan high risk status. The minutes continue in relation to HTLV III testing:-

> "Most companies are approaching RTD's (these are a ELISA tests). The preference within the NBTS is for an RIA technique. Dr. Gunson is to pass this information to the DHSS. The suggested cost is in the region of £2 per test. The meeting felt strongly that we should not be pressured by commercial sources to accept a test which is not ideal for our purposes and that we should act together. The DHSS should be pressed to make any test available to the community before its use in blood donor screening, otherwise unsuitable donors will be attracted."

778. This last point was a reference to people who were "at-risk" in the community presenting themselves for blood donation purposes simply to get a "free" test and the need to ensure that alternative test facilities for "at-risk" categories were introduced (ahead of BTS testing) and available at hospital clinics which they would ordinarily attend.

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779. The subject of AIDS testing came up at the CBLA meeting (the 16th) which took place on the 1st February 1985 (document no. 1932). The minutes record at pagagraph 8/85:-

> "The Director advised that if given the antibody BPL could produce a test as an alternative to the Chester Beatty's work in association with industry, at a much lower cost. Dr. Gunson confirmed the necessity for the test and referred to a Departmental Working Party considering the matter. It was noted that the CBLA role in this matter was not yet established, but there could be a related capital requirement for equipment for RIA tests. The Chairman stressed that revenue sparing was as important as saving. Dr. Gunson emphasised that the enzyme assay was a United States test and if the United Kingdom needed to be converted for enzyme testing, it would pose a serious problem for the continuance of RIA testing. It was therefore considered vital that a British test be developed."

780. The BTS was equipped for Radioimmunoassay testing for hepatitis B. The introduction of ELISA for HIV antibody would require alternative capital equipment in all centres. This explains Dr. Gunson's reluctance to convert to enzyme testing.

781. Mr. Williams and Dr. Gunson (in his capacity as Consultant Adviser to the DOH) represented the DOH at this meeting, and were therefore aware of the offer on the part of BPL to become involved in developing an RIA test. Nothing came of this suggestion.

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782. In a letter published in the Lancet on the 23rd February (document no. 1990), Dr. Pierce from Washington University School of Medicine commented that most haemophiliacs in the USA and Europe were sero positive.

783. On the 21st March, Dr. Snape prepared a note (document no. 2026) of a telephone conversation which he had with Dr. J.S. Finlayson of the Office of Biologics in the USA (FDA) on the subject of testing in the US. Dr. Snape records:-

> "Following release of HTLV III Ab test kits, all manufacturers have agreed to include the test in their plasma release protocol. Currently the statistics on testing show 0.6% positive on first test, 0.3% on best of three, 0.2% positive "confirmed" by Western Blot. (In retrospect these figures seem high for the general population."

784. The commercial tests for HTLV III had been licensed by the FDA in March 1985. I believe the Abbott test was the first test to be released. The tests at that time had an unacceptably high level of false positives, which had real implications for advice to donors and created problems with secondary testing.

785. The first reference in the CBLA's documentation to the RIA test which was eventually introduced in the UK, is to be found in the minutes of the CBLA meeting which took place on the 27th March (document no. 2033) where the following appears:-

> "23.1 <u>HTLV III virus - RIA test</u>
>
> "The Chairman said that he had written to Mr. A. Williams, DHSS, in the light of a request from Wellcome Diagnostics for the

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Authority's assistance by distributing their HTLV III test. Mr. Williams confirmed that Wellcome was still developing the test and they had not yet approached DHSS on this issue. He added that PHLS would need to carry out field trials on the product and that production would probably not take place until the end of the year. There was therefore a period of approximately 9 months to consider distribution arrangements.

"Dr. Gunson enlarged upon current trials taking place within the NBTS, and it was noted that the samples would be available in April."

786. Wellcome Diagnostics developed a test in conjunction with the Middlesex Hospital. The opportunity which BPL itself presented to the Middlesex Hospital was not taken up. The Transfusion Service at that time were using the tests as they became available. A serum bank of donor samples was set up, so that samples could be tested as and when better tests came along. The introduction and evaluation of tests was very much a concern of the Transfusion Service, who would in time be required to perform the tests anyway.

787. The US position featured again at the meeting of the CBLA Central Committee for Research and Development in Blood Transfusion which took place on the 2nd April (document no. 2038). At that meeting the Chairman confirmed that five US companies had been asked to set up screening tests in 1984 and that two firms had now been licensed by the FDA for the test which meant that exported tests from the USA could be used in other countries. Dr. Gunson who chaired the meeting highlighted possible problems for the Blood Transfusion Service as a result of the introduction of the test:-

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"(a) Obtaining a proper valuation (sic) with the US test on donor population would be difficult, and the UK might have to consider doing its own.

"(b) The implication of the test was not really known. Positive test indicated that donor had been exposed to virus but may exhibit no signs of illness. The 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 the test unilaterally.

"(d) If tests were not introduced simultaneously in the UK, public concern was possible if certain regions fell behind schedule.

"Dr. Smithies reported that evaluation studies of the tests had been set up. A protocol for the evaluation had been sent to manufacturers and results would hopefully be received by mid-May. It was noted that the DHSS expected to publish the results of the evaluation to the NHS....

"The importance of evaluation of the tests was emphasised and it was agreed that an adequate confirmatory laboratory service was required, especially in view of the high incidence of false positive results.

"In answer to a question raised by the Chairman about testing in the haemophiliac population in the UK, Dr. Rizza and Professor Luzzatto informed the Committee of tests they had carried out at Oxford and at

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the Middlesex Hospital, and the results of these had confirmed the importance of evaluation."

788. HIV antibody status became implicated in the transmission of the virus following the development of an HIV antibody marker test. As soon as an HIV antibody marker test was developed, it was applied to patients who had become infected with AIDS and to members of the epidemiological groups who were by that time implicated in the disease development. The first groups looked at were homosexuals and, within this group, positive tests were found in both individuals suffering from AIDS and individuals who were not clinically suffering from a defined disease at that time. The association developed quite rapidly thereafter. As soon as it was appreciated that haemophiliacs had AIDS they were tested. After the first reported case of an infant in Los Angeles who had developed AIDS following blood transfusion, high risk blood donors were looked at quite quickly and found to have significant levels of antibody marker positivity. Therefore from the outset of testing, there was an immediate association between infection and HIV antibody marker positivity.

789. The tests being used at Oxford were initially immunafluoresience and, after it became available for evaluation, ELISA. They were gathering data on the HIV antibody status of the haemophiliac population and to some extent they were investigating the efficacy of the tests themselves.

790. Our position on the introduction of testing was not to pre-empt the introduction of testing in the Regional Transfusion Centres insofar as it has always been a policy to adopt the standard of testing used by the BTS for the blood to be transfused and plasma to be used for fractionation. We were following the progress of testing which might be appropriate for validation on the finished products (but as I have already said, these are not representative of

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whole plasma). Our security of product was believed to come through the introduction of heat inactivation insofar as the antibody screen would not necessarily guarantee the non-infectivity of all plasma.

791. The validity of the tests becoming available created some real cause for doubt and there was the question of sensitivity: we did not believe the incidence of HIV in the donor community at that time was high and this was subsequently shown to be true. Therefore, there was a lot of uncertainty about the relevance of the test at that time.

792. At the 195th meeting of the Regional Transfusion Directors (which I did not attend) on the 17th April 1985 (document no. 2057), there was reference at paragraph 7 to the arrangements which were being made for the appraisal of HTLV III tests:-

> "Dr. Gunson informed the meeting that it is intended to collect 10,400 donor samples - this is to be funded by DHSS who are also being pressed to purchase the kits (the likely cost is £25,000).
>
> "The first 1,500 samples will be tested in the PHLS, together with known panels containing samples of high risk groups. If the initial appraisal is satisfactory, then the survey will be extended to the Transfusion Service. All kits will be tested against the same samples and all firms have agreed to comply. (Only two are approved at present). RTC samples will be required by mid-May and testing will be carried out during the summer. No decision has yet been taken on Centres undertaking this. The results will be available to all RTC's.

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"It is stressed that uniformity of action is essential amongst RTC's; 1st October is suggested as the starting date.

"A standard will be established by PHLS at Colindale who will send out samples for external quality control."

793. A circular published by the World Haemophilia AIDS Center appears in the CBLA's files during June 1985. I am not clear how this came to our attention and the circular itself is not dated, but it deals with events in the first few months of 1985 and contains some interesting information. The circular (document no. 2125) notes that:-

- HTLV III test kits were approved by the US Food and Drugs Administration on the 2nd March 1985 and that three firms, Abbott Laboratories, Electro-Nucleonics Inc., and Litton-Bionetics had been licensed to market kits.

- that the American Red Cross immediately signed an agreement with Abbott and announced plans to begin phasing in the test within days.

- US government officials had stressed that the new blood test must be used cautiously because it was neither error proof nor a diagnostic test for AIDS.

- the antibody test was a good test for screening of blood but a poor test for the diagnosis of patients.

794. The circular also contains a summary from the ABRA Newsletter circulated in March 1985. Part of this summary reads as follows:-

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"Blood and plasma collection facilities in the United States are preparing to implement HTLV III antibody testing. All major fractionators have stated their intent to test. Some reagent companies have decided to require testing. The German Bundesgesundheitsamt (BGA) has decreed that plasma and plasma products exported to Germany after October 1 1985 must be tested (which amounts to 15% to 20% of American plasma activities). By April or May, a blood/plasma industry standard will have been established so that anyone who is not testing will be potentially at risk to adverse legal consequences.

"The US Food and Drug Administration (FDA) is expected to call for testing of all blood and plasma collections used for transfusion and further manufacture into both injectable and non-injectable products.

"Further operational testing means: testing all blood and plasma collection; informing donors of testing programme in advance of donation; rejecting and destroying reactive blood or plasma; permanently deferring reactive donors from further donation; placing reactive donors on deferral lists; advising reactive donors of test results; referring donors to local medical or public health officials for more extensive tests; counselling and medical evaluation; and, where appropriate, reporting reactive donors to state or local agencies."

795. The US industry introduced tests once they were licensed. The test was applied on the donor at the time of donation. The same would have occurred with the US Red Cross: they implemented use of the Abbott test when it became available.

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796. The question of testing came up again at the 6th meeting of the Central Committee for Research and Development in Blood Transfusion held on the 9th July 1985 (document no. 2136). The relevant part of the minutes reads:-

"10.1 Anti-HTLV III Testing in the NBTS

"The Chairman **[Dr. Gunson]** confirmed that there were five company tests now available for anti-HTLV screening. It was his view, however, that 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. By not knowing the prevalence of antibodies in the donor population, the BTS was yet unaware of the most effective test especially as far as false positive results were concerned. It was noted that 6,000 donor samples were due to be tested at Edgware and Manchester and 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 referred to his capacity of Chairman of Haemophilia Centre Directors and 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 of Factor VIII. He therefore considered that any undue delay in introduction of the tests would be unreasonable.

"Dr. Lane informed the Committee that excess plasma products released onto the market from BPL were likely to require licensing by FDA and, in addition, any intermediates shipped to other manufacturers could also precipitate inspection of BPL's facilities and the plasma collection centres by FDA in due course. He said that part of the FDA requirement would

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be routine screening of donations by an FDA approved test for HTLV III antibody. The Chairman said that it was possible that an FDA approved test was not necessarily the most appropriate for the BTS.

"It was agreed that DHSS should be made aware of Dr. Lane's comments via the CBLA."

797. The five products undergoing evaluation at the time were produced by Organon, Dupont, Abbott, Electro-Nucleonics and Litton-Bionetics. A test panel was being established for use of any new test that came up. We did receive enquiries for the sale of Fraction II: I said that if we were to make any sales, we would be required to fall into line with FDA requirements of fractionation i.e. the receipt of tested donations. Further, the BPL should follow the requirements being established by the FDA. It is important to note that my comments were to be passed to the DOH. Any proposals to apply a test, would have referred to a test at blood donation level, which is the appropriate stage to do so.

798. The 196th Regional Transfusion Directors meeting (minutes document no. 2137) held on the 10th July 1985 (which I attended), involved further discussion of AIDS testing. The minutes record at paragraph 5:-

"AIDS

"The Chairman reported on a number of meetings. One group involving 2 RTD's from each division and Dr. W.B. McClelland from Edinburgh had met with Dr. A. Smithies (DHSS) and notes from this meeting had been circulated to all BTS consultants. It was stressed that a UK approach to the problem is essential. It was felt not essential to have the GP's name in all instances but that all donors must be informed that testing will be

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carried out. A leaflet would be helpful for donors and should be distributed by all means necessary.

"The NBTS 110 [an AIDS leaflet] should be updated.

"Obviously HTLV III positive donations would be destroyed. The initial approach to such a donor would be from the NBTS and afterwards counselling would be essential. We looked to the Expert Advisory Group [on AIDS] for guidelines but GP's should be involved, with the donor's consent.

"It was agreed that follow up of previous donations of plasma should be for 3-5 years.

"The Chairman requested the approval of the Meeting to let the Group draft a flow diagram for AIDS testing and follow up of donations. The meeting tomorrow will, if given approval, pass on recommendations to the Expert Advisory Committee (Group) and save considerable time.

"Dr. Gunson reported on the situation so far:

"(a) It is hoped shortly to begin the NBTS testing and evaluate the results rapidly since there is much media pressure.

"(b) Professor Glynn from Colindale had requested formally a BTS representative for the PHLS Working Party, and Dr. Fraser was nominated. **[This Working Party monitored the AIDS programme. It was felt that BTS should be represented on it.]**

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"(c) Dr. Taylor and Colindale have prepared a Quality Control panel of heat treated sera which are available on request. If any RTC has any weak confirmed positives, they are requested to send them. **[These are examples of sera which are borderline in tests for HIV antibody. To be sent to Colindale to be added to test panel of sera to be evaluated on new kits.]**

"Dr. Tedder has requested reporting of post-transfusion illnesses which are possibly infective.

"The reports of the evaluation will be reviewed and distributed through Regional General Managers and in journals.

"Concern was expressed that high risk members of the general public might be attracted to Blood Donor Sessions in order to obtain testing, and strong feelings were expressed that publicity should be used positively to deter this happening. Dr. Smithies reassured the meeting that concern was felt centrally on this matter and the message would be reinforced on testing and counselling. Dr. Smithies requested nomination of two representatives from each RTC to attend a Special Counselling Course.

"Directors felt that two types of course are needed. One approach is needed for a voluntary donor and advice and a suitable introduction into a specialised counselling service can be arranged. This is quite different from the present situation where the facts are concentrated on sexually transmitted diseases and known patients.

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"Stress was placed on the fact that Regions have been instructed to make provisions for undertaking testing although at present techniques are not yet decided. It was pointed out that time will be required for recruitment and training of staff and for obtaining equipment. The PHLS report will indicate the preferred tests and will trigger the full evaluation in the NBTS on donor samples. [I do not have the report produced by the PHLS]

"The results will be presented and RTD's will be able to decide on testing procedures. Firms have been asked for details of charges, equipment and availability. Regions have been asked to make provision but RTD's agreed that time would be required to establish routine testing, since accommodation, equipment and staff training will be necessary once it was known which test would be in use. A definite date had not yet been given but some time in October was the objective."

799. At its 19th meeting, the CBLA noted the position with regard to anti-HTLV III testing. The minutes of the 20th meeting on the 18th September 1983 (document no. 2171) contained at page 2 a more specific reference to test kits:-

"There followed discussion on test kits for the presence of HTLV III virus. The Chairman said that tests produced by Organon were nearing approval for use in the UK. Mr. Williams confirmed that DHSS were currently discussing the test with RTC's, whom it was noted were ready to place short term contracts for the tests with the two pharmaceutical companies mentioned. He expressed the view that short term contracts would be appropriate in the first instance in the likelihood that further tests, as time passed, would improve and be more convenient to use.

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The Director of BPL agreed to keep the Authority informed about progress in regard to HTLV III test developed in the UK."

800. The point had been reached where the Organon and Wellcome tests were nearing approval. This was information which came from informed sources being the manufacturers, the PHLS and the DOH. The assessment of all tests was being carried out by the PHLS at Colindale, who were reporting to the DOH about the observed effectiveness of the tests becoming available. The strengths or weaknesses of the tests were the presence or absence of significant numbers of false positives requiring re-testing or confirmatory results. The BPL were waiting for the Blood Transfusion Service to introduce donor testing. The choice of test was made on advice given by the PHLS and the DOH, as did the timing of its introduction.

801. On the 27th September 1985, a report entitled "Interim Report on Survey of HTLV Antibody in Haemophiliacs in the UK" (document no. 2176) was prepared by Drs. Rizza and Spooner at the Oxford Haemophilia Centre. This is a very useful report in that it provides a summary of all haemophilia patients tested for HTLV III up to August 1985. At the relevant time, returns had been received from 81 of the Haemophilia Centres (74%). A total of 2,570 patients had been tested. 44% of haemophilia A patients tested were found to be positive, and the prevalence in severe haemophilia A patients was 59%. The level of HTLV III antibody in patients suffering from Christmas disease was, however, much lower with only 6% of those tested being found to be positive. Although Factor IX was less likely to transmit HIV based on the manufacturing process used, I cannot help speculating, as indeed I have done previously, that this might in part be evidence supportive of the contention that blood products made from English and Welsh plasma donations would have been inherently safer than the equivalent commercial product so far as HIV was concerned.

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802. By 1985, Factor IX was being made at Elstree and finished off at Oxford. This being the case, the lower incidence of HTLV III antibody in haemophilia B patients cannot be attributable to treatment with smaller pool products (manufactured exclusively by PFL) than those used at BPL for the manufacture of Factor VIII. The figures are therefore indicative of the low incidence of HIV in UK source plasma. The incidence of infection in haemophilia B patients was very low as a result and the same incidence of infection might have been seen in the recipients of NHS Factor VIII. This supported the view that clinicians should be encouraged to treat their patients with UK non heat-treated Factor IX.

803. Factor IX had transmitted Non-A Non-B hepatitis effectively and was therefore known to be capable of transmitting virus. Severe haemophilia B patients are treated with substantial amounts of Factor IX concentrate and thereby exposed to an equivalent risk as patients treated with Factor VIII.

804. The introduction of screening at Regional Transfusion Centres may be seen from the minutes of the 197th meeting of the Regional Transfusion Directors held on the 9th October 1985 (document no. 2191) at which I was present:-

> "Anti HTLV III screening is in hand and training completed. All RTC's will start full testing by the 14th October 1985. Discussions took place over fresh blood products in stock, i.e. FFP cryo and frozen blood. The matter had been raised at Divisions and RTC's differed. Some felt they could not support discarding untested donations. Wherever possible back-testing would be carried out on in-date material. It was felt important that BPL should accept and process FFP and time-expired plasma for

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> heat-treated products. Dr. Lane stressed that such material must be clearly identified and BPL given notice."

Later in the minute there is reference to the fact that RTC's were apparently using the kits from Wellcome and Organon in the proportion of about 2 to 1.

805. The introduction of testing at the BPL was in December 1985. I refer to Appendix 8 "History of HIV Antibody Screening at BPL". **[Dr. Lane this history relates to tests on the finished product:. We need more detailed information on the introduction of testing of plasma upon receipt at BPL [P32]].** As a result of a directive from the DOH in 1986, NIBSC were required to perform tests on the finished product.

806. In a document prepared for the 11th meeting of the Advisory Committee on the National Blood Transfusion Service which took place on the 6th November 1985, the DOH set out the position with regard to the AIDS leaflet, HTLV III antibody testing, RTC staff training in counselling and confirmatory testing. The paper is designated AC(85)4 (document no. 2200). The document refers to the issue in September of the new national leaflet "AIDS - important information for blood donors". With regard to HTLV III antibody testing, the note records that:-

> "In February 1985, the Department alerted RHA's to the need to fund the introduction later during 1985 of routine testing for HTLV III antibody of all blood and plasma donations."

It records that the Department funded a two stage evaluation of various commercial kits; the first stage at PHLS being completed in July 1985 and the field work of the second stage involving two RTC's completed in September 1985. Preliminary advice arising from that second stage had, it said, been given to

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RTD's. The documentary evidence for this is doubtless contained in the records of the Regional Transfusion Centres.

807. With regard to confirmation testing, the note records that the Department had given £750,000 to the PHLS to provide laboratory facilities which would include confirmatory testing of samples from blood donors found sero positive in initial donation screening. The minutes of the meeting held on the 6th November (document no. 2202) record the simultaneous introduction throughout the UK of HTLV III antibody screening with effect from the 14th October. Dr. Smithies of the DOH is also reported as saying that the latest CDSC's figures showed 241 cases of AIDS with 134 deaths.

808. One of the documents which I believe was made available for the 16th meeting of the UK Haemophilia Centre Directors held on the 21st October and which was forwarded to us on the 12th November, is of interest. This is a note entitled "Surveillance of cases of AIDS and AIDS related illness" and its author is Dr. Craske. (document no. 2204(e)). This was a product of the UK Haemophilia AIDS Group and reported that:-

- By 1st October 1985, there had been 10 cases of AIDS or AIDS related disease in haemophilia A patients, one case in haemophilia B patients and one case in a spouse of a haemophilia A patient.

- by August, there were 834 HTLV III antibody positive haemophilia A patients, giving an incidence of 1.1% for AIDS

- 3 cases of AIDS occurred in patients with mild haemophilia where exposure to high risk blood products occurred on one or two occasions only

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- Dr. Craske, Dr. Snape and Dr. Spooner were to review the latest information on possible infected batches of Factor VIII concentrate (and especially HL3186)."

809. The problems of infected plasma follow-up are covered in Dr. Snape's Proof of Evidence, to which I refer.

810. At the 7th meeting of the Central Committee for Research and Development in Blood Transfusion held on the 19th December (document no. 2212), it was noted that:-

"Routine testing of blood donors had commenced in October

- all BTS Centres had commenced testing at the same time

- all but four Regional Transfusion Centres were using the Wellcome test. The other four were using the Organon test

- the MRC had set up a sub-committee of the Working Party on AIDS to carry out an epidemiological research programme on the transmission of HTLV III virus.

[Dr. Lane: you were awaiting more information from David Donald and Terry Snape - we need a retrospective summary of 1985 touching upon the FDA approval to the US tests identifying who took the decision not to introduce these tests for use by RTC's or BPL/PFL, but instead evaluate these and certain other tests. The evaluation process and time tabling needs to be briefly summarised with particular reference to what was eventually done within

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BPL/PFL. The possible argument that whatever the position with regard to RTC's, BPL/PFL should have introduced testing with whatever was available at an earlier date pending evaluation of all available test kits should be addressed and dealt with [P33]].

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SUMMARY OF AIDS/AIDS RISK CLAIMS AND SCREENING OF DONORS AND TESTING FOR HIV

AIDS/AIDS RISK

811. Those particulars of negligence and/or breach of statutory duty by the CBLA in relation to the AIDS risk in the NBTS which are at pages 112-113 of the MSC are dealt with below.

812. (95(ac)) From 1982 or such later time as may be justified on the evidence at trial, the CBLA should have been aware of the emergence of AIDS and its implications and acted in the light of that;

This is a very general allegation and, as will be seen from the description of events set out above, all interested parties including CBLA were as up to date as possible at any particular time given that the majority of information was, at least initially, generated in the United States and only subsequently was research undertaken in the UK. The CBLA pressed forward with its research into inactivation of viruses using heat treatment and development of processes to be applied to Factor VIII and Factor IX concentrates in the light of scientific information, confident that it would be a solution to the HIV problem, as events subsequently showed. For reasons I have touched on above, the alternative of small pool methods of manufacture would not have been practicable and in any event would not have offered total protection against HIV, given that we were only in a position to provide a proportion of the Factor VIII required for the treatment of haemophiliacs in England and Wales. We were committed to the research we were carrying out on heat treatment and by the time HIV was identified and found to be heat labile, we were poised to introduce a new high purity concentrate which was extremely tolerant to heat treatment and in the

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interim, we acted by making available the existing intermediate product in a heat treated form in replacement of non-heat treated Factor VIII.

813. Plasma screening per se cannot be taken as the definitive procedure for virus exclusion in the finished product. Whilst it will assist with a reduction of the viral load in a fractionation pool, it requires a defined process in fractionation to ensure that any virus present will be inactivated and therefore rendered non-infectious. The priority for any fractionator is an inactivation process for virus. Progress with the control of Non-A Non-B hepatitis is a precise example of this, where the fractionator controlled transmission of this virus before it had been defined, or visualised or a marker test produced. At the end of the day, screening does not avoid virus activity in the fractionation process.

814. (95(ad)) The CBLA should thereafter have been keeping itself informed of advances in learning and experience in respect of AIDS and acted in the light of that;

As will be seen, my membership of various Working Parties and my attendance at the regular meetings of experts in this field meant that at any given time, CBLA was, through me and through members of CBLA such as Dr. Gunson (who had an even wider attendance at these various meetings), as up to date as anyone could be with regard to AIDS.

815. (95(ae)) The CBLA should, in particular, from 1982 have known of the growing suspicion in the USA of a connection between AIDS and the supply and use of blood products and the facts and matters pleaded in paragraph 60 hereof and acted in the light of that;

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Paragraph 60 sets out the chronology of the development of knowledge and information regarding AIDS, but it should be noted that very limited information came from the US during 1981 and, of course, this was very early in the history of AIDS with the result that there were no clear indications at all as to quite what caused AIDS. **[Paragraph 60 will be considered in greater detail after a paragraph by paragraph review with Dr. Lane in the next draft].**

816. In or about the middle of 1982, the first suggestions that AIDS might be linked with blood transfusion and blood products appeared in the scientific literature. Again, whilst this link could be speculated upon, the agent at work was completely unknown, and there were only a few reported cases in the US and none in the UK.

817. It was not until the spring of 1984 that the causative agent for AIDS was confirmed by which time we were well advanced with our programme of research into heat treatment which was clearly the only practical solution to the HIV problem, aside from screening. Our first heat treated intermediate product was available on a trial basis from about the time HIV was identified and introduced from the start of 1985 in light of the information in the autumn of 1984 that the virus was heat labile.

818. Even if one accepts (which I do not) that it was possible to infer from what little was known in 1981, 1982 and, for that matter, 1983 about a causative agent of AIDS that it was indeed a virus and susceptible to heat treatment, it is difficult to see how our programme of research and development into heat treated products could have been accelerated, with respect to HIV (then generally undefined when the programme was orientated to inactivation of hepatitis NANB). It must be remembered that the various commercial companies who had heat treated products available from about 1983 onwards had developed these not as a

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result of any response to HIV, but because they had been working on programmes to tackle hepatitis B and Non-A Non-B. In the event, it seems in retrospect that the early commercial heat treated products which were available were not safe in respect of hepatitis B/hepatitis Non-A Non-B and subsequently showed that some regimes of heat treatment even failed to inactivate HIV.

819. (95(af)) Failed, from 1982 to pay any or any sufficient regard to the risk of AIDS to which haemophiliacs were exposed by treatment of Factor VIII and Factor IX concentrate, whether home produced or commercial.

This is really subsumed in answers to other points under this heading and Screening of donors and Testing for HIV.

820. (95(ag)) Failed, from 1982 to set in train any or any sufficient steps to remove, alternatively reduce the risk by:-

(i) eliminating the need to use imported (non-heat treated) commercial Factor VIII concentrate;

(ii) proper screening and/or surrogate testing of donors as hereinbefore particularised alternatively advising Health Authorities to perform such screening and/or testing;

(iii) heat-treating both Factor VIII and Factor IX concentrate;

(iv) requiring the reduction of pool sizes of donated blood for home-produced product; alternatively advising such reduction;

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As regards (i), this really relates back to self-sufficiency and the CBLA's efforts with regard to increasing production are dealt with elsewhere, save that this is not an allegation which can be supported on the facts. As regards (ii),

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this is dealt with above under screening for HIV. With regard to (iii), this is dealt with under the heading "Heat Treatment".

821. So far as (iv) is concerned, as I have indicated above, the Oxford small pool experiments were not successful in relation to hepatitis Non-A Non-B, and it is uncertain what, if any, protection small pools would have provided in relation to HIV. Such a massive re-ordering of the approach to producing concentrates would have been a major undertaking, even had it offered the prospect of material protection. Large pool methods of manufacturing concentrate were in general use not only in England but also in Scotland, the United States and in other countries in Europe (e.g. West Germany and France). For the severely affected haemophiliacs frequent recourse to treatment would involve use of equivalent Factor VIII related donor exposure, whether from fewer large pool products or greater numbers of small pool products.

822. By the time this solution could be considered, i.e. by the stage the HIV virus was identified in the spring of 1984, our work on heat treatment was advanced and was to provide the solution to the HIV problem and would have been applied to Factor VIII whether of large or small pool origin: in the latter case, economies of scale in yield would have been absent and the product output significantly reduced.

823. (95(ai)) Failed from 1982 until times which the Plaintiffs cannot yet particularise, either sufficiently or at all to volunteer advice, guidance and warnings in respect of the risk of HIV of Factors VIII and IX concentrates produced at the BPL to both the Department of Health and the Health Authorities;

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824. Given that BPL/PFL had no role (and no funds to perform one) in the research into HIV, we were in a position of having to interpret the results of research from the United States and from that which was undertaken in the UK. The results of that research was available to all parties including the DOH and the Health Authorities who were well aware, as can be seen from the meetings which they attended and to which I refer above, of the implications of that research. In this context, BPL/PFL volunteered such advice, guidance and warnings as could be given as is apparent from the records of the various meetings. The advice given to clinicians treating haemophiliacs was augmented by Directors from within the Haemophilia Service and the DOH. I refer also to Appendix 9 which covers advice given by BPL/PFL or by me (in conjunction with others) both in relation to the product and generally.

SCREENING OF DONORS

825. Turning to the specific allegations made in the MSC against the CBLA in relation to the issue of screening of donors and testing for HIV and dealt with at pages 109-111 in the MSC, there follows a summary of what I have said above.

826. (95(s)) Failed from 1982 to consider properly or at all the possibility of of screening donors by "surrogate testing" namely testing donated blood for evidence of abnormalities of the immune system thought to be associated with AIDS or testing for hepatitis B;"

As indicated above, surrogate testing was really not possible until such time as a reasonable amount of information regarding the cause of AIDS was available. In my view not enough was known until the actual identification of HIV which occurred in the early part of 1984, and the initiative taken by Dr. Wallington and others to pursue anti-HBc as a possible surrogate test followed

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very quickly thereafter. The same approach was adopted in the United States (there were no other surrogate tests in general use in the United States before this time) but was very quickly overtaken and rendered redundant by the work of commercial pharmaceutical companies on a test for the HIV antibody which was clearly much more productive than spending time and money trying to develop a surrogate test.

827. I think it is clear from the description of events set out above that 1982 and for that matter most of 1983 was a period of great uncertainty with regard to the cause of AIDS and that any consideration of surrogate testing before a positive identification of the cause (given the administrative and financial demands wholesale surrogate testing would have involved), was really unrealistic.

828. (95(t)) Failed from 1983 or such later time as may be justified on the evidence of trial, to appreciate properly or at all the categories of HIV high risk blood donors and act accordingly by confidential advice to Health Authorities;

It is a little difficult to understand this allegation and therefore to respond to it. The obvious high risk category of blood donor from about 1983 onwards, based on information from the United States, was the homosexual or bisexual and later those involved in drug abuse, and this was picked up in the leaflets which were made available to potential blood donors and were prepared at the initiative of the Blood Transfusion Service and the DOH. **[NB: the 1983 leaflet referred not to bisexuals but to "homosexual men who have many different partners": was this too narrow?].** These high risk categories were very well appreciated by all concerned as demonstrated from the publications which were put out and the discussions of the various experts during 1983 and 1984 which

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were attended by representatives of the Blood Transfusion Service, the DOH, the Haemophilia Centre Directors and BPL/PFL.

829. (95(u)) From 1983, or such later time as may be justified on the evidence of trial, CBLA should have advised Health Authorities to refuse and/or to mark for non-use and destruction blood offered by prospective donors who on enquiry revealed themselves to be or on impression and examination appeared to be homosexuals, bisexuals or intravenous drug abusers.

Again, I think the "at risk" categories with regard to blood donors were perfectly apparent to all concerned from about 1983 onwards. As a result of publications and donor leaflets, self-exclusion of donors in high risk categories was successful. Homosexuals and other people at risk behaved responsibly; so it would appear that people were aware of the problem.

830. (95(v)) Failed, from 1983, to consider sufficiently or at all whether Health Authorities were applying and enforcing what instructions as to screening of donors were in fact being issued by the Department of Health and to encourage and advise the Health Authorities to act accordingly.

Activities relating to donors are the concern of the Regional Transfusion Centres which were under the control of Regional Health Authorities, in line with such policy as may be laid down by the DOH. They were as aware as anyone of the problem then posed by AIDS and the need to do what was possible, given the absence of any screening test, to preclude donors from high risk categories. It was not a role that BPL or PFL had. In the circumstances, it was not part of PFL/BPL's responsibilities or for that matter the CBLA to police the action taken by Regional Transfusion Centres.

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831. (95(w)) Failed, from mid-1984 or such later time as may be justified on the evidence of trial, to encourage and advise Health Authorities to introduce and impose in their respective regions or districts or fields of activity, routine testing of donated blood for HIV;

There were no licensed tests available from mid-1984 until March 1985. There were two "prototype" tests (invalidated for use in production and with finished products) referred to previously, but here again it was not for BPL/PFL to enforce or police the use of these tests which were not entirely satisfactory with regard to the quality of their results. Activities concerned with the routine testing of blood for HIV were the responsibility of the National Blood Transfusion Service in accordance with policy laid down by the DOH. It is a duty of the Transfusion Service to deal with routine testing of donor plasma.

832. (95(x)) Failed, from mid-1984 or such later time as may be justified on the evidence of trial, to introduce routine testing of donated plasma received at the BPL for HIV antibodies and/or antigens and/or such routine testing of its final product;

833. Routine testing was introduced for final product in December 1985 following the co-ordinated introduction of testing by the BTS of blood and plasma donations, using evaluated tests approved by the DOH.

834. (95(y)) Accepted and/or adopted and/or encouraged the policy of the Department of Health of not introducing such testing, in the belief that the test methods were not sufficiently reliable; in accepting and/or adopting and/or encouraging such a policy, CBLA was in error and, given

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the nature and gravity of the HIV infection risk and the urgency of the situation, it was negligent;

As I have described above, validation of early HTLV III antibody tests produced a high rate of fale positivity, indicating a higher proportion of antibody carriers in the population than was in fact the case. Follow up of antibody positive donors (including counselling etc) was a legitimate concern of the Blood Transfusion Service, which was concerned with the interests of donors.

835. In July 1985 I pointed out that excess plasma products released on the market by BPL were likely to require licensing by the FDA: part of the requirement would be routine screening of donations by an FDA approved test, for HTLV III antibody. Moreover, my comments were to be passed to the DOH.

836. At BPL, our priority was to concentrate on inactivation of HIV by means of a valid heat-treatment process. By the time the FDA had licensed 2 HTLV III antibody tests in the United States, BPL were only issuing heat-treated Factor VIII.

837. (95(z)) The CBLA did not introduce routine testing of donated plasma received at the BPL and/or of its finished product until in or about October 1985 or such later date as may be revealed on discovery or in evidence at trial,

It has never been CBLA's role to test donated plasma received at BPL, for HIV antibody. The test was in fact introduced at BPL in [Dr. Lane please insert date], and on the finished product in December 1985. The test is carried out on a sample of a donor pool of some 15,000 donations: the diluting effect of

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the pool can be such as to place an infected sample below the sensitivity of the HIV antibody test and the antibody presence will not be found. For this reason, the most important test is that carried out (as a mandatory requirement) at the Regional Transfusion Centres.

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V. HEAT TREATMENT

OVERVIEW

838. Whilst it is true, as the Plaintiffs point out in the MSC, that heat treatment by pasteurisation had long been applied to one blood product, (albumin) over many years, it was not applied to products used to treat haemophiliacs until the start of the 1980's. Of course prior to the increase in the use of concentrates during the early 1970's treatment was mainly in the form of cryoprecipitate infusion, and cryoprecipitate was not stable during heat treatment. The implications arising from pooling of plasma had not arisen and treatment of haemophiliacs at that time involved lower levels of dose than is now practised. The emphasis was not on home prophylactic treatment, but on infusing cryoprecipitate in hospitals in response to bleeding. The investigation of hepatitis in haemophilia was necessarily in its early stage and possible applications for viral inactivation had not yet become apparent.

839. With the advent of concentrates, the studies by Dr. Craske and others of those treated with concentrates revealed through the 1970's that there was a problem with regard to hepatitis B infection (this of course was not unique to concentrates since cryoprecipitate carried a risk of infection as well).

840. The effect of hepatitis B in haemophiliacs was mitigated by the introduction of donor screening at Transfusion Centres aimed at eradicating hepatitis B transmission by blood and its derivatives. Thus it was, that control of hepatitis B in haemophiliacs was targeted through donor screening and later by active immunisation of patients rather than by applying some modification to the production process.

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841. Towards the end of the 1970's, again as a result of the research into hepatitis infection, it emerged clearly that other viruses collectively known as hepatitis non-A non-B could not be tested for, but could produce both clinical and sub-clinical infections in patients with potentially serious sequelae. By the early 1980's it was recognised that all Factor VIII concentrates were liable to transmit these viruses to a similar extent. In contrast to hepatitis B, NANB hepatitis could not be controlled through donor testing until very recently and there is no means of active immunisation of patients yet available.

842. It may be suggested that, notwithstanding the way in which hepatitis B was effectively controlled, thought might have been given to viral inactivation of product during the 1970's and, more particularly, when, towards the end of the 1970's, knowledge of the existence of NANB hepatitis had reached the point where it could be said that infection was virtually inevitable the moment a patient was treated with concentrate for the first time (whether commercial or NHS).

843. There are a number of answers to this. In the case of cryoprecipitate and early concentrates, it was believed that instability of the Factor VIII (and in particular accompanying proteins) would cause major problems if further process modifications were introduced. Support to this view came from the significant reduction in yield of Factor VIII which followed any attempt to increase purity of the product. This potential loss of yield required that any alteration to the process should be fully justified, for example by clinical demand. In the early 1970's demand was not clearly evident. Secondly, the economics of Factor VIII yield required that best use was made of the plasma source available at that time since the price benefits linked to the purer products made by the industry were not then relevant to the Blood Transfusion Service.

844. Early consideration was given in 1982 of ways in which virus in our products might be inactivated following the first confirmed reports that NANB hepatits, whilst not responsible for an acute severe illness, did after some years

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and in a significant number of patients cause chronic liver disease. We were aware that early attempts by commercial manufacturers to produce virus inactivated products by heat-treatment had resulted in severe loss of yield, which was not only unacceptable in our view but also failed to eradicate virus transmission. In a product required repeatedly by an individual patient, for virus inactivation to be effective, it must be virtually complete if transmission of infection is to be avoided in the long term. An early requirement in our virus inactivation programme was that serious penalities in yield be avoided.

845. Our first action was to review all the likely virus inactivation methods available to us. As Dr. Smith's Statement makes clear, there were a number of other possibilities around at the time. Our reasearch work began in the area of pasteurisation (that is to say heating in solution), since our only prevailing experience was with the inactivation of hepatitis in albumin solutions.

846. The advent of HIV and the rapidly clearing picture with regard to the nature of the source of infection during the latter part of 1983 and into 1984 gave considerable impetus to our reasearch and development work all of which Dr. Smith's describes in his Statment, and I do not propose to repeat.

847. The policy of the Tranfusion Service and the DOH was aimed at the maximum provision of Factor VIII concentrates for the treatment of haemophiliacs since it was considered that this represented the primary benefit to the patient, i.e. to arrest bleeding. Whilst it was understood that hepatitis B infection was a hazard of treatment, the risk benefit ratio was clearly with the control of bleeding. Early commercial studies had shown that severe yield penalties were attendant upon virus inactivation procedures and in any case it was becoming increasingly possible to control hepatitis transmission through the screening of donors using marker tests of increasing sensitivity. It was only in the early 1980's when Non-A Non-B forms of hepatitis in their sub-acute and chronic phases were unacceptably common and potentially life threatening and

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because no means of donor exclusion were available, that attention had to be given to a process variation which would inactivate viruses in the finished product. The first record of a discussion at BPL on this matter is in 1981. Following the reports of Dr. Craske and others in 1982, the national programme was put in hand.

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1981

848. It was against a background of resource availability, that I circulated a memorandum dated 13th February 1981 (document no. 1207), noting the availability of DHSS funds for research and development for appropriate and supported projects. I invited staff to set out projects with a simple outline of protocol which could be submitted to the Scientific and Technical Committee which was due to meet on 4th March. A Proposal dated 27th February 1981 (document no. 1221) was submitted for:-

> "The development of methods for the production of coagulation factor concentrates with reduced risk of hepatitis transmission".

849. The proposal referred to the fact that recent improvements in methods for the detection of hepatitis B surface antigen had dramatically reduced the incidence of hepatitis B in patients receiving Factor VIII and Factor IX concentrates. As a result, the importance of non-A non-B hepatitis as an undesirable side-effect, had been highlighted. The Proposal marked the start of a move towards a viral inactivation programme. It was stated that:-

> "The significance of a product demonstrably free of hepatitis risk cannot be ignored and it is essential that BPL/PFL be well placed to take advantage of such developments".

850. Research projects at the BPL were a subject for discussion at the 9th meeting of the Scientific and Technical Committee on 4th March 1981 (document no. 1229). I reported that a research project into the development of coagulation factor concentrates with reduced risk of hepatitis transmission, was an appropriate project for central funding.

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851. The removal of viruses from blood products was item 4.3 on the agenda for the 2nd meeting of the Working Party on Post-Transfusion Hepatitis (at the instigation of the Medical Research Council), held on 25th June 1981 (document no. 1325).

852. Hepatitis risk in plasma products was the subject of a paper prepared by the Research and Development Department at BPL (document no. 1331). It was recognised, in the opening paragraph of the paper, that:-

> "The known high risk of transmission of hepatitis B associated with plasma derivatives such as cryoprecipitate, Factor VIII and Factor IX concentrates exerts ethical pressure on clinicians in the use of such products, inhibits the search for new clinically useful plasma fractions, and restricts the development of alternative technology for the fractionation of plasma proteins".

853. It was noted at the bottom of page 3 that heating albumin products in the presence of a stabiliser for at least 10 hours at 60°C., had a good record in the elimination of hepatitis virus infectivity. Over the page, it was stated that:-

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

854. Dr. J.K. Smith's memorandum of 27th July 1981 (document no. 1344) sets out his thoughts on virus inactivation on therapeutic concentrates (with non-A non-B 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 by controlled tests in chimpanzees - "possibly the only evidence currently deserving credibility". At that time, work on heat treatment for Factor VIII had already been carried out

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by Behringwerke who were claiming a non-infective Factor VIII concentrate produced by heating. There was, however, no reputable evidence for the claim. In Dr. Smith's memorandum, he tentatively suggests that this area of research may be an appropriate R&D project.

855. The requirement for central funding for research and development was a continuous theme in 1981. On 14th September I discussed with Dr. Smith and Dr. Harvey approaches for reducing hepatitis antigens in plasma and final products with a view towards establishing protocols for research and development. My note of our discussions (document no. 1376) records that:-

> "The point was made that various commercial manufacturers have now produced both Factor VIII and Factor IX products claiming that in-process modifications have now substantially reduced the risk of transmission of hepatitis. The basis for these claims may lack scientific integrity but the ethical pressure brought on clinicians to use such products is clearly established".

856. My note sets out nine approaches for reducing hepatitis antigen, of which heat inactivation is one. I invited Dr. Smith and Dr. Harvey to prepare proposals for research and development projects for submission at the Scientific and Technical Committee meeting on 6th October 1981.

857. At the twelfth meeting of UK Haemophilia Centre Directors on 9th October 1981 (document no. 1394), I referred, at page 14, to the "active programme" concerned with the reduction of hepatitis transmission. At the same meeting, a discussion at page 20 centred around hepatitis-free Factor IX concentrates. There had been claims from commercial firms that a Factor IX concentrate was now available which was free of hepatitis:-

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"Dr. Craske thought that this may well be true but there were problems in proving the safety of each batch of concentrate made as only a limited number of laboratory animals were available for testing the materials".

858. This is not, in fact, a reference to heat-treated Factor IX but to chromatographic separations, 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 the case. Factor IX had for various reasons always been somewhat less infective than Factor VIII and whilst there may possibly have been some reduction in the infectivity of Factor IX using this method of production, it was later established that it was wrong to consider Factor IX produced in this way as "hepatitis-free". Although the chromatographic step in the production method was believed to achieve a measure of reduction in infectivity of Factor IX, it had been wrong to consider Factor IX free of risk of transmission.

859. At page 20 the minutes state that some Directors were:-

"Unhappy about the suggestion that the National Health Service concentrates might have 2 viruses and the US commercial concentrates only one virus".

Reference to the "2 viruses" was to two serotypes of Non-A Non-B hepatitis. Subsequently the comparison was shown to be unfounded.

860. The minutes then go on to state that it was suggested that Dr. Craske might get information regarding fractionation methods from the DoH, as all firms had to supply such information when applying for a product licence in the UK. However,:-

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"Dr. Walford of the DHSS said that the information on the fractionation methods held by the licensing department was strictly confidential and could not be revealed".

861. Dr. Smith gave a short address on the subject of inactivation of hepatitis in BPL products at the 11th meeting of the Scientific and Technical Committee on 24th November. His thoughts on the subject of inactivation were summarised in Annex A to the minutes (document no. 1436). Our thoughts were beginning to turn to this subject as the link between non-A non-B hepatitis and chronic active hepatitis increased and, with it, the desirability of inactivating the hepatitis virus if we could. Dr. Smith noted that the risk of hepatitis could be diminished by:-

- More specific and sensitive screening of blood donations intended for fractionation.

- Limiting the size of plasma pools for recovery of certain products.

- Neutralisation or adsorption of virus with an excess of hepatitis antibody.

- Vaccination of recipients.

- Selective removal of viruses during fractionation e.g. by precipitation with PEG (polyethelene glycol).

- Inactivation of virus e.g. with B-propiolactone or by heating in the presence of reagents preserving the biological activities of plasma proteins.

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862. Reverting to the body of the minutes, there was considerable discussion of the development work to be carried out at BPL (see paragraph 12) and a paper STC(81)16 prepared by me, was tabled. I do not have a copy of this paper and cannot recall the projects we had in mind.

863. A meeting of the Working Party to Advise on Plasma Supplies for Self-Sufficiency in Blood Products took place on 18th December 1981 (document no. 1495). The minutes record, at paragraph 3.2 that the need to produce hepatitis-free products in the future could act adversely against yields of Factor VIII. Heat treatment was in mind, together with the need to purify Factor VIII to make it more resistant to heat treatment.

864. In my annual report for the year 1981/82 and dated 20th April 1982 (document no. 1500) there is a list under the heading "Research and Development Department" of the various projects which were then underway. As will be seen from the Report, in 1981 no time was spent researching inactivation of viruses by heat treatment: this work only really started (in relation to Factor IX) in 1982.

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1982

865. During the course of 1982, discussions directed at viral inactivation were still aimed at reducing infectivity of the hepatitis B virus in blood products. It was only towards the end of the year, that there was real recognition of a possible risk of HIV infection for haemophiliacs treated with blood products.

866. Dr. Snape (the then head of Quality Control at BPL) was invited by Dr. Delamore to present a paper on "The removal of viral contaminants from coagulation factor concentrates" at the Haemophilia Symposium and confirmed in his letter to Dr. Delamore of 12th March 1982 (document no. 1490), that he would be pleased to contribute to the Symposium.

867. On 5th April 1982 I circulated a memorandum to Dr. Harvey and others at BPL (document no. 1496). It refers to Polyelectrolyte VIIIC, a process used to produce very high quality Factor VIIIC (not R). "R" is the Von Willebrand's carrier molecule for Factor VIII "C" which is the part of the molecule which effects clotting. For reasons which were unclear, the process itself resulted in a Factor VIII which did not appear to transmit non-A non-B hepatitis. 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. Considerable basic research was required to advance this project and the funding of this work could not be agreed with the Company. So far as I am aware, the process was not the subject of any further development by any other party subsequently.

868. On 4th August 1982 Dr. Smith and Dr. Snape prepared a memorandum entitled "Development projects related to prothrombin complex" (document no. 1538) reporting on projects commenced in February 1981. As I have mentioned above, a proposal dated 27th February 1981 was submitted for the development of

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methods for the production of coagulation factor concentrates with reduced risk of hepatitis transmission.

869. Dr. Smith noted that Einarsson had described an additional promising alternative to the reduction of HB markers in Factor IX concentrates, namely the use of substituted octylamine - Sepharose affinity reagents. As it turned out, the Einarsson method was not fool proof. Nonetheless, we kept reports of this nature under review in the hope that the research may lead to something of interest to us. Dr. Smith concluded in the memorandum that there was no further information on removal of NANB infective agents.

870. The UK Haemophilia Centre Directors' Hepatitis Working Party met on 13th September. The meeting was chaired by Dr. Craske and I was one of those present. Page 3 of the minutes (document no. 1548) records discussions about the evaluation of new brands of Factor VIII and Factor IX where attempts had been made to reduce the amount of virus contaminating the products, by biophysical methods. The minutes further record:-

> "There was also the "hepatitis reduced" brand of Hemofil, manufactured by Travenol Laboratories Limited. Biotest Laboratories in Germany had recently patented a method for the pasteurisation of Factor VIII and IX by heat in the presence of polysacharrides."

The minutes continue:-

> "The only way to evaluate the preparations for freedom from non-A non-B hepatitis viruses was by chimpanzee inoculation, or in a prospective study in susceptible human subjects".

871. I recall that there was in fact a German product called Humate produced by Behringwerke in about 1980 which, I believe, used a wet heat pasteurisation

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process 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 - estimated at 7% to 10%.

872. It should be noted that there was still no clear evidence that AIDS could be transmitted by blood or blood products, although the Working Party recognised that the AIDS syndrome had similarities in its epidemiology to that of hepatitis B virus infection. The likelihood of transmission by blood or blood products would be investigated and a further meeting of the Working Party would be held when more information became available. The chronology of AIDS (and recognition of HIV as a blood transmissible virus) is set out in detail above, but it should be borne in mind when considering the research and development programmes at BPL/PFL into virus inactivation.

873. As part of our review of potential methods of virus inactivation, I sent a memorandum to Dr. Harvey on 13th October (document no. 1563) proposing a meeting to set out plans for studies on pasteurisation of Factor VIII. I noted that some success had been achieved (by other manufacturers) with the addition of stabilisers, for example sugars and/or detergents. The use of stabilisers for coagulation factor products had been touched upon in a paper prepared by the Research and Development Department in 1981, to which I have referred above. I concluded my memorandum:-

> "I would be interested to know what information is available about detergents in a role which might be supportive to Factor VIII during the exposure to heat of pasteurisation".

874. An article was published by R.J. Gerety and D.L. Aronson, entitled "Plasma derivatives and viral hepatitis" in volume 22 of "Transfusion" (September - October 1982) (document no. 1572). There is passing reference on page 350 to heat inactivation:-

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"Plasma proteins cannot routinely withstand heat capable of inactivating HBV. The heating of albumin requires stabilisation with acetyltryptophanate and/or caprylate. Studies have been completed and others are currently underway to evaluate methods to stabilise clotting factors to heating as heat is capable of inactivating both HBV and the agent of non-A non-B hepatitis. Since HBV in albumin but not in whole serum can be inactivated by heat at 60°c. for ten hours, it would appear that information about HBV inactivation by heat will have to come from separate studies of each derivative".

875. On 10th December 1982 Dr. Rizza circulated details of the arrangements for a forthcoming informal meeting (to be held at BPL on 15th December) to discuss hepatitis-free/hepatitis-reduced coagulation factor concentrate (document no. 1576). It was at my request that the meeting took place: by that time I had the possibility of heat treating Factor VIII and Factor IX very much in mind.

876. The meeting took place on 15th December 1982. (Notes of it are document no. 1579). My purpose in calling the meeting was to ascertain 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 while it was appreciated that its sub-acute or chronic form was becoming a problem for haemophiliacs, on balance any method found which inactivated NANB virus was required, that had no unacceptable implications for other aspects of product safety or yield. The clinical consequences of HIV transmission, once fully appreciated (in 1984) immediately changed this balance of risk benefit.

877. The agenda for the meeting was:-

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

878. It was noted with some concern that:-

- "Hepatitis-safe" Factor VIII and IX products were appearing on the market and were being used on a named patient basis (that is to say without their having been licensed - a pre-requisite of which would be a properly documented clinical trial).

- The manufacturers were not obliged to reveal any data on process or product at the early stages of the development and trial in such patients.

879. There was a lack of information from the manufacturers as to how the products were rendered "hepatitis-safe" and there was considerable concern about the haphazard way in which the products were appearing and were being pressed into clinical use. The meeting concluded that:-

- The random exploitation of the Haemophilia Service by commercial organisations for the study of "hepatitis-safe" products should be discouraged.

- The Haemophilia Service should create a formal basis for controlled clinical trial of alleged "hepatitis-safe" products in line with the requirements of the Medicines Act.

- The Haemophilia Service, PHLS and the National Blood Transfusion Service should combine resources in a manner likely to advance economic treatment of NHS haemophiliacs with safe products.

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880. As paragraph 3 of the minutes demonstrates, 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 equally unclear what form of "heat treatment" had been applied.

881. The next document is a letter from Dr. Cash dated 17th December, which follows up on the meeting of 15th December, at which he was present. (Document no. 1580). Dr. Cash felt that it was not in the best interests of the NHS Fractionation Centres to encourage commercial manufacturers to undertake clinical trials with a view to obtaining product licences. His view was that the commercial manufacturers would undertake the trials, obtain product licences and in consequence there would be no doctors in the UK prepared, on ethical grounds, to look at the NHS product in patients (which would inevitably be falling behind). Towards the end of his letter, he refers to "furtive arrangements" between Dr. Smith and Dr. Foster (R&D Department at PFC), as regards Factor VIII and expressed the view that these arrangements were not a sound basis upon which NHS fractionators could combat commercial manufacturers. The arrangements he refers to were in fact not furtive, but quite open and were intended to share knowledge and information about heat treatment experimentation.

882. We needed to know whether the commercial manufacturers were indeed making a safer product and if so to establish whether we could replicate their experimentation.

883. I replied to Dr. Cash's letter on 21st December 1982 (document no. 1581). My letter records the fact that Dr. Cash had appeared to change his view since the meeting on 15th December regarding the wisdom of prompting commercial manufacturers to support their claims for their products, through proper clinical trials.

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884. There was a further letter from Dr. Cash on 22nd December setting out (in Appendix B) the FDA attitude to US "hepatitis-safe" products (document no. 1582). It appears that the FDA were prepared to license products on the basis of chimpanzee studies alone and that clinical trials (patient studies) were not then required for licensing.

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885. Following the informal meeting held at BPL on 15th December 1982, I prepared an "Aide memoire" on a policy for distribution of blood products for sale on a named-patient basis (document no. 1591). This was purely a file note, which I prepared to assist me in any later presentations or correspondence. On the first page under the heading "Hepatitis-safe Factor VIII" (whilst at the same time noting that the arguments applied equally well to Factor IX), I recorded the fact that certain companies, notably Armour, Immuno and Hyland were offering so called "hepatitis-safe" products and that production methods for reducing hepatitis centred mainly on the inactivation of virus by heat in a purified form which had been stabilised by detergent and sugars. I further noted that:-

- None of these end products was guaranteed free of transmission risk of hepatitis.

- Methods of treatment tended to carry substantial penalties in yield of product.

- Treatment methods in production could not be considered sufficiently close to existing production methods that they constituted appropriate examples for variation orders to existing licences.

- Methods for inactivation of virus in Factors VIII and IX cannot be considered in parallel.

- Evidence of satisfactory inactivation could only be demonstrated in chimpanzees for routine quality control purposes.

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886. Reverting to my penultimate point, it could not be assumed 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 having overcome problems of thrombogenicity, we decided 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 necessarily have proved to be the case.

887. My own view was that the commercial products should have been subject 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 licence it would have been necessary for the manufacturer to show the following:-

(i) A standardised process to eradicate hepatitis B (and hepatitis NANB);

(ii) How the process worked; and

(iii) That the process could be reproduced on a standard basis without variation.

888. 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.

889. On page 4, I referred once again to the meeting held at BPL on 15th December 1982 and noted that the general feeling of the Haemophilia Directors

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was that a formal clinical trial would be desirable. I went on to state that certain facts emerged, namely:-

- Whilst the introduction of hepatitis-safe Factor VIII was being encouraged in the UK, there was no evidence of movement towards clinical trials in the United States;

- It was surprising 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;

- Whilst it was accepted that heat may inactivate virus, it could have other equally detrimental effects on proteins normally present in the concentrates; these risks appeared to be unrecognised by FDA (i.e. they were not considered to be contrary to licensing by the FDA).

- It was suggested that both the companies and clinicians had now got "cold feet" over the introduction of the particular product, which seemed hard to reconcile with the previous pronounced interest.

890. My comments on the FDA were probably drawn from Appendix B supplied to me by Dr. Cash with his letter of 22nd December 1982.

891. We had certainly not heard of any clinical trials being conducted in the US in relation to the new "hepatitis-safe" products. In the United Kingdom it is relatively straight forward to get such trials underway economically. I do not know what the licence status of these products was in the United States; it was possible that for licensing purposes in the United States, heat treatment was regarded as a variation to an existing produce licence.

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892. I mentioned in my file note the likelihood of detrimental effects on proteins normally present in concentrates, when subjected to heat inactivation. I was surprised that these risks were not remarked upon by the FDA. We wished to know whether the application of heat to proteins could introduce structural changes which, for example produced new antigens or unfolding of the protein to expose antigens. This could induce antibody development against protein itself i.e. against Factor VIII. Our real concern was whether there was function impairment or a risk of new antigen creation. This is why studies were, we felt, important.

893. The effect of heat treatment on yield of Factor VIII from plasma did not go unnoticed. I wrote to Dr. Wagstaff, Director of the Sheffield Regional Transfusion Centre on 17th January, commenting on the report of the Blood Preservation Working Party documentation which had been discussed at a meeting on 14th January (document no. not found). In paragraph D of the extract it was noted that:-

> "There was concern that the new methods to produce hepatitis B free Factor VIII would cause an additional fall off in yield from the plasma. This plus the falling yield seen at the Central Laboratory immediately after thawing would be important factors in determining the amount of Factor VIII available for patient treatment".

894. The conflicting interests of plasma collectors and patients were recognised in all considerations on changes to the processes.

895. The implications of trials to evaluate the hepatitis risk of "hepatitis-safe" Factor VIII and IX on a prospective study of Factor VIII and IX associated hepatitis were considered at the 11th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party held on 19th January. (document no. 1599). I referred to several of the issues contained in my "Aide memoire" (referred to

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above) and in particular to the unsatisfactory state of affairs as regards proper clinical trials for "hepatitis-safe" products. On page 2 it is noted that Professor Bloom said that:-

> "As a result of the meeting he and Dr. Rizza had attended they 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 interests of the patient...."

896. Trials of products under the conditions of clinical trial exemption certification or other regulatory mechanisms require that the objectives of the trial are stated, that the product under test is shown to be likely to meet these objectives and that the methods chosen for the evaluation are valid.

897. In the third paragraph on page 2, I speculated that the likely consequence of the pasteurisation process would be a reduction in Factor VIII activity by about 50%.

898. It was suggested during the discussions that trials on a named patient basis often provided the best means of obtaining preliminary information about a new product. However, it was pointed out that this procedure did not provide the basis of safety defined in a product licence and there was a risk that companies might use the information obtained to influence the market so that it appeared unethical to withhold the product from clinical use. Three possible procedures were noted:-

- Evaluation on a named patient basis;

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- The granting of exemption from a clinical trial certificate by the licensing authority (National Institute of Biological Standards);

- A clinical trial certificate.

899. I commented that if all 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: HIV changed priorities and an orderly approach towards clinical evaluation of virus inactivation which might have proved possible in the context of hepatitis NANB was overtaken by events.

900. A detailed and chronological sequence of experimentation into both Factors VIII and IX is considered in Dr. J.K. Smith's Statement. However, I believe it is worth noting at this stage that experiments on the pasteurisation of Factor IX in a liquid state using a temperature of 60^{o} for 10 hours, were carried out at the PFL during the course of January 1983. A record of these experiments is contained in a note dated 24th January headed "9H4 pasteurisation of Factor IX concentrate" (Scientific/Technical (Factor IX) Report J). We were using the same heating regime as for albumin. The process used sorbitol and glycine. We attempted to identify the loss of activity: at the worst, there was a 48% loss of activity; at best, 27%. Sorbitol and glycine were needed to stabilize Factor IX protein if it was to escape damage in the heat treatment process. In this sense, Factor IX was different from albumin, which needed neither. Sorbitol and glycine were shown to stabilize various model viruses we sought to destroy, thereby reducing the efficacy of the heat treatment applied.

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901. The paper entitled "PFC method for heat-treated Factor VIII concentrate, 10.2.83" (document no. 1605) is evidence that the PFC were experimenting with a heat-treated zinc precipitated Factor VIII product. It was called "Factor VIIIZ". PFC introduced heat treatment of Factor VIII earlier than BPL, but they only applied marginal amounts of heat to their product. I could see no point in applying a method and degree of heat treatment which was unlikely to be wholly effective for NANB hepatitis, or HIV. The process itself involved pasteurisation, but eventually PFC adopted the dry heat treatment process developed by BPL.

902. In a memorandum to myself and others from Dr. Smith dated 15th February 1983, (document no. 1606) is an account of a visit to the Scottish National Blood Transfusion Service Protein Fractionation Centre and Headquarters, for a seminar which was held on 10th and 11th February 1983. Reference was made to heat inactivation of hepatitis viruses in coagulation factor concentrates, under the protection of glycine and sorbitol. I have already touched on this above. At the bottom of the first page, under the heading "Other information on virus inactivation" there is speculation, or "gossip" as to what the commercial manufacturers were 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 Beta PL/UV treatment of the concentrate (not the plasma); that Immuno were probably using dimethyl pyrocarbonate and a new unspecified virucide for Factor VIII. This was all unconfirmed speculation.

903. At the top of page 2, it is noted that:-

> "Scottish HCD's had expressed confidence in proceeding to clinical trial of PFC's products without chimpanzee studies, which were likely to take more than two years, even if animals became available. Medicines

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Inspectorate (and Professor Zuckerman) were quoted as being quite keen on work with more readily cultured model viruses as markers".

904. The latter reference is to a means of "spiking" the products with representative viruses and seeing whether the heating process inactivated those viruses. If it did, there was a possibility (but not a certainty) that the heat treatment may have a similar effect on hepatitis NANB.

905. So far as our own efforts were concerned, I prepared a memorandum on 24th February (document no. 1611) headed "BPL Research and Development Committee". The research projects having the highest priority were listed in paragraph 2 and item A was "Inactivation of transmissible virus in protein fractions".

906. A paper prepared by Dr. Smith in February, headed "Development projects related to prothombin complex" (document no. 1613) further evidences research work on BPL's part and touches, in several places, on heat treatment (particularly of Factor IX) aimed at improving the safety of the products. The paper chiefly evidences the fact that R&D was continuing at this time in a variety of areas consistent with available funds. Dr. Smith refers to various reports in the field of hepatitis-safe Factor IX. He adds that PFL have had "modest success" with the pasteurisation of conventional Factor IX concentrates under protection of additives.

907. I have mentioned in the section dealing with AIDS above, the expectation that as the AIDS risk heightened amongst haemophiliacs, there would come a time when a return to the use of cryoprecipitate as a desirable form of treatment would emerge. In a memorandum to Mr Mallory and others written on 24 March 1983 (document no. 1621) I further noted that:-

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> "....patients potentially at risk in the United Kingdom (notably haemophiliacs) are evidently concerned and resistance against the use of imported American coagulation factor concentrates is becoming apparent...".

908. I proposed a meeting between the key BPL staff to discuss the strategical alternatives which took place on 18th April 1983 and a note was prepared by Mr Pettet on 21st April (document no. 1625). It was noted that:-

> "The producers of concentrates are concerned, and expect the BOB [Bureau of Biologics in USA] to make a statement that no further clinical trials be carried out on materials that had not been rendered safe from the risk of transmittable disease".

The note continues:-

> "Dr. Snape stated that the BOB reaction was predictable and that an association was now being formed between heat treated concentrates in reducing the risk from AIDS".

909. Dr. Smith added that there was at that time little firm knowledge on how effective heat treatment was on NANB hepatitis virus or, for that matter AIDS, nor what the effect on yields would be. Other comments were raised during the course of the meeting, but notably the potential effect if BPL were only able to produce one half of the UK requirement for Factor VIII, if heat treated yields were much lower than those seen currently for normal material. In conclusion on page 3 of the note, it was nonetheless generally felt that BPL should proceed with both small panel and heat treated products.

910. The deadline for draft proposals was set as 15th July 1983. This confirms our commitment at that point to progress as far and as fast as possible

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the development of heat treated Factor VIII. Whilst inactivation through the use of heat could not be demonstrated to work, we nevertheless concluded that given all the uncertainties (and in the absence of any other apparent solution) we should try and accelerate the heat inactivation programme which was already underway for hepatitis NANB.

911. In February 1983 Dr Smith prepared a paper entitled "Proposal to develop a "hepatitis-safe" Factor VIII concentrate" (Scientific/Technical Report A). At the time his proposal was written, AIDS was not yet proven to be of viral origin, but this was "strongly presumed". In the introduction, he notes that:-

> "Factor VIII coagulant activity has always been regarded as exceptionally labile, and it is only recently that serious attempts have been made to apply to Factor VIII concentrates some physical and chemical processes designed to inactivate hepatitis viruses. As with other concentrates, the options open to fractionators (excluding screening and vaccination) are:-
>
> (i) Immunological neutralisation or immune adsorption on solid phase antibody.
>
> (ii) Physical removal of infective agents by e.g. semi-specific absorbence or precipitance.
>
> (iii) Inactivation by heat or virucides".

912. Having noted the potential pitfalls attributable to heat-inactivation of viruses, (and commenting that even brief boiling at 100^{o} may be ineffective), Dr Smith concluded that heating was considered the most promising approach to virus inactivation because:-

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"(i) It is likely to be of broad application i.e. conditions which inactivate the exceptionally robust HB are likely to inactivate other blood-borne viruses.

"(ii) The treatment is cheap, relatively easily controlled, recorded and scaled up with precision.

"(iii) Extensive experience with other successful pasteurised proteins such as albumin offers readier regulatory and clinical acceptance than the use of a novel or unfamiliar chemical virucide".

913. Dr Smith's proposal for inactivation of virus by heat is expanded upon on page 7 of his paper. He identified three sources of present information:-

(a) Behringwerke's process;

(b) Information, confidential at the moment, from PFC Edinburgh;

(c) Limited experience at BPL and PFL.

914. Subsequently Dr. Smith wrote a memorandum to Mrs Winkelman dated 23 June 1983 and headed "Formal R&D projects" (document no. 1648). Mrs Winkelman was engaged in research and development work at PFL. Dr. Smith asked Mrs. Winkelman to lead the research and development project on "Heat inactivation of viruses in Factor VIII concentrates". He stressed that:-

"The priority of this project at the moment is A1, i.e. most important to BPL/PFL's immediate product strategy".

915. I confirmed the priority level of this work.

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916. In Dr. Craske's paper (dated 11th July) prepared for the UK Haemophilia Centre Directors' Hepatitis Working Party (document no. 1652), he set out to classify the various products which were then available. There seemed to be three types of "hepatitis reduced" product:-

(i) Freeze dried product heated in the presence of compounds (e.g. sucrose) which stabilised the Factor VIII activity. Dr. Craske noted that there was no significant loss of Factor VIII coagulant activity, that the temperature was usually 60°c. and that the heat was applied after the freeze drying process, but that the exact conditions were a commercial secret. Two such products identified were Hemofil T and Factorate HT (the latter to be available in three months).

(ii) Product made from plasma treated with chemicals. Dr. Craske identified two examples: Factor VIII manufactured by Biotest in West Germany and Kryobulin, manufactured by Immuno.

(iii) Product pasteurised by heating at 60°c. in the presence of stabilisers for Factor VIII. He added that Factor VIII activity was reduced by 50%. Behringwerke had developed such a product which had undergone clinical trial in Germany.

917. As Dr. Craske's note demonstrates, there was a considerable degree 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. He concluded by hoping for a hepatitis-reduced product from the NHS. He identified the dilemma at the time:-

"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

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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".

918. Dr. Smith's memorandum of 25th July headed "Heat inactivation of hepatitis viruses in Factor VIII concentrate" (document no. 1658), set out the current position with regard to heat treatment, in the context of the introduction of project proposals for work on heat treated Factors VIII and IX concentrates, at PFL. He noted:-

- Inactivation by heat was chosen as the most promising method because of availability; extensive experience with albumin and other concentrates; clinical acceptability compared with the use of less familiar agents and probable general application to viruses as yet incompletely characterised (by which he meant, amongst others, AIDS).

- The only work on heat treatment of Factor VIII fully documented by the end of 1982 was that of Behringwerke who were heating Factor VIII in solution under the protection of sucrose and glycine, after quite extensive pre-treatment.

- The method adopted by PFC (which included heating Factor VIII in solution under protection of Sorbitol and glycine, after pre-treatment with zinc ions to reduce the fibrinogen content).

- That senior clinicians had been told by Hyland and Armour that their method of inactivation was to heat the freeze-dried vials.

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- The effect of heating freeze-dried vials of a single batch of 8CRV concentrate. Results suggested that temperatures between 60°C. and 70°C. for 48 hours, 75°C. for about 10 hours or 80°C. for about 4 hours could be held without loosing more than 5% of Factor 8CRV.

919. The work was continuing at the time that Dr. Smith produced his report and he concluded:-

> "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".

920. I prepared a memorandum dated 26th July entitled "AIDS - Progress with heat treatment of human plasma products" (document no. 1659). This paper was tabled at the CBLA meeting on 27 July 1983. I had not been asked to prepare the paper following the DOH Report on AIDS at the CBLA meeting on 22 June 1983. The opening paragraph of my paper refers to the long-standing use of pasteurised albumin products (without the complication of hepatitis), suggesting that the pasteurisation process was effective. I continued:-

> "Pasteurisation of other blood products has not been developed to this extent because these products are not amenable to the heat treatment process:- examples are fibrinogen, Factor VIII, Factor IX, which are all known to transmit hepatitis B and non-A non-B viruses".

921. I continued by saying that heat treatment of blood products was still primarily directed at the inactivation of transmissible viruses causing hepatitis in recipients. However, I felt that AIDS might include in its aetiology transmission

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of an infective virus with possible reactivation of an existing virus in individuals concerned. The fractionator's view was that as a virus it might, like hepatitis, be partially or completely inactivated by heat:-

> "This aetiological observation has promoted more activity in the area of blood products pasteurisation with the empirical view that a virus is involved (and) as with hepatitis virus, is likely to be partially or completely inactivated by heat".

922. The reasons for this were set out under the heading "Means of heat treatment of blood products", on page 2. Wet heat, which we used in relation to the production of albumin, appeared a less satisfactory route for research, than dry heat. I reported that the majority of commercial manufacturers were currently depending upon dry-heating of the finished Factor VIII concentrate to reduce the infectivity of the product relative to transmission of hepatitis. I continued by saying that:-

> "The associated claims (which are entirely unfounded in scientific and quality control terms) are that the heat process will inactivate the putative virus transmission causing AIDS".

923. I noted at the top of page 3 that BPL had undertaken preliminary studies to assess yield of Factor VIII intermediate concentrate after dry-heat. I continued:-

> "Since this form of product treatment will allow BPL to present to clinical managers of haemophilia a product carrying equivalent weight of claims for safety as those of rival commercial organisations, this product is being advanced with high priority to enable manufacture to become routine by the late summer 1984".

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924. The 12th meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party was held on September 14th 1983. With regard to Dr. Craske's prospective study of Factor VIII and IX associated hepatitis (which I describe in the Hepatitis section, above), it was noted that commercial Factor VIII products were at present being considered for trials. These were identified in the minutes (document no. 1667) as the dry heat treated Travenol Laboratories product, and the Armour product. The Travenol product had been granted an exemption from a clinical trial certificate and Armour had applied for exemption for their product.

925. It is also worth noting the following comment, at the bottom of page 1 of the Minutes:-

> "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".

926. The first meeting of the CBLA Working Group on AIDS in Relation to Blood Transfusion was held on 14th October (the minutes are document no. 1684). Under the heading "Treatment of blood products to eliminate micro-organisms" the following comment was noted:-

> "...with respect to non-A, non-B hepatitis the dry-heat treatment of Factor VIII and Factor IX had not initially been encouraging from the studies on chimpanzees. Wet-heat treatment appeared successful in the case of the albumin solutions and Dr. Lane expressed the opinion that

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further work was necessary and that such products should be subjected to evaluation before accepted".

927. The reference to the chimpanzee studies was to work carried out in the US, which had been published.

928. The 14th meeting of UK Haemophilia Centre Directors took place on 17th October 1983. It was reported on page 9 of the minutes (document no. 1687) that we were looking at methods for making Factors VIII and IX safer, with regard to the transmission of hepatitis. Dr. Snape stated that BPL hoped that not more than 10 to 15% of the Factor VIII yield would be lost in the manufacture of the virus free products. It was 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 conducted 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 the 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".

929. 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.

930. I have already touched upon the ethical dilemma facing clinicians, particularly in the section of my proof dealing with AIDS, above. However, I feel I should comment briefly at this point on the effect that the increasing

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knowledge of AIDS and HIV infection had on the studies then undertaken in relation to the infectivity of heat treated Factor VIII for non-A non-B hepatitis. AIDS very quickly eclipsed the idea of carrying out detailed studies on products which might potentially offer protection. By way of illustration, in the Minutes of the 12th Meeting of the UK Haemophilia Centre Directors' Hepatitis Working Party, it is noted under paragraph B that:-

> "The recent development of new preparations of Factor VIII where attempts have been made to reduce the contamination of preparations by hepatitis viruses by heat treatment has made it necessary to devise protocols for the evaluation of the residual infectivity of these preparations, since no tests of infectivity are available for non-A non-B hepatitis viruses".

The note continued:-

> "An internationally based trial was started with the Travenol product, and an Armour product will be available for evaluation in the next three months. However, the problem of AIDS has overshadowed these developments, as the ethical problems of exposing mild haemophiliacs to commercial material must be considered by each Director".

931. I refer next to the minutes of the 2nd meeting of the Central Committee for Research and Development in Blood Transfusion, which took place on 7th November (document no. 1692). I reported that a dry heat treated product was available at BPL and that I had approached the Haemophilia Directors on how they wished to proceed with its use. I had telephoned some of the Directors (namely Dr. Gunson, Dr. Delamore (Sheffield) and Dr. Jones) to advise them that we now had a product available for trial. The minute continues:-

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"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 on a trial of the BPL material was discussed and the difficulties with respect to the limitations of available patients were 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".

932. The Committee's recommendations that clinical trials should commence as soon as possible, were endorsed by the CBLA at its meeting on 23rd November 1983. A protocol was subsequently 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 had already approached showed no immediate enthusiasm to use the new BPL product on a trial basis. Our efforts in this regard culminated in our securing three patients only, on which to try out the new heat treated product. The trial in actual fact never got off the ground. These three patients were recipients of heated 8CRV in 1984.

933. 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 it had not been validated clinically in more than the 3 patients cited above.

934. In Dr. Smith's memorandum to me and others dated 14th December 1983 (document no. 1702) entitled "Animal and clinical testing of new coagulation

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factor concentrates", it was noted 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 have mentioned above, the trial was not completed but the memorandum also makes reference to our possible use of haemophilic dogs as part of the testing regime. In addition, it was likely that Dr. Rizza would be willing to use heat treated Factor VIII concentrate without a clinical trial certificate or formal exemption for the testing of the product, on patients he had accumulated for small-panel Factor VIII.

935. I replied to Dr. Smith's memorandum on 19th December 1983 (document no. 1703). I approved the idea of experimental work in haemophilic dogs and asked him to provide a full statement of costs and more programme details.

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936. The year commenced with Dr. Smith's memorandum dated 3rd January and headed "Proposal for special preparation - 8CRV pasteurised dry", (document no. 1712). Through the work being carried on by the commercial manufacturers, towards producing a "hepatitis-safer" concentrate of Factor VIII, it was clear that Factors VIII and IX had been heated by means of pasteurisation and dry heat.

937. It was "inferred" from publications, patents, discussions etc that Behringwerke were heating product in solution with glycine and sucrose and that Armour and Hyland were dry heating. Hyland took a decision in May 1984 to issue only dry-heated Factor VIII in future, although heating had almost certainly been introduced to combat NANB hepatitis. It remained only an "unsupported hope" that the transmissible agent of AIDS, if any, was heat sensitive.

938. Dr. Smith's memorandum summarised the reasons behind the decision to elect for dry heating of the existing product 8CRV:-

- The Haemophilia Centres felt the need to offer at least some hope that NHS products would carry a reduced risk of transmitting AIDS.

- Although the evidence from Hyland's study of (presumably) dry-heated Factor VIII in chimpanzees was unsatisfactory, there was a suggestion that the infectivity of NANBH had been reduced or attenuated by heat treatment.

- BPL/PFL recognised the lack of evidence for dry-heat inactivation of either hepatitis B or NANB hepatitis in Factor VIII. The work from PFC suggested that some hardy model viruses were inactivated only very slowly at 60°c., even in solution, and that one might

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predict that heating in the dry state should be less effective (and possibly more variable) than heating in solution.

- BPL/PFL's "late start" in more rigorous inactivation studies could leave BPL/PFL without a product for a year or more, by which time many of the small group of suitable patients would have been committed to testing other products.

- There need be no intention to convert all BPL/PFL product to dry-heating, at least on the grounds of NANB hepatitis reduction. Given the clear-cut pattern of infectivity of current concentrates, a few batches for clinical trial in a modest number of suitable patients might suffice, and a decision to widen this application might be taken on the success of this and commercial dry-heated Factor VIII.

- BPL/PFL could expect that, even if dry heating would not completely inactivate high concentrations of NANB hepatitis in commercial Factor VIII, heating Factor VIII from a potentially cleaner source of plasma might tip the balance towards non-infectivity in at least a proportion of patients.

939. The reference above to our "late start" is not to be misunderstood. The documentation I have discussed above indicates our intention to define a heat treatment process capable of full virus inactivation, probably requiring more severe heating than was currently recognised.

940. Dr. Smith detailed the experiments that had already been carried out by BPL/PFL and noted that the loss of Factor VIII on heating at 60°C. for 72 hours was acceptable, but that the losses at 70°C. were heavier and that there was a significant effect on solubility. Further, all samples heated at 80°C. for 24 hours

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lost more than 25% Factor VIII and became less soluble. Dr. Smith recommended that in the absence of T/t profiles (i.e. temperature and time) for the inactivation of hepatitis B and NANB hepatitis, 8CRV should be heated for 72 hours at 60°C. Preliminary work had also been carried out in Edinburgh to show that temperatures higher than 60°C. were required for inactivation of NANB and possibly HIV. Dr. Prince in New York considered that heating at 68°C. was only marginal. This was a first shot at a temperature definition for a specified time, which did not cause an unacceptable loss.

941. On page 5, Dr. Smith comments that although "scraps of information" were available from PFC, there was an urgent need for resources at BPL for spiking Factor VIII with model viruses. On the question of Factor IX, 9D concentrate was "extremely robust" to heating and it was intended that the principles relating to Factor VIII should be extended to Factor IX, with special care about thrombogenicity.

942. To coincide with the CBLA's first year of management, I prepared a report dated 16th January 1984 (document no. 1716) to cover the period between April 1982 and December 1983. In the summary of the report I noted that priorities in research and development had been directed towards improved product safety (inactivation or exclusion of hepatitis virus) and increased yield through more efficient processes. I noted that ways of reducing the transmission of viral diseases had been extensively reviewed and that programmes had been started with the aim of reducing or removing infectivity by heating under the protection of amino-acids and sugars. It seemed likely that Factor IX could be pasteurised with less than 50% reduction in overall yield, but Factor VIII presented more problems. I reported that conditions had been established for heating concentrates in the dry state and that the trial of these products was expected to preceed that of concentrates heated in solution.

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943. Whilst discussions continued as to the means of inactivating virus in Factor VIII, Dr. Smith's memorandum of 16th January 1984 (Scientific and Technical Report Q) directed attention to a hepatitis-safer Factor IX concentrate and the associated problem of thrombogenicity. I should add that whilst efforts were still directed at a "hepatitis-safer" form of concentrate, experience suggested that NANB hepatitis was a tough virus: if NANB could be inactivated, the treatment would affect a number of other less robust viruses.

944. Dr. Smith comments in his memorandum that:-

> "I believe 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 infective material".

945. The next document to which I shall refer is a letter from Dr. Delamore (at the Royal Infirmary Manchester) to Dr. Gunson, dated 3rd February 1984 (document no. 1727). The letter refers to the proposed "Northern Centres" trial for which cooperation was sought by Dr. Delamore from Haemophilia Reference Centre Directors at Sheffield, Liverpool and Newcastle. Manchester was the co-ordinating Centre. Newcastle and Liverpool Haemophilia Centres agreed to join Manchester in the proposed trial. The study to be undertaken was a trial of NHS heat treated Factor VIII concentrate (8CRV "H"). The details of the study are set out in a Protocol which is referred to in Dr. J.K. Smith's Statement. Accompanying the letter was a protocol for the study of heat treated Factorate, Armour's product. The Factorate protocol is dated May 1983 and is an indication of what the commercial manufacturers were doing by way of heat treatment.

946. At a meeting of the Central Committee for Research and Development in Blood Transfusion on 28th February 1984, (document no. 1732) Dr. Gunson

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reported that an approach had been made to Dr. Delamore for a collaborative study using heat treated Factor VIII.

947. A special meeting of the CBLA was held on 22nd February, to consider research and development. **[Dr. Lane to locate the Minutes [P35]]**. The CBLA's desire to be kept informed of progress in heat treatment of human plasma products is evidenced by Mr Armour's memorandum of 13th March 1984 (document no. 1740). In my reply (document no. 1741) I referred Mr Armour back to the project file prepared for the R&D meeting on 22nd February and explained that it would be more appropriate to re-evaluate the position in 6 months time since the projects were undergoing a 6 months' review.

948. Dr. Smith's memorandum to Dr. Snape of 14th March entitled "Factor VIII special preparations" (document no. 1739) summarised the position with regard to both small-pool and dry-heated Factor VIII products. The memorandum set out limited proposals for clinical quality control exercises. Although these trials were by their very nature limited, it was the only way we could do a proper control on the heat treatment process. Dr. Smith observed that the small pool unheated product was destined for particular users who could provide follow up on appropriate patients. Dr. Smith also noted that a batch of small pool heated product had been used at the Middlesex Hospital and the results were published.

949. An update on the "hepatitis reduced" Factor VIII products undergoing trials was circulated to Haemophilia Centre Directors in March. (I refer to Professor Bloom's memorandum dated 29th March 1984, document no. 1757).

950. Clinical trials had only been completed on one product, the "Hemofil HT" Factor VIII, prepared using the dry heat method. The results indicated that there was still a 63% attack rate of non-A non-B hepatitis on first exposure to this product in patients who had not received Factor VIII concentrate previously. From what I can recall, there was a cumulative attack rate close to 100% by the

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time of second or further exposure. A regular recipient of Factor VIII could be infected within weeks or months.

951. The products currently available were noted as follows:-

- Heated products from Armour, Cutter, Travenol and Alpha Therapeutics. The three former were "dry heat" preparations and the latter a "wet heat" product (the liquid phase being an organic solvent which was not miscable with water (i.e. didn't dissolve) therefore could not be a wetting agent).

- NHS Factor VIII prepared from a specially selected donor panel.

- One brand of heated NHS Factor VIII manufactured at PFC, Edinburgh would shortly be available; the second, manufactured at Elstree, would be available later that year.

- A heated preparation manufactured by Behringwerke (heated at $60^{o}C$ for a period known to inactivate hepatitis B in the preparation). Trials had been carried out in Germany, but no published information was available.

952. The 12th meeting of the CBLA was held on 23rd May (document no. 1772). It was reported to the CBLA that a trial of BPL heat treated Factor VIII was to take place in Manchester, Liverpool and Newcastle and it was hoped to commence by late summer. It is worth noting that at the same meeting, Dr. Gunson said that "it seemed most likely" that an HTLV virus was the causative agent of AIDS.

953. Dr. Craske's letter to Dr. Smith of 5th July (document no. 1787) conveys the fact that heat treatment of Factor VIII was not creating enormous

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confidence. He reports that two patients first treated with Armour heat treated Factor VIII concentrate contracted NANB hepatitis 2 to 3 weeks after their first transfusion with the material. Dr. Craske 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, but I thought that you should be aware of the results of the use of the Armour material. This case has been reported to the Medicines Division of the DHSS and the relevant batch of Armour Factor VIII has been withdrawn from the trial".

954. I received an update by way of a memorandum from Dr. Smith on 11th July (document no. 1791) on the cases where individual patients had been treated with NHS heated Factor VIII. One of Professor Stuart's patients had passed the twelve week mark without showing any signs of hepatitis. A patient of Dr. Colvin was to be followed vigorously over the next two months. Dr. Smith concluded that:-

> "I think this is an encouraging start, certainly in the face of poor performance from competition, and helps to justify the pattern of the Northern Centres' trial".

955. Dr. Smith's memorandum to me dated 6th September (document no. 1807) set out some "random notes" which he thought may be of interest. The areas he highlighted were noted in earlier documentation above, but I shall repeat the main points:-

- Hemofil HT had given a 63% NANB hepatitis attack rate in the "rather muddy" European trial;

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- Armour hepatitis-reduced Factor VIII had given 3/3 cases, one severe.

956. An article appeared in The Lancet on September 29th entitled "Recovery and inactivation of infectious retroviruses added to Factor VIII concentrates" (document no. 1824). Dr. Levy and others investigated the ability of infectious retroviruses to withstand the procedures used for Factor VIII concentrate. They noted that "lyophilised" (i.e. freeze-dried) material had to be heated at 68°c. for several hours before substantial quantities of infectious virus became inactivated. They concluded that these findings supported the possible role of retroviruses in AIDS and indicated that Factor VIII concentrates had to be heated to inactivate these infectious viruses. This pointed the way towards heat treatment and examined the effect of heat treatment on a number of marker viruses.

957. In October I asked Dr. Smith, Dr. Snape and Mr Wesley to give urgent consideration to the possibility of introducing, as routine, a dry-heating step in the finishing of Factor VIII and Factor IX concentrates. My request is recorded in a memorandum from Dr. Snape to Dr. Smith and Mr Wesley dated 12th October 1984 (document no. 1834). Dr. Snape noted that:-

> "This step would be aimed principally at the elimination of AIDS infectivity, accepting the dubious effectiveness of dry heating and the prevention of NANB hepatitis transmission".

958. Dr. Snape's memorandum prompted a meeting of Mr Prince, Mr Wesley, Dr. Harvey and Dr. Smith on 16th October. The meeting was to review the opportunities for heat treatment available to us, based on accumulating laboratory data and our preliminary clinical experiences in achieved safety in dry heated intermediate concentrate and potential application to routinely heated product. To be routinely applied, it had to be on the Elstree "HL" product because of the feasibility of transferring the technology to a large scale. We had

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to consider the inevitable situation where inactivation of an HTLV virus was a preliminary objective. Supporting data indicated that heat treatment would not be successful in inactivating Non-A Non-B hepatitis. Our objective was to deal with HIV first and then perfect the process for Non-A Non-B hepatitis. When it came to applying the 8CRV work to HL, the differences in the two products became apparent: HL as then formulated would not have been an appropriate product for dry heating. The matter was resolved by the introduction of 8Y. The meeting in fact conicided with the first studies of heat treatment on 8Y. By November, we realised it could tolerate much greater heat than HL or 8CRV.

959. Mr Prince's memorandum of 26th October 1984 (document no. 1836) examines the practical implications of my request for routine dry-heating. In particular, implementation of the procedure necessitated three heating cabinets for dry heating of Factor VIII and Factor IX (based on a 72 hour heating cycle).

960. A milestone document (to which I have already referred in the section of my proof dealing with AIDS, above) is the MMWR Update on AIDS in Persons with Haemophilia, dated 20th October (document no. 1835). 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. To physicians treating patients with haemophilia, they recommend that (i) 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; (ii) fresh frozen plasma be used in Factor IX-deficient patients in the same categories; and (iii) Desmopressin (DDAVP) be used whenever possible in patients with mild or moderate haemophilia A. The majority of haemophilia patients do not fit in categories (i) through (iii). For these patients, MASAC recommends that "because heat-

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> 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." [My emphasis]. They also recommend that all elective surgical procedures for haemophilia patients be evaluated with respect to possible advantages and disadvantages of surgical delays".

961. I would add that this was the first real recommendation that emanated from the MMWR.

962. A summary of the work conducted on the 8Y project for the six month period to October 1984 is reported by Dr. Smith in his note entitled "Unheated heparin 8: progress report. May - October 1984 (8Y1-8Y9)", (Scientific and Technical Report H). 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 the pasteurisation of Factor VIII concentrate. It was clear that 8CRV and HL were unsatisfactory 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.

963. I reported to Dr. Harris at the DHSS on 12th October (document no. 1833) that we were:-

> "...actively planning dried heat treatment of all our Factor VIII on the empirical basis that it has a satisfactory process efficacy for inactivation of HTLV - III".

964. Dr. Harris' response to my letter of 12th October was not favourable. In his letter of 8th November (document no. 1842), he stated that:-

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"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 HTLV III by heat is sufficient to warrant taking this step, particularly if a screening test can be made available" (my emphasis).

965. Dr. Harris went on to note that there could be implications for adequacy of the proposed plasma supply if heat treatment affected the yield of Factor VIII harvested. Nonetheless, we were by now 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 generally applicable test for HIV at the time, but we knew from our research work on heat treatment, 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 due to heating and greater possibilities of virus inactivation because of its tolerance to heat, was beginning to look a firm possibility.

966. I reported in some detail on the trials of heat treated Factor VIII manufactured at BPL, at the 4th meeting of the Central Committee for Research and Development in Blood Transfusion held on 9th November (minutes - document no. 1845). I stated that:-

"....the laboratory was currently dry heat treating Factor VIII with no great loss of yield and [he] felt that the time scale for the new product was approximately one year. The question now was whether Haemophilia Directors would be prepared to test the heat treated material using a small donor pool".

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967. My reference to no great loss of yield was of course in relation to the new 8Y product.

968. I referred to the fact that the CBLA had, in March, agreed to finance trials of the BPL heat treated 8CRV and that a draft clinical trial protocol for the Northern Centres had been circulated.

969. It was agreed at the meeting to recommend to the CBLA that I should commence dry heat treating material then being produced, whilst examining methods to obtain a better yield so that wet heat treatment might be feasible. It was also agreed to recommend to the CBLA that trials of heat treated Factor VIII should continue, but be extended to take into account anti HTLV III.

970. It was ironic that I was being asked to refer the policy on heat treatment to the CBLA to obtain approval, at a time when our work in this connection was well established.

971. Reference is also made in the minutes to trials of SNBTS heat treated Factor VIII. There were insufficient suitable patients in Scotland to test the heat treated Factor VIII, and Dr. McClelland explained that trials might have to be re-thought in view of the HTLV III virus. Dr. Rizza said he would be able to test the Scottish material, whilst continuing to test that supplied by PFL. Dr. Fraser considered that some assistance towards such trials could be forthcoming from the South West Region.

972. Dr. Smith considered the available options for heat treatment of coagulation factor concentrates at PFL and BPL in his memorandum of 12th November (document no. 1846). The memorandum was intended to survey what products had been developed to meet the demand for safer concentrates, what stage they were at, what they were expected to achieve and when clinical products might be provided, first from PFL and then from BPL.

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973. In paragraph 1.1, Dr. Smith comments on the restricted-pool intermediate concentrate, 8CRV. Evidence arising from the use of 8CRV from restricted plasmapheresis pools in patients who had not been treated before (or not for about two years), suggested a pattern of only one or two carrier donors (i.e. for NANB hepatitis) affecting a pool of about 1,000 donations. He noted that the chance of including a donor at risk for AIDS was reduced, but not eliminated.

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

975. The then current state of knowledge on the merits of dry heating, was summarised by Dr. Smith on page 2:-

> "Dry-heating of other commercial Factor VIII concentrates is said to result in negligible losses of VIIIC, but incompletely published results of clinical trials suggest that the incidence of transmitting NANBH is reduced only by about 30%. The concentration of infective particles in commercial plasma pools may of course be higher than in our pools. 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 border line 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 the suspicion that a 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

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inactivation of HTLV III spiked into Factor VIII concentrate, possibly five logs kill after 24-48h at 68°c., make dry-heating attractive as an immediately practical and minimally invasive way of reducing the transmission of AIDS, if not NANBH".

Dr. Smith continued:-

"A decision to adopt dry-heating of HL could scarcely be expected to yield product before 1st April, 1985, given a lead time for specification, construction, commissioning of ovens and quality control of heated products. If a date of about 1st April were adopted for issue of only dry heated HL, PFL would use this time to investigate and if possible reduce the current VIIIC losses in the light of recent experience with 8Y; success could not be guaranteed, so the current real loss of about 15% over 8CRV or HL should be assumed for the moment".

976. In paragraph 1.3 of the memorandum, Dr. Smith noted the intensive development of 8Y which had started in July and which was designed to be more suitable than 8CRV for heating in solution. It was noted that 8Y could be dry-heated with highest ability than 8CRV or HL. Initial heat treatment work on 8Y suggested no significant loss of Factor VIIIC or any other important quality after 72 hours at 72°C. The signs were encouraging and this information really prompted the decision at about this time to concentrate on developing 8Y. Dr. Smith noted that:-

"PFL's programme gives 8Y the highest priority".

977. In paragraph 1.4, consideration was given to Factor VIII heated in protective solution. It was noted that this had been the main long-term aim in 1983, primarily because of doubts about the effectiveness of dry heat inactivation of NANBH, before AIDS became a preoccupation.

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978. The options for heat-treatment outlined by Dr. Smith in his memorandum, were considered at an internal BPL meeting held on 13th November. I refer to the summary of the meeting prepared by Mr Wesley and dated 19th November (document no. 1849). It was reported that:-

> "...the size of the heating equipment, cost etc was dependant upon the precise heating conditions. Little definite information appears to exist about the efficacy of heat treatment in order to inactivate the causative agents of NANB hepatitis and AIDS, in freeze dried Factor VIII, nor upon the likely loss of specific activity in that preparation as a result of such treatment.
>
> "The meeting considered that (for the time being) 24 hours at 70°c. represented a reasonable compromise of the above factors; but recognised that these conditions may need to be changed in the light of future experience".

979. It was recognised at the meeting that every effort must be made to start heat treatment as soon as possible. Further:-

> "It was realised that undue delay may be caused because of the formal tendering requirements. Once the specification for the ovens was available it was agreed that Dr. Lane would be consulted in an attempt to by-pass some of the requirements".

980. The provisional date for full implementation of heat treatment was to be 1st April 1985 although it was recognised that it was impossible to judge its feasibility. Heat treated HL and 8CRV were issued from 1st February 1985. In the event, initial issues of heat treated 8Y became available from April 1st 1985 (on a named patient basis) and only 8Y was issued after August 1985.

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981. As a follow up to the meeting on 13th November 1984, Mr Prince sent a memorandum to Mr Wesley and others (myself included) (document no. 1848), which considered in greater detail the equipment requirements for the heat treatment of Factor VIII. This was further evidence of our efforts to respond to the need to introduce heat-treated product at BPL with the minimum of delay.

982. In a memorandum dated 20th November 1984 from Dr. Smith to myself, Dr. Harvey and Dr. Snape entitled "Clinical use of dry-heated restricted-pool 8CRV" (document no. 1852), Dr. Smith raised an issue which we were in danger of losing sight of in the rush to produce and issue heat treated Factor 8Y. Some stock of the dry heat treated restricted pool 8CRV 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 set out in his memorandum 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. Dr. Smith concluded:-

> "Now that CBLA have publicly stated that BPL issues from April will be heated, we will be seen as dragging our feet if the meeting on 10th December does not endorse some sensible immediate action. US companies say they can provide UK with more than enough heated product, today [my emphasis]. This is our last opportunity to get anything resembling rational trial without exposing patients to greater risks. I think the HCD's are in a mood to cooperate, but NHS sources may have the intuitive edge over imported products only until the next scandal hits the papers.

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"Anything going into PFL's oven on 11th December will not be issuable until January. Do we also need an interim policy on issue of what little dry-heated 8CRV we already stock"?

983. Dr. Smith circulated an internal memorandum to various personnel on 23rd November (document no. 1857), on the subject of the heat treated intermediate product 8CRV covering the week commencing 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.

984. A memorandum of 26th November from Mr Wesley (document no. 1858) again 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. Heat treated HL was released up to August 1985, at which time 8Y effectively took over (having been phased in over some months).

985. I referred above to Dr. Harris' comments questioning the need to heat treat product if a screening test could be made available. The agenda and supporting papers for the first meeting of the Working Group on AIDS which was held on 27th November have a section on arrangements for the collection and testing of blood donations in the NBTS. Under paragraph 8 of paper WGA(84)2 (document no. 1860(b)), the Working Group were requested to consider and discuss the following:-

"Should methods of heat inactivation of HTLV III be used in preparation of Factor VIII even if donations are screened for antibody. Is heat inactivation necessary if plasma is collected from small donor pools and screened...." **[We do not have the Minutes of the Meeting].**

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986. At the CBLA meeting held on 28th November, the minutes record at page 3 (document no. 1862):-

> "In regard to trials of heat-treated Factor VIII manufactured at BPL the recommendations made by the Central Committee were approved. The authority approved the spending of approximately £72,000 for ovens from within the intermediate capital cash limit".

987. The recommendation put to the CBLA emanated from the meeting of the Central Committee held on 9th November, above.

988. In Dr. Smith's undated memorandum of about that time to Dr. Harvey and others, including myself, (document no. 1864) he detailed a proposed programme of dog infusions of heat-treated Factor IX concentrate. This was a separate line of research we were pursuing in relation to Factor IX at the time.

989. On 29th and 30th November, Dr. Smith visited PFC Edinburgh. A summary of the conclusions from his visits are contained in a memorandum of 3rd December (document no. 1868). He noted, in relation to Factor VIII, that PFC had come under clinical pressure to "supply something or they will buy US heated concentrates" with the consequence that they were recalling large batches of Factor VIII and subjecting these and their current stock (approximately 1 year) to dry heat. He adds:-

> "Their concentrate will not stand 24 hours at 70°C and the exposure is much briefer, shorter than they or I could be happy about".

990. Both PFC Edinburgh and ourselves were using dog infusions as a way of checking the safety and efficacy of heat treated Factor IX.

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991. An important meeting of Haemophilia Reference Centre Directors took place at Elstree on 10th December 1984 (notes - document no 1874). The meeting attracted a wide variety of people to whom views could be aired, including three virologists (Drs. Mortimer, Craske and Tedder) a number of Regional Transfusion Centre Directors and Dr. Gunson, Dr. Rizza and Dr. Smithies (from the DHSS). At my request, the meeting was chaired by Professor Bloom. Under the heading "Advice to patients and donors" Dr. Jones, Haemophilia Centre Director in Newcastle, tabled the current Newcastle policy and made observations on its contents. The general policy and haemophilia policy for Newcastle is set out in a separate document (document no. 1870). Although it was noted that all commercial concentrate used was heat treated, I think it is fair to say that even at this stage clinicians were still not sure about the wisdom of using US heat treated product so far as HIV was concerned. The notes continue:-

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

992. With regard to Factor VIII, it was agreed that the heat treated product should be given to all patients, if freely available, to include those who were found to be antibody positive. In the case of antibody negative patients, it was agreed that from that time, treatment must be with heat-treated materials.

993. 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 and the possible downside of heat treatment in the form of increased thrombogenicity.

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994. For the remainder of the morning session, there was considerable discussion of the merits or otherwise of heat treatment. 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. The afternoon session commenced with the Chairman outlining the current position with regard to the commercial supply of heat treated Factor VIII. Cutter, Armour and Travenol products were dry heated preparations, whereas Alpha product was a wet heat treatment concentrate. Hoechst were also supplying a preparation.

995. I explained that so far as the NHS product was concerned, BPL had begun 1984 with two objectives:-

- A product with inactivation of non-A non-B hepatitis.

- A product acceptable for general use, with non transmittance of virus.

996. I added that research and development had been making good progress and coincided well with the AIDS problem. Dr. Smith went on to review the current work programme. He noted that:-

- The current product had been dry-heated at 60°C. This material had been available since March 1984 on a limited basis, in solution.

- Priority had been given to Factor VIII concentrate, although Factor IX was capable of being heat treated. No heat treated Factor IX would be issued even for clinical trial, before animal experiments had confirmed safety.

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- The present stock of Factor VIII was being considered for heat treatment. Not all batches were suitable and those would remain available as non-heat treated product.

- Current work was directed to making available limited supplies of heat treated product to April 1985, when it was expected that all batches would be heat-treated.

- A new product of higher Specific Activity was already being prepared which would withstand more severe heat treatment and other treatments designed to inactivate hepatitis viruses as well as HTLV III.

997. In response to a question I asked, Dr. Craske advised that it was too soon to know whether the AIDS implicated batch of NHS Factor VIII had caused the seroconversion. The batch referred to was HL3186.

998. It was agreed that on general evidence, the BPL heat treated product would be accepted for use. It was made clear, however, that heat treatment brought with it a 15-20% loss in terms of output.

999. On page 9 of the minutes, there is reference to Dr. Savage raising the problem of the treatment of haemophiliacs who had only received NHS product. Until heat treated NHS material was available, the alternatives were commercial heat treated or non heat treated NHS 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 advised that:-

"....under the circumstances, BPL would not issue non-HT product in December, unless these were required for use and a specific request was

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made. Non used vials should not 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. Some HT material will be available for clinical trial purposes, but the bulk will not be available until April...."

1000. It was also agreed that priority for NHS heat treated material would be given to children and past users of NHS material.

1001. As a result of these discussions, the Chairman concluded that:-

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

1002. As the notes of the meeting make clear on the last page, it was intended, following the meeting, to issue recommendations for the treatment of patients and this in fact is what occurred. The recommendations were written by Professor Bloom. These are the general advice and assistance for Haemophilia Centre Directors dated 14th December 1984 and sent to me on 9th January 1985.

1003. Following the meeting on 10th December, Dr. Smith set out the dry heating programme for Factor VIII concentrate that was to be followed, (document no. 1877). Dr. Smith stated that:-

- Without interfering with the progress on adoption of 8Y (dry-heated) the maximum amount of 8CRV and HL currently in stock or in quarantine should be supplied in heated form.

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- During 1984 PFL had issued a few batches heated at 60° for three days (conditions "HT1"). Heating should now be at 70° for one day (conditions "HT2").

- No entire batch should be heated which had not been heated on a trial scale to ascertain whether the total batch was suitable for heating.

- PFL would continue to produce the maximum amount of 8Y to be dry heated more severely ("HT3") and would support the adoption of 8Y at BPL.

- Small-pool unheated 8CRV was to be withdrawn unless specifically requested by clinicians.

- The Northern Centres' trial based on 8Y should start in perhaps February or March.

1004. With Dr. Smith's memorandum are "action" plans for the weeks commencing 10th December, 17th December, 24th December, 31st December and 7th January respectively. The stocks of 8CRV considered suitable for HT2 heating were to be heated in a continuous programme from 11th December. This would provide approximately 3,000 vials if quality control were satisfactory. A similar assessment of suitability for HT2 was being applied to HL batches. On 17th December, the trial heating of HL stocks was to be reviewed and advice given on the constitution of the issue of unheated HL and 8CRV on or about 19th December, "for January". By December 31st PFL expected to finish two to three batches of 8Y for further heat trials and to process a further 300 kilogram batch of 8Y. A further batch of 8Y would be processed in the week commencing 7th January.

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1005. In Appendix 2 to the memorandum, there were some suggestions made by Dr. Smith for priority of assignment of heated Factor VIII.

1006. NHS heat treated Factor VIII had to be issued on a "named-patient" basis. Mr Pettet corresponded with Haemophilia Centres asking for names of patients who could be selected for treatment with heat-treated product. The question of assignment of the material was very much for the Haemophilia Centre Directors to determine. Nonetheless, we supplied material as closely as possible to the pro-rata arrangements, to those patients.

1007. Mr. Pettet circulated a memorandum headed "Marketing gossip" and dated 13th December (document no. 1879). The note is prefaced by the statement that some of the comments may be commercial exaggerations. The main points are as follows:-

- Alpha, Cutter, Armour, Immuno and Travenol had all offered HT products.

- Immuno Kryobulin was currently dry heated for 12 hours at 60°c.

- Evidence so far was that no-one was making claims for HT Factor VIII to be AIDS-free or non-A - non-B free.

- Immuno claimed to have produced a new heat treated Factor IX which it was claimed was free from any thrombogenicic problems. The product was heated at 80°c. for 10 hours.

- It was admitted by at least two of the companies - at least off the record - that they had no real evidence as to the efficacy of the heat treatment methods.

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- The companies were also claiming that the majority of their users would not use non heat treated BPL product from then on.

1008. Mr Pettet wrote to all Regional Transfusion Directors in England and Wales on 14th December (document no. 1880). The letter 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 that 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 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".

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1009. We also touched on the situation with regard to Factor IX which was described as "somewhat more serious". Priority for heat treatment had been given to Factor VIII and in the meantime non heat treated 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 how best to treat haemophilia B patients.

1010. The stability of 8Y intermediates was the subject for a memorandum from Mrs Winkelman, dated 17th December (document no. 1882). This records the progressing experimentation with regard to 8Y. Mrs Winkelman concluded that more meaningful results could only be obtained in production on a large scale and that further studies on small samples were not planned.

1011. To some extent, the contents of the letter to Regional Transfusion Directors is reflected in Mr Pettet's memorandum to me of 18th December (document no. 1884) in which he confirmed despatch of the circular letter and that as far as possible, batches of our intermediate concentrates still in stock were being considered for heat treatment, although it was known some would not be suitable. He noted that requests for heat treated material had been coming in and he expected to receive more as the weeks went by. It was not yet known what the response would be to the use of BPL heat treated material. Any user would have to satisfy conditions of priority of use (children and/or no previous experience with commercial non heat treated concentrate) and willingness to provide detailed follow-up information.

1012. Dr. Smith considered the contents of a leaflet for heated HL and 8CRV, which he set out in a memorandum dated 20th December (document no. 1888). In paragraph 3, he suggests that:-

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"We have ... 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..."

He continues:-

"...until a "second generation" concentrate is available to everyone in 1985 we think this is the safest concentrate (from all points of view) which we can offer you [my emphasis]."

1013. An article was printed in The Lancet on 22nd December, entitled "Blood Transfusion, Haemophilia and AIDS" (document no. 1889). This is something of a landmark article, as I have mentioned above. There is reference to the fact that in the UK unheated large-pool concentrates, even those prepared from voluntary donations, had transmitted non-A non-B hepatitis and in addition, first generation heated (commercial) concentrate had similarly transmitted the disease. This is not the NHS product. The article also touched on the advice which had emanated from the National Haemophilia Foundation recommendations (which I have referred to above). It is stated at page 1434 that:-

"The aim of plasma fractionators should thus be to prepare factor concentrates from non infected donors and to ensure sterility before use. For England and Wales a new blood products factory should be in operation in 1986 and Scotland is already self sufficient, but the ability to provide all the products needed will depend upon increasing the supply of plasma at regional level... meanwhile, additional funds will be needed to purchase heat-treated concentrate. It would be indefensible to allow prescription and home use of material known to be at risk from HTLV III when apparently safer preparations are available".

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1014. A "Haemofact" leaflet was released by the Haemophilia Society in December 1984 (document no. 1891). This gave general information on AIDS and, to some extent, the ideal method of treatment for haemophiliacs. It stated that:-

- Heat treatment appears to destroy the HTLV - III (AIDS) virus. Heat treated Factor VIII has become available in the United States over the past few months and is now in universal use there.

- The Minister and the DHSS had issued the following statement on AIDS:- "Heat treated products will be available from Elstree in April 1985. The UK will be self sufficient in blood products from 1986".

- The NBTS had issued the following statement on AIDS:- "The Elstree plant will produce heat-treated products by April 1985".

The Haemophilia Society proposed pressing for the following measures:-

- The IMMEDIATE introduction of heat-treated product by importing this from the United States.

1015. The release continued:-

"We endorse our earlier advice to everyone with haemophilia, however mildly effected, to continue to accept medication as prescribed by medical staff..."

1016. This is followed by a recommendation that haemophiliacs should ask their Centre Director to make heat treated product available as soon as possible. The leaflet summarised current practice at major Haemophilia Centres as being the

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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 desmopressin where this could be used.

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1017. The very early part of the year saw a transition between non-heat treated and heat treated product as far as BPL was concerned and in relation to heat treatment the issue, on an interim basis, of heat treated 8CRV and HL diminishing as heat treated 8Y was phased in from April 1985 onwards. Reservations amongst some clinicians as to the wisdom of using heat treated product still persisted. There remained no satisfactory independent evidence that heat treatment at a particular level and for a particular duration worked in relation to HIV and, absent this evidence, there were lingering concerns that the heat treatment process itself might introduce unforeseen and detrimental changes in the product which would only manifest themselves in the form of side effects in patients treated, at some later stage. The haste with which heat treated product was introduced on the back of the HIV problem meant that very little comfort could be given by anyone with regard to these understandable concerns. The concerns and the uncertainty arising as a consequence were addressed in the Haemophilia Centre Directors Organisation AIDS Advisory Document (document no. 1902) which, though dated 14th December 1984, was actually sent to me on the 9th January 1985. The document sets out general advice and assistance for Haemophilia Centre Directors and was circulated, so far as I am aware, to all of them. The authors were Professor Bloom and Dr. Rizza although, as the opening paragraph indicates, the observations and recommendations were made in consultation with myself, Dr. Cash, Dr. Gunson, Dr. Mortimer, Dr. Tedder and Dr. Craske as well as others who are not named.

1018. By this time, as the background statement on the first page of the document makes clear, there had been three reported cases of AIDS in the UK involving haemophiliacs and a total of 52 in the United States. HTLV III antibody tests were available from PHLS, as the advice makes clear, as well as from the Middlesex Hospital Medical School.

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1019. The advisory document states that antibody positivity probably correlates with exposure to imported concentrates but also states that there have been two notable recent episodes concerning UK concentrates. One of these involved a BPL batch (HL3186) and the other a Scottish batch of Factor VIII.

1020. Batch HL3186 is the subject of more detailed consideration in Dr Snape's Statement, to which I refer.

1021. At this time, as the advisory document makes clear, evidence was accruing that the HIV virus was heat labile:

> "but the data from "spiked" concentrate is entirely related to US concentrates and is minimal. It seems that in concentrates HTLV III is inactivated by dry heat at 68°C for 24 hours. It is unlikely that this process completely inactivates non-A non-B hepatitis. Wet heat with stabilisers is probably more effective but evidence is lacking and loss of yield is up to 50%. Of current products, heat treated Koate HT and Factorate HT are dry heated...Travenol Hemofil T is dry heat treated...Alpha Profilate (heated) is wet heated...Immuno also have heated preparations".

1022. With regard to Factor IX the advisory document stated:

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

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1023. For reasons which I have mentioned above and elaborate on below, our own heat treated Factor IX was some months away. Whilst the authors of the note gave no firm guidance with regard to the use of heat treated Factor IX, it will nevertheless be seen from this reference that heat treated preparations were available as an alternative to unheated NHS Factor IX.

1024. The advisory document indicates that at the time BPL could dry heat 30% of its output from 30 January 1985 onwards and we anticipated heat treating the balance within about two months when two more ovens were installed at BPL 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.

1025. The authors then set out the options as they saw them in decreasing order of safety as far as Haemophilia A patients were concerned:-

(i) Heated UK concentrate (but still with Hepatitis NANB risk).

(ii) A single donor cryoprecipitate or FFP.

(iii) Heated imported concentrate (again still with Hepatitis NANB risk).

(iv) Unheated UK concentrate.

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

1026. For Haemophilia A patients requiring Factor VIII it was suggested that "virgin" patients (i.e. those not previously exposed to concentrate) and children should be treated with cryoprecipitate or heated NHS Factor VIII (if available).

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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.

1027. So far as Haemophilia B (Christmas Disease) patients were concerned, they were recommended to use fresh frozen plasma or NHS Factor IX concentrate if essential. Mild Christmas Disease sufferers were again recommended to use FFP 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 were well illustrated by the statement which appears on page 3 of the advisory document:-

> "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."

1028. 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 been issued some time before and how they had been handled during transportation and storage. In these circumstances we would not be willing to

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heat treat products which had been out of our control for a period and then reissue them. Aside from this, and on a more logistical level, we simply did not have the capacity to heat treat recalled product. If we had tried to heat treat this material, we would have received back only "part" batches. From the regulatory view point, it is not possible to take a sub-batch and re-issue it as a re-defined batch. Further, the system of heat treatment would have been inefficient: ovens would have been part filled, thereby reducing efficiency substantially. This was unacceptable. As the note makes clear, we had insufficient heating capacity at the time to heat our ordinary production and whilst we were awaiting two more ovens, their arrival would simply enable us to heat treat our normal production

1029. On the testing front (see page 4 of the advisory document) it was recommended that patients should be tested for the presence of HTLV III 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 several years later.

1030. In a memorandum from Mr. Prince to Mr. Wesley (both of BPL) dated 18th January 1985 (document no. 1913) Mr. Prince sets out the strategy for Factor VIII production at BPL at that time. As can be seen, we planned to heat treat all batches of HL from then on, even if this brought the activity in the vials down as low as 160 iu per vial as a consequence.

1031. On the 18th January 1985 (document no. 1914) Dr. Gunson wrote to Mr Pettet at BPL to advise him that his Region (North Western) 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.

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1032. In fact, with effect from the 14th December 1984 we no longer issued unheated Factor VIII concentrate save at the specific request of the relevant Transfusion Centre/Haemophilia Centre. Details of the batches produced at BPL from July 1984 to April 1985 are set out in Appendix 10 to my statement and demonstrate that 31 batches of unheated product were dispatched in that period. **[Dr Lane: please check and confirm this information from another source: please explain the author/source of this document. Do we have corresponding figures for Oxford? [P38]]**. Three batches of unheated Factor VIII were issued from BPL after 1st January 1985. Usage of unheated product already supplied prior to 14 December 1984 was a matter for the haemophilia clinician.

1033. By way of digression at this point I should mention that from about January 1985 onwards we received a great many letters from haemophilia centres nominating individuals they wished to be treated with our heated intermediate product which, like the 8Y product which followed, could only be issued on a named patient basis, being unlicensed. An example is the letter from Dr. Kernoff at the Royal Free Hospital Haemophilia Centre to Dr. Snape dated the 15th January (document no. 1906). His letter enclosed a list of patients which he wanted to treat with our heated product. In practice this meant the patient had to be identified by the Centre requiring the product and the vials containing the product would need to be specially labelled for that patient's use before despatch.

1034. As a separate matter I should mention that the protocol for the 8Y trial, which got under way in April, was in fact an adaptation of the excellent protocol which had been developed by Dr. Smith for use in relation to our heat-treated 8CRV and HL concentrate. Throughout 1984 this clinical trial documentation had been drafted, considered and revised and the final version of the documentation was in fact sent to me under cover of a memorandum from Dr. Smith on the 9th January 1985 (document no. 1901). Although, even at this stage, he was endeavouring to keep the idea of a proper clinical trial alive, the fact is that

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events had overtaken us and from January 1985 onwards heated 8CRV and HL was issued on a named patient basis without clinical trials having been carried out (beyond the treatment of the three patients I have mentioned previously) but the protocol and associated documentation was used, as I have indicated, for 8Y which was issued on a trial basis from April 1985 onwards and was the sole product issued by 1st September 1985.

1035. On the 21st January 1985 Dr. Smith prepared a memorandum (document no. 1917) summarising the results of the limited clinical use which had been made of our heated 8CRV product which was given to three patients during 1984. The 8CRV intermediate concentrate had been heated to 60°c. for 72 hours (HT1) and had been used on three Factor VIII deficient patients who were bleeding or were undergoing elective surgery. This was in fact the limit of the trial we managed to achieve for heat treated intermediate concentrate during 1984 and Dr. Smith's papers summarises the result of the trial and the effect of the 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 inactivation of Non-A Non-B hepatitis and HIV was difficult to assess in the absence of a marker for Non-A Non-B hepatitis and inadequate data on the seroconversion time for patients infected with HIV. We did not subsequently find any evidence of hepatitis Non-A Non-B or HIV manifesting itself in these particular patients. **[Dr. Lane please supply data from the trial [P39]]**.

1036. On the 22nd January in a memorandum from Mr. Prince to Mr. Wesley, Mr. Prince reported on the first 600kg batch (document no. 1918). At the same time as we were manufacturing heat treated HL and 8CRV we were of course developing and refining 8Y and the 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.

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1037. We tried to keep everyone informed of progress and on the 23rd January (document no. 1919) Norman Pettet, the Production 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 DOH, Mr. Armour and CBLA and Col. Deacon at The Army Blood Supply Depot. In his letter he explained the progress we were making towards the production of heat treated product following up on his previous letter of the 14th December 1984. He confirmed that since the 14th December BPL had issued restricted amounts of unheated 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. [Dr. Lane: do we know which regions these are? [P40]]. He said that 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 the heat treated products, he explained that the results of our investigations had showed a loss of between 20% and 25% of the original activity in the vials which were subjected to 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 heating 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 12,000 and 15,000 vials of heat treated Factor VIII for use on a named patient basis. This was of course HL and 8CRV intermediate concentrate rather than 8Y. With regard to our new 8Y formulation, he said that this was undergoing pilot production trials and hopefully 8Y would replace the existing products.

1038. In view of the loss of yield we were suffering as a result of having to heat treat HL and 8CRV, the balance of his letter was devoted to explaining how pro rata distribution would operate in the circumstances.

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1039. Again, in terms of keeping informed of progress with regard to the supply of heated NHS product, I attended the meeting of the Regional Transfusion Directors held on the 23rd January (document no. 1920) and reported (see paragraph 7) on the position with regard to heat treatment.

1040. On the 24th January (document no. 1923) Dr. Snape prepared a pro forma letter to be circulated to Haemophilia Centre Directors giving them information on BPL's proposals regarding the supply of heated Factor VIII concentrate. The letter invited Haemophilia Centre Directors to put their requests in writing to BPL for stocks of heated Factor VIII concentrate for use in the treatment of named patients. Dr. Snape explained 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% of what would otherwise have been supplied as unheated concentrate (this reflected the losses we were encountering 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 186iu per vial. The solubility of the product was also marginally impaired but Dr. Snape stated that resolution should be achieved within ten minutes if the vials of dried concentrate and the water for injections were pre-warmed to about 30°c. He went on to make it clear that our improved high 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.

1041. Dr. Snape 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 sufficient 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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1042. 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 a copy of the protocol for use of the new product with his letter. 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.

1043. On the 25th January (Scientific and Technical Report L) Mrs. Winkelman and Dr. Smith produced a report giving details of their attempts to improve the dry heating behaviour of HL and 8CRV. 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 production of 8Y. Although a technical document, it is reasonably clear from what is said, that dry heating was not a particularly easy exercise when applying it to our intermediate concentrate.

1044. The situation with regard to heat treated concentrate came up again at the CBLA meeting which was held on the 1st February (document no. 1932). At paragraph 4.3 of the Minutes there is a record of a fairly lengthy discussion which was prompted by Professor Bloom (then a member of the CBLA) 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 the general information to Haemophilia Centre Directors, the arrangements which were to apply to the distribution of heat treated intermediate concentrate and, thereafter, 8Y. I explained the arrangements in some detail and the problems which had been experienced due to the fact that not all intermediate concentrate could be satisfactorily heated and that even where it could, there was still a distinct reduction in activity. This had consequential effects on the pro rata system of distribution. As the Minutes record, the CBLA agreed to proceed with Factor 8Y

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from April and authorised 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 had been expressed regarding the safety and efficacy of BPL heat treated products. The comment was to the effect that if there were doubts about heat treated commercial concentrate, why did the DOH not put a stop order on BPL's heat treated HL and 8CRV.

1045. As a follow-up to the discussion at the CBLA meeting, Professor Bloom wrote to all Haemophilia Reference Centre Directors on the 4th February (document no. 1941).

1046. I regarded the letter as somewhat unfortunate. We had gone to the trouble of circularising all the Haemophilia Centre Directors who, as a consequence, would have been well aware of what our proposed course of action was, whereas Professor Bloom's opening paragraph suggests that what we proposed was known to a few Reference Centre Directors only who had the benefit of my confidence and advice. This again reflected that Professor Bloom had not properly read the material which we had sent out. Moreover, 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 back from Professor Bloom with the Haemophilia Centre Directors' views following his writing to them. Professor Bloom's letter refers to a meeting of Haemophilia Reference Centre Directors to take place on 18th February 1985. Although I do not have the minutes of the meeting on file, I understand that it took place on that date.

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1047. A further circular letter prepared by Dr. Snape dated the 7th February (document no. 1955) and intended for distribution to all Haemophilia Centre and Regional Transfusion Centre Directors was prepared with a view to keeping everyone advised of the steps that we were taking with regard to the distribution of heat treated intermediate 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 Centres 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 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 general issue of a product in replacement of non-heat treated Factor IX did not occur until October 1985.

1048. On the 7th February (document no. 1956) Dr. Snape wrote a memorandum to me which he copied to Dr. Smith, referring to the Haemophilia Centre Directors' Hepatitis Working Party meeting that had taken place on the 6th February. Dr. Snape attended in my absence and Dr. Smith was also present. 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 Dr. Kernoff arguing that Profilate (wet-heat treated) would, at that moment, be the material of choice in virgin patients, given indications of freedom from transmission of hepatitis 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 Non-A Non-B.

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1049. The memorandum indicated that various haemophilia B (Christmas Disease) patients had seroconverted. Dr. Snape commented that the circumstances suggested infection by one or two batches, but in any event, a significant number of HTLV III infected haemophilia B patients had been treated with only NHS Factor IX which strongly argued for haste in the manufacture of a heated Factor IX concentrate.

1050. On the 12th February (document no. 1961) Mr. Pettet, BPL's Product Services Manager, prepared a proforma 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% of the monthly allocation".

1051. On the 28th February Dr. Snape wrote to Dr. Duncan of the Medicines Division of the DOH (document no. 1999) setting out in some detail the approach which BPL were adopting with regard to the manufacture and issue for clinical use of heat treated concentrates of Factor VIII and Factor IX. (Dr. Snape's apology for failing to write sooner is, so far as I can recall, reference to the fact that they had spoken over the telephone and Dr. Snape had delayed in his response). It was necessary to keep the Medicines Division advised of our approach both in relation to 8Y and the new heat treated Factor IX since the approach we were adopting, and in particular the protocols which we would be using, would form, together with other information, the basis of licence applications for these products. We would normally advise of our approach, directly or through the DOH, of the protocols we would be using.

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1052. The timetable we were following is well set out in Dr. Snape's letter:-

"Stage 1 - 100 vials of the HL(H) concentrate were issued to each of the Haemophilia Reference Centres earlier this month for a preliminary evaluation of safety and efficacy in named patients. The first reports on these infusions are being received and indications are that the product was well tolerated and shows the expected in vivo recovery and half-disappearance time.

Stage 2 - General issue of the HL(H) concentrate will begin as soon as information from the preliminary evaluation has been assessed (probably first week in March). Issue will be to designated clinicians for the treatment of previously named patients, but dispatch will be via Regional Transfusion Centres in order that resources can be seen to be satisfactorily allocated between regions. A comprehensive protocol for follow-up of treatment was circulated in advance to all Haemophilia Centre Directors (I enclose a copy - App.I) but I do not anticipate a very complete response. We will, however, be making the strongest possible recommendation that the first dose of the concentrate to any patient be given under medical supervision.

Stage 3 - During the last week in February, limited supplies (~ 200 vials in all) of the heated high purity concentrate, 8Y, will be issued to selected Haemophilia Centres for a trial of immediate safety and efficacy in named adult patients. By mid-March, we expect to have observations on subjective and measured response to the infusions, absence of reactions and half-disappearance time of Factor VIII.

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Stage 4 - Towards the end of March, the summarised results on data from Stage 3 will be made available to other selected Haemophilia Centres, and Directors of these Centres will then be invited to request a supply of the 8Y concentrate for the treatment of named patients meeting the following criteria:

(a) not suspected of having liver disease at presentation;

(b) not having received more than two infusions of blood products in the last 12 months;

(c) not having received any blood products in the last 6 months;

(d) serum negative for HBsAg, anti-HBs and anti-HBc;

(e) giving informed consent.

I enclose a copy of the protocol for this study also (App.II).

Stage 5 - Armed with the safety and efficacy data from Stages 3 and 4, we would propose to make an abridged licence application for 8Y product (hopefully early in May). After licence for the 8Y product has been granted, and when stocks of the concentrate permit, general distribution of 8Y will begin, the HL(H) product being phased out.

We look forward to Stage 5 being completed by the end of June. You will notice that both protocols for patient follow-up place at least as much emphasis on hepatitis as on AIDS (HTLV III). This reflects our

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conviction that NANB and type B hepatitis viruses present a more severe challenge to viral inactivation procedures than does HTLV III."

1053. With regard to Factor IX concentrate, Dr. Snape summarised the position in his letter as follows:-

"Our approach here has been more conservative than that of fractionators in North America. Recognising the prothrombin complex concentrates are potentially thrombogenic, we were concerned that the freedom of heated Factor IX concentrates from potential thrombogenicity should be adequately demonstrated before any clinical trials. Although a small number of Christmas disease patients, whose only recorded treatment is with NHS Factor IX concentrate, are now known to be HTLV III antibody positive, we believe our original assessment of comparative risks was probably reasonable. We therefore intend to submit the heated Factor IX concentrate presently being developed to extended testing in a dog model prior to clinical trial.

We would see clinical trial of the heated Factor IX concentrate following the pattern of stages 3 to 5 above, but lagging 2 to 3 months behind 8Y concentrate at all stages. As with 8Y we intend to make an abridged licence application for the new heated Factor IX concentrate before commencing general issue."

1054. At about this time, we also prepared a data sheet to go to Haemophilia Centre Directors with the heat treated HL and 8CRV products (document no. 2001). Under the heading "Warning" the following statement appears:-

"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 benefit of treatment should be

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carefully weighed against the risk of transmission of virus before the product is used. Unpublished evidence suggests that heating conditions used may inactivate HTLV III added to similar concentrates but this remains to be confirmed by prospective studies. At least partial inactivation of NANBH virus(es) by heat is likely and heat inactivation of some model retroviruses has been described."

1055. Mr. Pettet of BPL prepared another circular letter to Regional Transfusion Directors and Haemophilia Centre Directors on the 19th March (document no. 2022) setting out more details of the arrangements being implemented for the issue of heated intermediate Factor VIII concentrate. He repeated that the amounts to be made available would be approximately 50% of those which would otherwise have been supplied as unheated concentrate, and also pointed out that the response to an initial request for named patients requiring treatment with heated product had been slow. In the circumstances, he suggested 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. BPL issued named containers and Regional Transfusion Centres were merely distribution agencies.

1056. Mr. Pettet's letter also makes reference to the anticipated introduction of 8Y in June/July, and advised that clinical trials were underway, 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 viral inactivation."

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1057. In her report on the progress of the 8Y project covering the period October 1984 to March 1985 (Scientific and Technical Report K), Mrs Winkelman indicated that by that time full quality control had been completed for five batches of PFL 8Y on both unheated and heated samples:-

> "Two batches failed on solubility grounds but we believe that greater purity resulting from recent processing changes will avoid that problem in the future. No significant changes have been found after heating other than the expected 5-10% loss of VIIIC activity.
>
> The first two batches of BPL 8Y passed all QC tests without problems."

1058. Heat treatment was raised at the meeting of the Central Committee for Research and Development in Blood Transfusion which took place on the 2nd April (document no. 2038). At paragraph 4.2 under the heading "Use of Heat Treatment on Factor VIII and Factor IX Preparations", I reported our hopes that the heat treated Factor VIII which we were producing would inactivate HTLV III. I reported on the work that 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. It will be seen that Dr. Rizza reported that his initial usage of the new 8Y product suggested that there were no adverse side effects. He was proposing to continue with longer term experiments with regard to the investigation of transmission of Non-A Non-B hepatitis.

1059. In his letter of the 4th April to Dr. Kernoff at the Royal Free Hospital in London, (document no. 2042) Dr. Smith reported on stage 1 of the clinical trial of 8Y:-

> "Three batches of new high-purity, severely heated Factor VIII concentrate type 8Y were distributed to Drs. Rizza, Kernoff and Jones at

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the end of February for evaluation of immediate safety and objective efficacy. The batches included the first and latest produced to date at PFL and covered the likely range of characteristics expected from PFL and BPL batches in future, except for minor changes in presentation.

Results on 4 Oxford and 3 Royal Free patients are summarised in table 1. Newcastle's will follow in May.

We interpret the immediate recovery and half-disappearance estimates as being well within the extensive experience with earlier concentrates. The patients were not actively bleeding and there is no final proof of haemostatic effectiveness. There have been no complaints about presentation or infusion and two patients commented on a subjective preference for 8Y compared with earlier NHS concentrate. On these grounds, we recommend progressing to stage 2 of the trial, viral follow-up of category 1 patients which have received little or no treatment in recent years and may be susceptible to infection with NANBH and HTLV III."

1060. Also on the 4th April, Dr. Smith sent a detailed report to me (document no. 2043) on the progress with regard to the heat treatment of Factor IX. 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 having regard to the potential problems of thrombogenicity. By the time the memorandum was written, these experiments were underway.

1061. In paragraph 2.1 of the memorandum, Dr. Smith identifies the difficulty which had arisen and which caused a 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

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that there was no significant problem with regard to the presence of thrombin. The full range of tests required by the British and European Pharmocapoeias were applied to the product. Heating had led to a level of thrombin not revealed earlier by the NAPTT test. This was surprising since the additional test(s) required by the British Pharmocapoeia and the European Pharmocapoeia, although not thought to have any physiological significance, required an additional modification to the process, hence further delay.

1062. The discovery of this problem at a late stage reinforced the need, once the problem had been tackled, to use dogs for testing before clinical trials were commenced. 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 anti-thrombin III). The programme for dog infusions is covered by Dr. Smith at paragraph 3 of his memorandum and at paragraph 4, Dr. Smith set out some alternative courses of action aimed at securing as early a release of the heated Factor IX concentrate for the 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 expressed as follows:-

> "...PFL will aim at the most rapid possible provision of finished 9D plus AT III for dog infusions and clinical trial (and potentially the most pressing treatment of little-exposed patients) but cannot greatly affect national supplies for severe haemophilia B. We will not interfere with the planned dog infusions this month of one batch of 9D minus AT III, but our second trial product would be 9D plus AT III."

1063. Mr. Prince's memorandum to Dr. Harvey and others at BPL dated 10th April (document no. 2044) records the installation of the two Pickstone heat treatment ovens which we had been waiting for in order to accelerate production

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of heat treated Factor VIII and Factor IX, and also records the fact that they were in the process of being commissioned and validated.

1064. On the 16th April, a PFL Working Party to deal with the introduction of heat treated Factor IX met for the first time (document no. 2053). The meeting concluded that the scientific evidence so far showed that 50ml of AT III added to Factor IX enabled heating at 80°C for 72 hours without detrimental effects 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 of the meeting, the effect of this on the dog trials programme suggested that this would be complete in time to allow for clinical trials by the end of May or the beginning of June.

1065. In his memorandum of the 18th April 1985 to me (document no. 2059), Dr. Snape confirmed the solution to the thrombin problem which had been decided upon in respect of heated Factor IX. As will be seen, it was decided to add 50ml of AT 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. This brought the product within the British and European Pharmocapoeia. Dr. Snape sought my authority to institute the appropriate change, which I subsequently gave.

1066. On the 24th April, Mr. Prince reported to me in a memorandum (document no. 2062) that Pickstone oven no. 2 had been satisfactorily 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.

1067. As can be seen from Mr Pettet's letter to Dr. French (a consultant haematologist at the Department of Haematology, Queen's Medical Centre,

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Nottingham), dated 2nd May (document no. 2079), the distribution arrangements with regard to heat treated Factor VIII were not ideal. 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 that initially it was 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 by Haemophilia Treatment Centres to enable this exercise to proceed, but the response from the majority of treatment centres was very slow with the consequence that by mid-March, BPL had received lists for only just over 50% of the treatment centres. At the relevant time, Mr. Pettet explained that through efforts at PFL we were in a position to issue heat treated Factor VIII on a limited basis, and the new ovens had been installed which allowed greater heating capacity from the 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. Mr. Pettet points out in his letter that it was apparent that the urgent need for NHS product outweighed the desirability 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 advised Dr. French that BPL would be in a position to issue an allocation of heated Factor VIII to each Transfusion Centre at between 50% and 60% of that for unheated product for May and June, and that by July, the new 8Y product would begin to replace the intermediate heat treated concentrate. He concluded by saying that the present heating methods appeared to have no effect on hepatitis NANB virus, at least

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from the published studies so far, but in fact as our later studies showed, the heat treatment we were applying to the BPL/PFL products worked so far as hepatitis NANB was concerned.

1068. In a memorandum from Dr. Snape to myself dated the 7th May (document no. 2084), Dr. Snape advised me that Dr. Kernoff had indicated that he might imminently decide to discontinue the use of non-heat treated NHS Factor IX for his Christmas disease 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 for that patient, but nevertheless the patient had seroconverted and was HTLV III positive. As the memorandum indicates, they were currently evaluating the heated Factor IX produced by Alpha Therapeutics, but their preliminary studies showed the tendency to raise FPA (fibrinopeptide A - a marker of increased thrombogenicity in vivo) levels in some patients.

1069. By the end of May, we were putting together teams to deal with the scaling up of production of 8Y now that we had the equipment (particularly the ovens) to facilitate this.

1070. Further evidence of problems with regard to distribution may be seen from a letter dated the 3rd June (document no. 2099) addressed to Dr. Smith by Dr. Michael McEvoy, a Consultant Haematologist at Harrogate General Hospital. He draws attention to the fact that when he received heat treated BPL Factor VIII, he did not, at the same time, receive the associated protocol and paper work from the relevant Transfusion Centre with the consequence that he used the concentrate to treat two patients on home treatment, both of whom were positive for HTLV III antibody. Dr. Snape replied to Dr. McEvoy on the 13th June (document no. 2120) and passed on proper copies of the protocol, and pointed out that the original protocol did not cater specifically for the follow up of HTLV III antibody positive patient. As he says, however,

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"it was assumed that, in the trial phase at least, heated NHS concentrate would be used primarily in HTLV III antibody negative patients."

However, as Dr. Snape pointed out in his 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 that we sent out with the heat treated Factor VIII intermediate concentrate, that it should not be used for HTLV III positive patients, although clearly the best use of what was a scarce resource was made by identifying those categories of patients who might benefit from what appeared to be a safer product than the unheated one.

1071. In July, Dr. Smith prepared two papers (probably as briefing documents for the meeting of the Central Committee for Research and Development in Blood Transfusion which took place on the 9th July), dealing with the Factor VIII and Factor IX heat treated concentrates.

1072. The first of these entitled "A new "Virus-Safer" Factor VIII Concentrate of high specific activity" (document no. 2130) sets out the basic details regarding the 8Y product which I have covered in one way or another above. He states, inter alia:-

"The concentrate is now in full scale (1,200 kg plasma) production at BPL, and the Factor VIIIC yield is beginning to overtake that obtained for the less severely heated intermediate purity concentrate (HLH) pressed into service early in 1985 in response to concerns about HTLV III transmission. Current limitations on centrifugation capacity preclude further scale-up for the moment, but a very active programme of process development is intended to remove such obstacles as well as improving efficiencies.

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The immediate safety and efficacy of the 8Y concentrate have been demonstrated by clinical trials. Eight patients at three Haemophilia Centres receiving 14 infusions of 3 batches of concentrate have shown dose response in the range 1.1 - 2.9 and a mean half-disappearance time of 10h **[10 hours]**, entirely consistent with recent experience of unheated concentrate.

Evidence for reduction or elimination of viral transmission is being sought after infusions in haemophiliacs who have been treated with concentrate either for the first time or after a long interval, and who are thought to be susceptible to infection with hepatitis B, NANBH and HTLV III. This trial is at a critical stage, but several patients have already safely passed the point at which the first evidence of NANBH transmission would have been expected."

1073. The second document entitled "Factor IX Concentrate Heat-Treated to inactivate Viruses" (document no. 2131) 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. Dr. Smith states:-

"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-affects. Any new concentrate, or new processing stages added, e.g. to inactivate viruses in the concentrate, should therefore be tested in animals before

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clinical trials; the preferred animal model in the UK is post-infusion detection of minimal DIC [disseminated intravascular coagulation] in dogs.

The new concentrate 9A, dry heated after the addition of AT III, has now been shown to be even less reactive than the parent 9D in dog DIC models. 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 precede to treatment of patients susceptible to NANBH and HTLV III transmission, starting in August. Current production of Factor IX concentrate at PFL and BPL has been easily adapted to incorporate the addition of AT III and heating in the ovens developed for heating Factor VIII."

1074. This effectively summarises the position we were at the start of July.

1075. A note of Factor VIII Issues dated the 9th July (document no. 2132) reveals that in the period January to July 1985, we issued a total of 3.9m. iu of unheated product against 4.3m. iu of heated product. **[The amount of unheated product seems much higher than would be anticipated given the decision to release only heat** treated product **from the** start of **January, save where clinicians requested non heat** treated product. **It does not seem to tally with the summary of batches which seem to show only three issued unheated batches in the period January to April 1985 (Appendix 10). Dr. Lane: please confirm these figures [P41]].**

1076. The CBLA Central Committee for Research and Development in Blood Transfusion met on the 9th July 1985. As the minutes show (document no. 2136), (paragraph 10.2), I reported progress with regard to the heated Factor VIII and Factor IX concentrates (probably using Dr. Smith's two memoranda on which I

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have commented above). I described the Factor VIII as "virus-safer". Our problem continued, in that we could not show the efficacy of viral inactivation in relation to HTLV III. By and large, this sort of experiment requires you to start with at least six logs of virus per ml, and with HIV at that time this was hard to achieve. 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 (PFC) suggested that heating at a similar level and for a similar length of time as ourselves killed four logs of vaccinia which is recognised to be an especially robust virus capable of withstanding 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 the heat treatment was working for HTLV III, but of course we could not describe our Factor VIII heat treated concentrate as "safe".

1077. I attended the meeting of the Regional Transfusion Directors which took place on the 10th July (document no. 2137) and at paragraph 13 of the minutes, I am quoted, under the heading "Factor VIII" 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 new product (8Y) will begin. Clinical trials appear satisfactory and a provisional licence is likely to be granted in the late summer."

1078. The desirability of obtaining a licence for BPL products was self-evident and in subsequent clinical trials a CTX (clinical trial exemption) was obtained. However, for regulatory purposes BPL's operations continued under Crown Exemption and would do so until new manufacturing facilities were commissioned permitting the grant of a manufacturer's licence and corresponding product licences.

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1079. In July we prepared an information sheet on 8Y which was issued to Haemophilia Directors and Regional Transfusion Directors (document no. 2149). The information sheet gave full particulars of heat to which the concentrate had been subjected. With regard to virus inactivation 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."

1080. 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 Centres. Allocations to the BTS will observe the pro rata requirements for distribution agreed between BPL and the BTS except for 8Y required to fulfil the special needs of clinical trials to provide information for product licence application.
>
> It is recognised that, until the new production unit at Elstree is completed, output of 8Y will meet about one third of current demand for concentrate and, for this reason, attempts have been made to define those patients likely to benefit most from the security inherent in 8Y.
>
> Therefore, Haemophilia Centre Directors are being asked to compile lists of their patients considered "at risk" and most Centres have complied. It is the considered view at BPL that, where possible, liaison between haemophilia services and the BTS should aim at directing 8Y to these patients, using the existing framework of distribution and supply.

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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."

1081. At this time we confirmed to Regional Transfusion Directors that only 8Y would be issued in September 1985 at the level of 7,500 vials (of 250 iu) per month (see the letter written by Mr. Pettet - document no. 2150).

1082. A similar information sheet was produced in October 1985 (document no. 2185) on heat treated Factor IX concentrate. This confirmed that from October, heat treated Factor IX concentrate would replace the previous product and the information once again gives details of the heat treatment. It states, inter alia:-

"Clinical trials at specified Haemophilia Centres are now in progress to gain evidence of reduction or elimination of viral transmission, particularly NANBH virus transmission. Further assurance is sought over freedom from risk of viral transmission."

1083. Dr. Snape also wrote a standard letter to Regional Transfusion Centres in October 1985 (document no. 2186) requesting them to return unheated Factor IX type 9D concentrate now that heat treated Factor IX concentrate was available.

1084. With the release of heat treated Factor IX in October 1985, we saw the end of the rush to develop heat treated NHS concentrates and get these to the patient. However, the work did not cease at this stage. Refinements to the processes for manufacturing 8Y and 9A continue enabling us, amongst other things, to increase the yield as we adjust the variables in the production process. We continue to receive information from clinicians regarding patients treated with

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the product, and to date we have received no evidence that patients treated with 8Y or 9A alone have become infected with hepatitis B, hepatitis NANB or HIV.

SUMMARY OF HEAT TREATMENT CLAIMS AND CBLA REBUTTAL

1085. Turning to the specific allegations made in relation to heat treatment, I would comment as follows:-

1086. (95m) Failed, from 1982, to have any or any sufficient regard to pressing and urgent need to heat-treat Factors VIII and IX concentrates, given:

(i) the ancient principle of pasteurisation;

(ii) the risk with such concentrates of contamination by hepatitis and/or other viruses;

(iii) from mid-1982, the risk of HIV contamination with such concentrates.

As I have explained above and as amplified in Dr. Smith's statement, 1982 saw the earliest consideration being given to viral inactivation of Factor VIII and IX concentrates. Heat treatment was merely one of a number of possibilities and when our research began in 1983, pasteurisation (or more correctly, heating in solution) was indeed one method of heat treatment we considered, and we did so largely because it was an established method which had been applied to albumin. However, heat treatment was not itself the only possible method of inactivating virus, and it was right that we should consider the alternatives before committing ourselves to a particular line of research. In 1982/83 when the foundations for our research work were laid, it should be remembered that the risk being addressed consisted of the long term potential affects in some patients of hepatitis Non-A Non-B infection. Although the MSC dates the HIV risk from

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mid-1982, this was really the earliest date that AIDS began to be appreciated and the dissemination of information regarding HIV did not lead to a tentative identification of the cause of AIDS as a virus until 1983. Confirmation of this in 1984 along with the news that the virus was heat labile places a different and more realistic perspective on events. The heat treatment of commercial products stemmed in the main from research done during the early 1980's which had nothing whatever to do with HIV at the time.

1087. (95(n) Failed, from 1982, either sufficiently or at all to require or commission and/or encourage and/or engage in research and development of heat treatment of home donated and produced Factors VIII and IX concentrates, given the reasons hereinbefore pleaded.

I think I can add little to what I have said above and what is amplified in detail in Dr. Smith's Statement describing the progress of research. Within the resources allocated (which were meagre), BPL and PFL accomplished a great deal producing ultimately the most successful of the Factor VIII heat treated concentrates and an equally satisfactory heat treated Factor IX concentrate.

1088. (95(o)) Failed, from 1982, to advise the Department of Health and the Health Authorities to use heat-treated Factors VIII and IX concentrates, in place of non-heat-treated product, given the risk of contamination with hepatitis and/or other viruses.

It was no part of BPL/PFL's role to provide advice of this sort. Clinicians and public health laboratories and the regulatory authority had as much information as anyone throughout this period regarding the need for use of heat treated products. There was an understandable reluctance to embrace a new and unknown product and we could not possibly have stepped into the arena to offer advice regarding the use of products which we had not developed or subjected to any sort of clinical trial. Moreover, as shown by subsequent events, some of the

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heat treatment applied to commercial products did not work as far as HIV or hepatitis were concerned. Again, one has to bear in mind that the chronology is different from that presented in the MSC. The use of heat treated products did not appear to become an imperative until 1984 when HIV was positively identified as a virus. At this time, along with many other experts, I contributed to debates leading to the production of guidance notes for haemophilia clinicians. There were a number of Working Parties working on AIDS at any given time with representatives of the DOH and the Haemophilia Clinicians sitting on them and, in the circumstances, it seems a somewhat bizarre suggestion that BPL/PFL as manufacturers of product should have set themselves up as advisers on the treatment of patients. Lastly, on the subject of chronology, I would state again that by the time the commercial heat treated products became available, much, if not all of the damage had been done and severe haemophiliacs in particular were, in the main, already infected with HIV.

1089. (95(p)) Failed, from 1982 or such later time as may be justified on the evidence of trial, to advise the Department of Health and the Health Authorities to use heat-treated Factors VIII and IX concentrates, in place of non-heat-treated product, given the risk of contamination with hepatitis and/or other viruses and the additional risk of HIV contamination.

As will be apparent from my Statement, I sat on a number of (but by no means all) expert groups considering, inter alia, hepatitis and later HIV. I contributed actively (drawing on my own experience and that of colleagues like Dr. Smith) along with many other experts, to discussions at the various meetings of these groups which were all attended by representatives of the DoH and individuals who represented or had close links with the Health Authorities. The advice given by all concerned at these meetings led to a consensus as to what reaction there should be at any particular point and, in this sense, BPL/PFL contributed as far as it could and should to the advice which the DoH and the

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Health Authorities drew from a variety of sources before determining upon a particular course of action.

1090. (95(q)) Failed to achieve production of home donated and produced heat-treated Factors VIII and IX concentrates; such production should have been achieved by 1980 or such later time as may be justified on the evidence at trial; as it was the CBLA failed to achieve such production from 1982 until 1985.

This does not materially add anything to the previous allegations. As explained in this Statement and in Dr. Smith's Statement, our first heat treated products were available for trial in the spring of 1984. We were not put under pressure by haemophilia clinicians to provide more of this product. It was our own decision in the autumn of 1984 (on the back of the news that HIV was heat labile) that we unilaterally determined to switch to entirely heat treated Factor VIII product; first our intermediate concentrates but subsequently our high purity 8Y products and to press forward as quickly as possible with our heat treated Factor VIII research. Unless specifically requested to the contrary from February 1 1985 onwards, we issued only heat treated Factor VIII. The earliest point at which we could have issued heat treated product would have been in the spring of 1984 when we produced a few batches for trial use, but it should be remembered that, at this point, heat treated commercial concentrate was also available and that there was no limitation on the amounts which could be supplied had clinicians required it. The reality was that there were misgivings amongst clinicians at that time about the use of heat treated products. Some feared side affects, some that the heat treatment was not effective and that the balance lay in favour of continuing to use what was perceived to be the "safer", albeit unheated, NHS alternative.

1091. (95(r)) The DHSS having, in late 1984, announced that home-produced Factor VIII would be heat treated at the BPL from 1985, the CBLA

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should thereupon have advised the Health Authorities to switch forthwith to imported heat-treated Factors VIII and IX concentrates in place of non-heat-treated product, and the CBLA should have forthwith invited and encouraged the Health Authorities to submit their existing stocks of concentrate to the BPL for testing and heat-treatment.

Advice, as will be apparent from my statement and from the documents that I have cross-referred to, was indeed provided to clinicians/other interested parties regarding products used for treatment. In particular, advice was issued in December 1984 and represented the distillation of views of many experts, not just fractionators, but virologists as well as clinicians treating haemophiliacs. As to the recall of stocks of concentrate for testing and heat treatment, I have explained in my statement that, in relation to testing, there was no satisfactory test available at that time although product is routinely tested and confirmed by NIBSC. At the relevant time, we did not have the capacity to heat treat stocks of Factor VIII retrospectively which might have been recalled. Additionally unheated Factor VIII produced by the NHS was still used by certain clinicians (conscious of all the risks involved), particularly in the treatment of those patients who were already sero-positive. Lastly, since we could not guarantee the integrity of products which had passed out of our control, the whole idea of retrospectively heat treating (even if this were feasible given our facilities at the time), was flawed. We had no idea under what conditions these products had been transported or stored and since we could not guarantee the safety of the product in vials which were recalled (and which we could not open to examine the contents without compromising the product), we would not have heat treated and re-issued it even if we had the facilities at the relevant time.

Signed.....

Dated.....

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