SNBTS DOCUMENT REQUEST No:

2010/00023

Witness Statement

Dr Brian McClelland

Surrogate testing of blood donors with the aim of reducing the incidence of non-A non-B hepatitis (NANBH) in patients receiving blood transfusions

A 1 Opinions of the importance of Non A Non B post transfusion hepatitis in the UK 1980-1989

1.1 Before considering the matters specified in the Schedule, I think it may be useful to the Inquiry to provide a personal view on the apparent persistence of the belief, over the years 1980 to 1989 that NANB post transfusion hepatitis (NANB PTH) was not an important problem in the UK. One of the themes underlying this history is the view that was taken of non-A non-B hepatitis in the UK from around 1980 to the discovery of hepatitis C in 1989. Many of the decisions taken, or not taken, can only be understood in the context of a widely held view, that despite an increasing body of evidence to the contrary, this condition was rarely transmitted by blood, and was usually not particularly serious. I have tried to assemble some evidence that illustrates how this view may have originated.

PTH in recipients of blood components in the UK

1.2 Medical Research Council Blood Transfusion Research Committee 1974. In 1974 the report was published of a study, carried out for the UK Medical Research Council (MRC), of hepatitis in recipients of blood components. (10125.tif) This study is described in some detail, since it is one of only four substantial prospective studies of PTH in the UK

From mid 1969 to the end of December 1971, patients at the Central Middlesex Hospital were invited to participate and to give a pre-transfusion blood sample for ALT and viral studies. The protocol required that patients who had been transfused be seen for clinical assessment and to provide a blood sample at intervals of 2 weeks after the transfusion. Patients attending outpatient clinics were used as non-transfused controls. Of the 2184 patients who were transfused during the study period, follow up was completed on 768 who received an average of 3.7 units of blood per

patient. Routine testing of donor blood for hepatitis B only began during the last 5 months of the study period.

1.3 Raised ALT values were found after transfusion in 158 patients. Six of these patients underwent liver biopsy. None showed histological features typical of acute viral hepatitis. The authors stated "These (158) patients were investigated for conditions other than viral hepatitis, (e.g. drug-induced liver injury). It was arbitrarily decided that where such other potential causes existed, the patient would not be regarded as suffering from viral hepatitis. On this basis, eight patients (1%) were judged to have had post transfusion hepatitis. Sustained elevation of ALT without other clinical features of hepatitis was present in 35 patients"

1.4 The authors concluded that "The overall incidence of icteric and anicteric hepatitis in the present survey (1%) is low compared with the incidence found in prospective studies in Japan (65%) ...USA (18%) ... and Germany (14%)" However, if PTH had been defined to include all the patients with persistently elevated ALT the PTH rate would have been 35/768 or 4.5%. If PTH had been defined to include patients with *any* elevation of ALT following transfusion, 158 of the 768 patients (21%) would have been defined as having PTH.

1.5 Although this study preceded the description of NANB hepatitis, it was later cited as making it unnecessary to conduct a further prospective controlled investigation of the impact of surrogate testing for NANBH.

1.6 Collins et al 1983.(10143.tif) In 1983, a UK study of 248 transfused cardiac surgery patients reported that 38 of the 248 patients (15.3%) had some elevation of ALT during the 5-30 days following the operation. The increase in transaminase levels was unexplained and reached over 100 IU/ml in six patients, all of whom had normal liver function tests when retested at six months. One patient had evidence of chronic persistent hepatitis six months after surgery and transfusion . The authors stated "We conclude that non-A non-B hepatitis after blood transfusion from a largely British blood donor group probably leads to clinically significant chronic liver disease very rarely indeed".

1.7 Vandervelde and Mortimer 1986. (1078.tif) At the meeting of the (BTS) Directors working party on transfusion associated hepatitis on 24 11 1986, a report was presented by two workers from the Public Health Laboratory Service on an epidemiological study of non A non B hepatitis in the UK. This extract gives a rather vivid view of the confusion surrounding NANB hepatitis and its relationship to blood, as late as the end of 1986.

1.8 "..It is still unclear how the putative agent(s) of sporadic NANB in England could be transmitted. One possibility is that it is a venereal infection...Another possibility is that sporadic NANB includes an agent such as described by Khuroo (1980) in Kashmir as a water borne form of hepatitis...Apart from seven patients who had received treatment with factor VIII preparations (cf Craske et al 1978) a history of parenteral exposure was uncommon. Only two had had blood transfusions and less than 10% gave a history of drug abuse. This contrasts with American experience, for instance the study in Los Angeles by Dienstag et al (1977) in which 11 out of 40 cases of NANB hepatitis had a history of parenteral exposure through transfusion or self injection, and several reports that most post transfusion hepatitis is not due to HBV but to NANB"

1.9 Contreras et al 1991 (10131.tif) A prospective study was carried out by the North London blood transfusion service, enrolling patients over the period July 1986 to July 1989. The authors noted that "London has the highest incidence of infectious markers in the donor population in the UK: the results of this study would therefore represent the worst case". The report covers 387 surgical patients who received 1176 blood components from a mean of 3 donors (range 1-10). Regular blood samples were obtained from the blood recipients over a period of 6 months with a final sample at 12 months. Three patients had increased alanine aminotransaminase levels "consistent with post transfusion NANBH". One patient had clear evidence of transmission of hepatitis C. One of the 8 blood donations received by this patient was also hepatitis C positive. The ALT level in this donation was normal but anti HBc was present. The report presents no data on routine surrogate tests on the donations, but it would appear from the evidence presented that the single episode of hepatitis C transmission would not have been avoided as a result of ALT screening, but would have been avoided by screening for anti HBc. In respect of hepatitis C screening, the authors stated that "The marginal benefit - the prevention of hepatitis C in 0.26% of recipients - must be balanced against the number of false positive donations which

would be lost to issue and the cost of confirmatory testing, counselling for repeatedly reactive donors and recruitment of replacement donors"

1.10 An abstract that I submitted for the 18th Congress of the International Society of Blood Transfusion in 1984 (SNB.008.6696) indicates that I was also of the view that "Clinically apparent NANB post-transfusion Hepatitis was also a small problem", that the importance of elevated liver enzymes as an indicator of NANBPTH was uncertain and that for the recipient of blood or single-donor components the benefits of improved donor testing were not quantifiable. Unfortunately I have not retained either notes or slides of the actual presentation.

1.11 In summary, the authors of clinical studies mentioned above seem generally to have considered that the 0.4% to 1.0% incidence of post transfusion hepatitis that they reported in the UK was very low in comparison to rates reported from other countries. It is also likely that because there are many causes of elevated liver enzymes (ALT), some cases that were in fact due to infectious hepatitis could be explained by evidence of another cause such as alcohol intake. The PHLS study illustrates how, at least in some circles, there was a view that NANB hepatitis was rarely transmitted by the parenteral route.

A 2 Surrogate testing as a means of reducing the risk transfusion transmitted hepatitis

2.1 Much of the early information comes from the United States, where as early as the 1940s it was recognised that patients often developed jaundice after blood transfusion. Jaundice, due to excessive levels of the pigment bilirubin in the body, is a manifestation of liver disease. A subset of liver disease, hepatitis, is inflammation of the liver. It may occur with or without jaundice.

2.2 Understanding of hepatitis grew as better tests were developed for clinical diagnosis of hepatitis. In 1955, tests were introduced that detected raised levels of enzymes in the blood that are released from liver cells. There are many causes of increased levels of liver enzymes in the blood; they include damage to liver cells caused by e.g. alcohol, drugs, including some anaesthetics and antibiotics, an association with obesity, or as a result of infection.

2.3 A commonly used liver function test is based on measurement of the concentration of the enzyme alanine aminotransferase (ALT) which is present in normal liver cells and is released when liver cells are damaged. It is important to say that tests like ALT were developed to help diagnosis of patients. They were not developed for screening populations of healthy individuals.

2.4 Tests of this type showed that some patients who were not evidently jaundiced had constantly or intermittently elevated levels of ALT in their blood, indicating the presence of some form of continuing damage to the liver cells. It became evident that following transfusion, some patients, although they did not have jaundice, did have transient or persisting elevations of ALT.

2.5 The term surrogate ('elect as a substitute') has come to be used in the context of NANB PTH to denote a test that may be applied to blood donors or donations and that detects a property that indicates the presence of some form of transmissible hepatitis, presumed to be due to the transfer of an infectious agent.

2.6 In the United States the Transfusion Transmitted Viruses (TTV) study was started in 1974 and collected samples from transfused patients and from blood donors up to 1979. An interim report in 1978 (10141.tif) indicated that transfusion hepatitis (diagnosed by the presence of elevated ALT levels) occurred in 12.6% of transfused patients and 2.6% of control non-transfused hospital patients. Of the patients who received only volunteer donor blood 7.5% developed PTH, whereas 43% of those who received only paid donor blood developed PTH.

2.7 Analysis of information about the donors' blood revealed that the risk of PTH in the recipient was associated with the level of ALT in the donated blood. Where the donor ALT was normal the attack infection rate for PTH was 3.4%. Where the ALT level in the blood was elevated the infection rate was 42.3%. In April 1981 10149.tif confirmed and extended these findings and led the authors to conclude "...that ALT testing is a potentially useful method of screening donors to reduce incidence of non A non B hepatitis... the observations in this report suggest that about 40% of the cases of non A non B post transfusion hepatitis in this study could have been prevented by discarding units with an ALT level in the upper 3% of the distribution..."

2.8 The use of a test for antibody to the hepatitis B virus core antigen (anti HBc) also emerged as an alternative or complementary approach to surrogate testing. In 1984, the TTV study group reported that the presence of anti HBc in donor blood was also associated with a rate of non-A non-B hepatitis in the recipients. 10150.tif In a parallel study published in 1986, (10144.tif) reported that "....of 193 recipients of blood positive for antibody to the hepatitis B core antigen (anti HBc), 23 (11.9%) developed NANB PTH compared with 12 (4.2%) of 288 recipients of only anti HBc negative blood". Both these studies concluded that an elevated ALT value and the presence of anti HBc acted independently on the attack rate for PTH.

2.9 The observed association between an antibody to the hepatitis B virus in donor blood and the transmission of NANBH has not been explained although it has been suggested that individuals who have anti HBc may be more likely to have exposed themselves to a variety of blood borne infections, and are therefore more likely to be infected.

2.10 As late as 1986, Dienstag and Alter described the important limitations of both ALT and anti HBc as surrogate tests (LIT.001.1675). "Both these indirect assays have the disadvantage of relatively low sensitivity and specificity (both in the region of 60%) and a very low positive predictive value (12% in the NIH study). If adopted, the anti HBc test will result in the initial loss of 4 to 8% of the donor population and the sustained loss of probably 2 to 4 %. Cost and time are both detrimental elements to the adoption of either or both of these non-specific assays". However, these authors went on to state that " despite these negative features, the accumulating data ....has served as compelling evidence for the need to rely on indirect assays as an interim measure until such time as specific NANB assays are developed".

2.11 Low test specificity, referred to in para 2.10, has serious consequences when a test is used to screen a member of a healthy population. A substantial proportion of the individuals who test "positive" and who therefore will be rejected as donors because of the risk of transmitting NANBPTH, will not in fact have NANBPTH nor will their blood contain the relevant infectious agent. Nevertheless, such individuals have to be informed that their donations can no longer be accepted and the risk that their blood could transmit hepatitis must be part of the explanation. This can have the effect of converting a person who correctly considers themselves into be in

good health into one who has been given information that indicates that they may be afflicted with a serious infection. This problem can only be avoided if there is some form of additional test (often termed a confirmatory test) that can reliably demonstrate the presence or absence of infection.

B Against this background, I will address the questions in the schedule

1 The consideration given by the SNBTS in the 1980s to whether or not surrogate testing of blood donors for non-A non-B hepatitis (NANBH) should be introduced.

1.1 I first became interested in this topic soon after I joined the SNBTS in 1979. On February 14 1980, the UK Medical Research Council (MRC) convened a meeting of a working party on post transfusion hepatitis, a subgroup of the MRC blood transfusion research committee. (1044.tif) Dr John Cash asked me to attend. One of the agenda items was non-A non-B hepatitis. There were reports of cases of NANB hepatitis in patients treated with both blood and with factor VIII concentrate. During this discussion I proposed the idea of a prospective study to determine the rate of NANB hepatitis in blood recipients and the relationship of infection in recipients to putative markers of infection in the donor's blood (1044.tif). For the second meeting of the MRC working party on June 25 1981 I put forward a draft protocol for a prospective study of surrogate testing for NANBH (1047.tif) which drew on the protocol for the US Transfusion Transmitted Viruses study (10142.tif). The need for such a study was challenged by Professor Arie Zuckerman, on the grounds that it would merely be repeating a completed study that had been funded by the MRC and published in 1974 (1045.tif). He suggested that retained samples from the patients who had participated in the earlier study would be available and could be used in studies of markers of infectivity. It later emerged that these samples had been mislaid or destroyed (1058.tif 1059.tif).

1.2 The MRC working party on post transfusion hepatitis had no further meetings and was disbanded in 1982. I do not know why this happened. Because post transfusion hepatitis was seen to be an important topic, Dr William Wagstaff, then regional transfusion director in Sheffield, called together a group, chaired by Dr Harold Gunson, to continue work on hepatitis (1051.tif). This was called the regional directors' working party on transfusion associated hepatitis (I have abbreviated this to WP TAH). It first met on September 27 1982 The working party set its own terms of reference as

> "...to promote the investigations of the epidemiology of transfusion-associated hepatitis, to promote research into the methods of prevention, and to make recommendations to the directors of the UK transfusion services regarding procedures and screening tests necessary for its prevention." (1053.tif).

I again agreed to provide an outline study protocol for the next meeting for (a) determining the incidence of recipients with "transaminitis" (elevation of liver enzyme levels in the blood) so that a library of putative non-A non-B recipients' samples could be collected (b) determining the incidence of PTH in recipients of blood positive for existing putative markers for non-A non-B hepatitis.

1.3 The WP TAH met again on January 18, 1983. (10111.tif 10112.tif). I presented a study protocol (1060.tif) and the members agreed to send comments to me. The comments received were favourable (1061.tif 1062.tif 1063.tif).

1.4 By the time of the third meeting of the WP TAH on April 20, 1983, Dr Gunson had been informed by the MRC that the samples from its 1974 post transfusion hepatitis study were no longer available (1058.tif 1059.tif) The protocol for the proposed prospective study on post transfusion hepatitis was discussed. Dr John Barbara, microbiologist in the North London NBTS centre, undertook to prepare a joint proposal that would include the North London RTC where the incidence of PTH was expected to be higher than in Edinburgh. It was minuted that this might then be submitted to the MRC on behalf of the working party (1066.tif).

1.5 Despite searching for any documentation, I have no recollection of the subsequent fate of this study proposal and it was the Inquiry's Preliminary Report that drew my attention to a statement made by Dr Harold Gunson referred to in the Judgement in A and Others *vs.* the National Blood Transfusion Authority, that he had submitted the proposal and that it had been turned down. At the time of writing this, I am awaiting information from Dr John Barbara who, although retired, may be able to shed some light on the fate of the proposal.

1.6 I have thought about why a prospective study was not pursued at this time. I do recall being surprised and dismayed by the notable lack of enthusiasm to commit any resources to

undertaking what I believed was a necessary study to try and determine if surrogate testing had any value in reducing NANB post transfusion hepatitis. However, I believe the main reason that the SNBTS lost sight of NANB PTH for a period is that by early 1983 concern about AIDS was increasing, I know that I became increasingly preoccupied with the actions that the BTS should be taking to protect patients against any possible risk of being infected by locally collected blood donations. During May 1983, SEBTS prepared the first donor information leaflet on AIDS and initiated discussions with the Scottish Homosexual rights group on how best this could be distributed. More detail of the response to AIDS over this period is to be provided in a separate witness statement requested by the Inquiry,

1.7 Looking back, I think it is the case that the work related to AIDS, firstly developing donor information and selection procedures and later evaluating and introducing the test for HIV antibody, distracted the attention of both the SNBTS and the National Blood Transfusion Service from non-A non-B hepatitis for about 3 years. The WP TAH did not meet after September 1983 until it was reconvened on November 24, 1986.

1.8 I missed the first part of this meeting due to travel delays. I have my own contemporaneous notes of the second part of this meeting (1079.tif) but have been unable to locate the minutes. A working paper had been prepared for the meeting by Dr Gunson (10116.tif) and is informative. I have reproduced below part of the text that details the matters that Dr Gunson proposed for consideration at the meeting, following his review of the literature from the USA and the UK.

Extracted from paper 10116

MATTERS FOR CONSIDERATION

1. Incidence of Transfusion Associated NANB Hepatitis in the U.K.

The best estimate of incidence from published data is 3%. If one assumes that the 2.3 million donations in the U.K. are transfused to 750,000 recipients annually, (possibly a more accurate assessment should and could be made), then one would expect 22,500 icteric or anicteric cases of NANB hepatitis each year. If the morbidity pattern of the disease is similar to that in the U.S.A. then one might expect half of these patients to have chronic ALT elevation and 10%, i.e. 2250, to develop cirhosis.

2. Projected value of ALT and anti-HBc screening in prevention of transfusion associated NANB Hepatitis

If 30-40% of NANB hepatitis could be prevented by the use of the above tests, then the reduction in the number of cases would be 6750-900 per year and by extrapolations; 675-900 cases of cirhosis.

Some qualifications should be made to (1) and (2) above.

(a) The course of the chronic disease in NANB hepatitis is mild and, therefore, many cases probably remain undiagnosed even when cirrhotic changes occur. This, I feel certain is why we have not been aware of what appear to be quite serious statistics. Of course, one must also bear in mind that approximately 50% of patients die of their primary disease within one year of transfusion, and this presumably applies in the U.S.A.

(b) The incidence of NANB hepatitis has been determined in the U.S.A. often with multiply transfused patients and in the TTV there was clearly dose relationship. Even in the two U.K. studies the patients in the second one (6) received an average of 6.28 units each.

(c) The data from the U.S.A. is from transfusions administered in the 1970's and early 1980's and even the more recent studies in the U.K. were undertaken before attempts to encourage self-selection of donors.

(d) One must question, therefore, whether the incidence of transfusion associated NANB hepatitis is as high now as the estimates suggest.

3. Effect of ALT and Anti-HBc Screening on Blood Collection

From the evidence available in the U.K. one might expect that ALT screening will cause the loss of 0.7-0.9% of donations and anti-HBc in the order of 1%.

Presumably there will be some overlap in the ALT and anti-HBc results but one might expect a loss of donations of approximately 1.5-1.75%.

Note: There is a typing error in para 2 line 2 of the extract above. The figures should read "6750 – 9000"

Despite the estimate that a substantial reduction in NANB PTH could result from the introduction of surrogate testing, the Committee did not proceed to recommend that it be

introduced. Instead, a multi centre study of surrogate markers in blood donors was proposed. This is described further in the response to question 3.

2 The research undertaken by the SNBTS in the 1980s into surrogate testing for NANBH.

2.1 During the 1980s two groups within SNBTS attempted to identify factors ("markers") in the blood that could be used to detect blood likely to cause NANBH. Some of this work is detailed in (10148.tif) and in (10151.tif)

2.2 In the West of Scotland SNBTS centre, epidemiological research on hepatitis B in blood donors had led to the observation of elevated levels of liver enzymes in some donors, suggestive of non A non B hepatitis. (See also my witness statement on "unsuitable donors" submitted to the Penrose Inquiry on October 22nd 2010). Dr Brian Dow in SNBTS West of Scotland was awarded a small research grant from the Scottish Hospitals Endowment Research Trust through the SHHD Chief Scientist Office and received his PhD for a thesis entitled "Non A non B hepatitis in the West of Scotland" (1985). In the summary of his thesis, Dr Dow states that "Transfusion associated non A non B hepatitis is a very rare occurrence with an average of only 3 reported cases annually. ...A study of haemophiliacs and renal unit patients has shown that there are occasional episodes of hepatitis (usually mild) in such patients. Some of these episodes in renal patients have been shown to be caused by cytomegalovirus (CMV) rather than NANB"

2.3 In SNBTS South East Scotland, Dr Robert Hopkins obtained funding from Wellcome Diagnostics for a PhD project (student Ms Sonya Field) whose PhD was awarded for a thesis entitled "Investigation of a serological marker detected in blood from a donor twice implicated in the transfusion of non A non B hepatitis" (1984). This work did not result in the development of a practicable test.

2.4 Research groups in other countries pursued the same goal and it has been estimated that 30 or 40 candidate tests systems were reported (10147.tif). None of these efforts were successful. In 1989 the discovery of the causative virus was reported and designated as the hepatitis C virus. At the same time, a test for antibody for the virus was described. Over the following months it became increasingly clear that this was a major breakthrough in the understanding and the prevention of a large proportion of what had till then been termed non-A non-B hepatitis.

3 Why the multi-centre study into surrogate testing for NANBH (conducted at Edgware, Manchester and Bristol) did not include a Scottish blood transfusion centre

3.1 The outcome of the November 1986 meeting of the WP TAH was to initiate proposals for a multi centre study that was essentially an expansion of that carried out by Gillon and colleagues during 1986 (1081.tif) and published in 1988 (10117.tif). The aim was to investigate the levels of surrogate markers, both ALT and anti hepatitis B core antibody (anti HBc) in large numbers of donors in several regions of the country. The proposed study was not intended to examine any samples from recipients of transfusion.

3.2 This study could never have provided any information about (a) the incidence, in blood recipients, of post transfusion disturbance of liver enzymes that might indicate hepatitis (b) the relationship of the presence or absence of a surrogate marker in a donor's blood to the risk of developing evidence of hepatitis after transfusion or (c) the possible safety benefits of introducing surrogate testing. A protocol for the study believed to be the final version and believed to be dated 1 May 1987 is attached (10118.tif) as is the final published report (10119.tif).

3.3 I cannot now be certain why there was no SNBTS participation in the multi centre study, but I am sure that several factors contributed.

3.3.1 Although I was a party to the development of the protocol, my own view was that the proposed multi centre study was unlikely to add much to the knowledge already available from the UK including the findings of a 1982 study from North London (10108.tif), Dr Brian Dow's

PhD Thesis (1985) and Dr Gillon's 1986 study (1081.tif). The letter that I drafted and that was published by the Lancet in 1987 (10128.tif) made the point that the time for further studies on the epidemiology of post transfusion non a non B hepatitis had passed.

3.3.2 It is evident that internal briefing in the SHHD expressed the view that non-A non-B hepatitis was a rare and relatively unimportant complication of transfusion (1090.tif).

3.3.3. It is also clear from internal SHHD correspondence during 1986 and 1987 that there was a distinct lack of enthusiasm among the senior medical personnel and also in the Chief Scientist Office (CSO) to grant funds (estimated as either £20,000 or £30,000) for a Scottish arm of the study. One memo describes the proposed work as "research of no great significance or scientific interest because the prospect of research would serve to counter pressure for example from haemophiliacs and haemophilia directors ...." (1092.tif).

3.3.4 Although I have not seen the relevant documents, it appears that an application to fund a Scottish arm of the multi centre study was finally submitted to Chief Scientist Office (CSO) of SHHD around August 1987. This was evidently rejected and the CSO was asked, on 1 October 1987, "...to ensure that the Minutes will confirm that the reason for rejection is not that research is superfluous (10145.tif).

4 Why it took until October 1988 before the multi-centre study into surrogate testing for NANBH commenced

4.1 I have already referred to the early proposals for prospective evaluations of the effectiveness of surrogate testing. Although the findings of the USA Transfusion Transmitted Viruses (TTV) Study emerged in 1978, the utility of surrogate testing remained highly controversial in the UK and the USA and was still untested in any scientifically rigorous study at the time the subject was considered by the FDA in 1983 (10147.tif). In January 1986 the American Association of Blood Banks considered recommendations for some form of surrogate testing to reduce non-A non-B hepatitis, and in February 1986 the FDA Blood Products Advisory Committee recommended, but did not require, that ALT and core testing be done routinely. In the UK, the WP TAH that had

been set up to advise the transfusion services on transfusion associated hepatitis had been in abeyance from 1983 to November 1986, probably because of the priority given to AIDS. The proposal for the multi centre study emerged at the very end of 1986, and was not finalised until around May 1987. Funding had to be obtained from the DHSS and I assume that this contributed a further element of delay. I have no knowledge of other factors that may have contributed to the October 1988 starting date

5 When the SNBTS sought funding from SHHD to introduce surrogate testing, including when it was proposed to introduce such testing

5.1 In response to the Question posed by the Penrose Inquiry earlier this year, SNBTS has submitted an account of documentation that indicates "the extent to which financial factors were taken into account in the consideration, between 1985 and 1991 of whether to introduce surrogate testing for NANB hepatitis in relation to the donation of blood in Scotland"
My understanding is that SNBTS submitted bids for funding for surrogate testing over the period 1982 to 1988 in the following documents:

Feb 1982	'SNBTS Forecast Development Estimates 1984-86' National Medical Director's paper to the CSA BTS Sub-committee
May 1986	SNBTS Public Expenditure Survey (1986)
May 1987	SNBTS Public Expenditure Survey (1987)
June 1988	SNBTS Public Expenditure Survey (1988)

5.2 I think that the first year in which it was considered that surrogate testing should commence was 1986, but I am not certain of this.

6 Why the SNBTS first sought funding from the SHHD, in 1986, for the introduction of surrogate testing in 1987 (PES 1986 (SNB.011.2637)).

6.1 By 1986 the American blood collection organisations had returned to the questions raised by the TTV study, and was moving towards the introduction of surrogate testing. I am sure that this was a factor in re activating interest in the topic in the UK. Dr John Cash corresponded with the

American Red Cross during 1986 and received detailed information from Dr James Aubuchon about their rationale for commencing testing. There was still a belief in the UK that NANB PTH was a less important problem than in the United States, and many of the more influential professionals in the UKBTS were opposed to the introduction of surrogate tests. I imagine that such opinions would have influenced professional officers in the SHHD.

7 Why the Directors of the SNBTS agreed at their meeting on 3 March 1987 that surrogate testing of blood donors for NANBH should be introduced, with implementation from 1 April 1988 (SGH.001.6653).

7.1 In 1987, I drafted a letter to the Lancet drawing attention to the potential liability and cost benefit issues related to surrogate testing (10128.tif). I think that it contributed to the SNBTS Directors' taking the view that the time had come to start surrogate testing, and all agreed to add their signatures to it. We were undoubtedly concerned that despite the persisting uncertainties about the real safety gains that might be achieved, failure to introduce testing could constitute a failure to protect patients from some degree of avoidable risk.

8 The steps taken by the SNBTS, and when, to prepare for the introduction of surrogate testing, including the evaluation of any surrogate tests and the preparation of guidance on testing and counselling donors.

8.1 Evaluation of surrogate testing for NANBH by the SNBTS included studies on the clinical features associated with elevated ALT levels and anti HBc in blood donors, the extent to which ALT levels fluctuate when donors are tested during the course of several donor attendances over a period of time, the age and sex distribution of ALT levels in the donor population and evaluations of a system designed for testing large numbers of samples. These studies are described below.

8.1 Clinical features associated with elevated ALT levels and positive Hepatitis B core antibody in Scottish Blood donors.

A study was published by Dr Jack Gillon and colleagues in 1988 (10117.tif) in which 1742 donors were tested for ALT levels and anti HBc, and a further 344 for antiHBc only. An ALT level greater

than 45 iu/l was found in 42 (2.4%) of the donors. Of these, 33 were 10-15% above ideal body weight and 11 admitted an alcohol intake above 40g per day. In 82% of donors with ALT levels above 45 iu/l a "non viral" explanation could be identified (excessive alcohol intake or obesity). Anti HBc was detected in 2.0% of donors and there was no overlap between those with anti HBc and those with ALT above 45 iu/l. Using both the screening tests would exclude 4.4% of donations. The authors concluded that the findings did not justify initiating surrogate testing until a prospective controlled trial had been done.

8.2 The extent to which ALT levels fluctuate when donors are tested during the course of several donor attendances

Dr Susan Lumley studied a group of donors who were donating plasma regularly by plasmapheresis (10103.tif). She found that the donors' ALT levels fluctuated from one attendance to the next, such that if ALT screening was used, a donor could be rejected at one attendance, but accepted at a subsequent attendance.

8.3 Evaluations of a system designed for testing large numbers of samples. Laboratory testing of ALT levels and the establishment of reference ranges for the Scottish Blood donor population. Age and sex distribution of ALT levels in the donor population

An evaluation of a commercial analyser (Eppendorf EPOS) was conducted by the SNBTS West of Scotland and reported in 1987 (10120.tif). Samples from 5000 donors of both sexes and ranging in age from 18 to 65 years were tested. The system was evaluated for reproducibility, and the range of values obtained was analysed to demonstrate the effect of various threshold levels. Because ALT level is a continuous variable, the definition of a positive result must be based on a judgement – essentially arbitrary - as to how an individual's test result relates to the results from the representative population. For any practical large scale application such as blood donor screening, a threshold value must be set, above which a sample is considered to be "positive". The West of Scotland study showed that if the threshold level was, for example, set as the population mean plus 2.25 standard deviations (SD) giving an ALT value of 55, then about 2.3% of donations would be considered "positive" and would require to be discarded.

The West of Scotland study mentioned above also analysed the effect of age and gender on ALT levels, providing data that indicated that the threshold ALT levels may well require to be adjusted to be age group specific for males and for females.

In 1988, the SNBTS undertook a multi centre evaluation of the Eppendorf EPOS system for ALT determination (10123.tif) and concluded that results were consistent between the centres. Taking a threshold value of the population mean plus 2.0 SD would lead to about 5% of donors being excluded, whereas a slightly higher threshold of mean plus 2.5 SD would exclude about 1.5% of donors.

I have no recollection of being involved in or being aware of work on the preparation of guidance on testing and counselling donors. However I am sure that there was concern about how we would manage donors rejected on the basis of a surrogate test, since we suspected that in most cases the test would not indicate the presence of infective non-A non-B hepatitis.

9 Estimates made at the time of the likely cost of introducing surrogate testing in Scotland

9.1 I am not qualified to give an authoritative response to this point, as I was never involved in any aspect of costing the test programme or submitting estimates for funding. I can however suggest that providing a reliable cost estimate of a surrogate testing programme would have been a difficult exercise. While the costs of equipment, reagents and personnel would have been relatively straightforward to determine, the costs that could be created in the blood donor programme would have been more difficult to predict. In addition to the costs associated with obtaining perhaps 5% more donations to replace those discarded because of surrogate test results, there would have been the costs of care and management of a large number of donors who would find themselves deemed unacceptable to donate.

10 Why surrogate testing of blood donors for NANBH was not introduced in Scotland

I think there are many connected reasons. I will attempt to summarise them as follows:
10.1 There was a persisting belief among most SNBTS (and NBTS) transfusion professionals that NANB hepatitis was a much less common consequence of transfusion than it appeared to be in the USA, and that it was generally not a particularly serious condition. I have dealt with this more fully above.

10.2 Medical advisers in the SHHD appeared to have shared this view.

10.3 This belief undoubtedly prevented serious consideration being given to undertaking a robust prospective clinical assessment of the effects of surrogate testing at a time when it should in my opinion have been undertaken.

10.4 SNBTS and NBTS medical professionals were unconvinced that surrogate testing would offer material safety gains and were concerned that it would lead to the loss of donors and donations and difficult problems in the subsequent care and management of donors rejected on the basis of a surrogate test result.

10.5 Requests to the SHHD for funding to undertake surrogate testing were repeatedly turned down by the SHHD.

10.6 The 1988 multi centre study of surrogate markers in blood donors was in my opinion essentially an irrelevance, yet it appears to have distracted a great deal of effort that could have been better directed to a dispassionate re evaluation of information that was already available and that strongly challenged the belief that non-A non-B hepatitis was a non serious condition that was rarely transmitted by transfusion.

10.7 Perhaps most importantly, SNBTS was not supported by SHHD in its expressed desire to adopt what Justice Krever would go on to describe as the "precautionary principle" by introducing surrogate testing for non A non B hepatitis.

11 If surrogate testing for NANBH had been introduced in Scotland, the extent to which the incidence of post-transfusion NANBH/hepatitis C is likely to have been reduced.

11.1 A number of studies provide some suggestions as the possible impact that surrogate testing might have made to the risk of transmission of hepatitis by transfusion. This is dealt with first for recipients of blood components and second for recipients of coagulation factors

Patients transfused with blood components

11.2 Blajchmann and colleagues in Canada had commenced a randomised controlled clinical trial of surrogate testing at a time when there was still doubt about when an effective hepatitis C test would become available (10136.tif). Patients who were likely to need a transfusion and who gave their consent to be enrolled in the trial were randomly allocated to one of two groups: patients in Group A (the control group) received transfusion according to the then standard Canadian Practice, that is, no surrogate test for NANBH risk was performed on the blood to be transfused. Patients in Group B (the "intervention" group) received blood that had been tested and shown not to be positive in surrogate tests for NANBH (elevated ALT level and/or the presence of hepatitis B core antibody). The patients were assessed for clinical and laboratory evidence of hepatitis at intervals for a period of six months after transfusion.

11.3 When hepatitis C tests became available, the stored donor and patient samples were tested for hepatitis C antibody. There was a 40% lower incidence of post transfusion hepatitis in the patients who received blood that had been screened for surrogate markers. Most of the effect of NANB surrogate testing was due to a reduction in hepatitis C.

11.4 However it must be pointed out that the authors suggest a need for caution in estimating retrospectively the possible benefits from surrogate testing in an earlier period. They state, with reference to published studies on archived blood samples:

> "The drop in the HCV hepatitis rate from 31.3 per 100 to 12.6 per 100 between 1984-5 and 1988-90 appears to have been associated with improved methods for the screening of donors, since the drop occurred *without* NANB surrogate markers. In the USA, a similar

drop occurred over the same period in association with the introduction of NANB surrogate marker testing."

11.5 During the first 6 months of donor screening for hepatitis C antibody in Scotland, 181,000 donors were tested and 0.088% were confirmed to have hepatitis C antibody. Among the hepatitis C positive donors, 59% had ALT levels above the upper limit of normal. Although this study did not determine ALT levels in donors who were hepatitis C negative, the findings suggest that the use of ALT screening would have allowed the detection of a substantial proportion of HCV positive units

Patients treated with plasma derived coagulation factor products

11.6 It is generally accepted that surrogate testing would have offered little or more likely no safety benefit to patients treated with these products. This is a consequence of the large number of donations included in each manufacturing batch of product and the introduction of heat treatment. (See SNBTS Document "Events concerning the safety of blood and blood products..." Section 5.4, page 35)

12 If surrogate testing for NANBH had been introduced in Scotland, the percentage of donations that are likely to have been rejected and the extent to which, if at all, that is likely to have caused difficulties in maintaining a sufficient supply of blood for the NHS in Scotland

ALT testing

12.1 If the level of ALT that had been set as the threshold for a "positive" result was the population mean plus 2.5 SD (about 45 iu /l), the loss of donors would have been of the order of 2.5 %. If Anti HBc had been used in addition, losses would, according to Dr Gillon's study, have been about 4.5%.

12.2 It is worth noting that a German report (10138.tif) describes much higher ALT threshold levels of 134 iu/l for males and 89 iu/l for females. Using these higher threshold levels, only 0.25% of donors exceeded the threshold. Information is being sought about ALT thresholds in use for donor screening elsewhere in Germany

Statement of Truth

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

Signed.....

Dated.....15-02-2071