CASE NO: 1998 - A - 458

On behalf of the: Defendant
Witness: H H Gunson
Statement No: 1
Exhibits:
Dated: March 2000
CASE NUMBER: 1998 - A- 458

IN THE HIGH COURT OF JUSTICE
QUEEN'S BENCH DIVISION
MR JUSTICE BURTON

RE: HEPATITIS LITIGATION

B E T W E E N : -

A AND OTHERS

Claimant

- and -

THE NATIONAL BLOOD AUTHORITY

Defendant

WITNESS STATEMENT OF:	**HAROLD HASTINGS GUNSON CBE MD DSc FRCPath FRCP FRCP (Ed)**
ADDRESS:	**International Society of Blood Transfusion PO Box 111 Royal Lancaster Infirmary Lancaster LA1 4GT**
OCCUPATION:	**Retired. Former Medical Director of the National Blood Authority**

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1 My full name is Harold Hastings Gunson. My full curriculum vitae appears at Appendix III of this statement. I have held appointments in the National Blood Transfusion Service (NBTS) since 1959, including the posts of Director of the Oxford and Manchester Regional Transfusion Centres. Between 1981 and 1994 I was Consultant Adviser in Blood Transfusion to the Chief Medical Officer at the Department of Health. In July 1988 I was appointed Director of the National Directorate for the NBTS. When the National Directorate was disbanded in 1993 I became National Medical Director of the National Blood Authority (NBA). I retired in July 1994 and became a part-time consultant to the NBA, which position I still hold today.

2 I should say that I have no formal training in virology. As part of my duties in the various posts listed above I have of course had to learn the essentials of the subject as it affects the prevention of transfusion-transmitted diseases. I have done so through extensive reading of the medical and scientific literature; through many discussions with colleagues in the Public Health Laboratory Service (PHLS) and with Prof. Tedder at the Middlesex Hospital Medical School; by attendance at meetings and by my membership of the Advisory Committee on the Virological Safety of Blood (with which I deal more fully below). Throughout my statement, I make reference to a number of specific academic texts. These are referred to in Appendix II. I was also aware at the relevant times of numerous other academic papers and there are additional key items included in Appendix II not specifically referenced.

3 The matters which I cover in this statement are as follows:-

A The organisation of the NBTS (1946-1993)

B The hepatitis C virus and its discovery

C Surrogate testing for hepatitis NANB

D The introduction of anti-HCV tests

Appendix I Dates of introduction of anti-HCV screening

Appendix II References

Appendix III Curriculum vitae and publications

A THE ORGANISATION OF THE NATIONAL BLOOD TRANSFUSION SERVICE 1946-1988

4 Organised blood transfusion began in England and Wales in 1921 with the introduction by Percy Lane Oliver of a blood transfusion panel in London later to come under the aegis of the British Red Cross Society. Oliver insisted that donations should be voluntary and unpaid, as remains the case to the present day. During the War the Ministry of Health approved the establishment of a number of blood depots (later re-named Regional Blood Transfusion Centres (RTCs)), initially in London and subsequently in the regions and in 1946 the wartime structure was formally recognised as a National Blood Transfusion Service (NBTS). The Service was centrally managed and funded by the Ministry of Health. A Blood Group Reference Laboratory (BGRL) and a Blood Group Research Unit were established at the Lister Institute and managed by the Medical Research Council (MRC) together with a Plasma Drying Plant producing freeze-dried plasma and a limited range of plasma fractions.

5 Shortly afterwards, however, the position was changed by the inauguration of the National Health Service in 1948. Under the new scheme the RTCs became the responsibility of the Regional Hospital Boards (subsequently Regional Health Authorities (RHAs)) within whose Regions they were situated. There were various changes over the years, but by 1970 there were fourteen RTCs - one in each Region except for South London, in which the RTC served two Regions, South East Thames and South West Thames, with a sub-centre at Hither Green Hospital. RTCs were responsible for the collection of blood from voluntary donors, the processing and testing of blood donations, and the supply of blood to hospitals within their area and (on some occasions) to other hospitals and bodies outside their Region (for example to the Ministry of Defence). In some instances the area of operation of an RTC did not correspond precisely to that of the Region of which it formed part. In the case of Wales, which did not have a regional structure, South Glamorgan Health Authority maintained and operated a Transfusion Centre in Cardiff for all the Welsh Districts save Gwynedd Health Authority and Clwyd Health Authority which were served by the Mersey RTC.

6 The position in Scotland was different. It retained its own, centrally-managed and independently funded, service – the Scottish National Blood Transfusion Service (SNBTS), founded in 1940 and comprising five RTCs (Masson, 1983, Ref. 82).

7 It is important to appreciate that each RTC was managed by its own independent medically-qualified Regional Transfusion Director (RTD), appointed by and answerable to his or her Region and concerned to meet the needs of that Region. The Regions were of course geographically and demographically diverse, and RHAs inevitably varied in their funding policies and priorities. Thus matters of policy relating to collection of blood within the Regions, and arrangements for the management and operation of the RTC came to vary substantially over the years.

8 The only other operational elements in the NBTS were the two central laboratories, the Blood Products Laboratory (BPL), and the BGRL. The BPL moved from the Lister Institute to Elstree in Hertfordshire in 1953 and subsequently the responsibility for it was transferred first from the MRC to the Lister Institute and in 1978 to the North West Thames RHA (on behalf of the DHSS) and later (in 1982) to a newly-created Central Blood Laboratory Authority (CBLA). At the BPL, plasma supplied by the RTCs was fractionated to produce blood products. None of the RTCs had a fractionation facility of its own.

9 There was no central organisation to ensure that those functions which were common to all RTCs operated in a uniform manner. Such central co-ordination as there was was vested in the Consultant Adviser to the Minister of Health. This was initially Dr. (later Sir) William Maycock, who was appointed Consultant Adviser in 1946 and Superintendent of the Lister Institute Laboratories at Elstree in 1949 (his title in the latter role changing to Head and subsequently Director of the BPL). He was succeeded as Consultant Adviser by Dr. Geoffrey Tovey in 1978. I succeeded Dr. Tovey in 1981. The Consultant Adviser chaired regular meetings of the RTDs, but these had no statutory basis or executive role. The most that the Consultant Adviser could do was to seek, where he thought appropriate, to encourage uniformity of practice and to make recommendations to the Ministry of Health (subsequently the DHSS). Whilst attempts were made to standardise certain functions, such as the medical selection of donors, these were only partly successful since there was no obligation for Directors to implement national agreements if these were not consistent with regional policies.

10 Various attempts were made in the course of the 1970s to improve the degree of co-ordination between the RTCs. The DHSS appointed a senior administrative officer to deal exclusively with blood transfusion and a senior medical officer to undertake blood transfusion duties. A multi-disciplinary Central Committee was set up with responsibility *"to keep under review the operation of the National Blood Transfusion Service, including the Blood Products Laboratory and Blood Group Reference Laboratory, in England and Wales and advise the Department of Health and Social Security on the development of the service"*. The Central Committee did not prove very effective in its intended central role. After 1978, the RTCs were grouped into three geographical "Divisions" – Eastern, Western and Northern. The Eastern Division comprised NW Thames (North London), NE Thames (Brentwood), SE/SW Thames (South London) and East Anglia (Cambridge). The Western Division comprised Oxford, South Western (Bristol), Wessex (Southampton), West Midlands (Birmingham) and Wales (Cardiff). The Northern Division comprised Northern (Newcastle), North Western (Manchester), Trent (Sheffield) and Yorkshire (Leeds).

11 In 1980 the DHSS, on the initiative of Dr. Tovey, replaced the Central Committee with a much smaller Advisory Committee with a membership restricted to persons closely involved with the Service, the terms of reference of which were: *"to advise the DHSS and the Welsh Office on the co-ordination of: (1) the development and work of Regional Transfusion Centres and the Central Laboratories in England and Wales and (2) as necessary the English and Welsh Blood Transfusion Service with that of Scotland"*. (This was the first occasion that there was an official liaison between the English and Scottish Services.) The Advisory Committee met on 14 occasions between 1st December 1980 and 8th February 1988 and a number of major decisions were taken which had a beneficial effect on the operations of the NBTS.

1988-1993: The National Directorate

12 Despite the formation of the Divisions and the improvement in central co-ordination by the Advisory Committee and by the formation of UK working parties to develop national policies, there were still major problems in achieving national standardisation. These became particularly apparent in the early 1980s as a result of the creation of the CBLA, which brought into focus major inconsistencies in the way in which different RTCs

supplied plasma to the BPL (which in 1990 had been re-named the Bio Products Laboratory), and of the difficulties in introducing testing for the HIV virus.

13 Accordingly I was asked to submit proposals for a centrally funded and managed service. Between 1986 and 1988 a team from the DHSS Central Management Services carried out an investigation of the organisation of the NBTS. The team identified a number of deficiencies and proposed the following options – (1) to maintain the status quo; (2) to create a Special Health Authority and (3) to retain management of RTCs by RHAs but with formal co-ordination of their work. The DHSS decided in favour of (3) and on 28th July 1988 the National Directorate of the NBTS was formed and I was appointed National Director. The National Directorate was funded by the DHSS and, as National Director, I reported to the Director of Operations of the NHS Management Board. A Co-ordinating Committee was established which reviewed the activities of the National Directorate.

14 It is important to stress that the National Directorate did not have any executive authority and its successes came about by persuasion. The RTCs remained the primary responsibility of the RHAs. There were inevitably difficulties when proposals from the National Directorate for a change in national policy required additional resources, since these had to be found from the budgets of the various RHAs. Despite these difficulties, the National Directorate did record several achievements, including the inter-regional transfer of blood; establishment of a management information system; quality assurance at RTCs, together with audits, and improved blood donor recruitment and retention.

1993: The National Blood Authority

15 However, despite these successes the National Directorate was overtaken by national events. The devolution of budgets to Districts proposed in the NHS and Community Care Act 1990 meant that RTCs had to recover their operating costs through reimbursement for products and services. Inevitably, RTCs had to work closely with the hospitals receiving their products and services, and there was a tendency for the National Directorate to become marginalised as a result. The lack of any central executive authority had to be addressed. Taken with the plans then under consideration to reduce the number of RHAs, it became clear that further change was necessary. On 1st April 1993, the Department of Health announced its intention to establish a single Authority, the National Blood Authority (NBA), with responsibility for both the central laboratories and the RTCs. The NBA took

over responsibility from the National Directorate, the CBLA and the BGRL with effect from 1st April 1993 and from the RHAs with effect from 1st April 1994. The position was thus restored to the structure that had existed between 1946 and 1948, with all elements of the NBTS under a single central authority.

16 The NBA inherited the legal liabilities of the various authorities which were previously responsible for the functions which it inherited.

B THE HEPATITIS C VIRUS AND ITS DISCOVERY

Hepatitis NANB

17 The data from which this section has been compiled has been reported in "50 Years in Blood Transfusion" (Gunson and Dodsworth, 1996, Ref. 58). Much of the early information was obtained from the Public Records Office, the contemporary medical archives at the Wellcome Institute and minutes of various meetings.

18 It has been known since the 1940s that hepatitis could be transmitted by transfusions of blood and plasma. At that time this type of hepatitis was called homologous serum jaundice. This name was changed to serum hepatitis to distinguish it from infectious hepatitis, now known as hepatitis A, which is transmitted almost entirely by the oro-faecal route, rather than by the transfusion of serum and plasma.

19 A major advance was made when an antigen, thought initially to be linked with leukaemia (Blumberg et al., 1965, Ref. 12), but later shown to be associated with hepatitis, was found in the serum of an Australian aboriginal (Blumberg et al., 1967, Ref. 13; Prince, 1968, Ref. 89). The antigen was specifically linked to type B viral hepatitis. A test was developed to detect this "Australia antigen" which is now called the hepatitis B surface antigen (HBsAg). Testing of blood donations for HBsAg was introduced for all blood from December 1972. Alter et al., (1972) (Ref. 4) demonstrated that exclusion of HBsAg positive blood donors and paid donors led to a reduction of 85% in transfusion associated hepatitis.

20 Initially, the tests for HBsAg had poor sensitivity, but even when that sensitivity was improved it was found that transfusion-associated hepatitis still occurred in 7-12% of blood-transfusion recipients in the USA (Alter, 1985, Ref. 3). In almost all instances this form of hepatitis was shown not to be of the types A or B, nor was there evidence of the existence of previously unrecognised hepatitis due to cytomegalovirus or E-B virus. In addition, drugs had not been administered that might have resulted in liver damage (Feinstone et al., 1975, Ref. 48). For the want of a better term this form of hepatitis was called non-A, non-B (NANBH) (Alter et al., 1975, Ref. 5; Dienstag et al., 1977, Ref. 33).

21 Transfusion-transmitted NANBH is generally a mild illness or is sub-clinical and in most instances jaundice does not result. In cases where there were no clinical signs NANBH

was diagnosed when the serum level of the liver enzyme alanine aminotransaminase (ALT) reached 2.5 times the upper normal limit between 2 and 26 weeks after a transfusion in a patient whose ALT was normal prior to the transfusion and whose ALT was more than twice the normal level in a further blood sample taken three weeks later (Aach et al., 1981, Ref. 1; Alter et al., 1981, Ref. 6).

22 As well as hepatitis A (HAV), hepatitis B (HBV) and hepatitis delta (HDV) (which occurs only in association with HBsAg (Rizzetto et al., 1980, Ref. 94; Tiollais et al., 1981, Ref. 106)), two forms of NANBH, enteric and parenteral, had been recognised by 1988. (It is now known that the enteric form of NANBH is caused by an agent now called HEV and is responsible for epidemics of hepatitis in countries with low standards of sanitation and is responsible for about 50% of sporadic hepatitis (Mollison, Engelfriet and Contreras, 1993, Ref. 85)). Parenteral transmission of NANBH due to HEV has not been reported (Purcell and Ticehurst, 1981, Ref. 90). It is the parenterally transmitted form of NANBH which is associated with the transfusion of blood, its labile products and certain plasma products. Subsequently it became apparent that HCV could be transmitted as a community disease.

The occurrence of parenteral NANBH

23 The occurrence of NANBH varied throughout the world. In general it was higher in the USA, Southern Europe and Japan than in Northern Europe and Australia, (Katchaki, et al., 1981, Ref. 69; Cossart et al., 1982, Ref. 29; Hernandez et al., 1983, Ref. 62; Tremolada et al., 1983, Ref. 107; Japanese Red Cross Non-A, Non-B Hepatitis Research Group, 1991, Ref. 66; Alter, 1985, Ref. 3). Within the UK, the Medical Research Council (MRC) established a Working Party to study NANBH. They concluded that the incidence was low (MRC Working Party Report, 1974, Ref. 83). Using the criteria defined by the MRC - that the diagnosis of NANBH should only be made when the ALT value exceeded 100 international units (iu) per litre - Collins et al., (1983) (Ref. 26) found 2.4% NANBH in cardiac surgery patients in the North East of England, but only 2 of 228 patients had a persistently raised ALT. Anderson et al., (1987) (Ref. 8) studied a group of cardiac surgery patients in North London who had received transfusions of at least three units of blood. Out of 186 patients, six had a mildly raised ALT and only one could be diagnosed as suffering from NANBH using the criteria from the USA. They concluded that the

frequency of transfusion transmitted NANBH was less than 1%. (This was a result consistent with a later study carried out in North London (Contreras et al., 1991, Ref. 28)).

24 Whilst a history of previous transfusion in patients with chronic hepatitis (42.8%), cirrhosis (37.1%) and hepatocellular carcinoma (15.1%) was frequent in a Japanese study (Kiyosawa et al., 1982, Ref. 71), this could not be confirmed in a UK study: Wood et al., (1989) (Ref. 121) found no significant association between chronic liver disease and transfusion in two groups of patients matched for age and sex treated in the same hospital. However, before the effective viral inactivation of clotting factors, chronic liver disease was a problem in haemophiliacs in the UK and elsewhere (Triger and Preston, 1990, Ref. 108), since many of them had a lifetime exposure to pooled plasma products.

25 In many countries the principal concern between 1980 and 1985 was the transmission of HIV infection. NANBH was not regarded as a major clinical problem.

The discovery of the hepatitis C virus

26 Many attempts were made during the 1980s to isolate the agent causing NANBH. It was found that the disease could be transmitted to chimpanzees and it was shown that the agent responsible for this was approximately 30 nm in diameter (Bradley et al., 1979, Ref. 15) and was destroyed by chloroform, suggesting that it had a lipid coat (Bradley et al., 1985, Ref. 17). Claims were made that antigen-antibody systems could be detected for NANBH by counterelectrophoresis (Tabor et al., 1979, Ref. 102), by double immunodiffusion (Shirachi et al., 1978, Ref. 97), by direct immunofluorescence (Kabiri et al., 1979, Ref. 67) and by a combination of immunodiffusion and immunofluorescence (Vitvitski et al., 1979, Ref. 114), but these findings could not be substantiated in later studies (Bradley et al., 1981, Ref. 16; Alter, 1985, Ref. 3).

27 Pooled plasma from the chimpanzees infected with NANBH by Bradley's group at the Center for Disease Control at Atlanta, Georgia was used by Houghton and his co-workers at the Chiron Corporation at Emeryville, California to recover and clone nucleic acids. It was this which led to the discovery of the hepatitis C virus. The Chiron Corporation issued a News Release on 10th May 1988 which stated:

> *"Scientists at Chiron Corporation have identified, cloned and expressed proteins from a long-sought blood-borne hepatitis non-A, non-B virus and have developed*

a prototype immunoassay that may lead to a screening test for non-A, non-B antibodies.

The research was carried out in part under the auspices of The Biocine Company, a joint venture of Chiron and Ciba-Geigy, which is responsible for researching, developing, manufacturing and marketing any vaccine, and with support from its partner Ortho Diagnostics Systems, a subsidiary of Johnson and Johnson, which will market any immuno-diagnostic products which result."

The News Release continues with a brief review of NANBH in the USA and the introduction of tests for anti-HBc and ALT to reduce the incidence of transfusion transmitted NANBH and it describes how the virus protein was expressed. It notes that "*.... Additional applications of research may include: confirmed clinical diagnosis of patients with symptoms of blood-borne hepatitis non-A, non-B and monitoring during therapy ....*". The discovery was subsequently formally written up in *Science* (Choo et al., 1989, Ref. 23).

Molecular biologic characterisation of HCV

28 Choo et al., (1989) (Ref. 23) described a clone, named 5-1-1, which encoded an antigen which bound circulating antibodies present in serum from several NANBH patients.

29 The understanding of the molecular biological characterisation of HCV developed over the period 1990-3. At the N-terminal region, there are the structural proteins comprising the core and the two envelope proteins, El and E2/NSI, (Choo et al., 1990, Ref. 24; Takeuchi et al., 1990, Ref. 105; Han et al., 1991, Ref. 60; Harada et al., 1991, Ref. 61; Houghton et al., 1991, Ref. 63; Takamizawa et al., 1991, Ref. 103; Weiner et al., 1991, Ref. 119; Grakoui et al., 1993, Ref. 57). The C-terminal region encodes the non-structural proteins, NS2, NS3, NS4 and NS5. which play a role in the replication of the virus (Choo et al., 1990, Ref. 24; Takamizawa et al., 1991, Ref. 103; Houghton et al., 1991, Ref. 63; Grakoui et al., 1993, Ref. 57). Significant sequence diversity in the HCV genome was found in isolates obtained from different parts of the world (Choo et al., 1991, Ref. 25; Chen et al., 1991, Ref. 21). As early as 1990 two different types of HCV were found (Enomoto et al., 1990, Ref. 42). Chan et al., (1991) (Ref. 20) defined a third type and pointed out that only one of four type 2 and one of five type 3 HCV infections reacted with the first generation assays

(see below). Later studies have shown that there were at least 11 distinct types (for references see Bresters, 1993, Ref. 18).

30 The complete sequence of the HCV viral genome has now been determined. It consists of about 9,400 nucleotides encoding a polyprotein of about 3,000 amino acids (Choo et al., 1989, Ref. 23; Kato et al., 1990, Ref. 70; Okamoto et al., 1991, Ref. 88; Inchauspe et al., 1991, Ref. 65; Takamizawa et al., 1991, Ref. 103; Chen et al. , 1992, Ref. 22).

Diagnostic assays for the detection of HCV

31 The first generation anti-HCV assay was based on the recombinant antigen c100 and was in the form of radioactive immunoassay (Kuo et al., 1989, Ref. 77). Anti-c100 reactivity was found in the majority of patients suffering from chronic NANBH (Sansonno and Dammacco, 1989, Ref. 96; Esteban et al., 1989, Ref. 43; Kuo et al 1989, Ref. 77; Roggendorf et al., 1989, Ref. 93; Sanchez-Tapias et al., 1990, Ref. 95) indicating that HCV caused most NANBH infections. Anti-HCV was found in 80-90% of patients with transfusion-associated NANBH (Kuo et al., 1989, Ref. 77; Sanchez-Tapias et al., 1990, Ref. 95).

32 The first commercial kits for detecting anti-HCV became available in late 1989. They were enzyme-linked immunoabsorbent (ELISA) assays and included recombinant antigen to the NS4 region of the genome only, but as two components, 5-1-1 and c100.

33 The sensitivity of the anti-c100 assay was restricted since only about 65% of transfusion transmitted NANBH was prevented by the transfusion of anti-c100 negative blood (Van der Poel et al., 1990, Ref. 110). Moreover, it was shown that anti-c100 might take one year to develop after onset of infection (Kuo et al., 1989, Ref. 77; Alter et al., 1989, Ref. 7). Also, some persons who were found HCV-positive by the polymerase chain reaction (PCR) test (which I describe below) lacked anti-c100 in their serum (Weiner et al., 1990a, Ref. 117; Zanetti et al., 1990, Ref. 122 and, subsequently, by Hagiwari et al., 1992, Ref. 59).

34 Not surprisingly, in view of the geographical variation of transfusion associated NANBH, the incidence of anti-c100 varied world-wide. In voluntary, unpaid blood donors in Northern Europe, Scandinavia, the USA and Australia it was in the range 0.2-0.8% (Kuhnl et al., 1989, Ref. 76; Weiner et al., 1990b, Ref. 118; Contreras et al., 1991, Ref. 28; Dawson et al., 1991, Ref. 32; Ebeling et al., 1991, Ref. 40; van der Poel et al., 1991, Ref.

111). In contrast, the incidence of the antibody was in excess of 1.0% in voluntary, unpaid donors in the Mediterranean countries and in Japan (Esteban et al., 1990, Ref. 44; Miyamura et al., 1990, Ref. 87; Katayama et al., 1990, Ref. 68; Sirchia et al., 1990, Ref. 99), and was approximately 10% in paid plasma donors in the USA (Dawson et al., 1991, Ref. 32). (Subsequent studies went on to confirm these findings (Hyland et al., 1992, Ref. 64; Takano et al., 1991, Ref. 104).

35 MacLennan et al., (1992), (Ref. 81) and Goodrick et al., (1992), (Ref. 56) found 46% and 58%, respectively, of HCV seropositive blood donors had been intravenous drug users in the past. This might partly explain why NANBH was found with less frequency following the introduction of self-exclusion procedures for donors at increased risk of transmitting the human immunodeficiency virus (HIV). There was, however, a disturbing feature of the association of anti-HCV positive blood donors and intravenous drug use since in some instances the experimentation with drugs occurred prior to 1977, the limiting date in the Department of Health AIDS leaflet giving advice to donors. This date limitation was removed in a subsequent leaflet issued in 1993.

36 In order to increase the sensitivity of anti-HCV testing, second generation tests were introduced early in 1991. The assays marketed by Ortho Diagnostics and Abbott detected antibodies against both the structural core proteins (c22), and the non structural regions NS3 and NS4 (Bresters, 1993, Ref. 18).

37 Other manufacturers in Europe and North America have since cloned HCV genomes from material distinct from the Chiron isolate. The assay marketed by United Biomedical Inc., (UBI), was based on synthetic peptides rather than expressed recombinant protein antigens. (It was subsequently found that it initially lacked the ability to detect antibodies against NS3 (Follett et al., 1992, Ref. 51). This was remedied later.) The assay supplied by Murex had an additional NS5 component.

Confirmatory tests for anti-HCV

38 Apart from the problems with the sensitivity of the first generation assays, as described above, which led to false negative results, they were also prone to yield false positive results, particularly in low risk populations such as blood donors (Weiner et al., 1990b, Ref. 118; Wong et al., 1990, Ref. 120). In order to deal with the possibility that a positive result may in fact be false, it is necessary to have a reliable confirmatory test. In 1990, Ortho Diagnostics introduced a recombinant immunoblot assay (RIBA-1). This comprised the two recombinant antigens, c100 and 5-1-1, present in the screening test absorbed on to a nitrocellulose strip. To confirm a positive result, a visual band had to be produced against both c100 and the 5-1-1 antigens: a single band against either was treated as an indeterminate result. Whilst RIBA-l was useful in distinguishing true from false positives (Ebeling et al., 1990, Ref. 39 and, subsequently, Contreras et al., 1991, Ref. 28), it was a supplementary rather than a confirmatory assay because it tested for the presence of the same markers as the primary assay, and unfortunately non-specific results continued to occur (as was confirmed by Follett, 1995, Ref. 49).

39 At about the same time, Abbott Laboratories introduced the HCV neutralisation ELISA as a different form of supplementary test. The principle of this test was that the c100 antigen would neutralise the corresponding antibody, but antibodies to other components in the assay, e.g. yeast, would not be neutralised. The performance of the neutralisation assay was similar to that of RIBA-1 (Wong et al., 1990, Ref. 120 and, subsequently, Evans et al., 1992, Ref. 45).

40 The unsatisfactory nature of these two supplementary assays led to the development of a number of others - RIBA-2 by Ortho Diagnostics; the MATRIX assay by Abbott Laboratories, and the INNO-LIA test by Immunogenetics. I will describe these briefly in turn.

41 The RIBA-2 assay contained, in addition to antigens c100 and 5-1-1, recombinant antigens to the core region (c22) and the NS3 region (c33). A positive result was obtained when a band was obtained against at least two recombinant antigens. A single band denoted an indeterminate result. Once again, it was not a true confirmatory assay, since the antigens

were not derived from an independent source; but, as described below, it was in due course shown to be much more reliable than RIBA-1. RIBA-2 was introduced in the UK for experimental purposes during the autumn of 1990 but was not in regular use until April 1991.

42 The MATRIX assay was a dot blot immunoassay in which the recombinant proteins c22, c33 and two c100 antigens (one derived from yeast and one from the bacterium E coli) were presented on a nitrocellulose-based solid phase. Several studies have subsequently indicated that the results using the Matrix assay were comparable to that of RIBA-2 Mimms et al., (1990) (Ref. 84) concluded that the Matrix assay was superior to RIBA-2. Another study has shown that it was comparable to RIBA-2 (Allain et al., 1992, Ref. 2).

43 The INNO-LIA assay comprised six antigens, four derived from the core region, one from NS4 and one from NS5, together with four control lines, on a nylon strip (Chan et al., 1991, Ref. 20; Kudesi et al., 1992, Ref. 75). Chan et al. (1991) (Ref. 20) found this assay proved successful for the confirmation of blood donors infected with HCV types 1, 2 and 3. With two of five examples of type 3 HCV only the c22 antigen was reactive in RIBA-2 and would have been declared indeterminate. Chan and his colleagues were using this test at the end of 1991.

44 A quite different form of confirmatory test was developed at the Middlesex Hospital and elsewhere in the course of 1990. The polymerase chain reaction (PCR) test detects the presence of the virus itself in the blood (viraemia) and is accordingly associated with infectivity (Garson et al., 1990a, Ref. 52 - and this was subsequently confirmed by Hagiwara et al., 1992, Ref. 59). It is thus a true confirmatory test. Because it does not detect antibodies it cannot identify donors who have once been infected but are no longer viraemic. It is extremely sensitive, and for that reason, and because of contamination of the sample, false positive reactions can occur (Kwok and Higuchi, 1989, Ref. 78). Despite its sensitivity false negative results can occur, e.g. if there is a delay of 2-3 hours or more in removal of plasma or serum from the blood sample before freezing, or if the levels of the virus present are below detectability: this can vary with technique and between laboratories (Bresters, 1993, Ref. 18). It is technically a more complex test than the ELISA assays described above and is not suitable for primary screening or for use in RTCs. PCR was first used in the UK to test selected samples from the Ortho/Abbott first generation study in September/October 1990.

45 It has been noted that the PCR assay might be helpful in understanding the significance of RIBA-2 indeterminate results. Other applications are the diagnosis of early HCV infection (Garson et al., 1990b, Ref. 53 and, subsequently, confirmed by Puoti et al., 1992, Ref. 91) and the investigation of HCV infectiousness since antibodies may persist after the virus has been cleared (Farci et al., 1991, Ref. 47 and, see Lelie et al., 1992, Ref. 79). (PCR can also be useful for monitoring the treatment of HCV hepatitis with anti-viral drugs (Bresters, 1993, Ref. 18)).

C SURROGATE TESTING FOR HEPATITIS NANB

The USA

46 Until the identification of the hepatitis C virus, as described above, there was of course no way of directly identifying infected donors and excluding their donations. But studies published in the USA in the 1980s suggested that other tests might allow the indirect identification at least some donors who were infected. First, two studies, the Transfusion Transmitted Virus Study (TTVS) and the National Institutes of Health (NIH) Study, concluded that there was a relationship between transfusion transmitted NANBH and raised levels of ALT (Aach et al., 1981, Ref. 1; Alter et al., 1981, Ref. 6). Secondly, these two groups subsequently also identified an association between NANBH and antibody to hepatitis core (anti-HBc) (Stevens et al., 1984, Ref. 100; Koziol et al., 1986, Ref. 74). This relationship with anti-HBc could not be confirmed by Reesink et al., (1988) (Ref. 92). So far as the former was concerned, it was concluded that, in the USA, exclusion of donors with high ALT levels might prevent 30% of cases of transfusion-transmitted NANBH at the cost of losing up to 3% of donors. As for the latter, it was concluded that the exclusion of donors with anti-HBc could lead to a reduction of 30-40% of cases, with a loss of 4-8% of donors. It was noted that ALT and anti-HBc appeared to identify two separate populations of donors since only 15% donors with a raised ALT were anti-HBc positive, and of anti-HBc positive donors, only 8% had a raised ALT (Stevens et al., 1984, Ref. 100).

47 On the basis of the TTVS and NIH studies, in 1981 the NIH introduced routine ALT testing at its own blood bank in order to study the clinical impact of such testing and to evaluate diagnostically all donors with a raised ALT value. Donors with an ALT greater than 50 international units (iu) per litre were excluded. The results (Alter, 1985, Ref. 3) showed that the incidence of transfusion-transmitted NANBH in a three-year period after ALT testing had been introduced was almost the same as that in the two years prior to ALT testing. The finding was unexpected: Alter suggested that an increase in use of platelet concentrates from paid donors might have accounted for the absence of the expected decline, but he acknowledged that it was unlikely that this factor could have masked the expected reduction of 30%.

48 The question whether the evidence justified the introduction of routine screening was controversial in the USA. I draw attention to some of the contributions to the debate.

- In the Medical News section of the Journal of the American Medical Association (1981) (Ref. 6), it is reported that the New York Blood Center intended to introduce ALT testing of blood donations. Dr Pindyck, Vice-President and Director of the New York Blood Program, defended the test itself although it had been criticised by the American College of Physicians for having widely varying results from different laboratories.

- In the same article, Alter raised the possibility of each laboratory setting its own standard deviation figure. Such an action would have led to blood being acceptable in one area and unacceptable in another. Holland commented that a donor might have to be told that he had been found positive with a test that had a 70% false positive and a 70% false negative rate. Dodd concluded that although a figure of 30% reduction of NANBH had been put forward, there was no agreement that this represented the real reduction that might be achieved.

- Dodd (1982) stated that a careful analysis of the advantages and disadvantages of ALT testing should be investigated before formulating such a policy.

- Hornbrook et al., (1982) (Ref. 62A) commented, after an economic appraisal of surrogate testing, that the current information concerning the frequency and severity of clinically apparent post-transfusion NANBH was not sufficient to provide the best advice for policy decisions. They regarded the lack of a randomised prospective study as important information to show that the exclusion of blood donors with a raised ALT would lower the incidence of post-transfusion NANBH.

- The contributors to the International Forum in Vox Sanguinis in 1983 did not advocate ALT testing at that time.

- In 1984, Alter and Holland (1984) (Ref. 4A) gave three options with regard to ALT testing: (1) to conclude that the data was inconclusive and that in view of the poor specificity of the results of such donor screening and other problems it was not justified; (2) that despite the difficulties the data was sufficient to warrant the immediate introduction of the test and (3) that a controlled study should be performed as soon as possible. Their preference was for the third.

- Barker (1988) (Ref. 10A) commented that randomised studies had not been performed and were not currently planned to study the efficacy of the use of non-specific tests. Although the tests had been introduced in the USA, he considered that other countries should query the value of such testing in the context of their own specific conditions.

- Klein (1990) (Ref. 71A) concluded that whilst ALT had emerged as one of the most effective laboratory determinants for reducing transfusion associated NANBH, it was not a perfect solution since it had not been calculated by prospective studies and now never would be. Also the determination of a proper cut-off was controversial. However, with regard to public expectations, it would be difficult to discontinue the test without compelling evidence that such a change would not impair transfusion safety.

49 In the event, testing of all blood donations for both ALT and anti-HBc was introduced in the USA in 1986. A two stage cut-off was employed for ALT, the lower cut-off being in the range 50-60 iu per litre and the higher at twice that level. If the donor's ALT was between these two levels the blood was discarded but the donor was allowed to donate again. If the ALT exceeded the higher level, or if two moderate increases were found within a given year, the donor was withdrawn and notified. The introduction of surrogate tests in the USA led to the rejection of between 4 and 6% of blood donors and placed a burden on the operation of blood centres, particularly with the need to quarantine a significant number of red cells and other components (Dodd, 1991, Ref. 36).

50 It is not possible to assess the value of these surrogate tests for NANBH markers in the USA in the late 1980s, since during that period measures were also undertaken to promote self-exclusion of donors at risk of developing infection with human immunodeficiency virus (HIV), together in due course with the introduction of tests for this virus. Both of these actions reduced the incidence of transfusion-transmitted hepatitis (Dienstag, 1990, Ref. 35). After the introduction of selective self-exclusion for HIV and before the introduction of surrogate tests the incidence of tranfusion associated NANBH decreased to about 1% in the USA (Alter, 1989, Ref. 3A). Also, the underlying effect of sporadic NANBH was not taken into account in assessing the efficiency of surrogate markers in the reduction of transfusion transmitted NANBH.

51 Screening of donated blood for either form of surrogate marker was not introduced in Canada.

Australia

52 In Australia, Cossart et al., (1982) (Ref. 29) found a raised ALT in 2% of 842 cardiac surgery patients. Her criterion for abnormality was 2.5 x upper limit of normal. Of the 18 patients three raised ALTs were caused by HBV and one by cytomegalovirus. The remainder were assumed to be NANBH. Since a significantly higher proportion of blood given to these patients was anti-HBc positive it was concluded that the rejection of such donations could reduce the incidence of NANBH by up to one-half. The association with ALT had less significance.

53 Discussion within the Australian BTS Executive in 1986, following the introduction of ALT and anti-HBc testing in the USA, concluded that there should be a further study before a decision was made to introduce surrogate tests. This study began in 1987, but in the meantime Dr Ian Young had introduced surrogate tests in Queensland. Woodfield argued in a paper presented at the 1988 meeting of the Australian Society of Blood Transfusion that surrogate testing had been "too much, too soon". The proposed study of 500 patients in Western Australia and a similar number in New South Wales proceeded and it was agreed to defer the introduction of non-specific tests for NANBH until the study had been completed. The study revealed an incidence of post-transfusion NANBH of 1.1% and the conclusion was that non-specific tests would not have significantly reduced this incidence (unpublished - personal communication).

Europe

54 Non-specific tests for the diagnosis of transfusion associated NANBH were considered by the Committee of Experts on Blood Transfusion and Immunohaematology (code named SP-HM) of the Council of Europe in 1987, 1988 (WTD/8785-8845) and 1989 (J/69-123).

55 I was a member of the Committee (which reports to the European Health Committee of the Council of Europe) and in 1987 I conducted on its behalf a survey of surrogate testing of blood donors in European countries (MINV/77-84). It will be seen that at that time, there were ten countries not performing either test routinely - Cyprus, Denmark, Finland, France, Greece, Iceland, Ireland, Netherlands, Norway, and the UK. Of these countries, France,

under the aegis of the French Society of Blood Transfusion, had conducted a study of ALT and anti-HBc tests and had concluded that the introduction of these tests routinely would reduce the incidence of transfusion transmitted NANBH. In other European countries, either ALT or anti-HBc (or both) were being carried out routinely either on all blood donors or on selected groups. By way of example:

- In West Germany ALT tests had been performed on blood donors for more than 20 years. The German representative on SP-HM claimed that there was a reduction of 29% in NANBH, with a loss of 1.2 % of blood donors.

- In Italy (which had a particularly high incidence of NANB) and Luxembourg ALT tests were also carried out routinely.

- In Belgium plasmapheresis donors were tested for both ALT and anti-HBc, but not donors of whole blood.

- In Switzerland, red cells sent from Berne to the New York Blood Center had to be tested for ALT and anti-HBc to meet US requirements; but the other regional transfusion centres did not perform surrogate tests.

It was clear that there was considerable divergence in policies throughout Europe and the Committee appointed a working group to propose recommendations for advice to Council of Europe members. The members of the working group were Prof. van Aken (Netherlands), Drs. Habibi (France) and Leikola (Finland) and myself.

56 It will be seen that on the basis of information available it was concluded that:

- The use of non-specific tests for the purpose of reducing the incidence of transfusion associated NANBH and its possible value as a public health measure remained a controversial issue.

- If the stance was taken that blood should have maximum safety then the tests would be introduced, but the benefits derived from this testing would not be uniform

throughout every country. Also, there was no guarantee that, in any given country, there would be any significant reduction of NANBH as a result of surrogate testing.

- The introduction of non-specific tests could lead in some countries to a severe depletion of donors which could compromise the blood supply and this was a factor which must be taken into account.

- Where non-specific testing was introduced in a country, provision must be made for interviewing, counselling, further medical examination and treatment which might be required for donors found to have a raised ALT or who were anti-HBc positive.

- The working group could not give a general recommendation on the routine introduction of non-specific tests for the evidence of NANB infectivity of blood donors. Individual countries would have to assess the situation locally and decide on the appropriate action to take. (MINV/87-89)

- The conclusion was that the introduction of surrogate tests remained a controversial issue. The recommendation to SP-HM was that individual countries would have to assess the situation and decide on the appropriate action to take. This was accepted by the Committee.

57 I repeated my survey in 1988 (WTD/8785-8845). Among the points to note are that:

- France had commenced ALT testing but anti-HBc testing was not compulsory.

- There were no uniform policies in Austria, or in Belgium where 20-30% donations were screened for ALT.

- Some, but not all, centres in Portugal were screening for anti-HBc and there was a similar situation in Spain with respect to ALT tests.

- Nine countries were not routinely carrying out surrogate tests.

58 I repeated the questionnaire again in 1989. The results can be found at J/28-29. However only ten countries responded. Of these, four were performing ALT tests on blood donations (West Germany, France, Malta and Switzerland). Additionally France was screening for anti-HBc and Ireland was testing selected donations for ALT. Studies to assess whether surrogate testing should be introduced were under way in Norway (as well as the U.K., with which I deal below). The paucity of information in this survey limited its usefulness.

59 Among the countries which did not introduce either form of surrogate testing during the period of my surveys was the Netherlands. A study carried out in Amsterdam in 1984-6 (Reesink et al, 1988, Ref. 92) concluded that exclusion of donors on the basis of raised ALT levels would be of value, though screening on the basis of anti-HBc positivity would not. The issue was considered by a Committee of the National Health Council in 1989. The conclusion (Ref. 92A) was that neither form of screening should be introduced (though by the time that the Committee reported the identification of the HCV virus had been announced, and it was influenced by the prospect that a direct screening test might soon be available.)

The UK

60 The question of surrogate testing was discussed (among other things) in a UK Working Party on Transfusion-Associated Hepatitis which I chaired (unfortunately the relevant minutes have not been found). Dr. D.B.L.McLelland and I applied to the Medical Research Council (MRC) in 1981 for a grant to set up a prospective study to investigate transfusion associated NANBH. This request was made under the aegis of the Blood Transfusion Research Committee, a standing MRC committee formed in 1939. I was Chairman of the Committee at the time. The grant was refused and the Committee was disbanded in 1982.

61 As Consultant Adviser I was of course very much interested in the issue of surrogate testing of donors for NANB (though it must be borne in mind that there were many other important issues at this time). I followed developments in the U.S.A. and, as I have explained above, I took a central role in the European SP-HM Committee. The report of the SP-HM working party in 1987 reflects my views in the aftermath of the American decision in 1986 to introduce surrogate testing. I was very aware of the absence of clear

evidence as to the value of either form of surrogate testing, and of the need to have regard to the characteristics of the donor populations in different countries: there was reason to believe that the prevalence of NANB was at its lowest in Northern European countries. I did not believe that the introduction of surrogate testing could be justified until a proper study had been carried out in the UK.

62 In April 1987 I submitted an application to the DHSS for a grant for a multi-centre study of ALT and anti-HBc screening of donations. It was proposed that three RTCs in England - Manchester, North London and Bristol - and one in Scotland – Edinburgh - would carry out the study. The plan was to test 12,000 donors in a period of six months and, by interviewing the donors with elevated ALT levels and those who were anti-HBc positive, determine not only the rates but also any aetiological factors contributing to elevated ALT values and the significance of anti-HBc positive donors.

63 It was agreed that a prospective study was needed. In the event, while the application was pending, Edinburgh undertook its own study (Gillon et al., 1988, Ref. 54). This study was completed in 1987, and I was aware of the results from my contacts with the authors. Of donors found to have raised ALT levels 82% were found to have a "non-viral" clinical explanation, typically either obesity or excess alcohol intake. There was no overlap between the donors with raised ALT levels and those with anti-HBc. The conclusion was that a screening programme based on either form of surrogate test could not be justified.

64 The DHSS approved my application on 28th April 1988 (S/18) and the trial proceeded in the three English RTCs. 3,000-3,600 donors were tested for ALT and anti-HBc at each RTC. The study was managed by a steering committee, of which I was a member. The Chairman was Dr. Marcela Contreras, the Director of the North London RTC, the Secretary was Dr. John Barbara, the Head of Microbiology at North London, and the Co-ordinator Dr. Alaeddin Rafaat, also of North London. The results were published in 1992 (Anderson et al., 1992, Ref. 9), but I was of course aware of them as they emerged. The study demonstrated the importance of standardising the methodology for ALT testing, since at the Manchester RTC ALT values greater than 45 iu per litre (regarded as the upper limit of normal) showed a lower incidence than in the other two. In summary, the results showed a significant difference in alcohol intake and obesity between those donors with a raised and those with a normal level of ALT. There had been similar findings in comparable studies in the USA (Alter, 1985, Ref. 3) and, as mentioned above, in Scotland

(Gillon et al., 1988, Ref. 54). With respect to anti-HBc, initial repeatable positive results were similar in the three centres, averaging about 0.9 %. This was reduced to an average of 0.6 % on confirmatory testing.

65 The issue of surrogate testing for hepatitis NANB was kept under review by both the U.K. Advisory Committee on Transfusion Transmitted Diseases (ACTTD), of which I was the Chairman, and the U.K. Advisory Committee on the Virological Safety of Blood (ACVSB), of which I was a member, from their respective inceptions. As I set out more fully in section D below, it was ACVSB which was intended to be, and was, the appropriate forum for the development of policy as regards (among other things) the screening of donated blood for hepatitis NANB; but the issue arose in both Committees. The consideration of the issue of surrogate testing by these Committees appears from their minutes, but the key developments in the ACVSB can be summarised as follows:-

- In a short paper presented to the first meeting of the Committee on 4th April 1989 headed "Overview of Problems for this Committee" (MINV/6-7) the issue was identified as one of some urgency, though it was noted that a final decision might have to await "UK research currently in progress", i.e. the multi-centre study referred to above. (The ACTTD had similarly concluded at its meeting on 24th February 1989 that "there should be no recommendation to institute ALT testing until the current study was completed in England" – minute 7.4 (MINT/58-62).) It was decided that the next meeting of the ACVSB would concentrate on the issue of viral hepatitis.

- At the next meeting of the Committee, on 22nd May 1989 (MINV/104-106), two papers were tabled in which the issue of surrogate testing was raised (ACVSB 2/6 and 2/7 - MINV/68-76), one of which appended extracts from the SP-HM materials from 1987. A decision was made not to introduce such testing prior to the results of the multi-centre trial (minute item 20).

- On 3rd July 1989 I tabled my analysis, prepared for the European SP-HM Committee, of the results of the 1989 questionnaire, together with a paper presented to that Committee by Prof. Van Aken of the Netherlands (ACVSB 3/4 - MINV/125-134). The Committee was also given a progress report on the multi-centre study (ACVSB 3/5 - MINV/136-138), but results were not yet available.

- For the purpose of the meeting of the Committee on 6th November 1989 I was asked to obtain from the ACTTD a briefing paper on policy regarding anti-HCV testing of blood donors. At its meeting on 9th October 1989 (MINT/170-173) the ACTTD approved the use for this purpose of a version of a paper which I had initially prepared for them as a report following my attendance in Rome at a meeting in September to discuss the hepatitis C virus: see minute 4.1. The paper was duly tabled at the meeting of the ACVSB on 6th November (ACVSB 4/3 - MINV/155-166). By this time, of course, early versions of the assay for the HCV virus were available, and the paper discussed both direct and surrogate testing (and the relationship between the two): the sections of direct relevance to surrogate testing are paras. 5, 6.7 and 7.5. In para. 7.5 I (as Chairman of the ACTTD) recommended that *"the routine introduction of non-specific tests should be deferred"*. I also tabled a paper giving the provisional results of the multi-centre study (MINV 185) and pointing out the conclusions to be drawn from it. I noted the variability of the ALT testing in the three centres, and I made the following points in particular:

    - That overall 3.2% of donors would have been rejected for raised ALT and 0.63% for anti-HBc seropositivity. The loss of almost 4% of donors cannot be regarded lightly. During the period 1988-1993, when I was National Director, there was an annual loss to the national blood panel of 12-15% of donors due to retirement or donors who had to retire due to ill health. Considerable efforts had to be expended to replace these donors so that the 9,000-10,000 donations per day could be maintained. The recruitment of an additional 4%, which would have amounted to a additional 120,000 donors, would have caused serious difficulties.

    - That it was not possible, without a prospective study, to determine how many of those donors would have transmitted NANB viruses, but that the ALT test was non-specific, giving a striking correlation with both alcohol intake and obesity;

    - That once HCV testing were introduced the justification for performing, in addition, routine ALT and anti-HBc testing was much reduced.

The paper was fully discussed (minutes paras. 23-30 – MINV/199). The view of the Committee was that there was no case for introducing surrogate tests.

66 I do not believe that the NBTS should have introduced surrogate testing for NANB, whether by screening for raised ALT levels or for anti-HBc, at any time between 1988 and 1991. I do not believe that recipients of blood or blood products derived from donors who had not been so screened – whether in the U.K. or in the Netherlands or any of the other countries which decided not to introduce such screening - were receiving a product which was less safe than they were entitled to expect.

ALT testing of plasma

67 I should deal with one other point which I understand has been raised by the Claimants' solicitors. In 1989 the CBLA, which managed the BPL, made approaches to commercial firms (initially Immuno, but subsequently Cutter) to supply plasma for use in fractionated products. It was a requirement of the firms in question that the plasma be ALT-tested, in Immuno's case because of regulatory requirements and in Cutter's as a matter of company policy. At the request of Dr. Lane, the Director of the BPL, I arranged for RTCs to ALT-test plasma derived from apheresis (which is a technique used with a limited number of donors by which plasma is collected and the red cells returned to the donor). The use of ALT testing in these special circumstances was expressly identified in my paper to the ACVSB meeting on 6th November 1989 (MINV/185-191) (previously approved by the ACTTD, where the issue was expressly discussed): para. 7.4 of the paper recommends deferral of routine ALT testing *"unless this is necessary for the acquisition of product licences in the U.K. for fractionated plasma products"*.

68 In the event it was not possible to provide BPL with sufficient plasma, and their request for ALT-tested plasma was withdrawn in February 1991 (except for a small quantity to supply the German market with anti-thrombin III).

69 I do not believe that this has any relevance to the general question whether routine ALT testing of donated blood should have been introduced during the relevant period.

D THE INTRODUCTION OF ANTI-HCV TESTS

Introductory

70 I have set out in section B the discovery of the HCV virus, announced in May 1988, and explained the various screening and supplementary and confirmatory tests which were developed over the following three years. The NBTS introduced routine screening of all donations of blood with effect from 1st September 1991. In this section I describe the process by which that decision was arrived at and implemented.

71 Consideration of the question of screening for the HCV virus, once that became practicable, plainly fell within my remit as National Director of the NBTS. The old Advisory Committee described in section A had been disbanded as a result of the creation of the National Directorate and in order to be in a position to respond to new developments with respect to transfusion transmitted infections, I set up the UK Advisory Committee on Transfusion-Transmitted Diseases (ACTTD). The aim of this Committee was to consider the implications of transfusion-transmitted infections on the transfusion services in the UK and provide advice for the DHSS (MINT/4). I chaired the Committee and its membership initially comprised:

- Dr. Contreras, Dr. Wagstaff – NBTS
- Prof. J.D. Cash, Dr. R. Mitchell, Dr. E.A.C. Follett – SNBTS
- Dr. P.P. Mortimer – PHLS.

Prof. R.S. Tedder, Consultant Virologist at the Middlesex Hospital, joined the Committee in March 1991. Drs. Barbara, Head of Microbiology at the North London RTC (with whom, as noted above, I had worked closely on the surrogate testing study) and P. Minor, of the National Institute for Biological Standards and Control (NIBSC) and Mr. A. Barr (Glasgow) joined in June 1991. The Committee held its first meeting in February 1989 and continued to meet during the next three years.

72 However, the Department of Health established the UK Advisory Committee on the Virological Safety of Blood (ACVSB) in April 1989. Its terms of reference were "*to advise the Health Departments of the U.K. on measures to ensure the virological safety of blood whilst maintaining adequate supplies of appropriate quality both for immediate use*

and for plasma processing" (MINV/4-5). This was a multi-disciplinary committee chaired by a senior Deputy Chief Medical Officer of DHSS and the membership comprised:

- Prof. A.J. Zuckerman - Royal Free Hospital School of Medicine
- Dr. (later Prof.) R.S. Tedder - Consultant Virologist at the Middlesex Hospital
- Dr. P.P. Mortimer - PHLS
- Dr. P. Minor - NIBSC
- Dr. E. Tuddenham - Consultant Physician at the Hammersmith Hospital
- Dr. G.P. Summerfield - Consultant Haematologist at the Middlesborough
- Dr. R. Mitchell - SNBTS
- Dr. R.S. Lane - Director of the BPL
- Dr. R. Perry - Director of the Scottish Plasma Fractionation Centre (PFC)

and myself. There were observers from the DHSS, the Medicines Control Agency, the Scottish Home and Health Department, the Welsh Office and the Department of Health, Northern Ireland. The DHSS provided the Secretariat.

73 The ACVSB was a powerful committee. As was noted at the outset (see the "Terms of Reference" note tabled at its first meeting on 4th April 1989 – MINV/4), it was appreciated that it would be covering many of the same issues as the ACTTD. The relationship between the two Committees was formally addressed at the meeting of the ACVSB on 24th April 1990, where the Chairman proposed that it would be the responsibility of the ACVSB to advise Ministers on the virological safety of blood, while the ACTTD would consider the operational implications of policy, advise the Department on non-viral threats to blood and contribute to the advice on viral safety through input to the ACVSB. I confirmed that I shared this view of the respective roles of the two Committees and did not believe that it involved any conflict (see para.32 of the minutes ACVSB - MINV/303-307).

74 It was accordingly the ACVSB which was the leading Committee in formulating policy with regard to the introduction of HCV testing. Of course neither the Committee nor I, as explained in Section A, had any direct authority to impose decisions on the Regions, which retained operational responsibility for the RTCs. It was my role, once policy had been

determined within the Committee, and where necessary approved by Ministers, to communicate the decisions to the RTDs and to make every effort to ensure their co-operation.

Initial evaluation of anti-HCV tests

75 On 11th October 1988 Dr. Barbara and I met Drs. Polito and Chien of the Chiron Corporation, which had been responsible for the discovery of the HCV virus, in Kansas City (S/80-81). They explained that reagents for HCV testing were available on an "investigative new device" basis. They offered to carry out tests on samples which had been taken by the three RTCs contributing to the multi-centre surrogate testing trial which I have described above. This would be for research purposes only and a confidentiality agreement was required (B/4-5). (This was standard practice: when alternative kits became available from Abbott Laboratories in July 1990, it was on the same basis.) At a meeting in April, however, it was agreed that Ortho Diagnostics test kits would be supplied to North London for use there (S/183-185). The testing of the samples with the new kits was, in effect, an extension of the original surrogate testing trial.

76 Testing was completed by November 1989. I received provisional results on an informal basis from Dr. Rafaat and Dr. Barbara – see, e.g., faxes dated 3rd November 1989 (S/222) and 9th November 1989 (B/29-30). The results of the study were in the event never published. I was able to give some figures to the meeting of the ACTTD on 9th October 1989, as part of my report of the Rome meeting (MINT/129, 171). Revised figures were incorporated in my report given to the meeting of the ACVSB on 6th November 1989 (MINV/163-5). The final figures showed 9,684 samples tested for anti-HCV. The repeat reactive rate (two successive positive results on a given sample) averaged 0.67 %. (There was a variation in this rate between the samples from the three regions.) The HCV seropositive rate for donors with a raised ALT (greater than 45 iu/l) averaged 1.65%: the rate was highest in donations collected in North London (3.2%). With respect to donations which were anti-HBc positive, only one out of 62 (1.6%) was positive for anti-HCV.

77 An evaluation was also carried out in Scotland, where Prof. Cash arranged for two batches of Ortho anti-HCV test kits to be supplied to SNBTS (WTD/2360-2389). The SNBTS study commenced in August 1989 and was completed in October 1989. A total of 2745 random blood donations were tested from three SNBTS regions - North East (Aberdeen),

East (Dundee) and West (Glasgow). Fifteen were initially positive (0.55%) and 13 (0.47%) were repeatedly positive. The repeatedly reactive rate was highest in the Glasgow donations (0.55%) and lowest in those from Aberdeen (0.35%), but the difference was not statistically significant. When donor samples obtained during the ALT study (Gillon et al., 1988, Ref. 54) were tested for anti-HCV an average of 2.4% were repeatedly positive when the ALT value was greater than 45 iu/l. This percentage increased in those samples with ALT values 2.5 times greater than the upper limit of normal. In a limited number of patients diagnosed as suffering from non-A, non-B hepatitis, only 21% had been transfused with blood which was anti-HCV reactive. On the other hand, 63% of haemophiliacs were repeatedly reactive for anti-HCV. There was a variation in sensitivity between the two batches used.

78 As far as I am aware the tests carried out by NLRTC and SNBTS were the only evaluations of first generation Ortho kits in the UK during or prior to the pilot trial.

79 Results from other countries, reported at the First International Meeting on the Hepatitis C Virus held in Rome on 14-15th September 1989 (D/27-103), to which I have already referred above, showed a greater degree of correlation between the finding of an abnormal ALT value and HCV seropositives – e.g. France 5.3%; Italy average 7.9%; Switzerland 4.1% and USA, 12.7%. With respect to correlation between anti-HBc positives and HCV seropositives, the highest percentage was reported from the USA (7.3%). Despite the variations in the results there was an association between a raised ALT and anti-HBc positives and HCV seropositives since in every instance the seropositive rate is higher in these two classes of donors than in the population of donors as a whole.

Consideration of HCV screening by the ACVSB – 1989/90

80 The question of whether, and if so when, routine screening of donations for the HCV virus should be introduced in the NBTS was considered by the ACVSB at a series of meetings between 1989 and 1991. The deliberations of the Committee appear from the Minutes and the materials submitted to the Committee, and I do not propose to set them out in detail in this statement. The main milestones can be set out as follows:

- On **6th November 1989** I presented the report which, as mentioned above, had been approved by the ACTTD in October (MINV/156). This covered the discussions at the Rome meeting in September and the preliminary evaluations described above. I recommended (see sec. 7 - MINV/160-161) that the Committee should approve in principle the routine testing of donations when practical (though no earlier than the Ortho test had been licensed by the FDA); but I drew attention to a number of issues including the need for a policy on counselling seropositive donors; the need for a confirmatory test and the additional resource implications. The Committee, after a lengthy discussion, acknowledged the importance of the test but felt that much more information was needed before it could be implemented and recommended the carrying out of pilot studies at three Centres (Birmingham, Sheffield and Brentwood); the Committee would support the general introduction of the Chiron test if the FDA approved it and the pilot study showed it to be feasible and non-problematic (Minutes paras. 28-29 – MINV/199). Funding was available for the pilot study (para. 30).

- The **pilot study** proceeded accordingly over a two-week period commencing early December 1989 (MINV/203-204). Its objectives were as set out in a document dated 8th November 1989 (Q/11-12). Matters to be studied included ease of operation, how the test could be fitted into a work schedule, interpretation of results, validity of results, repeatability of results and recognition of any adverse factors. Ortho Diagnostics provided the equipment for the tests on loan. As far as I am aware, these were the only pilot studies of the Ortho kit in the UK at this time.

- I reported on the results of the pilot study to the next meeting of the ACVSB on **17th January 1990** (Minutes paras 13-15) (MINV/242-248). The Committee discussed fully the question whether the time had now come for the introduction of screening (Minutes paras. 16-35): this involved the consideration of letters tabled from Prof. Zuckerman (MINV/205) and Dr. Elias (MINV/207). I will not attempt to summarise the discussion here; but factors discussed included the number of false positive reactions, the absence of a confirmatory test and the need to counsel donors. The consensus of the Committee was that testing should not be introduced in advance of approval by the FDA. The Committee were informed that both Ortho (the makers of the only test then available) and Abbott (who

were expecting to launch a test shortly) would be holding symposia, in London and Chicago respectively, in February, which members of the Committee would be attending.

- At the meeting of the ACVSB on **24th April 1990** reports were received of the two February symposia and of a conference (Minutes, paras. 8-19 – MINV/304-305). The Committee were informed about the RIBA 1 "confirmatory" test, whose deficiencies were pointed out by Prof. Zuckerman (para. 17) and Prof. Tedder tabled a paper about the development of a PCR test (para. 20). There was then a further full discussion (paras. 21-31 - MINV/305-307). The conclusion was that there was inadequate scientific data to support the introduction of the Ortho test for routine screening. Among the continuing concerns was the absence of a reliable and practicable confirmatory test and the continuing uncertainty about the false positive rate.

- The ACVSB was reconvened, three weeks earlier than planned, on **2nd July 1990** (MINV/369-372), in order to consider again the question of the introduction of screening following the approval of the Ortho test by the FDA in May 1990. A conclusion was reached (Minutes, para. 22 – MINV/371) that the UK should introduce HCV screening, but that there should first be a pilot study to evaluate the Ortho test as against that recently introduced by Abbott.

- The **pilot study** was carried out at three RTCs (Newcastle, North London and Glasgow), in the course of September and October with confirmatory testing being carried out by the PHLS laboratories at Colindale (Dr. Mortimer), Middlesex Hospital Medical School (Prof. Tedder) and Glasgow (Dr. Follett). As far as I am aware these were the only laboratories to receive Abbott or Ortho kits at that time. A report containing the results was sent by me to the Department of Health on 30th October 1990 (MINV/373-383).

- The ACVSB met again on **21st November 1990** (MINV/402-407). The results of the pilot study were discussed. The decision was to recommend that the UK should introduce HCV testing as soon as practicable (Minutes, para. 18 – MINV/405): the choice of which test to use was left to individual RTCs. I submitted a paper on the counselling of HCV-positive donors. I also raised the question of the date of introduction of screening (para.

21). I explained that some RTCs with which I had informally discussed the question had asked for a six-month period to set up the procedures. I said that I thought this was excessive but that I would need to consult with other RTDs. It was agreed that this consultation would be deferred until a submission had been put to Ministers. The Chairman stressed the importance of a common date of introduction throughout the UK. I think it is important to comment on the importance of a common starting date. When HBsAg was introduced during the 1970s there was a period of over one year before all RTCs were testing all donations. This meant that patients in some regions had the advantage of receiving tested blood whilst others did not. This was clearly unacceptable and when the next test was introduced (anti-HIV) considerable efforts were made to ensure that the test was introduced simultaneously throughout the UK. The same priority was given to the introduction of anti-HCV.

81 It was effectively at the meeting of 21st November 1990 that a final decision was made to proceed with HCV testing, although that decision had to be confirmed by Ministers, and I was not informed that approval had been received until shortly before 22nd January 1991. The issues thereafter related to implementation.

82 I do not believe that the decision of 21st November 1990 was one which ought to have been made earlier. The factors which influenced the ACVSB in not making a final recommendation earlier appear from the minutes. But I should emphasise in particular the related problems of false positives, confirmatory testing and donor counselling. The early indications were that the Ortho ELISA test threw up a very large number of false positives. Wong et al., (1990, Ref. 120) estimated a false positive rate of 72% using the Abbott neutralisation assay as a supplementary test; Wiener et al., (1990b, Ref. 118), using RIBA-1 followed by PCR, found 69% false positives and in our own study comparing Ortho/Abbott first generation tests, the false positives totalled 77%. A study using the first generation Ortho tests at three RTCs has been referred to in paragraph 76. Matters of concern included the definition of a true positive result and the failure to confirm initial positive reactions using serum with the plasma of the donation, an essential step for quality assurance: the latter suggested that false negative results could occur. SNBTS found differences in sensitivity in the two batches they received (paragraph 77). Unless these could be reliably checked by a supplementary or confirmatory test, the consequences would be very serious. Not only would it mean discarding large quantities of donated blood which

was not in fact infective, with consequences for the blood supply; but large numbers of donors, few of whom would in fact be infected, would be left in complete uncertainty as to what their true condition was. That was unacceptable. I would not have regarded it as justifiable to proceed with screening unless and until reliable and practicable supplementary or confirmatory tests were available. The RIBA 1 test did not fill those conditions as pointed out by Professor Zuckerman at the meeting of ACVSB on 24 April 1990. The PCR test was a reliable confirmatory test, but it was not ready for use until the latter part of 1990 and was not available on a regular basis until well into 1991. RIBA-2 likewise became available on an experimental basis in late 1990 but was not available for regular use until spring 1991.

83 Even when the decision had been taken to introduce routine testing on 6 November 1990, it was evident that this would not be without problems. During the Ortho/Abbott study, the initial test kits supplied by Ortho to North London RTC were found to give negative control optical density results which invalidated the quality control of the plate. There were difficulties with the computer equipment installed by Abbott at the Newcastle RTC and the equipment installed by Ortho caused some blank wells to read as positive. It is clear that the first generation tests were not ideal for routine blood donor screening, but by November 1990 it was evident that the decision to plan for the introduction of testing could be delayed no longer.

Implementation planning

84 The ACTTD met on 8th January 1991, while confirmation from Ministers of the ACVSB recommendation was still awaited. It discussed a number of operational matters concerning anti-HCV testing of blood donations (MINT/311-314). Dr. Mortimer submitted a paper on the introduction of such screening and put forward four proposals which he considered to be essential for the management of the screening process and the donors (MINT/279-281). A flow-chart for the testing process prepared by Dr. Mitchell was discussed in detail. A report on the counselling of HCV-positive donors by an SNBTS working party was produced to the Committee (MINT/282-294). The contents of this paper and one prepared by Dr. Contreras were discussed and it was agreed that this information should be combined and a set of recommendations prepared. It was agreed

that an information leaflet should be prepared for donors prior to the introduction of routine tests.

85 On 22nd January 1991, having been notified on the telephone by Mr Canavan of the Department of Health that Ministers had approved the introduction of routine screening, I wrote to all RTDs (with a copy to Prof. Cash), asking for the earliest date on which testing could begin at each RTC (U/6). I told them that operational proposals from the ACTTD would be circulated when they had been approved by the ACVSB. The written responses from the RTDs are summarised below (though I also spoke to most if not all of them personally):

Newcastle: Commence testing approximately from the 1st April 1991. It would be advantageous if the commencement of testing could be associated with the availability of a second generation test with improved specificity (E/17).

Leeds: Commence testing at the beginning of May 1991 with a universal release of HCV tested product on 1st June, providing satisfactory financial arrangements have been agreed nationally (E/14).

Sheffield: Possible commencement on 1st April 1991 but more probably 1st May. However, a list of conditions accompanied the dates - finances to be secured; the company who supplies the RTC to produce both disposables and hardware in time and provided there was not the prospect of even more frantic activity with land based action in the Gulf. The response concludes by stating that consideration should be deferred until there was a resolution of the Gulf affairs (E/12).

Cambridge: Commence testing on 1st October 1991 if additional funding was made available and adequate progress with other matters, viz. development of a computer program, a degree of retraining of staff and recruitment to cope with an anticipated 10-15 cases per week, requirements for counselling and to decide which screening test to use (U/8).

Brentwood: Earliest date for commencement of testing, 15th April 1991. However delays until 1st May or even 1st June would be preferable; the reasons for this were given as a move into a new microbiology department and the recruitment of additional staff (E/13).

North London: Not possible to give a date for commencement of testing until there is definitive information on financial arrangements to cover screening, supplementary tests, counselling, follow up etc. Dr. Contreras, the Director, had flagged up concern regarding finance to cover the costs of anti-HCV tests as early as January 1989 (E/2).

South London: Commence testing on 1st June 1991. Questions were asked about the test system manufactured by Ortho, the likely number of positives which would be found at that RTC, whether the protocols to be issued would include guidelines on follow up of donors. Also stated that necessary building work had been arranged to accommodate the testing and upgrading of the computer was taking place (E/15).

Bristol: Commence testing on 1st July 1991. Main problem was the lack of sufficient staff and operational difficulties with evening preparation of platelet concentrates (E/7).

Birmingham: Commence testing by April, given the financial support, including two additional members of staff. Development funds have been devolved to Districts and Dr. Ala, the Director, could not foresee the Districts collectively releasing the £0.6 million required (E/4).

Liverpool: Commence testing on 1st August 1991, due to a changeover from the radio-immune assay for HBsAg on 1st April and a reluctance to introduce two tests simultaneously as HBsAg tests had to be carried out. Dr. Martlew, the Director, commented that her budget would not support routine anti-HCV testing and requested confirmation that there would be a financial allocation from the Department of Health (E/5-6).

Manchester/Lancaster: Commence testing on 1st June 1991. The major issue to be resolved was the financial arrangements; were these to be provided centrally or would the Department of Health instruct Regions to release the necessary money? (E/16)

Oxford/Southampton: Replies from these RTCs cannot be traced. I cannot now recall whether any were received.

Scotland: Unanimous opinion of the RTCs in SNBTS that commencement of testing should be delayed until after the Gulf conflict was over or until such time as confidence could be obtained that blood collection and microbiology testing teams could cope with the substantial changes and increased workload involved. If pressed, a date of May/June 1991 might be appropriate, but Prof. Cash would prefer to delay the decision for one month due to his concern that Good Manufacturing Failures might result in overstretched existing programmes (E/8-9).

86 These responses require some explanation. The introduction of a new test is not at all a straightforward matter. The necessary equipment would of course have to be bought and installed. Careful training will always be necessary, both as regards test procedures but also as regards counselling of donors. Depending on the circumstances of the particular Centre, there might be a need for recruitment of additional staff and for additional premises. All these requirements will need to be funded. I understand that a statement has been obtained from Mr Garwood, the National Processing, Testing and Issue Director of the NBA, in which these practical aspects are explained in greater detail. There was genuine concern that if the introduction of the test were rushed, safety would be compromised. References to the Gulf War reflected the fact that RTCs had been alerted to a potential need for supplies of blood on a large scale in the event of serious casualties. The air campaign had begun on 18th January 1991, prompting a huge surge in donations, but it was not known whether or when a land campaign would start.

87 In view of the number of enquiries concerning the financing of routine testing of blood donations for anti-HCV, I held discussions with Department of Health officials. As a result of those discussions, I wrote to all RTDs on 5th February 1991 informing them that it was proposed that the costs for the implementation of testing would be charged on products issued from RTCs and thus would be borne by the users (U/10). I should say that, despite the concerns expressed (in particular by Dr. Contreras at the North London RTC (U/11)), this approach gave rise to no serious difficulties in practice, and I do not believe that it had any consequences for the implementation date eventually achieved. The usual pattern was

for the RHA to make funds available until April 1992, after which the costs would be incorporated into the recovery cost for products and services.

88 I wrote to all RTDs on 15th February 1991 (E/19-20) enclosing various materials and informing them that following my discussions with all RTCs an agreed date of 1st July 1991 had emerged for the commencement of anti-HCV screening, provided that blood collection was not being disrupted by the Gulf War. The Department of Health were informed and Ministers authorised this starting date (H/2-5).

89 In fact, despite the agreed starting date of 1st July, the Newcastle RTC introduced routine HCV testing of samples with effect from mid-April. Dr Lloyd, the RTD, notified other RTDs by letter dated 2nd May 1991 (U/38). His action provoked a number of critical letters from his colleagues (U/39-47, 52-53, 57-58, 62-63) and was criticised by the ACVSB at its meeting on 29th May 1991 (Minutes, para. 32- MINV/555). Nevertheless, he was strictly within his rights to do so. As explained in section A, I had no power as National Director to impose a common starting-date.

The second generation assay

90 By early 1991 it became known that both Ortho and Abbott were planning shortly to launch the "second generation" tests referred to above, which it was expected would be far more sensitive than the first generation tests. The impending availability of these tests was discussed at a meeting of the ACVSB on 25th February 1991 (Minutes, para. 6 – MINV/480). Members agreed that it was important that proper evaluation of the new tests be carried out before RTCs decided which test they would adopt. When the ACTTD met on 25th March 1991 (MINT/343-346), it was reported that Dr. Barbara had tested approximately 2,000 donations with a pre-production batch of the Ortho second-generation assay (together with a similar number of tests with the United Biomedical Inc. (UBI) and Organon assays). It was known that the Ortho pre-production batch differed from the production batches, which were to be available from mid-April. It was not known when the Abbott second generation assay would become available. Neither version had been approved by the FDA. It was agreed that the 10,600 specimens from the trial carried out in September 1990 would be tested with both second generation assays (and with the UBI and Organon tests.)

91 The uncertainty about when these tests could be performed led to doubts whether the date of 1st July could still be met. I wrote to RTDs on 3rd April 1991 informing them that the Department of Health had agreed that there should be a further comparative evaluation of the second generation anti-HCV assays at Newcastle, Glasgow and N. London RTCs. The delay in obtaining these tests meant that it was unlikely that the date of 1st July could be met and the revised date of 1st September should be aimed for (U/28-29). A copy of the letter to Prof. Cash led to the response that the change in the starting date had the SNBTS Directors' fullest support (L/88).

92 Evaluation of the new assays by reference to the 10,000 samples already held took place during May and June 1991 and the results were published on 3rd July 1991 (I/145-151). Of the original 10,633 samples used in the first trial, 10,545 remained available. In summary, the six positive results confirmed with RIBA-2 and PCR with the first generation assays were repeatedly positive with the second generation assays of Ortho, Abbott and UBI. The SNBTS found that the UBI test missed one positive because it was not detecting the NS3 region of the virus because the test itself did not contain the NS3 antigen (Follett et al., 1992, Ref. 51). It is important to remember that the Organon test was also withdrawn by its manufacturer. Valuable findings were therefore revealed during this time which should not be underestimated. A total of 110 sera gave repeatedly positive results with the three assays, compared with 69 with the first generation tests. Only one serum from the additional positives was considered to show evidence of HCV infection by RIBA but neither that sample nor a further 28 selected samples were shown to contain HCV RNA by PCR. Once again there was an overlap between the repeatable positives indicating false positive results.

93 On 8th May 1991, Prof. Cash faxed me suggesting that the evaluation of second generation tests should be extended beyond the 10,000 samples. He suggested that two RTCs should use the Abbott second generation test and two RTCs should use the second generation Ortho test (L/110-112). I followed this up in discussions with several RTDs and held discussions with the Department of Health (O/2-8), and it was decided to adopt Prof. Cash's suggestion. Leeds and Liverpool RTCs were to use the second generation Ortho kit, while Newcastle and Glasgow would test the second generation Abbott kit (Newcastle indeed was already doing so – see above - and its introduction into the trial served to defuse some of the controversy). Subsequently, at the request of the Procurement Directorate,

UBI were included in the extended trial, the tests being carried out at Sheffield and Bristol RTCs; unfortunately, UBI amended their cut-off value during the trial which affected the number of positives found.

94 The conducting of these expanded trials did not involve any further postponement of the date of introduction of screening. Indeed they meant that screening was introduced at an earlier date (around the beginning of June) at four further English RTCs (Leeds, Liverpool, Sheffield and Bristol – plus Newcastle) and at Glasgow. Routine screening of blood donations in the UK duly commenced on 1st September 1991.

95 Given the date at which the decision to proceed was taken, with which I have dealt above, and given the importance reasonably attached to adopting a common start-date for HCV screening, I am sure that a start-date could not reasonably have been set much (if at all) before 1st July 1991. There was a great deal of work for the RTCs to do before screening could have been effectively introduced. The further postponement to 1st September 1991 was the consequence of the decision to carry out a trial of the second generation assays. I am sure that that decision was reasonable, given the deficiencies of the first generation test and the absence of any independent evaluation of its successor. But I accept that it would have been possible to adhere to the earlier date, using the second generation test and collecting data from all RTCs until the second generation tests had been fully evaluated. With hindsight, I think that it would have been better if we had done so. However, it would only have meant that tests would have been introduced two months earlier, and in five English centres that occurred in any event.

Discussion

96 The timing of the introduction of screening was controversial at the time. Towards the end of August 1991, Reviews in Medical Virology published a debate on the issue (Brown, J.L., Thomas, H.C. and Barbara, J.A.J., 1991 - A/114-118) .

- Dr. Brown and Prof. Thomas argued that the NBTS should have begun screening for hepatitis C when an antibody assay first became available. [They estimated that in the UK the incidence of anti-c100 in blood donors was 0.55% (Garson, et al., 1990, Ref. 52), although it was higher in other studies (Esteban et al., 1990, Ref. 44; Kuhnl et al., 1989, Ref. 76; van der Poel et al., 1990, Ref. 110; Sirchia et al., 1989, Ref. 98; Stevens et al.,

1990, Ref. 101). They assumed that there would be an incidence of 0.5-1.0% in the UK leading to a loss of 12,500- 25,000 blood donations each year. They concluded that between 2,500 and 5,000 cases of post-transfusion hepatitis could have been prevented with the sequelae of chronic liver disease in 1,250-2,500 and cirrhosis in 250-500 transfused patients. (This last figure is however very questionable, since in the nature of things, blood transfusions are generally given to patients who are already ill: 50% of patients who receive a transfusion die of their primary condition within one year).

- Dr. Barbara responded that, whilst chronic liver disease had been associated with blood transfusion in Japan (Kiyosawa et al., 1982, Ref. 71) there was striking contrast in the report by Wood et al., (1989) (Ref. 121) of transfused patients in the UK when no such correlation could be found. He pointed out that the use of the first generation assay, without initially the availability of supplementary tests, was not appropriate for screening blood donations in a country with low rates of post-transfusion hepatitis and little association with chronic liver disease. Also, the anti-c100 had a low predictive value, the response had a low titre, it disappeared in a significant number of patients and there was a long delay before seroconversion.

- Support for action taken by the transfusion services was expressed by Fagan (1991) (Ref. 46) who wrote:

> *"The reluctance to begin widespread testing of blood donors in the United Kingdom before the introduction of the second generation tests seems justified in view of the poor correlation between C100-3 antibody positivity based on first generation tests and results using second generation tests and the polymerase chain reaction".*

97 Bove (1990) (Ref. 14) has pointed out that whilst the major consideration for the introduction of an additional test has to be whether it is in the interests of the patient, pressures often arise to introduce the test before adequate data is available. There are many parties who demand immediate action, eg. researchers, physicians, kit manufacturers and the press. A reliable assessment of the reliability, sensitivity, and specificity of the test is essential before a new test becomes routine. Without this the patient is not best served and donors may be compromised if it is not possible to advise them concerning their future

health and there may be a significant loss of donors. Bove cites the introduction of surrogate testing for NANBH as an example. He comments that the experimental work which led to the introduction of these tests was performed during the 1970s but it was a decade later when testing began. During this period there had been many changes in transfusion practice and it was doubtful whether surrogate testing had significantly improved transfusion safety.

98 In my view the decision to introduce hepatitis C screening on 1st September 1991 was taken on the basis of careful and thorough advice from a highly qualified Committee, who acted at all times in accordance with the development of the scientific evidence. I do not believe that any patient who prior to that date received blood or blood products derived from an unscreened donation was receiving a product which was less safe than he/she was entitled to expect. The cumbersome and lack of centralised management structure of the NBTS undoubtedly caused difficulties but it is unlikely that such difficulties were responsible for the implementation taking any longer than it otherwise would given the basic advice being received.

99 I am of course aware that screening was introduced earlier in the United States and in most European countries, though the dates vary and some were only marginally, if at all, earlier than the UK. A table showing dates of introduction, so far as I am aware of them, is at Appendix I. But the fact that some countries acted earlier than the UK does not mean that the UK should have acted as soon as they, for reasons stated earlier in this statement. Both as regards collection arrangements and as regards the characteristics of the donor populations different countries differ widely.

100 I should also like to say that at all times during this difficult period I received solid support from the majority of RTDs and Prof. Cash on behalf of SNBTS. Whilst we were criticised for the delay in introducing HCV antibody screening of blood donations by some clinical colleagues, we received support from others.

101 I believe that the facts stated in this witness statement are true.

Signed: .....

Dated: .....