CAL13(110511)

Witness Statement in respect of viral inactivation in the period up to 1985

in response to request of

3rd November 2010.

Professor Christopher A Ludlam

Para 1 (Schedule031110).

This paragraph highlights endeavours at SNBTS during the 1970s to remove infectious viruses from clotting factor concentrates. Complementary and in parallel to this, the Edinburgh Haemophilia Centre was undertaking clinical studies to assess the ongoing hepatitis B virus infection rate in haemophiliacs, treated with SNBTS products, following the introduction of screening for hepatitis B virus in individual blood donations. This is described in Appendix 1 (Long term safety monitoring for transfusion transmitted infections).

Para 14 (Schedule031110)

Paragraphs 11.96 to 11.114 (Preliminary Report) These paragraphs set out some of the deliberations within SNBTS in relation to developing viral reduced clotting factor concentrates as well as some of the wider discussions and meetings. The minutes of the SHHD/Haemophilia/SNBTS meetings in 21st January 1983 and 22nd March 1983 ring true although I do not recall most of the details as set out in the records. I do remember the difficulty of being keen to support SNBTS endeavours by testing new concentrates in patients, whilst also being aware that commercial fractionators might have viral reduced products which could be of benefit to patients under my care. As I was not aware of any available commercial concentrate that was likely to have a good hepatitis safety record in 1983/4, I did not consider that I was denying my patients access to a virally safe product at that time by 'reserving' my patients for NHS factor VIII trials. My view was set out in a letter to UKHCDO on 10th April 1984 declining to test commercial 'hepatitis reduced concentrates' (para 7.58 and SNF.001.3211).

I remember the discussions nationally about trying to avoid using commercial 'virally reduced' concentrates on a 'named patient basis' and to use them in 'clinical trials' if possible under a 'clinical trial exemption' arrangements. This was set out by Professor Bloom in a letter to all haemophilia directors of 24th June 1983 as well as being stated at the Immuno meeting on 24th January 1983 (SGH.002.2175).

Para 11.96 reports a letter of 10th January 1983 from the PHLS to DHSS enclosing a 'letter' (authors name redacted) which it was proposed to submit to the Lancet. The text sets out data from a study in which liver function tests were monitored serially after patients were given an infusion of non-heat treated factor VIII concentrate. Non-A non-B hepatitis

developed in 9 or 10 individuals who had not previously received concentrate, in 3 or 4 who had previously received between 1 and 4 batches and in 0 of 7 who had previously received more than 4 batches. These data are almost identical to that which appeared in a paper in the BMJ in December 1983 by Fletcher, Trowell, Craske, Pavier and Rizza (1) and this is presumably the paper referred to in reference 1 of the 'letter'.

Para 23 (Schedule031110)

See Para 26 below

Para 26 (Schedule031110)

By way of a letter to me, Dr Cash on 13th June 1983 invites me to infuse 3 patients with heat treated factor VIII batch NY761 (SNB.001.5311). Infusions were given on 9th September, 5th October and 2nd November 1983. The patient also received an infusion of unheated SNBTS factor VIII (batch 727) on 7th December.

At the meeting on the Haemophilia Directors with SNBTS at SHHD on 14th November the Minutes record that I reported that there had been 'minor adverse reactions on each occasion' when the heated product was infused. This was how the Minute-taker recorded what he thought had been said and may not have accurately recorded what had actually been stated. I have no recollection of exactly what I said. I might have indicated that the reactions were 'minor' but this does not make them acceptable. A 'major' reaction would have been an anaphylactic one in which there is severe hypotension and is immediately life-threatening – this occasionally is seen with infusion of blood products especially cryoprecipitate.

Further details of the infusions and the reactions are given in my letter of 11th January 1984 in which I recorded that 'infusions were accompanied by reactions on all three occasions. On the first the recipient had a short episode of diarrhoea beginning an hour after the infusion. On the second and third occasions he felt ill towards the end of each infusion. He developed transient central chest pain, pallor and retching. There was no change in his pulse, BP or temperature.' The reaction to each infusion was sufficiently marked that an injection of piriton (antihistamine commonly given to reduce 'allergic' reactions) was given on each occasion. If I had considered that these reactions were not clinically significant I would not have gone to the trouble of inviting the patient to receive a further infusion of a different batch of non-heated product (which he had been told had been heat-treated) which was given on 7th December. I concluded that the reactions were therefore due to the heated concentrate.

The Schedule (031110) para 26 enquires whether the letter 'of 11th January 1984 was written at the request of Dr Cash'. I do not have any recollection of Dr Cash asking me to

write the letter. I would have done so of my own volition as a formal summary of the result of the infusions.

Para 29 (Schedule031110) This paragraph highlights the circular from Professor Bloom, Dr Craske and Dr Rizza listing virally inactivated concentrates. The question posed as to how Dr Craske knew of the different heat treated concentrates. The letter of 29th March 1984 (DHF.002.8963) was written by Professor Bloom, Dr Craske and it appears Dr Rizza (although the scanned copy apparently fails to include the whole of the foot of the last page). Certainly Professor Bloom and Dr Rizza would have known of commercial heat treated concentrates under development. In addition Dr Rizza was asked to test Scottish products (letter from John Watt 22nd Feb 1983 and he was probably kept updated). Furthermore Dr Craske was chairman of the UKHCDO Hepatitis Working Party and it this capacity he is likely to have become knowledgeable of developments.

Para 31 (Schedule031110) The summary of presentation by Professor Mannucci is principally concerned with the clinical study of 'hepatitis' transmission by the dry (60 degrees 72 hours) heated Hemofil T factor VIII concentrate. The study clearly demonstrated transmission of hepatitis in at least 11 of 17 patients (2). It was noteworthy that there were no LAV seroconversions.

Para 32 (Schedule031110) The way in which the Edinburgh Cohort was discovered is set out in Appendix 1.

Para 36 (Schedule031110) This paragraph raises the question as to whether the Edinburgh cohort would have been prevented if heat treatment has been introduced at the beginning of 1984. If effective heat treatment against NANBH virus(es) had been part of the routine manufacturing process and all concentrates issued after the beginning of January 1984 then it is likely that batch 023110090 would not have contained infectious HIV. However the question suggests that there is a misunderstanding about the initial reasons for developing heat treatment – it was to prevent hepatitis (and heat treatment had not been demonstrated to be efficacious even by the end of 1984) not HIV.

Clearly heat treatment was not introduced early in 1984 because it was being developed to render concentrates free of infectious NANBH virus and at that time there was no proven technique available which could guarantee this. Furthermore there were concerns about heat treatment modifying the factor VIII molecule so that it might develop neoantigens with anti-factor VIII antibodies arising in the recipients. Thus heat treatment would have introduced a further risk of therapy without known benefit with respect to NANBH virus.

Whilst there was evidence in Scotland that heating at 68 degrees for 2 hours appeared to have inactivated HIV in several batches of SNBTS concentrate, it is not possible to know

whether it would have inactivated HIV in batch 023110090, as it was clear from use of commercially manufactured concentrates that dry heating at 68 degrees for 72 hours may have been inadequate (Pierce, JAMA 1989 261 3434-38). The efficacy of 'dry' heating is probably critically dependant on the HIV viral load in the concentrate and also the physical state of the 'freeze dried concentrate', e.g., its moisture content and possibly its physical characteristics. One view of batch 023110090 is that it may have either had a relatively high HIV viral load or contained an 'aggressive' subtype of HIV and both of these might have rendered it less heat labile.

Additionally batch 023110090 was manufactured in the ?Autumn of 1983 and presumably shortly thereafter completed its quality checks and was cleared for issue and possibly even transferred to the Regional Blood Transfusion Centres. Operationally it thus might have missed a dry heating stage in its manufacture had it been introduced in early 1984 (unless a decision was made to heat treat all existing stock, as occurred in December 1984).

In summary the reason why heat treatment was not introduced in early 1984 is because it was being developed to render concentrates non-infectious for NANBH virus(es) and at this time there was no proven effective technique which would prevent its transmission.

Reference List

(1) Fletcher ML, Trowell JM, Craske J, Pavier K, Rizza CR. Non-A non-B hepatitis after transfusion of factor VIII in infrequently treated patients. Br Med J (Clin Res Ed) 1983 Dec 10;287(6407):1754-7.

(2) Rouzioux C, Chamaret S, Montagnier L, Carnelli V, Rolland G, Mannucci PM. Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated Factor VIII concentrate. Lancet 1985 Feb 2;1(8423):271-2.