Review of Documentation Relating to the Safety of Blood Products 1970 – 1985 (Non A Non B Hepatitis)

May 2007

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Summary

1. This review was commissioned in June 2006. The need to assess the extent and content of documents held by the Department of Health (DH) in relation to Non-A, Non-B hepatitis (NANBH) was prompted by calls for a Government backed public inquiry and the return of documents, previously considered missing, from a firm of solicitors. The objective of the review is to consider all documents related to NANBH held by the DH and report on their content. The review covers the period 1970 to 1985 as in September 1985 a heat-treated factor VIII product, Factor 8Y, was introduced by the Blood Products Laboratory (BPL) to inactivate the virus. BPL was accountable to the Central Blood Laboratories Authority (CBLA), which was established as a special health authority in 1982. Prior to this a Joint Management Committee had managed the Laboratories on behalf of the DHSS and NW Thames Regional Health Authority.

2. The DH became aware that documents relating to the safety of blood products were mislaid/destroyed some time during the period between 1990 and 1998. The incidents of the mislaid/destroyed DH files were the subject of an internal audit in February 2000[1]. Following publicity of this loss, photocopies of 610 documents were returned in May 2006 to the DH by a private firm of solicitors who had acted for claimants during earlier HIV litigation. There was also the realisation within the DH that some documents held in unregistered files might be pertinent to the issue of the safety of blood during 1970 and 1985. These unregistered files held 4,629 documents.

3. The above figures represent a substantial number (5,239) of documents. It is presumed that the majority of documents from 1970 to 1985, previously identified as missing in paragraph 2 above, have been located.

4. The review identified that in the mid 1970s it was recognised that as well as hepatitis A and hepatitis B there were other hepatitis agents which were not hepatitis A or hepatitis B. There was at this time a push towards achieving self-sufficiency in clotting factor concentrates, initiated by the increased use of dried concentrates from large pools of donors and concern that commercially produced and imported products ran a higher risk of transmitting hepatitis than NHS products. It would appear that based on the scientific knowledge available at the time, there was a general view that the benefits resulting from the use of plasma concentrates far outweighed the potential risks from NANBH.

5. The additional impact of the cost of commercially produced imported products provided the impetus to plan for the UK to become self-sufficient.

6. By the early 1980s the incidence of NANBH was recorded as being similar in commercial and NHS products. The need for research into NANBH and the need to devise a diagnostic test was recognised and promoted.

7. In the 1980s published research into NANBH expanded. NANBH was by then thought to be the main cause of post-transfusion (viral) hepatitis, although more than one agent was suspected. The severity of the chronic hepatitis related to NANBH virus remained unrecognised, with most patients in this group being

symptomless. With no specific diagnostic tests available NANBH remained a disease diagnosed by exclusion; if hepatitis A and hepatitis B had been excluded, the hepatitis was diagnosed as NANBH.

8. In the early to mid 1980s, there was an emerging recognition that the long-term clinical significance of NANBH had not been determined. There was some evidence during the early 1980s that NANBH could lead to progressive liver disease and might be an understated problem.

9. By 1985, it was realised that NANBH might not be as benign as previously supposed and that progression from chronic mild NANBH to a more severe outcome of cirrhosis may be protracted and only identified with long-term studies. Research in 1986 identified the need for retrospective studies, recognising that the disease might be quite mild but progression to severe symptomatology may be very protracted.

10. After 1985, it was possible to undertake longer duration follow-up studies. There were indications that studies in which the length of the follow-up was less than 10 years had underestimated the importance of the disease.

11. An effective heat treatment to inactivate the NANBH virus was sought from the early 1980s. A heat-treated product, BPL Factor 8Y, was generally introduced in September 1985. This replaced an intermediate product that was introduced early in 1985 in response to concerns about HTLVIII (HIV) transmission. The hepatitis C virus was identified in 1989. It has since been shown to account for the majority of cases of post-transfusion NANBH. A series of studies in 1989, 1992 and 1998 provided evidence that the BPL Factor 8Y product appeared to have prevented transmission of hepatitis C and HIV/AIDS. When reliable and validated assays for hepatitis C antibody became available the screening of donor blood was introduced in the UK in September 1991.

12. This review of documents summarises the information on NANBH in relation to the safety of blood products held by the DH during the time period 1970 to 1985.

Introduction

13. The aim of this review was to identify, and consider the content of, all documents held by the Department of Health (DH) in relation to the safety of blood products, specifically the viral inactivation of blood products for non-A non-B hepatitis (NANBH), during the period 1970 – 1985. The review summarises the information in the documents related to NANBH. NANBH was the name first used in 1974 to describe a number of post-transfusion hepatitis cases that were caused by neither the hepatitis A nor the hepatitis B viruses. The hepatitis C virus was identified in 1989 and has since been shown to account for the majority of cases of post-transfusion NANBH. This review focuses on the period 1970 to 1985 as in September 1985, heat-treated factor VIII, BPL Factor 8Y, was introduced to inactivate the virus. Research undertaken after the identification of hepatitis C provides evidence that BPL Factor 8Y effectively removes risk of NANBH (hepatitis C).

14. It was identified that there were two instances of documents relating to blood products being inadvertently destroyed or mislaid.

15. In the first instance, large numbers of documents were mislaid following their retrieval for the DH solicitors use in the 1989 HIV litigation. These documents were removed from their original files and provided to Counsel. The trial folders were returned to the DH. These mislaid files were the subject of an internal audit review in February 2000. The DH was not able to respond to a later request in January 2005, under the Freedom of Information Act (FOIA), for the release of documents that were subject to a Public Interest Immunity (PII) claim by the DH during the HIV litigation. These missing files, including those subject to PII, are thought to cover the period from 1970 to 1990 although the internal audit report[1] commissioned in February 2000 does not specify the number of documents or the period covered by the loss.

16. In the second case and some years later, between September 1994 and March 1998, a number of files documenting the work of the Advisory Committee on the Virological Safety of Blood (ACVSB) were inadvertently destroyed. These files contained the minutes and background papers of the Committee between May 1989 and February 1992. The internal audit report[1] found that the files had initially been marked for a review and then soon afterwards sent to the Departmental Records Office for destruction. The report concluded that the person who sent the files for destruction had probably been unaware of their importance and offered a number of recommendations for improved induction and guidance. The ACVSB files relate to a period post 1985, after the introduction of heat-treated factor VIII and are therefore outside the scope of this review.

17. The loss of documents, summarised in the two instances above, contributed to demands for a public inquiry into the issue of patients infected with hepatitis C through contaminated blood products during the 1970s and early 1980s.

18. A report 'Self-Sufficiency in Blood Products in England and Wales A Chronology from 1973 to 1991'[2] was published by the DH in February 2006. The report

considered the emerging and developing understanding of the seriousness of NANBH, later known as hepatitis C. It concluded that the prevailing medical opinion in the late 1970's and early 1980's was that NANBH was perceived as a mild and often asymptomatic disease and the advantages of treatment with factor VIII concentrates were perceived to far outweigh its potential risks. The focus of the 'Self-Sufficiency' report was the achievement of self-sufficiency in the UK between 1973 and 1991 to secure both health and economic benefits. The fact that self-sufficiency was not achieved appears to be linked with the increase in demand for clotting factors at the time. Although the production target for factor VIII was achieved within the two-year timescale it was not enough to achieve self-sufficiency and demand for clotting factors increased during the 1970s partly because treatment practices were developed.

19. In May 2006 a firm of solicitors who acted for claimants during the earlier 1989 HIV litigation, returned to the DH photocopies of 610 documents provided to them by DH solicitors as part of this earlier litigation process. These are presumed to be some of the missing documents identified in paragraph 15 above.

20. During the review process, a large group of documents, held in unregistered files were assessed as relating to the safety of blood. Process records accompanying these documents indicate that some of them were the mislaid documents in instance one above (paragraph 15). With the exception of the ACVSB files, known to be destroyed, it is therefore presumed that these comprise the majority of the documents previously mislaid.

21. The review therefore aimed to deliver the following:

    - An inventory of all documents held by the DH, these being those returned by the firm of solicitors and those held in unregistered files at DH (Wellington House), relating to the safety of blood products between 1970 and 1985.
    - The identification, where possible, of missing documents.
    - The preparation and release, in line with FOIA, of two sets of documents. Set one relates to the referenced documents referred to in the published report 'Self-Sufficiency in Blood Products in England and Wales'. Set two are the photocopies of documents returned to the DH in May 2006 by the firm of solicitors who had represented claimants during the 1989 HIV litigation. Both these sets of documents have been released in line with FOIA during the course of this review.
    - A report (this document) on the content of documents dating from between 1970 and 1985 on post-transfusion NANBH.

22. A chronology of the key events is provided in Annex A.

Background

23. Haemophilia is a rare hereditary bleeding disorder in which clotting factor VIII (haemophilia A) or factor IX (haemophilia B) is deficient. Both haemophilia A ('classic haemophilia') and haemophilia B ('Christmas disease') are caused by defects on the X-chromosome. This implies that, with few exceptions, all patients are men[3]. The classification of haemophilia into severe, moderately severe and mild is based upon the basal clotting factor activity; severe <1%, moderately severe 1-5%; mild 5-40%. Most bleeding in severe haemophiliacs occurs spontaneously in the larger joints and in muscles. In mild haemophilia, bleeding does not usually occur except after trauma. Moderately severe haemophilia has clinical features between severe and mild haemophilia. Repeated bleeding in joints causes arthropathy, the major chronic complication of haemophilia, often worsened by muscle atrophy.

24. The identification of hepatitis C using molecular biological techniques was published in 1989. Its presence had been predicted as far back as 1974 when it had been shown that there were cases of post-transfusion hepatitis not related to either the hepatitis A or hepatitis B viruses (then referred to as post-transfusion NANBH). The DH is of the view that only after the virus had been identified was it feasible to develop a screening process for hepatitis C. Screening of blood donations for hepatitis C was introduced in 1991: prior to this no reliable and validated assays for hepatitis C antibody were available.

25. The review of all documents, relating to NANBH, held by the DH was undertaken to assess their content. The review focuses on the period 1970 to 1985 as in September 1985 heat-treated factor VIII, BPL Factor 8Y, was introduced to inactivate the virus.

26. From an historic perspective, the medical developments in the treatment of haemophilia are significant in terms of life expectancy and quality of life (Rosendaal et al, 1991)[3]. Rosendaal's study found that the introduction of purified clotting factors in the 1960s dramatically improved life expectancy and cited the introduction of home treatment in the early 1970s as one of the cornerstones of modern haemophilia care. Before 1960 patients with severe haemophilia had a life expectancy of 25 years, the clotting factor preparations increased life span almost to normal; severe - 63 years, moderate – 65 years, mild – 69 years (Rosendaal et al, 1989)[4]. Rosendaal's 1990 study found that home treatment had several advantages: bleeding can be treated without delay; reduction in the days spent as hospital in-patients; great enhancement of the patient's possibilities to lead as normal a life as possible. The development of clotting factor opened the possibilities of modern haemophilia treatment by adequate replacement therapy and revolutionised haemophilia care. The increasing number of patients, related to the longer life span, as well as the increasing intensity of treatment with a shift from on-demand treatment to prophylactic treatment (not waiting for bleeding to start) increased the demand for clotting factor concentrates.

27. Most patients with haemophilia treated with blood products in the 1970s through to the mid 1980s were infected with NANBH and many with HIV/AIDS. The technology for eliminating NANBH from plasma products, whilst maintaining their effectiveness, was developed by BPL and issued across the NHS in September 1985. The risk from hepatitis was known as evidenced in this review but it was not possible until the mid 1980s to produce effective virucidally treated clotting factors for the treatment of haemophilia that were free from that risk.

28. In February 2006, the DH published 'Self-Sufficiency in Blood Products in England and Wales A Chronology from 1973 to 1991'[2]. Self-sufficiency was not achieved in England and Wales. The initial target was met but by then demand had increased. In relation to NANBH, the report concluded that the prevailing medical opinion in the late 1970's and early 1980's was that NANBH was perceived as a mild and often asymptomatic disease.

29. There have been a series of calls for a Government-backed public inquiry. Given these calls and the return of documents from the firm of solicitors, this review was initiated in June 2006.

30. A Grade 6 DH civil servant undertook the review between July 2006 and March 2007.

Methodology

31. The documents held by the DH were at their offices at Wellington House, London in unregistered files. These documents were reviewed to assess information and advice available to the DH in relation to NANBH.

32. The documents included in this review were initially categorised under the following headings.

- Wellington House files, located at Wellington House in unregistered files. At some point, in preparation for the HIV litigation in 1998, these documents were presumed to have been removed from registered files and grouped into unregistered lever arch files. The documents date from 1970 to 1990.
- The documents 'returned by solicitors'. These were returned to the DH in May 2006 following press articles on documents destroyed in error and were in 11 lever arch files. The documents date from 1969 to 1988.
- The documents referenced in the report, 'Self-Sufficiency in Blood Products A Chronology from 1973 – 1991', published in February 2006.
- Files scanned at Departmental Record Office (DRO) at Nelson. A scan of files at DRO Nelson for the period 1970 to 1985 identified four documents relating to NANBH. Copies of these documents are now at Wellington House.
- Documents released by the Scottish Executive.

33. An inventory was created to record, for each document: the reference number; the title or subject; the type of document and the date. All documents were then transferred to registered files. The registered files were recorded as:

- HIM 22/1 Documents located at Wellington House, 102 registered files.
- HIM 22/2 Documents returned by the firm of solicitors, 20 registered files.
- HIM 22/3 Published and Unpublished references to the 'Self-Sufficiency' report, 4 registered files.
- HIM 22/4 Documents obtained from DRO Nelson, 1 registered file.
- HIM 22/5 Documents released by the Scottish Executive; 351 documents, held on CD.

34. There are 127 registered files, identified above and one CD within the scope of the review. Each document was categorised under one of the following subjects:

- NANBH;
- Self-Sufficiency. Government policy in the 1970s was for England and Wales to achieve self-sufficiency in the production of plasma products for haemophiliacs to avoid expensive commercial products. The U.K. has always been self-sufficient in blood components, but not in plasma products;
- HIV/AIDS ;
- Hepatitis B;
- Hepatitis;

- Other;
- Development at Central Blood Laboratories (primarily BPL) and re-organisation of National Blood Transfusion Service (NBTS).

35. An analysis of the distribution across the time range and coverage of the subject was completed. This identified the number of documents within the 1970 – 1985 period and their subject category (paragraph 34 above). One document relating to NANBH fell outside this period, dated February 1988. This was a letter to BPL from the New England Medical Centre Hospitals, Boston, USA. The letter requested BPL to apply for Food and Drug Administration (FDA) approval of the BPL process for heat-treatment of factor VIII (Factor 8Y).

36. Some documents, not related to NANBH, fell outside the scope of this review but were included in the inventory. The percentage of documents falling within each of the subject categories is identified in Table 1 at Annex B.

37. Every document identified in paragraph 21, has been inventoried and categorised. This report, however, does not summarise every document where mention of NANBH is made. It has not included documents where the information relating to NANBH had already been cited or where the reference was minor. The aim was to summarise the information objectively and all documents relating to NANBH, whether cited in the report or not, will be released with the report, in line with FOIA.

38. A diagrammatic representation of the methodology is displayed below in Figure 1.

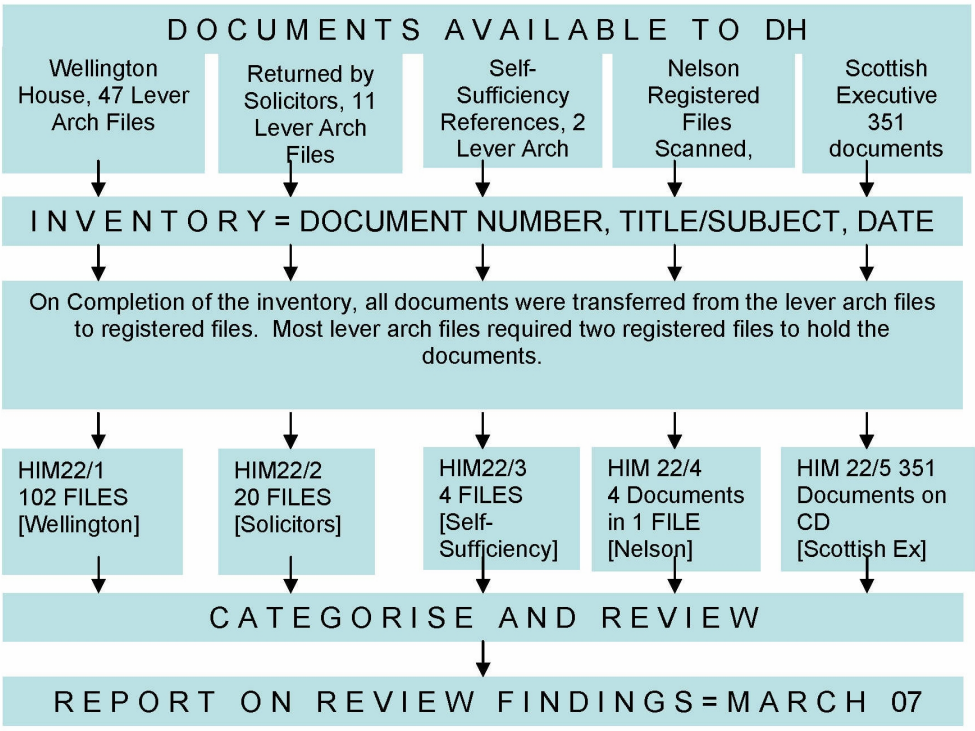

Figure 1 Methodology

Inventory

39. Over 5,500 documents were inventoried. Approximately 7% of documents were identified as duplicates within the Wellington House files. Whilst effort has been made to remove duplicates, given the number of documents it is not possible to ensure that all were identified. The breakdown by location is given in Table 2.

Location and File Reference	*Number of Documents*
HIM 22/1 (Wellington House)	4629
HIM 22/2 (Solicitors)	610
HIM 22/3 (Self-Sufficiency)	72
DRO Nelson	4
Scottish Executive	351
Total	***5,675***

Table 2. Number and Location of Documents

Review of 1970 to 1975

40. The majority (over half) of documents in this period focus on Government policy to achieve self-sufficiency in blood products. See Table 3.

Period	*NANBH*	*Self-Sufficiency*	*AIDS*	*Hepatitis B*	*Hepatitis*	*Other*	*BPL/NHS Re-org.*	*% in this period*
1970-75	0.0%	57.4%	0.0%	18.5%	3.7%	17.2%	3.2%	9.6%

Table 3: Coverage of Documents relating to 1970-1975

41. Although no mention is made of NANBH in the unpublished documents, the Haemophilia Centre Directors meeting of March 1971[5] discussed the incidence of post-transfusion hepatitis. They considered that the number of potential donor exposures would increase with the use of dried concentrates from large pools of donors, but the view was that the increased risk of clinical illness was not so great as to outweigh advantages of using concentrates. The greater reliability, ease of administration and economy of manufacture were in favour of concentrated materials.

42. The published study, by Prince et al[6] in 1974, implied that neither hepatitis B nor hepatitis A agents caused a substantial number of post-transfusion hepatitis cases. The author suggests the existence of additional virus(es), type C. In the conclusion the authors point to the long-term complications of acute hepatitis B infection following anicteric infection and suggest that consideration must be given to the possibility that a non-A, non-B hepatitis may also play a role in the aetiology of some forms of chronic liver disease.

43. It is observed (Rosendaal et al, 1989)[4] that during this period, the treatment for haemophilia had developed, providing a significantly increasing life span and, with the introduction of home treatment, improved quality of life to those with haemophilia.

Review of 1976 to 1980

44. The majority of documents within this period refer to self-sufficiency in the provision of blood products in England and Wales and on the re-development of BPL. 2.7% of documents in this period relate to NANBH. See table 4 below.

Period	*NANBH*	*Self-Sufficiency*	*AIDS*	*Hepatitis B*	*Hepatitis*	*Other*	*BPL/NHS Re-org.*	*% in this period*
1976-80	2.7%	37.8%	0%	3.8%	2.7%	16.9%	36.0%	19%

Table 4: Coverage of Documents relating to 1976-1980

45. A Department of Health and Social Security (DHSS) internal minute of February 1976[7], on anti-haemophilic globulin (AHG) concentrate, reaffirms the Ministerial aim of NHS self-sufficiency. The minute notes that the alternative of buying the commercial product (with its higher hepatitis risk) is more costly than producing the NHS product.

46. The World Health Organisation (WHO) Report presented in 1976 on viral hepatitis,[8] discusses the problem of viral hepatitis and the fact that a new type of hepatitis had been revealed, NANBH. No laboratory tests are available currently for identifying this agent or agents.

47. The report of the Haemophilia Centre Directors' Hepatitis Working Party 1978[9] refers to NANBH surveillance. Comparing the prevalence of hepatitis in 1978-79 to 1976-77 the report identifies an increase in the proportion of NANBH reported in patients with mild haemophilia receiving concentrate for the first time to cover operative procedures. It is suggested that the observed increase in mild haemophiliacs contracting hepatitis is probably because most severe haemophiliacs have already been exposed to viruses present in all brands of concentrate and are therefore immune to re-infection. Patients with mild disease have not so been exposed.

48. Referring to mortality, the report identifies that no further fatalities directly due to acute hepatitis had been reported (in this period). One patient had acute NANBH followed by persistent raised enzyme levels in 1978. He died following a retroperitoneal haemorrhage, post mortem was refused but it is possible that his hepatitis indirectly contributed to his death. A second patient, who died of causes unrelated to liver disease, was found at post mortem to have evidence of liver disease because of the presence of portal cirrhosis in one who was HBsAg negative.

49. The minutes of the Medical Research Council (MRC) Meeting held on 12 February 1979[10] record that parenterally-transmitted hepatitis was discussed and also the state of knowledge regarding NANBH and the potential for non-parenteral spread and post-transfusion hepatitis. In discussing a study on post-transfusion hepatitis (that suggested that some cases were not due to hepatitis B) the view was that post-transfusion hepatitis must now be rare and that it would be difficult to find many cases. One and three-quarter million units of blood were

transfused in 1978 and very little had been heard about NANB post-transfusion hepatitis. It was pointed out however that post-transfusion hepatitis might be anicteric and that the risk of progression to chronic liver disease remained, however mild the initial infection. In agreeing that post-transfusion hepatitis was rare in the U.K., concern was expressed about the continued use of commercial plasma products, many of which were produced in the U.S. and carried a high risk of transmitting NANBH. Among some 1800 haemophiliacs treated in 1978, 15 had developed hepatitis B and 20 had developed NANBH, nine of the later associated with blood products of NHS origin. In referring to the need for research, it was suggested that sera should be gathered and stored until specific tests for NANBH viruses were available.

50. One person attending this MRC meeting recalled evidence from haemophiliac studies that NANBH infection might severely damage a liver already compromised by previous viral hepatitis. A second attendee quoted the view of American and German workers that up to 40% of NANBH infections progressed to chronic liver disease. It was also pointed out at this meeting that it remained uncertain whether NANBH virus was present in the British population or whether British blood products were causing NANBH. It was thought that cases certainly did occur, but there was no evidence that this spread from recipients of British blood products to other members of their family group.

51. A letter from the MRC dated 7th February 1979[11] regarding an ad hoc meeting on NANBH states that the Chief Scientist of the DHSS had informed the MRC Council that the subject was being given high priority by the DH and identifies the need for further research. A letter to DHSS in January 1979[12] refers to re-convening an advisory group and the belief that the stimulus for re-convening the group came from a desire to up-grade the viral safety of UK factor VIII. In proposing terms of reference for such an advisory group on viral hepatitis,[13] NANBH was included as, although hepatitis B presented the majority of problems, NANBH may also become a major source of concern. The Advisory Group on Hepatitis was subsequently established.

52. An internal DHSS minute[14] made reference to NANBH that could not (unlike hepatitis B) at that time be detected by testing donor blood. The comment was made that this form of hepatitis can lead to progressive liver damage and/or chronic carrier state and referred to patients with pre-existing liver disease where NANBH could prove fatal. This internal note may have been referring to a report in the Lancet in March 1979[15] that reported three fatalities in jaundiced patients (who did not have haemophilia) subsequently shown to have severe cirrhosis due to either alcohol (two patients) or Wilsons disease (one patient), who were given factor IX concentrate to correct clotting abnormalities prior to liver biopsy.

53. The MRC Blood Transfusion Research Committee Working Party on Post-Transfusion hepatitis met for the first time on 14 February 1980[16]. Their function was to promote research to assess the nature and size of the problem of post-transfusion hepatitis in the UK with particular reference to changes in transfusion practice, such as products prepared from pooled plasma from large numbers of donors and the introduction of commercial products from abroad. It was decided that such studies should also include investigations to assess the incidence of

NANBH in the UK and the position of research to characterise the agent(s) associated with this form of hepatitis and devise diagnostic tests.

54. Extracts from a Pitman Medical publication on Haemophilia Home Therapy[17] published in 1980, refer to 'Rules and Reasons for Home Therapy', 'Hepatitis Warnings' and 'Choice of Therapeutic Material. Under 'Rules and Reasons for Home Therapy', the text states, "Every family knows that the use of human blood products carries the risk of hepatitis. They are aware that this risk has been linked particularly to commercial concentrates prepared from the blood of paid donors, and they know that these risks still exist despite the increased sensitivity of donor tests for hepatitis B." The extract on 'Hepatitis Warnings' refers to the use and disposal of potentially hazardous equipment, with advice on what families and parents should do should a mistake (such as needle-stick) occur.

55. In 'Choice of Therapeutic Material', reference is made to the introduction of new commercial products and clinical trials underway that hold the promise of producing therapeutic materials free of all forms of hepatitis. The text mentions that with the present state of knowledge there is no way to remove this threat, apart from rigorous testing for hepatitis B, because it is probable that changes in liver function and architecture reflect challenge by more than one NANBH viral agent. The suggestion that large pool factor VIII concentrates should not be prescribed for children, who should receive only cryoprecipitate is considered impractical if severely affected children are to benefit from the early cessation of haemorrhage which home therapy affords.

56. The Pitman Medical publication also refers to a study that demonstrates that abnormalities in liver function were as prevalent in haemophiliacs treated only with cryoprecipitate prepared from voluntary donor plasma as in those who had been subjected to multiple transfusions with commercially prepared concentrates. The view is expressed that it is difficult to understand why the reported histopathological features of liver disease do not seem to be reflected in an increased morbidity or mortality even in those populations of haemophiliacs subjected to very high doses of large pool preparations for many years.

57. An article in the New England Journal of Medicine, (1980)[18] reports on a six-year study on one patient. The study was designed to determine the duration of infectivity during chronic asymptomatic NANBH by inoculating into chimpanzees four serum or plasma samples obtained over a six-year period from one patient.

58. The third annual report of a three year study (Project Number J/S240/78/7) by the Oxford Haemophilia Centre on behalf of the UK Haemophilia Centre Directors in 1980 refers to two proposed publications[19] [20] and report upon a series of cases of factor VIII and IX related hepatitis in the UK reported to the Oxford Haemophilia Centre. NANBH is described as an acute illness that is clinically mild and clinically indistinguishable from hepatitis A and B. The reports are concerned primarily with epidemiology (e.g. the incidence of infections with both hepatitis B and NANBH in patients receiving replacement therapy, the possible rates of transmission associated with different clotting factor products and different rates of transmission to household members in these two groups). They do make clear

that chronic hepatitis can follow from infection with NANBH. However, they do not report to any extent upon the severity of these conditions.

Review of 1981 to 1985

59. HIV dominates this period with 55% of the documents focussing on this subject; NANBH is referred to in 1.9%. See Table 5 below.

Period	*NANBH*	*Self-Sufficiency*	*AIDS*	*Hepatitis B*	*Hepatitis*	*Other*	*BPL/NHS Re-org.*	*% in this Period*
1981-85	1.9%	11.9%	55.1%	4.2%	2.0%	7.6%	17.3%	61.5%

Table 5: Coverage of Documents for 1981-85

60. The Third Report of the (DHSS) Advisory Group on Testing for the Presence of Hepatitis B Surface Antigen and its Antibody in 1981[21] mainly covers screening for hepatitis B of blood donations. The report notes that at present there are no screening tests for detecting NANBH viruses in blood donations. The report recommends that research be undertaken in the UK to determine the extent and severity of post transfusion hepatitis due to NANBH virus. The report states that unless this is done, there will not be the knowledge on which to base possible future recommendations on screening blood donations for these viruses.

61. The Haemophilia Centre Directors' Hepatitis Working Party Report for 1980/81[22] identified that, of the 283 cases of hepatitis related to factor VIII or IX therapy, 197 were non-B hepatitis and therefore probably NANBH. There is strong evidence that different types of NANBH are related to different products and most patients in this group are still entirely symptomless. Figures for hepatitis B and NANBH in patients receiving only one product in any year for the period 1977-1979 shows that there is a 4 – 20 times higher incidence of overt NANBH associated with US commercial concentrate compared with NHS products.

62. An article by Seeff in 1981 cited in the British Medical Journal in July 1981[23], points out that in the absence of specific markers for NANBH, overall protection against hepatitis appears remote, referring to the more likely possibility that hepatitis free plasma products will become available through processing by chemicals, ultraviolet light or heating. An editorial in the British Medical Journal in July 1981[24] cites the same article by Seeff and refers to NANBH agents thought now to be the main cause of chronic liver disease in patients with haemophilia.

63. Realdi et al (1982)[25], in a long term follow up of patients who developed NANBH following blood transfusion after open-heart surgery, discuss recent prospective studies accumulating evidence that those patients who develop post-transfusion NANBH often progress to chronic liver disease. The study also notes that the long-term evolution of NANBH in the patients followed by this study was more severe than suggested by previous studies, citing Berman et al (1979)[26] and Koretz et al (1980)[27]. The study notes that the long-term outcomes of this chronic condition and its clinical significance have not yet been determined. Collins et al (1983)[28], illustrate the developing knowledge regarding the significance of NANBH in a prospective study in a single British centre, of post-transfusion hepatitis after cardiac surgery. The study concludes that the incidence of

significant chronic liver disease after blood transfusion possibly attributable to NANBH agent was only 0.4%.

64. A study by Mannucci et al in 1982[29] supports the above view, that in haemophiliacs with NANB chronic hepatitis, progressive liver disease is not the rule. The authors observe that only two of the 91 haemophiliacs followed-up since 1974 have died from cirrhosis and both were also infected with hepatitis B.

65. A discussion on the safety and efficacy of commercially produced "hepatitis-safe" factor VIII and IX took place at a meeting at BPL on 15 December 1982[30] with representatives from the NHS haemophilia services. There was concern regarding price instability in the world market introducing price battles for factor VIII intermediate concentrate in the UK. It was proposed that random exploitation of the haemophilia services by commercial organisations for the study of "hepatitis-safe" products should be discouraged. Haemophilia services should create a formal basis for controlled clinical trials for alleged "hepatitis-safe" products. They further propose that the haemophilia services, the Public Health Laboratory Service (PHLS, now the Health Protection Agency) and the NBTS should combine resources to advance economic treatment of NHS haemophiliacs with safe products.

66. In 1982, Rizza and Spooner[31], on behalf of the Directors of Haemophilia Centres, report on a survey of the treatment of haemophilia between 1976 and 1980. The survey identifies an increase in the number of patients receiving treatment with a substantial increase in the total amount of clotting factor concentrates used. The authors note that home treatment became established for severely affected patients during this time and this accounted for about half of the total amount of clotting factor concentrates used. In reference to the widespread concern about the transmission of hepatitis viruses by giving plasma products, they note that only two deaths were attributed to hepatitis during this five-year period. A near normal median expectation of life in patients with severe haemophilia A is found. The authors note the recent reports of persistently abnormal liver function values and abnormal histological findings in liver tissue from haemophiliacs treated with plasma products. Most haemophiliacs treated were asymptomatic but it remained to be seen how many would develop severe chronic liver disease with the passage of time.

67. In 1983, the Advisory Group on Hepatitis considered a summary of a report of a three-year survey of viral hepatitis in West London[32]. This summary notes that among adults, hepatitis B was only slightly more severe than hepatitis A but NANBH is a much milder disease. The severity of the illness (hepatitis) increased with age. This was most marked with hepatitis A.

68. A letter to DHSS dated January 1983 from the PHLS[33] includes an attached draft letter that PHLS intend to submit to the Lancet. The letter relates to the current situation with regard to the risk of NANBH after first exposure to large pool factor VIII concentrates and the implications for trials of 'hepatitis reduced' factor VIII and IX. The attack rates for NHS and US commercial factor VIII (un-treated) appear similar but the number of patients so far studied is not sufficient to be certain. The paper reports that there is no evidence to indicate that re-exposure to

NANBH viruses present in concentrates received by patients with severe coagulation defects predisposes them to a higher incidence of serious chronic liver disease than patients with mild coagulation defects who received less frequent transfusion. The draft letter refers to several attempts to render factor VIII and IX concentrates free of NANBH viruses by biophysical methods. It is proposed that if 'hepatitis reduced' concentrates prove to be associated with a reduced risk of NANBH then these products should be reserved in the first instance for patients with no prior exposure to factor VIII concentrates or those who received less than five batches of factor VIII in the past.

69. The UK Haemophilia Centre Directors Hepatitis Working Party in July 1983[34] notes an ethical problem in relation to the factors to be considered in the selection of 'hepatitis reduced' products for clinical trials. As the only way of ensuring that participants had not previously been infected with NANBH viruses is by using patients who have not previously received factor VIII or IX concentrate a choice will have to be made between using heat-treated products from commercial sources or NHS concentrate that appears to carry a 100% chance of transmitting NANBH.

70. The Self-Sufficiency Report[2] refers to attempts to develop viral inactivation processes to treat plasma/blood products in the early 1980s. Available techniques resulted in a substantial loss of yield and were not capable of producing sufficient quantities of concentrates for the UK market. Heat-treated factor VIII commercial products, and applications for product licences for these products, are referred to in a letter from DHSS in July 1983[35].

71. An unpublished paper on AIDS[36] by the Central Blood Laboratories Authority (CBLA) on the progress of heat treatment of plasma products, mentions that the severity of NANBH in haemophiliacs is probably associated with the co-existent impaired immune responsiveness of these patients. This has motivated plasma fractionation organisations to re-examine the means to inactivate the hepatitis virus in large-pool concentrates. It notes that heat treatment of plasma products is still primarily directed at the inactivation of transmissible viruses causing hepatitis in recipients.

72. A study on infrequently treated patients in 1983 found a high incidence of NANBH after treatment with factor VIII (Fletcher, et al[37]). All those who received commercial concentrates developed hepatitis. All those who received NHS factor VIII who had not been treated before developed hepatitis, whereas 8 of the 15 patients who had previously been treated with NHS factor VIII did not develop hepatitis. In trying to analyse their findings the authors speculate that the pool size of NHS concentrates had increased to the point where the benefit conferred by using plasma from volunteer donors has been lost. The study raises the prospect of at least two types of NANBH. Such an observation had been made earlier in 1980 at an NHS meeting[38] where the characterisation of NANBH antigens were under discussion. Kernoff et al (1984)[39] reaches similar conclusions and the Haemophilia Society in their letter to DHSS (August 1983) supports the importation of US commercial products[40]. The Haemophilia Society's Blood Products Sub-Committee also refers to Fletcher et al's work in January 1984[41]. The Sub-Committee suggests that British clotting factor

concentrate is no better (and may be worse) than imported material in respect of post-transfusion NANBH.

73. The first meeting of the Central Blood Laboratories (CBLA) Working Group on AIDS, held on 14th October 1983[42] discusses the use of plasma pools containing smaller numbers of donors. Also considered is the plasma supply for self-sufficiency in blood products. The Working Group notes that in regard to NANBH in studies on chimpanzees, the dry heat-treatment of factor VIII and IX had not initially been encouraging and that further work is necessary.

74. The minutes of the 14th meeting of the CBLA on 26th September 1984[43] refers to NANBH and intravenous immunoglobin where it is agreed that further proposed chimpanzee studies to establish safety of product should be carried out.

75. A report from the London School of Hygiene and Tropical Medicine[44] to the DHSS in May 1984 notes that NANBH viruses have not yet been identified and that the development of specific laboratory tests for NANBH remain a matter of high priority.

76. Notes on Transfusion[45] were revised in 1984 by a Committee of the Regional Transfusion Directors and published by DHSS. The Notes contain a section on post-transfusion hepatitis, "Very similar illnesses can also be caused by other viruses including the so-called NANBH viruses. The latter are also transmissible by transfusion, but as yet, no specific laboratory tests have been developed to identify them. The incubation period is also variable extending up to 70 days or more. The clinical course may be acute or chronic leading to cirrhosis".

77. A DHSS minute of November 1984[46], in reference to heat-treated factor VIII notes that pilot trials have shown that heat treatment does not inactivate NANBH agent against which the heat treatment had originally developed. BPL is asked by DHSS to provide a programme of the intended introduction of heat-treated factor VIII to ascertain how soon the first batches will be available to haemophiliac patients in the UK.

78. In 1984, the Haemophilia Society[47] notes concerns at the time gap while the supply of a UK heat-treated factor VIII product caught up with product demand, urging that heat-treated commercial concentrates be introduced. In response, the DH advise[48] that BPL will start heat-treating their product in April 1985. The choice of treatment, including prescribing unlicensed heat-treated factor VIII, is a matter for the judgement of the clinician responsible and the cost will be borne by Health Authorities.

79. Minutes of the 5th Meeting of the CBLA Central Committee for Research and Development held on 2nd April 1985[49] record that BPL has been looking at heat treatment for two years. The primary aim is to inactivate NANBH virus, though it is hoped that the HTLV III virus (now called HIV) would also be dealt with in the heat treatment programme. A high purity factor VIII product had now been achieved and three trial batches sent out and an abridged licence is to be applied for in the near future.

80. The WHO report on a meeting in Munich on the 11-13th June 1985, Viral Hepatitis in Europe-Further Trends and Targets,[50] provides information on the state of knowledge regarding NANBH and the lack of specific tests; it is still a diagnosis of exclusion.

81. The 6th, meeting of the CBLA Central Committee for Research and Development held on the 9th July 1985[51] refers to the new "virus-safer" factor VIII concentrate. The new concentrate (Factor 8Y) is now being introduced in England and Wales and is dry heated at 80° for 72 hours. The yield is beginning to overtake an intermediate purity concentrate that had been introduced early in 1985 in response to concerns about HTLV III (HIV) transmission. The trial (of Factor 8Y) 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 and an application is being prepared for a product licence for Factor 8 Y, with only provisional evidence of reduced infectivity.

82. An information sheet issued by BPL[52] in July 1985 advises that general issue of Factor 8Y will begin from September 1st 1985. BPL recognises that, until the new BPL plant is complete, output of Factor 8Y will meet about one third of current demand. A letter from the DHSS[53] in August 1985, to all Haemophilia Centre Directors, advises that the output of heat-treated Factor VIII concentrate has been increased to the maximum possible in the current BPL plant. Until the new BPL plant comes into production there will continue to be a need to obtain additional supplies of (heat-treated) Factor VIII from commercial sources.

83. The assessment of the state of knowledge in 1985 is confirmed in Morbidity and Mortality Weekly Report[54] of June 1985. The report refers to NANBH and comments that it is probably caused by at least two different agents and lacking specific diagnostic tests, remains a disease diagnosed by exclusion.

84. An article published in the Lancet in July 1985[55] considers the transmission of NANBH by heat-treated factor VIII. The authors note the preliminary results on 13 haemophilia A patients, not previously treated with blood or blood products, who were given a dry-heated factor VIII. Over the next 12 months hepatitis developed in 11 (84%) and was invariably NANBH. During the follow-up period signs of the disease disappeared in 10 patients (90%). However, these findings contrast with the absence of NANBH in chimpanzees given the same heated concentrate. Thus, clinical studies in first exposure haemophiliacs are essential for the true evaluation of the safety of new heat-treated concentrates.

85. In a letter in the BMJ[56] in July 1985, the authors raise concern at the recommendation that cryoprecipitate be no longer used, and the implications of this for those with mild haemophilia. The authors suggest that treatment needs to be more tailored to individual cases and agree that only heat-treated concentrates (as opposed to non-heat treated) should be used since these may protect from HTLV-III (HIV) infection.

86. In a study to define the spectrum of liver disease in liver biopsy specimens in haemophiliacs Aledort et al (1985)[57] find the incidence of cirrhosis to be 15%, which is less than previously reported. The authors warn that the lack of severity

of the histopathologic findings in the current material might not be reassuring as recent evidence is suggestive of insidious progression of NANBH to cirrhosis (Koretz, 1982)[58].

87. In an 8-year study of patients with haemophilia who received clotting factor concentrates Hay et al (1985)[59] reports that there is evidence of chronic progressive liver disease in at least 21% (17) patients; 8 had chronic active hepatitis and 9 cirrhosis. Histological evidence suggests that NANBH is mainly responsible, although the influences of other viruses cannot be excluded. Serial liver biopsies shows progression from chronic persistent hepatitis to chronic active hepatitis and cirrhosis within 6 years, suggesting that chronic persistent hepatitis in haemophiliacs is not as benign as hitherto supposed.

Post 1985

88. The contents of the following documents, whilst post 1985, were selected from the published papers for review as they provide an overview and refer to the period of the review.

89. One unpublished document, dated 1988, on NANBH fell outside the period of the review and is included in this section, see paragraph 94.

90. Dienstag, Harvey and Alter (1986)[60], present an overview of the evolving epidemiologic and clinical perspective of NANBH. They state that our understanding of NANBH is unsettled and evolving and that diagnosis is imprecise. The authors note that by observing the disease for more than a decade, insight has been gained into its natural history and its unusual pattern of insidious, silent progression. Referring to transfusion-associated hepatitis and citing estimated cases of NANBH in the US, Dienstag, Harvey and Alter consider that the conversion from a blood donor population which included paid 'commercial' donors, to an all-volunteer donor population has had the most dramatic impact on reducing the frequency of hepatitis after blood transfusion.

91. In considering the clinical features of NANBH, Dienstag, Harvey and Alter (1986)[60] note that although the acute illness associated with NANBH is similar to other types of viral hepatitis, as a rule, acute NANBH tends to be less severe. Despite its usually benign course, acute NANBH may be severe and even fulminant, with fulminant cases often occurring among patients with transfusion-associated hepatitis B.

92. In their examination of chronic NANBH, the authors note that in the decade since its discovery, the concept of NANBH has evolved from that of a benign elevation of aminotransferase activity to that of a serious disease with significant long-term consequences. Referring specifically to NANBH in haemophiliacs the authors record that symptomatically, chronic NANBH may be quite mild but progression to severe symptomatology may be very protracted. Although chronic hepatitis in haemophiliacs has been reported to be non-progressive, the authors cite the study by Hay et al[59] (above) as a more recent study that demonstrated the presence of severe, progressive liver disease in a large number of patients.

93. The authors consider that because the maximum prospective evaluation time for chronic NANBH is now, in 1986, only 10 years, we may find increasing NANBH-related morbidity and mortality occurring in this patient population over the next decade and beyond. There has been no significant advance in the development of a specific detection system for this agent or groups of agents.

94. One unpublished document relating to NANBH fell outside the period of the review, dated February 1988. This was a letter to BPL from the New England Medical Centre Hospitals, Boston, USA[61]. The letter requested BPL to apply for Food and Drug Administration (FDA) approval of the BPL process for heat-treatment of factor VIII (Factor 8Y). The Medical Centre expressed the view that BPL Factor 8Y is the safest concentrate available.

95. A series of studies undertaken in1989 by Pasi and Hill[62], in 1992 by Rizza, Fletcher and Kernoff[63] and in 1998 by Brown, Dasani and Collins[64], demonstrate that the BPL Factor 8Y product, introduced in 1985 appears to have prevented transmission of hepatitis C and HIV.

96. Seeff et al (1992)[65] undertook a study on long-term mortality after transfusion-associated NANBH. The background to the study was that acute NANBH after blood transfusion often progresses to chronic hepatitis and sometimes culminates in cirrhosis or even hepatocellular carcinoma. The frequency of these sequelae and their effects on mortality are not known. To address this, the authors trace patients with transfusion-related NANBH who had been identified in five major prospective studies conducted in the US between 1967 and 1980. Vital statistics are established on 94% of the 568 patients. After an average follow-up of 18 years, the estimate by life-table analysis of mortality from all causes is 51% for those with transfusion-associated NANBH, as compared with 52% for the first controls and 50% for the second controls. Mortality related to liver disease is 3.3%, 1.1% and 2.0% respectively among these three groups. Seventy-one percent of the deaths related to liver disease occurred among patients with chronic alcoholism. The authors conclude that there is no increase in mortality from all causes after transfusion-associated NANBH, although there is a small but statistically significant increase in the number of deaths related to liver disease. The timing of death, whether from all causes or from liver disease, is virtually identical among the subjects with NANBH and the controls.

97. In a review (2003) of hepatitis C, alcohol and liver disease, Jamal and Morgan[66] report that prevalence of hepatitis C is 7 to 10-fold higher in alcoholics than it is in the general population and that up to 60% of patients with hepatitis C have a history of alcohol use. They conclude that in patients with hepatitis C, chronic alcohol consumption increases the rate of liver fibrosis and the risks of cirrhosis, hepatocellular carcinoma and, possibly, death from liver disease.

98. In an editorial in 1992, Czaja[67] observes that initially retrospective analysis of patients with NANBH emphasised the relatively benign short-term prognosis. In time, the indolent nature of chronic NANBH became apparent and it became clear that a longer duration of follow-up was required to assess the full consequences of the disease. Studies in which the length of the follow-up was less than 10 years had undoubtedly underestimated the importance of the disease. Long-term follow-up of asymptomatic patients with persistent viremia and of those with chronic hepatitis is warranted.

99. Czaja cites a study by Alter et al[68] in 1992 that reconfirms earlier observations that chronic hepatitis is common after acute NANBH infection regardless of how the disease was initially contracted, but that progression to cirrhosis and liver failure is unusual in the short term.

100. Czaja stresses in 1992 that the natural history of HCV infection has not been fully described and that additional late consequences are likely. Czaja concludes that the observations by Alter[68] and Seeff[65] above heighten awareness of the disease potential of HCV infection and provide a realistic hope that dire

consequences are unusual. Until the natural history of HCV infection is fully delineated the worst-case (unspecified) scenario must also be kept in mind.

Other Subject Areas

101. The focus of this review is NANBH. The documents held by the DH however, refer to a range of subject areas over the period of interest, predominantly AIDS, self-sufficiency and the redevelopment of BPL.

102. The papers relating to the redevelopment of BPL document Ministers' decision in 1982 on the major redevelopment of BPL, work began in May 1983 and the foundation stone laid in March 1984. The increasing scope and cost of the development and DHSS concern as to the effectiveness of the financial control and project management is documented. The original £22.6m budget (November 1981 prices) increased to £35.5m in September 1984 with an increase in scope; a cost limit of £38m was set. The completion date slipped from an original prospect in November 1983 of July 1985, to an estimate in July 1985 of June 1986. In May 1986, a formal submission was made for the cost limit to be raised from £38m to £50m. The forecast completion date, in June 1986 was January 1987 with commissioning in mid 1987 and production levels consistent with self-sufficiency during 1988.

Missing Files

103. There were two instances of documents relating to blood products being mislaid or destroyed. This loss of documents was the subject of an internal audit report commissioned in February 2000.

104. In the first instance, documents were removed from their registered files and passed to solicitors for use in the HIV litigation in 1990. The trial folders were returned to the DH, but when a subsequent request for disclosure of records was made in January 2005, the DH was unable to retrieve some of the records requested.

105. In the second instance, between September 1994 and March 1998, a number of files recording the work of the Advisory Committee on the Virological Safety of Blood between May 1989 and February 1992 were inadvertently destroyed.

106. From the review of documents, an assessment is made that there is little duplication between the documents returned to the DH by a firm of solicitors and those already held at Wellington House. The documents returned by the firm of solicitors are believed therefore to be some of the documents previously thought to be mislaid.

107. Similarly, from the inventory and review of documents, those documents now held at Wellington House in 102 registered files are thought to be those removed from registered files for use in the HIV litigation in 1989 (paragraph 105 above) and previously thought to be destroyed or mislaid. It is suggested that the nature of these files was not subsequently appreciated as they were no longer stored in registered files and staff and location had changed over time.

108. 24 of these 102 registered files contain documents that, at that time, were subject to a Public Interest Immunity (PII) claim by the DH that they should not be disclosed in civil litigation on the grounds of public interest. These documents relate to Ministerial correspondence and submissions to Ministers and briefing notes and draft replies to letters. An earlier request (paragraph 104) for the release of these documents under FOIA could not be met, the documents being presumed lost. The report therefore concludes that these documents are those previously considered missing.

109. It is not possible to state that all documents, previously recorded as missing, have been located but a very substantial number relating to the time in question have been and are included in the inventory and, if related to NANBH, in the review. These documents include those that were subject to a PII claim during the HIV litigation. The ACVSB files that were destroyed relate to the post 1985 period.

110. During the review process, two sets of documents were released into the public domain in line with FOIA (paragraph 21). These were firstly, the documents referenced in the report 'Self-Sufficiency in Blood Products in England and Wales and Chronology from 1973 to 1991' and released in August

2006 and secondly, the documents returned to the DH by the firm of solicitors were released in November 2006.

Conclusion

111. This report and the previously unpublished documents reviewed that relate to NANBH should be released, in line with FOIA, into the public domain.

112. It is presumed that the majority of documents previously considered missing, with the exception of the Advisory Committee on the Virological Safety of Blood (ACVSB) files, have now been located.

113. The ACVSB files destroyed were post 1985. This Committee did not come into existence until after the heat-treatment of plasma products was introduced in September 1985.

114. A number of the documents, subject to a Public Interest Immunity (PII) claim by the DH that they should not be disclosed in civil litigation on the grounds of public interest, were identified. These had previously been considered missing (paragraph 108). FOIA gives a right to request information from the documents, subject to exemptions. Many exemptions require a consideration of the public interest. (This consideration has begun).

115. The predominant subjects covered in the documents are HIV/AIDS, self-sufficiency and the redevelopment of BPL. The treatment of NANBH in the correspondence and notes of meetings gives no indication that NANBH was considered a life threatening disease over the period to which this review relates i.e. 1970 to 1985.

116. Since the confirmation that papers had been destroyed existing papers have been reviewed and a number of documents released in line with, but not under, FOIA. The documents referenced in the report 'Self-Sufficiency in Blood Products in England and Wales' were released in August 2006 and the papers returned by the firm of solicitors were released in November 2006.

117. The BPL heat-treated Factor 8Y product was introduced for evaluation in July 1985 with general issue across the NHS in England and Wales in September 1985. A series of studies in 1989, 1992 and 1998 demonstrated that the BPL Factor 8Y product appeared to have prevented transmission of both hepatitis C and HIV.

118. This review of documents summarises the information and advice on NANBH in relation to the safety of blood products available to the Department during 1970 to 1985.

ANNEX A

Chronology of Events

Date	Event
March 1973	DHSS Expert Group on the Treatment of Haemophilia recommends that the NHS should be self-sufficient in blood products as soon as possible
August 1974	Non-A Non-B Hepatitis (NANBH) first predicted by Prince et al
December 1974	Minister of State (David Owen) earmarks central funds of £0.5m, half of which is recurring, to increase the output of plasma from Regional Transfusion Centres to 275,000 donations annually for the preparation of factor VIII and 100,000 donations for cryoprecipitate
Beginning of 1975	Expert Group on the Treatment of Haemophilia estimated that 275,000 donations of blood would be required to achieve self-sufficiency in factor VIII.
May 1975	WHO resolution states that each country should be able to supply sufficient quantities of its own blood and blood products to meet clinical needs
August 1975	Mannucci et al. reports 45% of patients with NANBH had raised ALT levels; Craske et al. links an outbreak of hepatitis (some NANBH) after intravenous injections of commercial factor VIII concentrate.
April 1976	DH issues a press release re-affirming the aim of the UK to become self-sufficient in the supply of plasma products by mid 1977.
June 1977	Factor VIII production target set in beginning of 1975 attained; however demand has increased
Early 1980	Plasma products begin to be heat-treated; yield is very low and not shown subsequently to inactivate NANBH.
October 1980	Craske states that NANBH is mild and often asymptomatic, but might cause chronic liver disease not associated with overt disease.
1982	Central Blood Laboratory established as a Special Health Authority
1982/1983	Studies published that indicate that NANBH is more serious than previously thought.
1983	Studies confirm that commercial and BPL concentrates carry equal risk of transmitting hepatitis.
1983	US patients with haemophilia contracted AIDS strengthening concerns over the safety of imported plasma.
May 1984	Trial issues of Heat-Treated factor VIII (60° C for 24 hours)
1985	Studies revealed almost 100% transmission of NANBH following administration with untreated large donor pool clotting factor concentrate

1985	Hay et al. reported that progressive liver disease in patients with haemophilia was an understated problem
February 1985	First issues of heat-treated factor VIII (70ºC for 24 hours}
July 1985	Trials of a new, high purity product, Factor 8Y, conducted
September 1985	BPL start general issue of its new Factor 8Y heat-treated factor VIII
1986	Research identifies the need for retrospective NANBH studies, recognising that the initial disease might be quite mild but progression to symptoms associated with severe disease may be very protracted.
September 1988	UK was not self-sufficient in plasma products due to errors in estimating both the amount of plasma stockpiled and the net yield for factor VIII production at BPL and could not expect to be so for a couple of years.
1989	Identification of hepatitis C.
1989	Studies provide evidence that the heat-treated product BPL 8Y introduced in 1985 appears to have prevented transmission of hepatitis C as well as HIV.
September 1991	Second generation hepatitis C virus screening assays become widely used in the screening of donor blood in the UK
1992	A retrospective study questioned whether hepatitis C virus infection was a disease in waiting and confirmed that the acute infection was perceived in the 1970s as mild and that in 1980 analysis emphasised its relatively benign short-term prognosis.
1992	A study on long-term mortality after transfusion-associated NANBH concluded that there was no increase in mortality from all causes after transfusion-associated NANBH after an average of 18 years follow-up, although there was a small but statistically significant increase in the number of deaths related to liver disease.
1995	Look-back exercise started in UK to trace as many people as possible who had contracted hepatitis C through blood transfusions. Carried out between 1995 and 1997 and covered all donors who tested positive for the hepatitis C virus from the date of introduction of testing in September 1991 and a subsequent search for recipients of each donation to offer counselling and treatment where appropriate..
October 2000	Hepatitis C litigation against the National Blood Authority began. Action was taken under the Consumer Protection Act. All 117 claimants won damages. (Note the Government was not party to this litigation).
October 2000	Identified that files relating to the Advisory Committee on the Virological Safety of Blood between May 1989 and February 1992 were missing. Independent audit identified that they were destroyed in error.
	Demands for a public inquiry in response to loss of documents. Lord Owen stated that as Minister for Health he had allocated finance in 1975 to increase the production of factor VIII to attain self-sufficiency and that the DH did not fulfill this policy.

January 2005	Subsequent to the identification of missing ACVSB files, a request for papers that were subject to a PII claim during the HIV litigation were requested and found to be missing.
February 2006	The report 'Self-Sufficiency in Blood Products in England and Wales A Chronology between 1973 and 1991 published.
May 2006	Documents relating to the HIV litigation returned to the DH by claimants' solicitors, independent Counsel appointed to review documents.
August 2006	Release, in line with FOIA, unpublished documents referenced in the report 'Self-Sufficiency in England and Wales A Chronology 1973 and 1991.
November 2006	Release, in line with FOIA, of documents returned to the DH by a firm of solicitors.

ANNEX B

Distribution and Coverage.

The number of documents reviewed is in the order of 5,500. The distribution and coverage across the periods, pre 1970, 1970-75, 1976-80, 1981-85 and post 1985 is illustrated in Table 1 below, as is the distribution and coverage across the scope of the review, 1970 – 1885.

Period	*NANBH*	*Self-Sufficiency*	*AIDS*	*Hepatitis B*	*Hepatitis*	*Other*	*BPL/NHS Re-org.*	*Total*
Pre 1970	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.1%
1970-75	0.0%	5.5%	0.0%	1.8%	0.4%	1.7%	0.3%	9.6%
1976-80	0.5%	7.2%	0.0%	0.7%	0.5%	3.2%	6.8%	19%
1981-85	1.2%	7.3%	33.9%	2.6%	1.2%	4.7%	10.7%	61.5%
Post 1985	0.1%	0.5%	7.6%	0.2%	0.0%	0.7%	0.5%	9.7%
1970-85	**1.8%**	**20.5%**	**41.5%**	**5.3%**	**2.2%**	**10.3%**	**18.3%**	**100%**

Table 1: Distribution and Coverage of Documentation.

The overwhelming focus of the documents is HIV/AIDS (41.5%), followed by Self-Sufficiency (20.5%) and BPL/NBTS Redevelopment/ reorganisation (18.3%). Fewer than 2% of documents relate to the subject of this report, NANBH.

Of the above, some 72 unpublished documents were referred to in the report 'Self-Sufficiency in Blood Products in England and Wales A Chronology from 1973 to 1991', published by the DH in February 2006. The references were released in line with FOIA in August 2006.

Of the total documents inventoried, 610 documents were returned to the DH by a firm of solicitors and were released in line with FOIA in November 2006.

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