PATIENT INTEREST CORE PARTICIPANTS - SUBMISSIONS FOR THE C3A TOPIC

Ambit of the topic

C3A) The use of blood product concentrates in Scotland in the period between the introduction of NHS heat treated products in 1984 and the supply of NHS products sufficiently treated to inactivate Hepatitis C

The identification of patients as suffering from a bleeding disorder

1. How were previously untreated patients identified as suffering from haemophilia or some other bleeding disorder over this period?

Patients who had never before received treatment were most likely to be mild patients who had had little experience of bleeding episodes in the past. In his evidence, Professor Lowe spoke of the system at the GRI over this period whereby newly diagnosed patients with mild haemophilia would be tested for their response to DDAVP and, as most had the predictable response, they would be told that this was the treatment which would be used for them.\(^1\) He accepted that at the GRI there was quite a large group of patients with mild haemophilia.\(^2\) This system does not appear to take account of the category of patients who would only present for treatment once they had been injured and their resultant bleed did not stop. We would refer, in particular, to the submission which we have made in the B2 section which identified that the WHO classification for mild haemophilia resulted in there being certain patients who still had a good chance of suffering a bleeding episode who would not have been classified as haemophiliacs at all with the result that they would not have been registered within the system or undergone the types of analyses to which Professor Lowe referred. Professor Lowe accepted the importance of establishing what the reason for the bleeding was and the nature of the deficiency before any treatment decision could be taken.\(^3\) However, his earlier remark about DDAVP suggested that it was the designated treatment for mild patients. This may not have been appropriate in all circumstances.

\(^1\) Transcript for 13/10/11 (day 54); 24 (14 to 24) (Professor Lowe)
\(^2\) Transcript for 13/10/11 (day 54); 25 (8 to 10) (Professor Lowe)
\(^3\) Transcript for 13/10/11 (day 54); 61 (20) to 62(16) (Professor Lowe)
Professor Ludlam gave evidence to the effect that the haemophilia department would do quite a lot of clotting screens for patients who had presented to the accident and emergency department with a haemorrhage.\textsuperscript{4} One would require to make a diagnosis before any treatment could be administered.\textsuperscript{5} With borderline cases, he told the Inquiry that he would be reluctant to make a diagnosis of haemophilia but that the patient should be told that they should tell other doctors that they may have a bleeding disorder when presenting for treatment.\textsuperscript{6} In our submission, it is important to understand that this all depends on those involved in primary care linking the haemorrhage with a possible diagnosis of haemophilia. Professor Ludlam thought that an A&E doctor would have a "low threshold" for sending the blood off for a clotting test.\textsuperscript{7} That they would think to do that in response to unexplained bruising would simply have been part of their general medical education, in his view.\textsuperscript{8} There was no clear evidence, however, of any particular system other than reliance on general medical education to ensure that such patients were indeed identified and taken into the haemophilia care system. This is addressed further below.

For some significant period of time, the value of previously untreated patients had been recognised for research purposes as their reactions to products would give an invaluable insight in clinical trials. At a meeting of the SNBTS Haemophilia & Blood Transfusion Working Group on 14 November 1983, Professor Cash reminded those in attendance about collection of data of liver function tests of virgin haemophiliacs. Dr Forbes responded that ‘there were not enough virgin patients in Scotland’ and he was writing up his experience of hepatitis in 12 mild cases treated with PFC factor VIII.\textsuperscript{9} Attention continued to be paid to previously untreated or "virgin" patients into the period with which this topic is concerned.\textsuperscript{10} Professor Colvin told the Inquiry in his evidence that untreated patients were ones he would have been interested in for putting into a clinical trial.\textsuperscript{11}

In light of the attention paid to such patients, it is surprising, in our submission, that greater care does not seem to have been paid to the ways in which such patients might be identified and referred into the haemophilia treatment system. Further, the attitude towards the identification and

\textsuperscript{4} Transcript for 14/10/11 (day 55); 69(1 to 3) (Professor Ludlam)
\textsuperscript{5} Transcript for 14/10/11 (day 55); 70(9 to 10) (Professor Ludlam)
\textsuperscript{6} Transcript for 14/10/11 (day 55); 72(1 to 6) (Professor Ludlam)
\textsuperscript{7} Transcript for 14/10/11 (day 55); 74(6 to 8) (Professor Ludlam)
\textsuperscript{8} Transcript for 14/10/11 (day 55); 75(25) to 76(3) (Professor Ludlam)
\textsuperscript{9} SNB.001.5188
\textsuperscript{10} See SNF.001.2890 (24 March 1984); SNF.001.3212 (25 April 1984); SNF.001.3213 (April 1984); SNB.001.5352 @ 5354 (15 May 1985) and SNB.005.1522 (1 July 1986)
\textsuperscript{11} Transcript for 7/12/11 (day 74); 92 (17 to 20) (Professor Colvin)
treatment of such patients for their own safety and care does seem to have played a subsidiary role to their value to the advancement of knowledge about products in clinical trials. In our submission, a sophisticated system was necessary to identify such patients to allow them to receive advice from a specialist and be fully appraised of the risks involved. In our submission, such a system was necessary in order to maximise their chances of avoiding having to have a concentrate by giving them appropriate lifestyle advice and instigating appropriate non-concentrate treatment at an early stage which would be less likely to infect them with NANB hepatitis. However, there is, as far as we are aware, no clear evidence that such sophisticated systems existed in Scotland over this period (see below).

The background knowledge of the risks of infection with NANB hepatitis over this period

2. What was known about the risk of contracting NANB hepatitis from the administration of factor concentrates (in particular factor VIII concentrate) or other blood products over this period?

Early evidence of a link between the treatment of patients with bleeding disorders and the emergence of NANB hepatitis

In a paper by Mannucci and Ors published Journal of Clinical Pathology on 10 February 1975 data from a study of 91 multi-transfused severe haemophiliacs was presented which suggested that repeated and prolonged contact with the agents responsible for post transfusion hepatitis may cause chronic liver damage not associated with overt illness. All 91 patients were asymptomatic but there was a high incidence of abnormal liver function tests showing damage to the liver. The incidence of abnormal liver function tests tended to increase with age. It was not possible to establish a link with any particular type of product as the 91 patients had received the full range of haemophilia treatment.

Dr Rosemary Biggs, the director of the Oxford Haemophilia Centre, published the 2nd edition of "The Treatment of Haemophilia A and B and von Willebrand’s Disease" in 1978. One of the four complications that was said to arise from treatment with plasma fractions was the transmission of

12 LIT.001.0132
13 PR, para 6.62
an infective organism, in particular hepatitis, to the patient. It was suggested that mildly affected patients who had never or rarely been transfused should not receive large pool commercial concentrates. Instead, they should be given cryoprecipitate or small pool concentrates. There was no overt mention of NANB Hepatitis in the book. However, in our submission, we can assume that she was talking about NANB hepatitis due to the fact that hepatitis B testing had been instituted by this stage. In our submission, the increase in knowledge between 1978 and the mid 1980s about the severity of NANB hepatitis (see below) and the introduction of screening blood for HIV in October 1985 (resulting in the greater safety of cryoprecipitate) mean that her advice to use small pool products for mild patients should have become all the more relevant in the period with which this topic is concerned. In our submission, small pool products were being recommended for mild patients based not on the fact that their bleeds were less severe but on the fact that they carried a lesser risk of transmitting NANB hepatitis. This was clearly understood in 1978 as was the need for such action to be taken.

In an important paper by Preston & Ors entitled “Percutaneous liver biopsy and chronic liver disease in haemophiliacs” (published in the Lancet on 16 September 1978), data from the screening of 47 haemophiliacs in Sheffield showed that 77% of them had abnormal liver function tests with a tendency for those abnormalities to persist. Importantly, a liver biopsy was carried out on 8 symptom free patients who had had abnormal liver function for 6 months or more in order to elucidate the importance of the abnormal liver function tests. These biopsies demonstrated a wide range of chronic liver disease including chronic aggressive hepatitis and cirrhosis. It was observed that the hope that the incidence of liver disease amongst haemophiliacs would fall after the introduction of hepatitis B testing had been unduly optimistic. Further, it was concluded that the high incidence of chronic liver disease was probably related to factor concentrate replacement therapy with 4 of the 8 patients having indications that their liver disease is not caused by HBV but by NANB hepatitis. It is also suggested that patients with mild haemophilia may possibly benefit from the newly developed DDAVP treatment against a background of it being discovered that two mildly affected patients who only required occasional transfusion with factor VIII had cirrhosis.

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14 Pages 181–2
15 LIT.001.0387
16 LIT.001.0387 @ 0389
17 LIT.001.0387 @ 0389
18 LIT.001.0387 @ 0389
The minutes of UKHCDO centre directors meeting on 13 September 1982 contain a report from the chairman of Hepatitis Working Party (Dr Craske) which had not met for 6 months. The report points to interesting results from mildly affected or seldomly transfused patients as regards hepatitis in Oxford and records that a study was being prepared for publication at that time. A separate note of the same meeting records the Oxford data as showing that the risk of contracting hepatitis from large pool NHS concentrates was unexpectedly high.

The UKHCDO Hepatitis Working Party report for the year 1982/83 refers to the Oxford study, started in 1981, of hepatitis in infrequently treated haemophilia patients. It was noted that the study appeared to demonstrate that the risk of contracting NANB Hepatitis from Factor VIII concentrates was 100% on first exposure, whether of NHS or commercial origin. It was noted that the problem of AIDS had overshadowed these developments. The availability of commercial heat treated products was also discussed. Directors required to consider the ethical problem of exposing persons with mild haemophilia to heat treated commercial material. The ethical problem was expressed as follows:

“Since the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received factor VIII or IX concentrate, a choice will have to be made between using heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non-A, non-B hepatitis.”

The Oxford research by Fletcher, Craske & Ors was published in the British Medical Journal under the title "NANB hepatitis after transfusion of factor VIII in infrequently treated patients" 10 December 1983. All nine of the patients who had not had factor VIII concentrate (whether NHS or commercial) before contracted NANB hepatitis. It was stated that the pool size of NHS concentrates had increased to the point where the benefit conferred by using plasma from volunteer donors had been lost. In his evidence to the Inquiry, Professor Thomas confirmed that what was taken from this

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19 SNB.001.7419 @ SNB.001.7428
20 DHF.001.6837 @ DHF.001.6838
21 SNF.001.0948 (dated 28 September 1983)
22 SNF.001.0948 @ 0949
23 SNF.001.0948 @ 0952
24 LIT.001.0239
study was that there was a very high rate of development of NANB hepatitis in people given concentrates for the first time whether of NHS or commercial origin.  

Similar research was being done in Scotland by 1983. At a meeting of the Scottish Haemophilia & Blood Transfusion Working Group on 14 November 1983 Professor Cash reminded those in attendance about collection of data of liver function tests of virgin haemophiliacs. He raised a question about the number of virgin haemophiliac patients in Scotland. Dr Forbes responded that ‘there were not enough virgin patients in Scotland’ and that he was writing up his experience of hepatitis in 12 mild cases treated with PFC factor VIII concentrates. In a letter to Dr Forbes dated 28 March 1984, Professor Cash pointed out that he was beginning to ‘plan ahead with regard to getting our product put into SHS ‘virgin’ haemophilia A patients’. He asked Dr Forbes for his data about the incidence of hepatitis in his patients which he had indicated to the working party was identical to the Oxford data and was needed for use as retrospective controls. This would appear to suggest that the results in Scotland at this time had also indicated a 100% transmission rate from PFC concentrates. In a talk given by Dr Brian McClelland at the International Society for Blood Transfusion Congress in Munich on 22 July 1984 he indicated that present day coagulation factor concentrates had a very high risk of transmitting NANB hepatitis.

The period with which this topic is concerned

In an article by Kernoff, Thomas and Ors published in the British Journal of Haematology in July 1985, it was reported that 9 out of 9 UK patients developed NANB hepatitis after first transfusion of commercial factor VIII concentrate. Further, 10 out of 12 UK patients developed NANB hepatitis after first transfusion of NHS factor VIII concentrate and 4 out of 4 UK patients developed NANB hepatitis after first transfusion of NHS factor IX concentrate. It was concluded that whether prepared from volunteer or commercial donor plasma, clotting factor concentrates carried a very high risk of acute NANB hepatitis in first exposure recipients. Given that this was a collaboration
between Professor Thomas and haemophilia clinicians, one would have expected the haemophilia treating community to have been aware of it.

Oral evidence heard by the Inquiry

Professor Thomas expressed the view that between 1970 and 1990 the prevalence of HCV in the UK blood donating general community was around 0.5%.\(^{31}\) He accepted that the levels were found to be lower than that in blood tested in the first 6 months to a year after anti-HCV screening was introduced and pointed out that the level had fallen to around 0.01%. However, he observed that that (even using that prevalence) still meant that one in 10,000 donors would be positive at that prevalence level meaning that one would still expect to see "some carry over into a factor VIII concentrate if its derived from 30,000 donors".\(^{32}\) Professor Thomas explained that the figure he had been using was derived from a paper by Minor\(^{33}\) (whom he thought would be privy to the accurate figures) which reported "a frequency of 0.4% consistent with previously reported figures" in the plasma from UK donors used to make factor concentrates.\(^{34}\) As was accepted by Professor Thomas, this demonstrates that the UK donor plasma, although it had a smaller amount of the virus than the equivalent US plasma, had more than the critical level of infection at which the vast majority of recipients would be infected with hepatitis C.\(^{35}\) This explains the epidemiological basis upon which factor concentrates available over this period were nearly always infective for NANB hepatitis.

As far as the then available Scottish product was concerned (heated to 68 degrees for 24 hours) the PFC did not receive regular reports of apparent infections as it was assumed that most patients, if not all patients, who received concentrate prior to 1987 became infected with NANB hepatitis.\(^ {36}\)

Conclusion

By the start of the period with which this topic is concerned, it was or should have been known on the basis of the evidence which had been accumulated over a number of years that it was almost certain that a patient who was not infected with NANB hepatitis would contract the disease on first infusion with a factor concentrate of any origin. This inevitability should have featured highly in the

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\(^{31}\) Transcript for 11/10/11 (day 52); 78 (21 to 23) under reference to his report (Professor Thomas)
\(^{32}\) Transcript for 11/10/11 (day 52); from 79 (Professor Thomas)
\(^{33}\) SGF.001.1380
\(^{34}\) Transcript for 11/10/11 (day 52); 113 (Professor Thomas)
\(^{35}\) Transcript for 11/10/11 (day 52); 115 (2 to 9) (Professor Thomas)
\(^{36}\) Transcript for 7/12/11 (day 74); 61 (8 to 16) (Dr Perry)
treatment decisions made for patients who were unlikely to have been infected with the disease at the time when the treatment under consideration was received.

3. What was known about the potential consequences of contracting NANB hepatitis over this period?

The late 1970s to the early 1980s

In "Non-A, Non-B hepatitis" by Purcell, Alter and Ors (published in the Yale Journal of Biology and Medicine on 26 February 1976)\(^{37}\), it was noted that, generally, NANB hepatitis had been associated with less severe acute illness than hepatitis B. However, judged by frequency of jaundice and magnitude of SGPT elevations it was observed that the prognosis for the two diseases may be similar. Further, for 3 patients in whom transaminase elevations were documented at the NIH over a period of several years and who had a liver biopsy, 2 had histopathologic changes in the liver compatible with chronic active hepatitis and the other was diagnosed as having chronic persistent hepatitis. It was concluded that chronic NANB hepatitis was not necessarily a benign infection and may be the cause of a significant proportion of chronic hepatitis not identifiable as hepatitis B.

The Lancet article "Percutaneous liver biopsy and chronic liver disease in haemophiliacs" by Preston and Ors of 16 September 1978 (referred to above) recorded that 4 patients were thought to have NANB hepatitis from factor concentrates including 2 only occasionally treated mild patients who had advanced liver disease. \(^{38}\)

An article entitled "Progression of hepatitis non-A, non-B to chronic active hepatitis" by Iwarson and Ors (Journal of Clinical Pathology, 25 September 1978)\(^{39}\) contained details of a follow up of 2 cases with no hepatitis A or hepatitis B markers, assumed to be NANB patients). They progressed to chronic liver disease (one from a blood transfusion). One of the patients had died and the other was still alive 8 years after follow up. The article concludes that NANB hepatitis may progress to chronic liver disease in certain cases and refers to a study by Knodell et al (1977) reporting 10 cases of chronic liver disease amongst 44 patients with NANB hepatitis.

\(^{37}\) LIT.001.3932
\(^{38}\) LIT.001.0387
\(^{39}\) LIT.001.0196
In a further article entitled "Long term follow up of acute and chronic NANB post transfusion hepatitis: evidence of progression to liver cirrhosis" by Realdi and Ors (GUT, 10 September 1981) the long term development of NANB hepatitis was studied in the cases of 21 patients who developed the condition after open heart surgery. The histological chronic sequelae were documented in 13 patients over 5 years. The progression to the chronic state was in most cases symptomless but 5 developed cirrhosis and one had died.

A paper entitled "Clinical and histological features of a group of patients with sporadic NANBH" by, among others, Professor Thomas and Dame Sheila Sherlock (1981) also related to the issue of the severity of the consequences of the disease. Professor Thomas gave evidence about this study to the Inquiry. This was a study of non-haemophilia patients. The results constituted an affirmation of what was seen in the 1978 Preston paper where there was one patient with cirrhosis. Half of the patients in this study had chronic active hepatitis (which had a poor prognosis according to Professor Thomas). Professor Thomas summed this up by saying that the study was a confirmation of the message from the Preston paper and other groups (in particular in Italy).

The mid-1980s

In an article entitled "Blood product concentrates and chronic liver disease" by Preston & Ors (The Lancet, 6 March 1982) it was noted that the presence of chronic liver disease in patients with post transfusion NANB hepatitis was now well established but that the rate or likelihood of progression was unknown. The article gave details of one patient (infected from a single infusion) showing significant progression in the disease after 2 years but with no symptoms.

A further article entitled "Non A, non B post transfusion hepatitis: Disaster after decades" by Koretz and Ors, UCLA Medical school (Hepatology, 1982) 35 - 53% of patients (66) with post transfusion NANB hepatitis had chronic liver disease. 6% had cirrhosis (after between 4 and 9 years of follow up). It was concluded that the disease developed in a clinically silent fashion and recommended that

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40 LIT.001.0529  
41 LIT.001.0759  
42 Transcript for 11/10/11 (day 52); 123 to 124 (Professor Thomas)  
43 Transcript for 11/10/11 (day 52); 128 (22 to 23) (Professor Thomas)  
44 Transcript for 11/10/11 (day 52); 129 (7 to 10) (Professor Thomas)  
45 LIT.001.0398  
46 LIT.001.3738
patients with post transfusion NANB hepatitis should be followed for many years. In his evidence, Professor Thomas noted that this was one of the bigger studies into this subject at the time.47

In a further article entitled "Liver disease in haemophiliacs - an overstated problem?" by Stevens, Craske and others (British Journal of Haematology, January 1983)48 the significance of the disease was questioned after liver biopsy had been performed of 12 multi-transfused patients in Manchester. It was found that only one had chronic active hepatitis with progression towards cirrhosis and that 4 had mild chronic active hepatitis but 7 have signs of good prognosis from chronic persistent hepatitis. It was noted that the incidence of chronic active hepatitis/cirrhosis may be around 16% (consistent with other worldwide studies). In our submission, even the content of this article is perhaps not as reassuring as its tone might suggest. The content of the article was summed up in his evidence by Professor Thomas when he said that "there are some worrying things in there but in the main most of that histology is encouraging". 49 Further, Professor Thomas noted that most of the studies available at that time were small and so one needed to look at the overall picture.50

However, the tone of this Manchester paper was rather eclipsed in 1985 by a further paper from the Sheffield group entitled "Progressive liver disease in haemophilia - an understated problem" by Hay, Preston and Ors (The Lancet 29 June 1985).51 The paper presented data from an 8 year study of 79 haemophiliacs in Sheffield who had received concentrates which showed that 21% of them had chronic progressive liver disease (8 had chronic active hepatitis and 9 had cirrhosis). There was therefore evidence of cirrhosis in 12% of patients with chronic active NANB hepatitis. The histological evidence showed that NANB hepatitis was mainly responsible. Liver biopsies (done on 34 of the patients) showed progression from chronic persistent hepatitis to chronic active hepatitis within 6 years (suggesting that chronic persistent hepatitis was not as benign as had been hitherto thought). It was noted that symptoms and abnormal physical signs were uncommon in these patients and it was anticipated as a result of this protracted study that liver disease in haemophiliacs would become an increasing problem in future.

47 Transcript for 11/10/11 (day 52); 131 (18) (Professor Thomas)
48 LIT.001.0008
49 Transcript for 11/10/11 (day 52); 145 (14 to 16) (Professor Thomas)
50 Transcript for 11/10/11 (day 52); 133 (from 17) (Professor Thomas)
51 LIT.001.0335
The UKHCDO Hepatitis working party report 1984/85 referred to the results of the Sheffield research (above) and the fact that previous reports may have seriously underestimated the risk of serious chronic liver disease resulting from infection with NANB hepatitis amongst haemophiliacs. There can be no doubt that the Preston/Hay research was communicated to the haemophilia directors. Professor Thomas described this paper as the turning point in the understanding of the severity of the disease which came to light when Dame Sheila Sherlock was writing the 8th edition of her textbook. Professor Ludlam pointed out that it was the progressive nature of the disease which was not understood adequately before this paper.

In "A study of liver biopsies and liver disease among haemophiliacs (Blood, 66, 367 – 372) by Aledort & Ors dated August 1985 biopsy and autopsy results from 155 haemophiliacs were examined in order to study the relationship between severity of liver disease and treatment history. The article noted that published results on increasing numbers of liver biopsy studies being conducted around the world which had stressed (a) the severity of the pathologic lesions observed and (b) the safety of the biopsy procedure. The incidence of cirrhosis was found to be 15%. This was less than had been previously reported in other studies but, in our submission, still represented a significant marker of the potential severity of the disease.

In a letter from Dr Schimpf and others in The Lancet (8 February 1986) 16% of patients were found to have chronic active hepatitis and a further 13% had cirrhosis in his centre. The authors aligned themselves with the Sheffield study to the effect that the progressive nature of liver disease in haemophilic was deemed to be an understated problem. The lead author was described as a very distinguished haemophilia treater by Professor Ludlam.

As Professor Ludlam said in his evidence, the important thing which is emerging from this data was not necessarily the numbers with the more advanced forms of liver damage at this point in time but the fact that the disease was being shown to be progressive. Professor Thomas was asked whether any haemophilia patients had actually died from the complications of liver disease at the time of the

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52 SNB.001.7589
53 Transcript for 11/10/11 (day 52); 146 (21 to 24) (Professor Thomas)
54 Transcript for 13/10/11 (day 54); 85 (25) to 86 (2) (Professor Ludlam)
55 LIT.001.0506
56 LIT.001.0341
57 Transcript for 13/10/11 (day 54); 92 (21 to 22) (Professor Ludlam)
58 Transcript for 13/10/11(day 54); 93 (21 to 22) (Professor Ludlam)
articles upon which he placed some reliance between 1978 and 1982. He answered that they had not. However, we would submit that the nature of the disease was (by this time) known to be a progressive one and that it could progress to a cirrhotic stage which, as Professor Thomas told the Inquiry, meant that the condition was irreversible. At the very least what was known was that, in some cases, the disease could progress to a serious level of morbidity. We would submit that the knowledge about the potentially severe consequences of the disease and its progressive nature were clearly established by this stage. We submit that, in light of that knowledge, it was not reasonable and certainly not in the best interests of patients for treatment decisions to be without regard to the potential consequences of almost inevitable infection based simply in the fact that nobody had died amongst the haemophilia population at that time. The progressive nature of the disease meant that it was predictable that the serious consequences of it would emerge some period into the future. Professor Thomas agreed with the proposition made by Professor James that the approach of haemophilia clinicians was perhaps based on an underestimation of the severity of NANB hepatitis based on the fact that screening techniques had minimised infections with hepatitis B by 1981. We submit that such an approach was not sufficiently cautious and did not sufficient account of the known risks to the patient of almost inevitable infection with NANB hepatitis from factor concentrates. Further, the evidence of the potential severity of the consequences increased in the following years up to the early part of the period with which this topic is concerned.

Conclusion

As was the position of Professor Thomas in his evidence, it became increasingly clear between 1978 and 1985 that NANB hepatitis was a more serious disease. Early assessments about the likely severity of the progression of the disease appear to have been based on what transpired to be erroneous assumptions about the likelihood of similarities between the progression of hepatitis C and hepatitis B as well as problems, in particular with haemophiliacs, of evaluating the progression of the disease based on uncertainties about the date of infection. The advent of the liver biopsy

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59 Transcript for 11/10/11 (day 52); 143 (7 to 10) (Professor Thomas)
60 Transcript for 11/10/11 (day 52); 144 (2 to 4) (Professor Thomas)
61 Transcript for 11/10/11 (day 52); 143 (18) to 144 (2) (Professor Thomas)
62 Transcript for 12/10/11 (day 53); 82 (Professor Thomas) - under reference to the development between the 6th and 8th editions of the textbook by Dame Sheila Sherlock which was referred to by Professor Thomas as approaching the status of “absolute truth” on 11/10/11; 122(20)
63 Transcript for 11/10/11 (day 52); 119 (3 to 7)
64 Transcript for 11/10/11 (day 52); 119 (19 to 24)
allowed a more accurate picture of the disease and its likely progression to be evaluated.\textsuperscript{65} It was the position of Professor Thomas that the view of the disease changed (as reflected in the Sherlock text) on the basis of the study in which he was involved and which was reported in the Journal of Clinical Pathology.\textsuperscript{66} Even in the sixth edition of the Sherlock textbook the position had been stated as being unclear as the disease was referred to as "probably benign".\textsuperscript{67} The development of the understanding that the disease was more severe, Professor Thomas stated in evidence, was the result of this article which, in itself was a confirmation of the results of the Preston paper published in 1978.\textsuperscript{68} Professor Thomas accepted that once this data started to become available, one would not take what comfort existed in the sixth edition of the Sherlock text.\textsuperscript{69} The view expressed in the eighth edition of the Sherlock text (which was prepared in the 2 or 3 years prior to its publication in 1989\textsuperscript{70}) was that evidence suggested that the disease was potentially very serious. In our submission, Professor Thomas's evidence is clear that the genesis of this changed opinion was the overall picture emanating from the papers published resulting from the liver biopsies, the results of which were published in 1978 and 1981/82.\textsuperscript{71}

4. Access for those treating patients with bleeding disorders to current information and opinions on (a) the risks of transmission of NANB hepatitis from blood products and (b) the potential severity of NANB hepatitis over this period

Evidence

Professor Ludlam gave evidence that in Edinburgh they had regular educational meetings.\textsuperscript{72} The Inquiry heard no evidence about what went on at those meetings, in particular whether any consideration was given at them to the position of virgin or minimally treated patients and how they might be handled.

As far as awareness of the research referred to above was concerned, Professor Lowe (who became a consultant at the GRI in October 1985) told the Inquiry that the studies between 1983 and 1985 resulted in it being very much on people's mind that there was a virtually 100% risk of contracting

\textsuperscript{65} Transcript for 11/10/11 (day 52); 118 (15 to 22) (Professor Thomas)
\textsuperscript{66} LIT.001.0759 and PEN.017.1071 @ 1079
\textsuperscript{67} Transcript for 11/10/11 (day 52); 129 (25) (Professor Thomas)
\textsuperscript{68} Transcript for 11/10/11 (day 52); 129 (7 to 8) (Professor Thomas)
\textsuperscript{69} Transcript for 11/10/11 (day 52); 139 (4 to 9) (Professor Thomas)
\textsuperscript{70} Transcript for 11/10/11 (day 52); 130 (5 to 6) (Professor Thomas)
\textsuperscript{71} Including LIT.001.3738 also referred to by Professor Thomas on 11/10/11 (day 52); 131; 11/10/11; 133 (25)
\textsuperscript{72} Transcript for 14/10/11 (day 55); 57(7) (Professor Ludlam)
NANB hepatitis from concentrates at that time. He accepted that it was known from 1985 that in the absence of serial studies conducted in Scotland, one would have thought that the SNBTS concentrates were equally 100% infective with NANB hepatitis.

Professor Thomas pointed out that information would be exchanged between haemophilia centre directors around a year before it would be published in a journal. This suggests that, even on the assumption that junior members of staff had access to and kept up to date with developments in knowledge which might be relevant to their practice, there was a significant time delay between information being available and its publication. No evidence was heard about the extent to which any information communicated to centre directors in Scotland via the UKHCDO would be disseminated more widely beyond their centres. Indeed, one of the reference centre directors, Professor Ludlam made it clear that he had no managerial responsibility for any other of the haemophilia centres and that it was not until the factor VIII working party was established in 1988 that there was a forum for a regular exchange of views. Further, that Professor Ludlam suggested that there might be a system whereby treatment decisions for virgin or minimally treated patients should be referred to a consultant rather suggests that this information was not disseminated to enable others to use it. In his evidence, Professor Lowe stated that information from Dr Forbes (who attended the UKHCDO meetings) came more frequently to him once he became a consultant than when he was a junior doctor. Professor Ludlam felt that it should have been a matter of medical policy for information and guidance to be circulated about this difficult period. This suggests that within Scotland no responsibility was taken for mutual assistance within the NHS.

Conclusion

The evidence available to the Inquiry suggests, in our submission, that little formal structure existed to ensure that important information and opinions about the risks of transmission of NANB hepatitis to uninfected patients, the known severity of the disease, what treatment options were available and how treatment decisions might be affected by this information was conveyed clearly and efficiently to anyone other than the most senior staff at Scottish haemophilia reference centre (ie Edinburgh and Glasgow). In particular, there would seem to be little evidence of formal efforts being

73 Transcript for 13/10/11 (day 54); 22 (2 to 8) (Professor Lowe)
74 Transcript for 13/10/11 (day 54); 32 (19) to 33 (1) (Professor Lowe)
75 Transcript for 11/10/11 (day 52); 43 (21 to 24) (Professor Thomas)
76 Transcript for 14/10/11 (day 55); 61(3 to 8) (Professor Ludlam)
77 Transcript for 13/10/11 (day 54); 37 (4 to 11) (Professor Lowe)
78 Transcript for 14/10/11 (day 55); 62(20 to 21) (Professor Ludlam)
made to communicate any such information to junior staff or to hospitals where such treatment decisions may have to be made outwith these main centres.

5. The factors which should have influenced the choice of product to be used in the treatment of virgin and minimally treated patients with bleeding disorders over this period

The significance of virgin and minimally treated patients over this period

As noted above, the literature which existed over this period tended to suggest that patients would be likely to be infected on first infusion of a factor concentrate. Therefore, it is highly likely that patients who had previously been treated with factor concentrates would have been infected by the commencement of this period, in particular more severe haemophiliacs who had been multiply so infused due to the severity of their condition (their position is addressed below). In reality the significance of the severity of an individual's bleeding disorder was that it was an indicator of (a) the likelihood that they would already have been exposed to concentrates and therefore already infected with NANB hepatitis (in addition to their ALT test levels)\textsuperscript{79} (b) the extent of the treatment which they might require to achieve haemostasis (addressed below) and (c) the likelihood that they would require to have treatment which might infect them in the future. Equally, those who had not been treated or who had received treatment with products other than concentrates in the past were likely not to have been infected when presenting for treatment over this period. Therefore, such patients deserved special and careful product selection.

The severity of the bleed

The choice of treatment for a patient will inevitably depend to a certain extent on the severity of the bleeding incident for which the treatment is being administered. The requirement to stop the bleeding requires, however, to be considered in the balance with other factors in the selection of treatment. However, in response to questioning about the position where there would require to be greater weight placed on the urgency of the procedure for which the coagulopathy was being administered, Professor Thomas restricted his answer to referring to the most severe types of

\textsuperscript{79} Transcript for 13/10/11 (day 54); 37 (4 to 11) (Professor Lowe)
surgery, where very good coagulopathy would be needed such as major brain surgery or liver surgery. 80

The size of the patient

The requirement to consider not overloading the patient with fluid in achieving haemostasis was an important factor in the choice of treatment for young children. 81 However, this does not, in our submission, correlate with a suggestion that concentrates would be preferable to cryoprecipitate in the treatment of children for this reason per se. Indeed, there is evidence that at one stage Professor Ludlam counselled against the abandonment of cryoprecipitate specifically on the basis that it required to be used in the treatment of small children. This proposal was agreed to by Professor Hann, who was the director at Yorkhill at that time. 82

The likely NANB infectivity of the product

The Inquiry has heard evidence that various different products might have been used in the treatment of virgin or minimally treated patients in this period. It is most likely that such patient would be either (a) a patient who had not required treatment or much treatment in the past due to the mildness of his condition or (b) a child who had not required treatment or much treatment in the past due to his age. The possibility of using DDAVP would have ruled out the infection risk completely. However, as is considered below, there were limited situations in which this product would have been clinically suitable. If treatment was necessary, the choice for doctors treating haemophilia A patients was, therefore, between cryoprecipitate and a factor VIII concentrate. As noted above, it was understood by the time of the period which the topic is concerned that a patient would almost inevitably contract NANBH on first infusion with a factor concentrate. As far as likely infectivity with NANB hepatitis for the probably uninfected patient was concerned, it is our submission that over this period, cryoprecipitate was by far the preferable option in this situation. This conclusion is supported by a large body of evidence available to the Inquiry, as follows:

As noted above, Dr Rosemary Biggs, the director of the Oxford Haemophilia Centre, published the 2nd edition of "The Treatment of Haemophilia A and B and von Willebrand’s Disease" in 1978. 83

80 Transcript for 11/10/11 (day 52); 161 (15 to 20) (Professor Thomas)
81 Transcript for 11/10/11 (day 52); 162 (13 to 15) (Professor Thomas)
82 SNB.001.5252 @ 5253 (2 February 1984)
83 PR, para 6.62
Even at this time, it had been suggested that, due to the hepatitis risk, mildly affected patients who had never or rarely been transfused should not receive large pool commercial concentrates. Instead, they should be given cryoprecipitate or small pool concentrates.

By October 1980, in his paper entitled “The epidemiology of factor VII and IX associated hepatitis in the UK”84 Dr Craske advised that small pool concentrates or cryoprecipitate should be considered for patients with mild coagulation defects until testing was available for the NANB virus where they require treatment cover for surgery only. This was on the basis that ran a high risk of contracting transfusion hepatitis if exposed to concentrates for the first time.85

At the time of the AIDS crisis, the use of small pool products to minimise the risk for mildly infected/untreated patients was clearly recommended to minimise the risk of exposure. In a letter from Professor Bloom and Dr Rizza to Professor Ludlam dated 24 June 1983, it was recommended (a) that DDAVP should be considered for mild patients with haemophilia A or vWD (this was the practice of many directors at this time anyway due to the risk of hepatitis from large pool concentrates) and (b) that it would be circumspect to reserve stocks of NHS products (cryoprecipitate or freeze dried) for children, mildly infected patients or unexposed patients as a result of the discussions at the Reference Centre directors meeting on 13 May 1983.86 The minimisation of the risk of viral transmission by not exposing probably uninfected patients to concentrates was, therefore, a recommendation at the time of the AIDS crisis. It would appear that this may have been forgotten about when the HIV crisis was over after HIV-safe factor VIII concentrate arrived. The principles being proposed here apply equally to the prevention of HCV as HIV.

In an article from 1985 submitted by Professor Thomas and others in June 1984, it was observed that "the absence of hepatitis amongst our cryoprecipitate treated patients probably reflects their relatively low exposure as none received more than 70 donor units."87 Professor Thomas gave evidence about this article to the Inquiry on day 52 to the effect that patients who required relatively small amounts (such as mild patients and children) could avoid infection if treated with cryoprecipitate.

84 DHF.003.0649
85 DHF.003.0656
86 SGH.002.2175
87 LIT.001.0800
In an article entitled "A prospective study of cryoprecipitate administration: absence of evidence of virus infection" by Colvin & Ors (Clinical and Laboratory Haematology, 2 October 1986) looked at NANBH infection rates amongst the recipients of cryoprecipitate. 88 6 patients previously untreated with concentrates were treated with cryoprecipitate tested for a year and no signs of hepatitis developed. The article observed that "until the recent epidemic of AIDS, cryoprecipitate was widely used as the safest form of treatment for patients with mild coagulation defects who were unsuitable for DDAVP injection". It recommended that following the screening of blood donors for HIV in October 1985, the use of cryoprecipitate in selected cases should be reconsidered. The study was carried out between October 1982 and July 1984. By the time it was published (in 1986) Professor Colvin indicated that the world had really moved on 89 but this was really because of the apparent success of viral inactivation making concentrates more attractive. He was of course speaking from an English perspective. 90 At the time when this data was collected (prior to the availability of heat treated concentrates which were NANBH safe in Scotland) it demonstrated the genuine advantages of cryoprecipitate from the point of view of NANBH infection.

The decline in the use of cryoprecipitate is considered in our B2 submission. By February 1986, Professor Cash commented in a paper designed to help for future planning for the needs of blood and blood products by SNBTS that over the previous few years ‘it is probable that a substantial proportion of the issued cryo was not used in the management of haemophilia A patients’. 91

Professor Thomas gave evidence in connection with the position as regards the relative safety of cryoprecipitate in the 1980s. He gave evidence to the effect that cryoprecipitate was relatively safe in terms of its likelihood to transmit NANB hepatitis given the relatively small numbers of donors per batch. It was for this reason even in the early years of the 1980s according to Professor Thomas, that infants would be "first up with a call on cryo". 92 In his study (referred to above) none of the patients who had been treated with cryoprecipitate only were infected with NANB hepatitis 93. In his evidence, he made it clear that none of those patients had been treated with more than 70 donor

88 LIT.001.0640
89 Transcript for 14/10/11 (day 55); 136 (22 to 25) (Professor Colvin)
90 Transcript for 14/10/11 (day 55); 137 (13 to 15) (Professor Colvin)
91 SNB.001.5454 @ 5456
92 Transcript for 11/10/11 (day 52); 99 (21) to 100 (2) (Professor Thomas)
93 LIT.001.0800

18
units of cryoprecipitate.\(^{94}\) In the conclusions of the paper, it was pointed out that "Whether prepared from volunteer or commercial donor plasma, clotting factor concentrates carry a very high risk of acute NANB hepatitis in first exposure recipients".\(^{95}\) In our submission, the material in this Thomas and Kernoff study constitutes contemporaneous evidence of the strong likelihood that patients who would be likely to require low doses of cryoprecipitate, such as mild patients or infants, would have a good chance of avoiding infection with NANB hepatitis. In his evidence, Professor Thomas expressed the view that in the period between 1985 and 1987 cryoprecipitate would be "a way forward" for mild patients based on this evidence that it did not have a high risk of transmitting NANB hepatitis\(^{96}\) (the risk of HIV from cryoprecipitate is addressed below).

Professor Lowe expressed the view in his evidence that faced with a mild patient who had a bleed that was not stopping post October 1985, he would have preferred cryoprecipitate over a concentrate.\(^{97}\) Professor Ludlam indicated that he had expected that his patients who had received pooled concentrates or "a great deal of cryoprecipitate" would have been infected in appear published in the Lancet on 2 September 1989.\(^{98}\) No such expectation was applied to those who had received lesser amounts of cryoprecipitate.

Professor Ludlam gave evidence to the effect that cryoprecipitate started to be used less in the period between 1984 and 1988. This was partly, at least, due to the greater number of patients on home treatment.\(^{99}\) This would seem to imply that considerations of safety required to be subordinated to considerations of practicality.

**The likely infectivity of the product with other diseases**

\(^{94}\) Transcript for 11/10/11 (day 52); 104 to 105 (Professor Thomas)
\(^{95}\) LIT.001.0800 @ 0808
\(^{96}\) Transcript for 11/10/11 (day 52); 156 (4 to 7) (Professor Thomas)
\(^{97}\) Transcript for 13/10/11 (day 54); 30 (4 to 6) (Professor Lowe)
\(^{98}\) Transcript for 13/10/11 (day 54); 83 (21 to 22) (Professor Ludlam) and LIT.001.3859
\(^{99}\) Transcript for 13/10/11 (day 54); 141 (5 to 11) (Professor Ludlam)
Professor Thomas expressed the view in his evidence that it was known that it was improbable that cryoprecipitate would transmit HIV due to its low frequency within the population.\textsuperscript{100} Further, by the second half of the 1980s, he was of the view that it was known that there were no cases of HIV occurring from cryoprecipitate over the C3A period.\textsuperscript{101} He considered the risk of HIV from cryoprecipitate prepared from plasma where the gay community had been excluded as donors to be negligible\textsuperscript{102}. We would submit that the safety of cryoprecipitate as far as HIV was concerned must have increased even further (to the point of a non-existent risk) from the point where blood used in its preparation was screened for anti-HTLV III in October 1985. Professor Thomas accepted that for patients at the mild end of the spectrum, cryoprecipitate would be the treatment of choice.\textsuperscript{103} Though Professor Thomas qualified his answer by pointing out that he is not a haemophilia clinician, he clearly, in our view, demonstrated throughout his evidence a deep knowledge of haemophilia care through his contact with patients with bleeding disorders in the preparation of his research, his experience on general medicine and contact with haemophilia doctors like Dr Kernoff.

The severity of the condition and the likely future exposure to blood products

In selecting the most appropriate treatment for a virgin or minimally treated patient, one would legitimately also consider the likelihood of the patients requiring future treatment with blood products which would be likely to infect him anyway. In patients who be likely to have frequent future bleeds, Professor Colvin pointed out that cryoprecipitate would have "diminishing benefits as the number of treatments went up".\textsuperscript{104} However, he did also point out that he had treated one or two patients who were heavy users who were treated with concentrate who did not develop hepatitis C infection.\textsuperscript{105}

We would also submit that this consideration also requires to be judged against the background of the emerging likelihood of a Scottish NANB free concentrate being available. The nearer such a product was, the more it became clear that future treatment would be unlikely to be infective and the greater the need to avoid infection in the current treatment.\textsuperscript{106} This appeared to be the

\textsuperscript{100} Transcript for 11/10/11 (day 52); 100 (2 to 6) (Professor Thomas)
\textsuperscript{101} Transcript for 11/10/11 (day 52); 156 (8) (Professor Thomas)
\textsuperscript{102} Transcript for 11/10/11 (day 52); 156 (25) to 157 (7) (Professor Thomas)
\textsuperscript{103} Transcript for 11/10/11 (day 52); 159 (8 to 10) (Professor Thomas)
\textsuperscript{104} Transcript for 14/10/11 (day 55); 152 (4 to 5) (Professor Colvin)
\textsuperscript{105} Transcript for 14/10/11 (day 55); 151 (10 to 14) (Professor Colvin)
\textsuperscript{106} Transcript for 13/10/11 (day 54); 140 (3 to 10) (Professor Ludlam)
reasoning adopted by Professor Colvin in treating the children in his care with cryoprecipitate. Further, the availability of a supply of BY for future treatment (considered in more detail below) would also have made the current treatment decision tend towards favouring cryoprecipitate.

The treatment of the more severe patients

As far as more severe haemophiliacs are concerned, there was an attitude prevalent over this period that the fact that such patients would most likely have been infected due to their previous treatment, in particular with factor concentrates, meant that there was no need for consideration of the nature and extent of their treatment as far as the risks of NANB transmission were concerned. However, the Inquiry has also heard evidence that there are multiple genotypes of the hepatitis C virus. In our submission, the failure to consider the possibility of reducing the amount of treatment to which more severe patients were exposed, in fact, increased the chances of them being infected with multiple genotypes of the disease. Given there are "significant differences" in the success rate of treatment depending on the genotype with which a patient is infected, the infection with multiple genotypes will lessen the likelihood of successful treatment. Professor Thomas recognised the existence of infection of haemophiliacs who were treated around this period (a) with multiple genotypes of the virus (which he described as not uncommon) and (b) with multiple viruses (which may have been the case with severe haemophiliacs treated before this period but who continued to be exposed to the hepatitis C virus during it), which would also create a worse prognosis. Further, the fact of repeated multiple exposure to infected products would reduce the chance of the infection which one received being one which would not progress to the chronic phase of the disease based on the likelihood of constant re-infection by multiple exposures. Haemophilia patients have tended, therefore, to be infected with genotype 1 hepatitis C which is less susceptible than genotypes 2 or 3 (the other genotypes prevalent in the UK population) to treatment. According to Professor Thomas, the level of viraemia increases the likelihood of rapid progression of the disease to the irreversible cirrhotic phase. Haemophilia patients exposed regularly to infected products would, therefore, be more likely to progress to the worse stages of the disease.
We do not contend that this is something which could have been known over the period with which the C3A topic is concerned. It is not something which could have been appreciated until knowledge emerged about (a) the existence of different genotypes and (b) the varying responses of the different genotypes to treatment, in particular in the case of multiply infected patients. Knowledge about genotypes emerged only gradually from the end of the 1980s, by which time factor concentrates were already heat treated to inactivate the hepatitis C virus. Professor Thomas informed the Inquiry that there would not have been knowledge about genotypes until around 1991. However, thus is a factor which, in retrospect and as a matter of fact, can be seen as having increased the risk that treatment would be unsuccessful for more severe patients.

Conclusion

In light of the evidence available to the Inquiry, we submit as follows:

- Minimally treated patients included those who had received treatment in the past for their bleeding disorder, but not with factor concentrates or with large volumes of cryoprecipitate
- The treatment of virgin and minimally treated patients over this period merited special consideration by treating doctors on the basis that (a) the state of knowledge was such that it was highly likely if not certain that they would be infected with a potentially lethal disease if treated with the then available Scottish factor VIII concentrate (NY) and (b) it was probable that such patients would not yet be infected with that disease
- The then available Scottish factor VIII concentrate (NY) should not have been given to virgin or minimally treated patients unless it was unavoidable over this period
- The priority in the treatment of bleeding episodes in such patients should have been to try to achieve haemostasis with other treatments which carried less of a risk of transmission of NANB hepatitis, such as DDAVP (for mild patients) or cryoprecipitate or alternative products sourced outside Scotland before resorting to the use of SNBTS factor VIII concentrate.

The systems in place in Scotland for managing the risks of patients with bleeding disorders contracting NANB hepatitis over this period

115 Transcript for 11/10/11 (day 52); 36 (10) and 39 (5 to 8) (Professor Thomas)
116 Transcript for 12/10/11 (day 53); 64 (24 to 25) (Professor Thomas)
117 Transcript for 13/10/11 (day 54); 19 (20) (Professor Lowe)
118 The concept that the correct approach was to try less risky treatments first was accepted in the context of a discussion about DDAVP with Professor Lowe - transcript for 13/10/11 (day 54); 73 (2 to 6) (Professor Lowe)
6. The extent to which patients presenting for treatment for bleeding disorders in Scotland were treated in a way which minimised the risk of them being infected with NANB hepatitis including (a) the systems in place at the point of first presentation of such patients and (b) the systems in place for others responsible for treating bleeding incidents

As was accepted in his evidence by Professor Ludlam, the general guiding principle over the C3A period was (or should have been) to avoid treatment unless it was unavoidable. However, given that the likelihood of requiring treatment for an untreated bleed would rise with time, in our submission, there should have been proper systems in place within primary care to deal with patients who were having a bleeding incident and for whom early intervention would have lessened the likelihood that they would require infective treatment.

Systems within haemophilia care

Professor Ludlam was unable to explain when questioned on the subject what systems existed for the vertical dissemination to his staff of guidance such as that emanating from the UKHCDO on treatment. In the case of previously untreated patients, Professor Ludlam suggested that he would almost certainly have been contacted by more junior members of staff. When asked as to how junior doctors knew to contact him in these circumstances, he could not point to any clear method by which this system was communicated to them. There was no written document to which Professor Ludlam could point which made it clear to staff members that in situation where virgin or minimally treated patients presented for treatment at the RIE over this period, the protocol was to contact the consultant. Whilst on the one hand suggesting that the consultant could not be too prescriptive in his guidance given junior staff, he also suggested in his evidence that it would have been useful for the CMO to have provided some guidance to him.

We submit that the objective of getting the person with the most experience and knowledge of the risks to such patients and the most likely chance of selecting the most appropriate treatment was, in

119 Transcript for 13/10/11 (day 54); 74 (20 to 25) (Professor Ludlam)
120 Transcript for 14/10/11 (day 55); 45 to 47 (Professor Ludlam)
121 Transcript for 14/10/11 (day 55); 51(1) (Professor Ludlam)
122 Transcript for 14/10/11 (day 55); 51 to 52 (Professor Ludlam)
123 Transcript for 14/10/11 (day 55); 126(7 to 8) (Professor Ludlam)
theory, the appropriate one for virgin and minimally treated patients over this period. Professor Thomas pointed out that information would be exchanged between haemophilia centre directors around a year before it would be published in a journal. This, in our submission, would place an even greater requirement within haemophilia centres for the directors (who may be privy to current information which more junior members of staff do not have) to make themselves available to make treatment decisions about the most at risk patients. The Inquiry heard no evidence of the existence of any such system in any other hospital in Scotland over this period.

Systems in accident and emergency

As far as the systems in primary care are concerned, the Inquiry heard initial evidence from Professor Ludlam to the effect that, in Edinburgh at least, there existed at this time a non-written system for how patients presenting in the accident emergency department for treatment for a bleed should be managed. Subsequent to this period, according to him, a written protocol of this nature was produced. He then corrected himself and suggested that there was indeed at this time some written form of guidance for accident and emergency staff as to how to deal with patients with potential haemophilia presenting. Amongst the documentary evidence presented to the Inquiry in this section, there was, however, no such protocol at all, either in this period or subsequently. No evidence was heard in this section about any other hospital having such a system.

One of the core participants whom we represent was infected in May 1986 after an infusion of SNBTS factor VIII concentrate at the Edinburgh Royal Infirmary. He has been referred to during the oral hearings as "patient A". As is pointed out in his signed statement to the Inquiry, no member of the haemophilia department was contacted on his first visit to the accident and emergency department with an ongoing bleed at the beginning of May 1986. Further, on his admission on the night of 13 May 1986 (when he was infused with a factor VIII concentrate) he was treated by doctors within the haemophilia department. No consultant was involved in his treatment.

We are unaware of any other evidence available to the Inquiry about the systems to which reference has been made by Professor Ludlam in his oral evidence, both in connection with the accident and emergency department and his own. In light of this evidence, we would invite the Chairman to reject the evidence of Professor Ludlam about the existence of the systems on which he has given

124 Transcript for 11/10/11 (day 52); 94 (9 to 14) (Professor Thomas)
125 Transcript for 14/10/11 (day 55); 81 (Professor Ludlam)
126 Transcript for 14/10/11 (day 55); 86 (Professor Ludlam)
evidence. If the Chairman were to accept that evidence, we would invite him to find that the systems were ineffective in achieving their apparent aim, namely to ensure that at risk patients such as patient A received the fastest and most well informed treatment for his bleed available.

**Conclusion**

In our submission, the Chairman should be slow to accept that the primary care management system spoke to by Professor Ludlam did indeed exist in Edinburgh in the absence of any documentary evidence to substantiate that assertion. Even if the existence of the system were accepted, we would submit that the Chairman should not accept the evidence of the details of it without such documentary support.

As far as the systems at the Glasgow Royal Infirmary were concerned, Professor Lowe gave evidence to the effect that the policy in Glasgow over this period continued to be that moderately severe haemophilia A patients or vWD sufferers who had not previously been treated or received "very minimal" previous treatment would be treated with cryoprecipitate due to the pool size of around 20, rather than thousands of donors.127 As far as mild patients were concerned, he then gave evidence to the effect that the treatment of choice for mild patients at this time in Glasgow was DDAVP and that, even in unplanned treatment, most of the time DDAVP would be effective.128 Given the evidence of Professor Ludlam in the B2 evidence about the mild patients usually being in the most distress, given their inexperience of dealing with bleeds, it seems that such a standard instruction to use DDAVP (appropriate for only the most minor trauma)129 would be unlikely to be able to cope with many mild patient bleeds.130

In any event, there is no evidence of any such consideration being given to mild patients and their possible treatment in any of the other haemophilia centres. Patients were also treated for bleeding outwith the 5 recognised haemophilia centres in Scotland. Previously untreated or minimally treated patients would be least likely to have an existing connection with a major haemophilia centre and would, therefore, be most likely to present for treatment elsewhere. No evidence of any systems in such hospitals has been heard.

127 Transcript for 13/10/11 (day 54); 12 (16) to 13 (7) (Professor Lowe)
128 Transcript for 13/10/11 (day 54); 24 (14 to 24) and 25 (23) (Professor Lowe)
129 Transcript for 28/04/11 (day 17) 109 (3 to 5) (Professor Forbes)
130 Transcript for 03/05/11 (day 18); 53 (5 to 25) (Professor Ludlam)
7. The effectiveness of systems for ensuring that all reasonable steps were taken for the proper assessment of such patients and the avoidance, where possible, of them being exposed to SNBTS factor concentrates

The objective at this time should have been, as stated above, to avoid patients who were to this point uninfected becoming infected with what was now understood to be a potentially lethal disease. Patients with bleeding disorders did, however, become infected over this period with hepatitis C through the administration of blood products (see below). Whatever systems were in place, they were, therefore, not effective in achieving their aim. In our submission, given the advanced knowledge about the potentially lethal character of NANB hepatitis at this time and the fact that the relative risks of cryoprecipitate and factor concentrates were well understood, we submit that such infections should not have occurred over this period (even without the availability of the NANB safe 8Y product, which is considered further below). In light of the unsatisfactory nature of the evidence about the systems in this period in place in Edinburgh and the lack of such evidence about other hospitals in Scotland, we submit that the risks to patients who were probably uninfected were not appreciated or assessed as they should have been. In particular, we invite the Inquiry to conclude that, at this time, there was a failure to ensure that clinical decisions about the treatment of virgin or minimally treated patients were taken by those with the greatest knowledge of the risks inherent in the alternatives. Early warning systems designed to achieve the involvement of those with greatest knowledge at the earliest stage possible in such decision making did not exist and would have been, in our submission, relatively easy to institute given the small numbers of such patients likely to present for treatment. Such strategies as did exist, such as the standing instruction in Glasgow aimed at treating mild patients with DDAVP, were divorced from reality of practice.

8. The information given to untreated and minimally treated patients with bleeding disorders of the particular risks to them of contracting NANB hepatitis during this period and the involvement of such patients in treatment decisions

Professor Ludlam gave evidence in the B2 section to the effect that mild patients who bleed (who are most likely to be virgin patients) often present in distress.\(^{131}\) In very general terms, Professor Lowe gave evidence to the effect that it was very much part of the unit policy at the GRI to discuss

\(^{131}\) Transcript for 03/05/11 (day 18); 53 (5 to 25) (Professor Ludlam)
the risks of NANBH with the patients.\textsuperscript{132} Even in emergency situations, he was of the view that it would be a bad doctor who did not discuss with the patients the pros and cons of the different treatment options with an untreated or minimally treated patient.\textsuperscript{133}

The Inquiry has heard no evidence that any specific information was given to virgin or minimally treated patients over this period about the particular risks inherent in treatment for their bleeding disorders, in particular about the high probability that they would be infected with a potentially lethal disease if treated with SNBTS factor VIII concentrate. The Inquiry has heard no evidence that these patients were involved in treatment decisions, despite the almost inevitably severe consequences of certain decisions being taken. Further submissions about the importance of properly informed patient involvement in treatment decisions are made in our responses in connection with the B5 and C5 sections.

In his evidence to the Inquiry, Professor Thomas expressed the view that patients would have to be told about (a) the fact that of treated with a concentrate they would probably develop NANB hepatitis and might go on to develop cirrhosis\textsuperscript{134} and (b) the different treatments which might be available to them, especially in the case of mild patients\textsuperscript{135}. Current UKHCDO guidance (considered in more detail below) contained no suggestion that patients should be given this information. In response to questioning about information given to patients or parents about first infusions, Professor Ludlam pointed out that they would have given leaflets to patients after they had received their treatment. As he accepted, this measure was rather \textit{post hoc}.\textsuperscript{136}

\textbf{Guidance made available to hospitals involved in the treatment of patients with bleeding disorders over this period}

9. The guidance in place for hospitals around Scotland as to the recommended treatments for patients with bleeding disorders and, in particular, as to the appropriate treatment for virgin or minimally treated patients including the quality and currency of that guidance (including the roles played by the UKHCDO and the government in providing guidance)

\textsuperscript{132} Transcript for 13/10/11 (day 54); 24 (9 to 12) (Professor Lowe)
\textsuperscript{133} Transcript for 13/10/11 (day 54); 31 (22 to 23) (Professor Lowe)
\textsuperscript{134} Transcript for 11/10/11 (day 52); 141 (23) to 142 (2) (Professor Thomas)
\textsuperscript{135} Transcript for 11/10/11 (day 52); 141 (12 to 17) (Professor Thomas)
\textsuperscript{136} Transcript for 13/10/11 (day 54); 163 (21 to 23) (Professor Ludlam)
As is explained above, difficult treatment decisions required to be taken by clinicians over this period, in particular concerning the treatment of patients who required some treatment but who were (based on their treatment histories) probably not infected with NANB hepatitis. Despite this, in his C3A statement, Professor Brian Colvin maintained that over this period "clinicians were obliged to make their own judgements on product safety".\(^{137}\)

**Guidance from the government**

Professor Ludlam indicated in his evidence that, as a clinician, he would have found some guidance from the CMO on these difficult treatment decisions to have been of assistance to him. None was available.\(^{138}\)

A response to this suggestion from the then CMO (Dr Iain Macdonald) was provided in written form to the Inquiry.\(^ {139}\) It was pointed out that decisions of this nature would have been considered to have been medical policy and not public policy. The fact that Dr Macdonald (in the final paragraph) feels that he would have been bound to decline a request from Professor Ludlam for guidance on this matter rather shows, in our submission, the defect in the system. If Professor Ludlam was asking, one could take it that the medical profession was doing nothing about the development of a medical policy. If the government declined, no policy would be developed at all. It seems that the system left important gaps like this which, with the application of a bit less of a territorial attitude, could have been resolved in the interests of the safety of patients. Just because a decision is a clinical one does not mean that useful guidance cannot be given to make that decision easier to take in the interests of public health.

**Guidance from the UKHCDO**

Professor Ludlam explained in his evidence that UKHCDO guidance would be sent directly from its secretariat in Oxford to the haemophilia centres who would issue advice on haemophilia care to other non-centre hospitals.\(^{140}\) The most up to date guidance available from the UKHCDO over the C3A period was contained in the AIDS advisory documents dated 14 December 1984.\(^{141}\) As the title suggests, this material was intended to deal primarily with the HIV risk at that time. It notes that

\(^{137}\) PEN.017.1674 @ 1675, para 3.2
\(^{138}\) Transcript for 14/10/11, (day 55); 62 (20- 21) (Professor Ludlam)
\(^{139}\) PEN.018.0620
\(^{140}\) Transcript for 13/11/11 (day 54); 147 to 148 (Professor Ludlam)
\(^{141}\) SGF.001.2388
there would still be a risk of NANB hepatitis from UK heated concentrates.\textsuperscript{142} It recommends that DDAVP be used in the cases of mild haemophilia A or vWd patients if possible.\textsuperscript{143} For patients not previously exposed to concentrates and children with haemophilia A, the recommendation is "cryoprecipitate or NHS heated factor VIII (if available)" (meaning factor VIII heated so as to eradicate HIV but not NANB). For severe or moderate patients with haemophilia A previously treated with concentrates, the recommendation is heat treated UK factor VIII or US commercial factor VIII. As far as patients not previously exposed to concentrates and mild patients with haemophilia B are concerned, the recommendation is that they be treated with fresh frozen plasma. It is noted that in individual patients there may need to be a choice.\textsuperscript{144} This document is fraught with uncertainty (for example about funding supply and the long term effects of using heat treated products) and appears to have been issued in recognition that some guidance was necessary to deal with the variety of products available and the HIV crisis. It is not clear what is being recommended for mild virgin patients. Despite this, Professor Lowe told the Inquiry that the unit policy at the GRI from December 1984 was very much in accordance with these recommendations.\textsuperscript{145} However, Professor Ludlam made it clear that such guidance documentation could only exist in situations where there had been consensus at the UKHCDO.\textsuperscript{146}

We would also wish to refer to the evidence given by the witness "Alex" as illustrative of the kind of guidance which might have been passed on during this period. A letter, described as a letter from a consultant paediatrician to Alex's GP after his admission to Raigmore Hospital, Inverness (referred to in evidence at page 6 of the transcript of "Alex" on 10 January 2012) described the circumstances of his diagnosis with haemophilia A\textsuperscript{147}. Guidance as to further treatment is given in the following terms:

"\textit{Obviously he will require replacement therapy with cryoprecipitate or factor 8 infusions from time to time following trauma and before any operative procedure}\"

He received an infusion of cryoprecipitate at this time, as detailed in the letter and referred to on page 10 of the transcript. This letter was written by a consultant paediatrician at the hospital where Alex was diagnosed, in part advising as to the future care of his haemophilia. Despite the fact that he had been given cryoprecipitate there, the future treatment options include cryoprecipitate or factor

\textsuperscript{142} SGF.001.2388 @ 2389
\textsuperscript{143} SGF.001.2388 @ 2389
\textsuperscript{144} SGF.001.2388 @ 2390
\textsuperscript{145} Transcript for 13/10/11 (day 54); 16 (15 to 16) (Professor Lowe)
\textsuperscript{146} Transcript for 13/10/11 (day 54); 149 (10) (Professor Ludlam)
\textsuperscript{147} WIT.005.0950
VIII. No further guidance is given in the letter as to the circumstances in which one would be preferable over the other. The terms of the guidance mirror the terms of the recommendations for treatment of an infant with haemophilia A in the UKHCDO guidance of December 1984. Alex later received treatment with factor VIII concentrate in January 1987 at his local hospital (as referred to in the transcript of his evidence at page 12 under reference to a letter from Dr Hann dated 22 January 1987148). His subsequent treatment as an infant was at Yorkhill hospital, where he was looked after in the early months of January 1987 with cryoprecipitate. By this time, it was clear to Dr Pettigrew at Yorkhill that (a) at that time treatment with cryoprecipitate was preferable in an infant from the point of view of NANB hepatitis and (b) that his future treatment needs would be likely to be able to be catered for with heat treated factor VIII concentrate, the arrival of which was imminent at that time.149 The result of the guidance given by Raigmore to those responsible for Alex's care locally appears to have been that it was not until after he arrived at Yorkhill (by which time we was already infected) that cryoprecipitate was even mentioned (page 17 of the transcript).

Conclusion

In our submission, the responsibility for providing adequate guidance for the safety of patients with bleeding disorders fell over this period to the UKHCDO, whose guidance was issued to all hospitals (be they recognised haemophilia centres or not) as to the risks inherent in treatment and with broad recommendations as to how to treat patients at risk of infection. Such patients over this period included patients who were not already infected with NANB hepatitis, namely patients who had never been treated for their bleeding disorder or who had received only minimal treatment, to the extent that they had not yet been infected. The existence of guidance showed that it was possible to draft broad guidelines to assist with treatment decisions. The UKHCDO failed to update its guidance from December 1984 (which was principally designed to deal with the HIV crisis) to take account of (a) the updated knowledge of the potential severity of NANB hepatitis and (b) the increased protection against HIV afforded by the screening of blood used in the manufacture of products like cryoprecipitate from October 1985. New guidelines should have been introduced from 1985 which (a) made it clear to hospitals that virgin or minimally treated patients who may not yet be infected presenting for treatment should be treated by senior members of staff and (b) the preferred treatment in such patients should be cryoprecipitate. In his evidence, Professor Lowe pointed out that guidance documents were designed for the guidance of wise doctors not for blind obedience150

148 WIT.005.0952
149 WIT.005.0954 and the transcript of Alex's evidence at page 15
150 Transcript for 13/10/11 (day 54); 37 (15 to 16) (Professor Lowe)
He also concluded that treatment decisions were multi-factorial and that one had to decide as a doctor on the basis of “gut feeling”. The purpose of the guidance should have been to make that process as educated an estimation as possible, in our submission. The existing guidance did not achieve that aim.

In our submission, the government also had a role to play in assisting in the provision of guidance to deal with situations like this. We submit that the government should, in light of the HIV crisis at least, have recognised that virgin and minimally treated patients were an at risk group and that they were likely to be a group for whom a particular policy framework required to be established (in particular when virgin patients started to be infected with NANB hepatitis in Scotland). We accept that the precise medical content of that guidance was a matter for the UKHCDO and that clinical decisions for the treatment of individual patients fell to the treating doctors. However, we submit that it was the government which could and should have recognised the potential problem with these patients, that this problem could be solved and that there were many hospitals which would benefit from broad guidance to assist with clinical treatment decisions.

**Action after May 1986**

10. Steps taken by the NHS and/or the government in Scotland to minimise the risks of a virgin or minimally treated patient contracting NANB hepatitis in the aftermath of the infection of a virgin patient in Edinburgh in May 1986 or any earlier such infections within the relevant period of which the Inquiry is aware (other than the procurement of a supply of the English 8Y product)

A virgin patient was infected with NANB hepatitis as a result of the administration to him, for the first time, of Scottish factor VIII concentrate heated at 68 degrees centigrade for 72 hours in the early hours of 14 May 1986.152

**Guidance**

We have made our submission above about the guidance which should have been in place for the treatment of virgin or minimally treated patients from 1985. Given that it was not, we would submit

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151 Transcript for 13/10/11 (day 54); 39 (17 to 19) (Professor Lowe)
152 This patient has been referred to in the hearings as “patient A” out of respect for his confidentiality. He is also referred to in paragraph 10.197 of the preliminary report.
that emergency measures should have been taken to put in place such guidance from May 1986 when a virgin haemophilia patient was infected with NANB hepatitis in Edinburgh for the protection of other such patients who may present for treatment over the C3A period. We address below the possibility that a supply of English 8Y might have been made available to meet the modest needs of these patients in Scotland pending the introduction of a concentrate product heat treated so as to inactivate the NANB virus.

Safer Scottish factor VIII

Further, in the aftermath of this infection, Dr Boulton wrote to Professor Cash that Professor Ludlam had indicated that he would be happy to treat patients such as the virgin patient infected in Edinburgh with a concentrate produced by SNBTS which had been subjected to a similar heat treatment regime to the then available English 8Y product. In a letter to Dr Perry of the same date, Dr Boulton suggested that Professor Ludlam was a bit "ruthful with his own staff" as he thought that the patient could have received 8Y or "an equivalent product". It is submitted that greater efforts could have been made to make a small amount of the Scottish factor VIII concentrate then in development available to meet the likely modest needs of patients who were not yet infected with NANB hepatitis in Scotland.

By letter dated 2 July 1986, Dr Perry informed Dr Boulton that it was anticipated that trial versions of the Scottish factor VIII concentrate heated to same degree as English 8Y would be available before stocks of the previous product were exhausted but that that could not yet be announced as a policy. By letter dated 7 July 1986, Dr Perry stated:

"While there will be no PFC product virucidally comparable to 8Y until September ’86, after that time it would be my intention to supply the Phase III product to “virgins” since we hope to demonstrate by that time that it is virucidally equivalent thus removing the need to go South"

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153 SNB.007.5869 (27 June 1986)
154 SNB.007.5871
155 SNB.007.5909
156 SNB.007.5913
In his evidence, Dr Perry clarified that the intention was that that product would be used from that time for both virgin and minimally treated patients. An "eleventh hour problem" was encountered with freeze drying the new product in around August 1986. By 22 December 1986, Z8 (dry heated at 80°C for 72 hours) was issued to Edinburgh for clinical trial. We would submit that it is likely, as was anecdotally described by Professor Colvin, that in rare situations, small supplies of new products might be made available. This should have been done as a matter of urgency and supplies for clinical trial been made available for virgin and minimally treated patients around Scotland.

As far back as May 1983 in a memo from John Watt to Dr Foster referring to overriding concern leading to experimentation with heat treatment to that point having been to try to eradicate hepatitis from SNBTS products, the strategy to that point had been to benefit mild and moderate haemophiliacs in the foreseeable future as severe patients would already be infected. The plan at that time had been that 30% of the concentrate produced would be heat treated as this was the amount of the total which the mild and moderate group would need. A safe Scottish factor VIII concentrate did not actually become available until the end of the C3A period. In a document entitled "The Development of Hepatitis-Safe Factor VIII Concentrates by the Scottish National Blood Transfusion Service" (by Peter Foster dated 9 February 1999), it was pointed out that Scotland was believed to be the first country in the world to be able to provide sufficient hepatitis safe factor VIII for all of its patients with haemophilia A.

It would appear that at some point over this period, the focus of the PFC changed from being on producing a quality product for a minority of the patients (predominantly virgin and minimally treated patients) for whom it was likely to be of help to producing a quantity of product sufficient to meet the needs of all haemophilia A patients.

Conclusion

We would submit that inadequate steps were taken in light of the infection of a virgin patient in May 1986 in Edinburgh with NANB hepatitis to avoid a re-occurrence of this infection in similar patients around Scotland.

157 Transcript for 7/12/11 (day 74); 24 (15 to 19) (Dr Perry)
158 SNB.007.6080
159 SNB.009.4073
160 Transcript for 7/12/11 (day 74); 98 (11) to 99 (2) (Professor Colvin)
161 SNB.007.3635
162 SNB.001.6647, para 1.4
The possibility of alternative concentrate products being made available for Scottish patients over this period

11. The advantages in this period of the English 8Y concentrate over the available SNBTS factor VIII concentrate and the effectiveness of information exchange between England and Scotland on this issue

Evidence on the safety of the Scottish factor VIII concentrate available over this period

The Scottish factor VIII concentrate available over this period (NY) was heat treated to 68 degrees centigrade for 24 hours. That heat treatment regime had rendered the product free from infectivity with HIV. However, there was no evidence to suggest that that heat treatment regime would inactivate the NANB virus. Dr Perry accepted that the product available in March 1986 was known to infect with NANB hepatitis or, at least, that it was probably not free from that virus. That a virgin patient became infected with NANB hepatitis in May 1986 as the result of a first infusion with the Scottish concentrate was "not wholly surprising" according to Dr Perry.

Professor Ludlam gave evidence to the effect that they did not know until the infection of a virgin haemophilia A patient who had been treated with this factor VIII concentrate that it was known that the product was infective. In our submission, this was entirely the wrong attitude towards the likely infectivity of the product. Given the historical infectivity of domestically produced concentrates (see the literature references in response to issue 2 above), the new product should have been presumed to be infective until the contrary was proven. In the case of the Scottish concentrate in use at that time, there was not even a hypothesis, never mind proof, that the product was non-infective (see position of the PFC as expressed by Dr Perry below). At another part of his evidence, Professor Ludlam did accept that the product was thought to be infective. Therefore, the potential attractiveness of other concentrate products required to be judged in comparison with a Scottish product which, would be highly likely, if not certain, to infect a recipient with NANB hepatitis on first infusion.

Evidence on the safety of 8Y

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163 See preliminary report paragraph 11.249 and SNB.007.5202 - Dr Perry was informing BPL as late as July 1985 that as far as this product was concerned “it is unlikely we will achieve freedom from NANB”

164 Transcript for 7/12/11 (day 74); 7 (20 to 23) and 8 (13 to 16) (Dr Perry)

165 Transcript for 7/12/11 (day 74); 10 (15 to 16) (Dr Perry)
In England, a factor VIII concentrate product heat treated to 80 degrees for 72 hours (known as 8Y) was routinely available from September 1985. The product was discussed at the CBLA research and development committee meeting on 9 July 1985. It was noted that a number of patients in a clinical trial of 8Y, had already passed the point at which it would be expected that they would be infected. An application for a product licence was being prepared. This meeting was not attended by anyone from Scotland. Indeed, the meeting received the apologies of Dr Forrester, who was the SHHD representative who was meant to have been in attendance. It is understood that the meetings of this committee were carried out confidentially. However, one assumes that the subsequent minutes would have at least allowed those within government to be made aware of the existence and potential benefits of the 8Y product. Professor Ludlam gave evidence to the effect that he was not aware of the existence of the CBLA. He indicated that maybe that high level guidance on 8Y would have been something which haemophilia clinicians would have appreciated.

The launch letter for 8Y dated 24 July 1985 (addressed to haemophilia directors in England and Wales) asked clinicians to identify "those patients likely to benefit most" from the new product. As had been pointed out at the CBLA meeting, clinical trials of the product were underway in 6 haemophilia centres and several patients had passed the point at which it would normally be expected that they would have been infected with NANBH by an unheated concentrate. The letter does not appear to have been sent to haemophilia directors in Scotland. However, in his evidence, Dr Perry thought that haemophilia directors in Scotland would have been likely to have seen this launch documentation through their contacts. The English directors were asked to identify the patients who were most at risk so that the products could be directed towards them. It seems to have been an omission on the part of Scottish directors, once they found out about this trial, not to have sought to have their "at risk" patients included in this trial. The letter presupposes that there was some benefit to those patients most at risk. This comes from the manufacturer. However, even at this early stage participation in such a trial would have given an uninfected patient who needed...
concentrate some chance of avoiding infection which would not have been available if treated with an SNBTS concentrate. This letter (as Professor Lowe also confirmed in his evidence) indicated that the product was also achieving the appropriate rise in factor VIII levels.\textsuperscript{175}

By the time of the meeting of the CBLA research and development committee on 19 December 1985, Dr Rizza had reported that he had been using 8Y in a clinical trial for 9 months and that none of his patients (including children) had become clinically ill. He considered this to be encouraging. This contrasts with his report on the heat treated factor IX product, in which he reported that the incidence of NANBH was hard to assess.\textsuperscript{176} It is interesting to note that this meeting was the first attended by Dr Forrester on behalf of the SHHD.\textsuperscript{177} He is not minuted as having made any contribution at the meeting. There is no evidence of which we are aware of him having reported these encouraging findings to anyone.

At a joint meeting between representatives of the BPL and the PFC on 24 March 1986, Dr Smith outlined that after 12 months of trials there had been no infections in virgin haemophiliacs from the 8Y product.\textsuperscript{178} The BPL annual report to March 1986 (which was not published until September 1986 but which is indicative of the position as it stood at that time) pointed out that there were still no reported cases of NANB transmission.\textsuperscript{179} The document also refers to the BPL’s “promotional activities”.\textsuperscript{180} We submit that by this stage, the superiority of the 8Y product over the Scottish factor VIII concentrate was well established in a relative sense. This was known in Scotland but no action was taken.

In a report by Dr Perry, PFC, for an SNBTS/Haemophilia Directors meeting on 5 March 1986\textsuperscript{181}, Dr Perry noted that “Directors will be aware that [BPL] are currently issuing a FVIII product which has been heated at 80 degrees/72 hrs and preliminary clinical data indicates that this material is non-infective with respect to HTLV III, NANB and Hepatitis B.” In an “Addendum to Development of New Products 1986/87” it was observed that “The heat-treatment procedure now being applied to FIX

\textsuperscript{175} Transcript for 13/10/11 (day 54); 42 (22 to 23) (Professor Lowe)
\textsuperscript{176} PEN.016.1152 @ 1153
\textsuperscript{177} PEN.016.1152
\textsuperscript{178} SNB.007.5664 @ 5666
\textsuperscript{179} DHF.002.1590 @ 1594
\textsuperscript{180} DHF.002.1590 @ 1621 - 1622
\textsuperscript{181} SNB.001.5469
concentrates (PFC & BPL) and to FVIII (BPL) may well be effective in ensuring non-infectivity of products.” 182 Further, Dr Perry accepted in his evidence that by March 1986, the signs [as regards the emerging evidence non-infectivity of 8Y] were looking promising. 183 It was clearly thought that 8Y was safer in July 1986 as it was contemplated that it would be used for Edinburgh virgin patients by Dr Boulton and Dr Perry. 184

Professor Ludlam’s response to this data in his evidence was to say that it was unreliable because (a) they did not know how many patients had been tested (b) they were not all previously untreated patients and (c) the frequency of liver testing applied did not meet international standards. 185 Therefore, Professor Ludlam was of the view that the viral safety of the product was unknown with respect to NANB hepatitis. 186 This, in our submission, indicated the application of the wrong approach to the data.

The data on 32 patients (the emerging data which had been reported upon by Dr Smith above) who had received 8Y was presented by Dr Smith to a UKHCDO meeting in September 1986. This was described by Professor Ludlam as being "soft data" (under reference to a comment made by Dr Kernoff at that meeting). However, Professor Ludlam also accepted that it was interesting and reassuring data. 187 That the data was soft did not mean, in our submission, that it contained no indication at all that 8Y was not looking like it might be non-infective. Against a background of increasing concern about the severity of NANB hepatitis, we submit that there should have been greater weight accorded to this data (the thrust of which had been available at least since the start of 1986, if not the middle of 1985) especially when one considers that it would otherwise take many years for sufficient virgin patients to prove anything conclusively. In his evidence, Professor Ludlam was of the view that it was in July 1986 that evidence became available which convinced him of the merits of 8Y. That was before Dr Smith’s report was presented to the UKHCDO. There would appear, in our submission, to be no good reason why at that point it should have suddenly become apparent that 8Y was safer than the SNBTS factor VIII. In our submission, this could and should have been realised earlier that year, at the latest. As we will address below, the evidence shows that it was not

182 SNB.001.5484
183 Transcript for 7/12/11 (day 74); 7 (9 to 12) (Dr Perry)
184 SNB.007.5911 appended to SNB.007.5910
185 Transcript for 13/10/11 (day 54); 101 (22) to 102 (1) (Professor Ludlam)
186 Transcript for 13/10/11 (day 54); 104 (1 to 3) (Professor Ludlam)
187 Transcript for 13/10/11 (day 54); 116 (10 to 16) (Professor Ludlam) and SNF.001.1123
the emergence of greater information that prompted the move on Professor Ludlam’s part to procure a supply of 8Y but the infection of a virgin patient in his hospital with NANBH.

The interim report presented containing this data had studied patients with no previous exposure to large pool concentrates but did have variable previous exposure to cryoprecipitate based on difficulties getting people for the study.\(^{188}\) None of the patients had an ALT above 2 and a half times the upper limit of normal. This included a number of virgin patients.\(^{189}\) No cases of HIV conversion in over 100 patients. There was a great deal of caution about not making unjustified claims of safety for products at this time, according to Professor Colvin, based on the disappointments of previous commercial products which had claimed to be non-infective but had not been.\(^{190}\) As far as use for untreated or minimally treated patients was concerned, Professor Colvin gave evidence to the effect that he used cryoprecipitate for children until he started using 8Y around July 1985.\(^{191}\) Thus, one requires to differentiate between claims being made for the conclusive safety of a product and there being sufficient evidence for it to be used as the treatment of choice for the probably uninfected patient.

In letter from Mr Pettet to Dr Perry dated 24 July 1986, Mr Pettet appeared to want to make it clear to Dr Perry what the possible risks of the products were. He raised one point and one point only, concerning the lack of HIV screening of the plasma. No issue was raised about possible NANB infectivity from the product.\(^{192}\) There was no reluctance on the part of BPL to supply some 8Y to Scotland when it was asked for.

**Conclusion on evidence about the safety of 8Y**

This evidence, in our submission, makes it clear that by 1985 the English 8Y product offered advantages over the Scottish factor VIII concentrate as far as infectivity with NANB hepatitis was concerned. That is not to say that claims could be made at that stage on the basis of strict scientific proof that the English heat treatment regime had inactivated the NANB virus. However, in our submission it was not the question that those responsible for the treatment of bleeding disorders

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\(^{188}\) SNF.001.1123

\(^{189}\) SNF.001.1123 @ 1126

\(^{190}\) Transcript for 14/10/11 (day 55); 144 (18) to 155 (7) (Professor Colvin)

\(^{191}\) Transcript for 7/12/11 (day 74); 89 (11 to 14) (Professor Colvin)

\(^{192}\) SNB.007.5980 @ 5891
should have been asking themselves. The appropriate question was whether the available evidence demonstrated that there was any increased margin of safety in the English 8Y product when compared with the Scottish factor VIII of which there was no evidence of non-infectivity and which was, according to the evidence, thought to be infective with NANB hepatitis. Against a product with a perceived 100% chance of infection, even one with a 99% chance of infection would be the safer product. The question should not have been whether 8Y was safe but whether it was safer than the Scottish factor VIII. In his evidence, under reference to the then almost 100% rate of infection with NANB hepatitis with both NHS and commercial concentrates, Professor Thomas pointed out in response to questioning about a paper he had written193 that "when the inactivation procedures started to become a possibility then if there were even one or two patients who didn't develop NANB then that would be significant". In our submission, this is the attitude which should have been adopted by haemophilia clinicians in Scotland towards the apparently safer, and therefore, significant 8Y product.194 Further, he pointed out when comparing the partially heated concentrates to the non-heated concentrates that "with that [virtually guaranteed infection] as the worst scenario, anything that was potentially better than that would be preferably used, whether it was proven to be better or just possibly better. I think ethically that would be the material you would want to use.195" Therefore, Professor Thomas equated the use of a product which was just possibly safer as imposing an ethical duty on clinicians to try to use it. In his evidence, Professor Ludlam was keen to point out that when he heard about the 8Y product, he was thinking that it might be safer against NANBH than the then available Scottish concentrate, rather than safe.196 In our submission, this distinction, on the basis of the approach outlined by Professor Thomas, should have resulted in greater steps being taken to procure a supply for probably uninfected Scottish patients. That it appeared safer, to whatever degree, should have started the process. The approach of Professor Thomas notwithstanding that he is a hepatologist as opposed to an haemophilia clinician preferable. His CV showed that he had had a distinguished career and that he was a founding editor of the Journal of Viral Hepatitis.197 He had a long list of academic distinctions and also appeared able to talk in his evidence about different aspects of haemophilia care.198 His CV also demonstrated that he had a general knowledge of medicine and that he had practised acute case receipt.199 He had involvement with haemophilia patients due to their infections with HIV and hepatitis (B and C) and also wrote papers in conjunction with haemophilia clinicians, like Dr Kernoff (see above).

193 LIT.001.0800)
194 Transcript for 11/10/11 (day 52); 89 (21) to 90 (1) (Professor Thomas)
195 Transcript for 11/10/11 (day 52); 158 (22) to 159 (1) (Professor Thomas)
196 Transcript for 13/10/11 (day 54); 100 (14 to 20) (Professor Ludlam)
197 PEN.017.1617 @ 1619
198 See his evidence on home treatment in transcript for 11/10/11 (day 52); 92 (Professor Thomas)
199 PEN.017.1617 @ 1622
It was claimed in evidence that it was not until 1988 or perhaps until 1993 that it could be shown that 8Y was free from NANB hepatitis. That may be so by the standards of scientific proof which may be required before a product can make such claims on the mass market. However, in our submission the evidence was available much earlier for the correct test (detailed above) to be met for a supply of 8Y for virgin or minimally treated Scottish patients. Professor Van Aken confirmed in his C3 statement that “An interim review of the clinical trial with 8Y in March 1986 showed that it was likely that the product was free of NABNH.”

**Information exchange - production level**

Both at the level of production and at the haematology level, the Inquiry has heard evidence about the information exchange between England and Scotland. As can be seen above, information about the emerging data on 8Y was communicated to people at the PFC by the BPL. Dr Foster explained that in his experience there was a very free exchange of information about products in the not for profit sector, in particular between the BPL and the PFC. It appears that nobody at PFC thought to act on this information in the interests of virgin and minimally treated patients in Scotland.

**Haemophilia clinicians**

Professor Ludlam gave evidence to the effect that he first became aware of the development of the 8Y product at some point in 1985 and that he received information about it at the UKHCDO meetings which he attended. Professor Ludlam could not remember what evidence had been made available to him about the early indications of NANB safety in the 8Y product. He attended 5 directors meetings between the launch of 8Y and the spring of 1986, at which time he could have discussed the clinical trial progress with those involved, such as Dr Rizza and Dr Colvin. In his statement, Professor Colvin alluded to discussion amongst haemophilia directors about infectivity

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200 PEN.017.1597 @ 1600
201 Transcript for 10/05/11 (day 22); 93 (23) to 94 (1) (Dr Peter Foster)
202 Transcript for 14/10/11 (day 55); 91(15 to 22) (Professor Ludlam)
203 Transcript for 13/10/11 (day 54); 107 (10) (Professor Ludlam)
204 LOT.003.2698 - 30 September 1985 (21st meeting of the Reference Centre Directors); LOT.003.3964 - 21 October 1985 (16th meeting of the UK Haemophilia Centre Directors); LOT.003.2693 - 9 January 1986 (22nd meeting of the Reference Centre Directors); LOT.003.3955 - 17 March 1986 (17th meeting of the UK Haemophilia Centre Directors); and LOT.003.3100 - 14 April 1986 (23rd meeting of the Reference Centre Directors)
issues and other product risks as well as to the results of trials being known and shared before publication. Dr Perry expressed the view that the emerging data about the apparent safety of 8Y would have been discussed at the UKHCDO meetings. Professor Thomas points out that information would be exchanged between haemophilia centre directors around a year before it would be published in a journal. However, Professor Lowe did not recall seeing the launch letter or any information about the emergence of 8Y being given to him by his centre director at the time, Professor Forbes.

**Conclusion**

We submit that there was an inadequate response in Scotland at PFC, SNBTS, SHHD and the haemophilia centres to information available to all of them about the apparent freedom of the English 8Y product from infection with NANB hepatitis. We submit that it is likely that the actual response was due to (a) a failure to ask the right questions about and appreciate the apparent advantages of the 8Y product over the then available Scottish factor VIII concentrate and (b) a failure properly to consider the probability of a patient who was likely to be uninfected presenting for treatment in Scotland.

12. The action taken in Scotland in light of that state of affairs, including the reasons why action was or was not taken

The Inquiry has heard no evidence that any steps were taken in the interests of securing safer treatment for patients with bleeding disorders in light of this emerging information of the relative safety of the English 8Y concentrate until after the infection of a virgin patient with NANB hepatitis in Edinburgh in May 1986. No steps were taken to procure a supply of English 8Y for Scotland before the aftermath of the infection of a virgin patient in Edinburgh in May 1986. Dr Perry was of the view that by the time a request was made in the summer of 1986, he "probably" be able to get some, given the small requirement. The question of what might have been done is addressed below.

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205 PEN.017.1674 @ 1675, para 3.2
206 Transcript for 7/12/11 (day 74); 12 (16 to 18) (Dr Perry)
207 Transcript for 11/10/11 (day 52); 43 (25) and 44(24) (Professor Thomas)
208 Transcript for 11/10/11 (day 52); 43 (21 to 24) (Professor Thomas)
209 Transcript for 7/12/11 (day 74); 13 (9 to 11) (Dr Perry)
210 Transcript for 7/12/11 (day 74); 26 (9 to 14) (Dr Perry)
13. Whether, when, how, in what quantities and on what conditions a supply of English 8Y for treatment of previously untreated and/or minimally treated patients in Scotland could practically have been made available and whether, when and by whom efforts should have been made to secure such a supply

The likelihood of an earlier supply

Dr Perry said in his evidence that once it was suggested that a supply of 8Y might be procured from England by Professor Ludlam via Dr Boulton, he and Dr Bouton considered it to be a feasible proposition which was well worth exploring.\(^{211}\) Despite the short supply of 8Y in England, that did not seem to them to prohibit the likelihood of a small supply being made available to Scotland for probably uninfected patients, especially as such a request might provide BPL with interesting data on how these rare patients reacted to the product.\(^{212}\)

Given that no attempts were made to secure a supply of English 8Y for Scotland before the summer of 1986, it cannot be said with certainty how, if such attempts had been made, what would have been likely to have happened. However, given that a supply of 8Y was made available and Dr Perry's stated views on the likelihood at that time that such a supply would be forthcoming, we can see no reason why an earlier request would not also have been received favourably. The possibility of a product swap was also not considered and that possibility is also addressed elsewhere in this submission. Professor Ludlam gave evidence to the effect that if he had had a supply of 8Y available in May 1986, he would have used it on the untreated patient at that time.\(^{213}\) Professor Colvin gave evidence to the same effect.\(^{214}\)

The conditions upon which such a supply might have been made available at an earlier date

At the time when a supply was made available, Dr Perry did not think that participation in a clinical trial was being made a mandatory condition of the supply from BPL.\(^{215}\) Though follow up information from the reaction of probably uninfected patients to the product would have been useful, there is no reason to think that an earlier supply would have had any such mandatory condition attached to it either. When the supply was actually produced, Mr Pettet at BPL pointed out to Dr Perry in a letter

\(^{211}\) Transcript for 7/12/11 (day 74); 22 (2 to 4) (Dr Perry)
\(^{212}\) Transcript for 7/12/11 (day 74); 21 (11 to 15) (Dr Perry)
\(^{213}\) Transcript for 13/10/11 (day 54); 131 (3 to 18) (Professor Ludlam)
\(^{214}\) Transcript for 7/12/11 (day 74); 96 (2 to 7) (Professor Colvin)
\(^{215}\) Transcript for 7/12/11 (day 74); 34 (8 to 9) (Dr Perry)
dated 24 July 1986 that he could provide 8Y set aside for trial purposes but also suggested that some can be put aside for patients who did not meet the criteria for the trial. Dr Perry was clear that the product was there to be used freely in the treatment of probably uninfected patients in Scotland. By the latter part of 1985 the product was available for routine use in England and not just as part of a clinical trial (as Dr Perry pointed out in his evidence). The 50 vials which were procured were not provided with a requirement that they be administered only as part of a clinical trial. Given that by the latter part of 1985 the product was available for routine use in England and not just as part of a clinical trial, we would submit that a request for an amount to meet the requirements of virgin and minimally treated patients in Scotland would have been likely to have been fulfilled at any point in 1986.

The quantity of product which might have been made available to Scotland

It is, of course, the position that relatively small quantities of 8Y would have been needed to cater for the eventuality of probably uninfected patients requiring treatment with a concentrate in Scotland in the time period between 1986 and the introduction of Z8 in April 1987. The fact that the supply would only be used in those patients would be likely to have made BPL interested in making more product available to Scotland in the hope that data might be reciprocated about the effects of the product on the treated patients. As is shown above, they had had trouble in England securing patients for the evaluation of the product. The possibility of a product swap is discussed below.

As noted above, 50 vials were procured in the aftermath of the infection of the virgin patient in Edinburgh in May 1986. A request for this amount, apparently for Edinburgh patents, was made by Dr Boulton to Dr Perry by letter dated 7 July 1986. The 50 vials is described as amount which would be enough for initial treatment of a presenting virgin patient. He anticipates in the letter that if more were needed they could call it in from Oxford over the next 24 hours. He indicated that Professor Ludlam had no untreated patients on his books at that time. This letter is clearly the genesis of why an amount was procured. It was procured in that amount for the reasons set out by Dr Boulton, not because anyone was of the view that more would be impossible to obtain. Dr Boulton (a former haemophilia centre directors in Liverpool and therefore, no doubt, used to dealing with the BPL) appears to express the view that more would be available from Oxford if needed. From

216 SNB.007.5980
217 Transcript for 7/12/11 (day 74); 41 to 42 (Dr Perry)
218 Transcript for 7/12/11 (day 74); 49 (15 to 17) (Dr Perry)
219 Transcript for 7/12/11 (day 74); 50 (9 to 12) (Dr Perry)
220 SNB.007.5914
this and in light of the observations made above, we submit that an earlier supply, in greater quantities, would have been forthcoming, if requested. In our submission, the approach of Dr Boulton was to open the door to the supply with a small request, with an anticipation that more would be forthcoming once the door was open.

**By whom such an earlier supply should have been procured**

In the event that such a supply had been procured earlier, Dr Perry gave clear evidence to the effect that it was the responsibility of the haemophilia clinicians to instigate this process. It could not have been part of the role of SNBTS/the PFC in his view actively to promote a potentially better product from outwith the SNBTS. In the letter from Dr Boulton to Dr Perry dated 27 June 1986 (referred to above) it was reported that Professor Ludlam thought that the patient infected in May 1986 should have got 8Y or some equivalent. In our submission, the reason why Professor Ludlam was ruthless with his staff, or "a bit sad" as he described it in evidence was, because he had regretted not acting upon the data available earlier that year, which he himself accepted indicated that 8Y might not be hepatitis free but that it might be less infective than the then available SNBTS concentrate which was highly likely to transmit NANB hepatitis. It was only when a virgin patient became infected that a supply of 8Y was procured, after the horse had bolted (for that patient at least). This indicates that he knew that it was his responsibility to instigate such an action, which he later did.

To us, it seems reasonable that it would have been expected that the haemophilia clinicians would require to instigate the process as they would have been most likely to recognise the need for such a product for particular patients. However, the system described by Dr Perry does seem deficient in that it is clear from the material available to the Inquiry that both at PFC and within the SNBTS more generally, there was knowledge of the clinical trials going on with the 8Y product in England. Further, the development of the Z8 product and the delays with that forms an important part of the background (as the correspondence between Dr Perry and Dr Boulton demonstrates). In our submission, a less territorial system based on information sharing might have resulted in it being realised at an earlier date that there was a gap in the Scottish market for a factor VIII concentrate to

221 Transcript for 7/12/11 (day 74); 39 (22) to 40 (1) (Dr Perry)
222 Transcript for 13/10/11 (day 54); 120 (3 to 4) (Professor Ludlam)
223 Transcript for 13/10/11 (day 54); 119 (14 to 23) (Professor Ludlam)
224 Transcript for 14/10/11 (day 55); 104(8 to 11) (Professor Ludlam)
treat probably uninfected patients, which could be filled by the procurement of a modest supply of 8Y. The procurement system is addressed in some more detail below.

14. The systems in place for the procurement of blood products (including the projection of demand), in particular for virgin and minimally treated patients, over this period and the effectiveness of those systems

Dr Perry said in his evidence that it was the treating doctors' responsibility to determine which patients particular products should be given to (and not that of SNBTS). It seems unrealistic, in our submission, that Dr Perry would have been able to describe to treating doctors the situations in which the supply which he had procured would be suitable for use. Dr Perry gave evidence to the effect that the supply of 8Y did not have to go through the PFC but that he considered that it was best for it to do so, so that a degree of central control could be exercised over what would have been a very scarce product. It was not normally the case that non-SNBTS products were procured through SNBTS/PFC but in the case of the 8Y supply, that was what happened due to the specific request for assistance made by Professor Ludlam.

The actual procurement of 8Y happened as a result of a request being made by Professor Ludlam to Dr Perry at the PFC. Professor Ludlam told the Inquiry in evidence that there he made the request through that channel as he thought that it would be the best way to get a supply of the product. He thought it unlikely that he would be able to secure such a supply, though by this time he had been a haemophilia centre director for around 16 years. Further, he gave evidence to the effect that he was subsequently able to procure a further supply from the haemophilia centre in Newcastle.

There is no evidence of others having considered the PFC to be a channel through which favourable products could be procured. Further, Dr Perry gave evidence to the effect that, in the early 1980s, the haemophilia doctors had strongly rejected the proposal that the PFC should be responsible for the procurement of all products for use in Scotland, given their specific interest as a manufacturer.

225 Transcript for 7/12/11 (day 74); 15 (16 to 23) (Dr Perry)
226 Transcript for 7/12/11 (day 74); 29 (5 to 19) (Dr Perry)
227 Transcript for 7/12/11 (day 74); 37 to 39 (Dr Perry)
228 Transcript for 13/10/11 (day 54); 130 (18 to 23) (Professor Ludlam)
229 Transcript for 7/12/11 (day 74); 54 (15 to 25) (Dr Perry)
The mechanics of the procurement process appeared flexible enough to enable the person most likely to get the product to be the person who asked for it. In our submission, the issue arose as a result of a failure of information sharing and on the part of the haemophilia clinicians to realise that there was a gap in their treatment which needed to and could be filled with the 8Y product.

15. Consideration given in Scotland to the possibility of swapping a quantity of SNBTS factor VIII concentrate for a supply of 8Y

Evidence

The Inquiry heard no evidence that the possibility of swapping a quantity of the then current SNBTS factor VIII concentrate for a small quantity of English 8Y was considered. The available supply of 8Y in England was not sufficient to meet the treatment of all English patients.\(^\text{230}\) The Inquiry has, however, heard evidence that the English and Scottish manufacturing centres worked in close cooperation with one another and there were precedents for "mutual assistance."\(^\text{231}\)

Conclusion

In our submission, the failure to consider this option is indicative of a failure on the part of the SNBTS and the haemophilia doctors (a) to appreciate the urgent need for a safe concentrate product in Scotland given the likelihood that virgin or minimally treated patients would be infected on first infusion of the Scottish product (b) to undertake a proper risk assessment in connection with the advantages of 8Y and (c) to anticipate the likely response of the English transfusion services to a request for a supply of 8Y. As far as (b) is concerned, we have addressed in response to issue 11 above the approach which we submit should have been taken. As far as (c) is concerned, we submit that there was a failure to appreciate that the English doctors would be likely to be hesitant about the release of a quantity of the 8Y product not just because of the apparent advantages which it offered as far as NANB infection was concerned, but also because in England it was the first HIV safe product. To use the alternative would, therefore, be to have exposed patients not only to the risk of NANB hepatitis (with which, of course, the majority would already have been infected) but also to the risk of HIV infection. A swap would have alleviated concerns about the latter of these two points as the Scottish product was thought to have been free from HIV infection from December 1984. It would also have resulted in the likelihood of greater quantities of 8Y being made available to

\(^{230}\) Transcript for 13/10/11 (day 54); 130 (6 to 7) (Professor Ludlam)

\(^{231}\) Transcript for 7/12/11 (day 74); 66 (7 to 17) (Dr Perry)
Scotland, in our submission. As far as NANB infection was concerned, it seems unlikely that this would have prevented a swap from taking place as (a) the evidence was not conclusive on the infectivity of 8Y with NANB hepatitis in 1985 and (b) the literature suggested that most patients in England previously exposed to concentrates would be infected with NANB hepatitis anyway.

Professor Cash gave evidence to the effect that it was unlikely that he would have considered possibility of obtaining a quantity of 8Y in the C3A period as that would have been to deprive English patients of the product against a background of there being serious shortage of the product even for English patients.232 This passage, in our submission, demonstrates that Professor Cash could have made such an approach but did not. The possibility of a swap for a small quantity of 8Y to cater for the needs of probably uninfected Scottish patients would have dealt with concerns that depriving England of 8Y would have resulted in patients becoming exposed to potentially HIV infective products. As was the case in Scotland, the majority of patients who had been treated before (if not all of them) would have been infected with NANB hepatitis already.

We submit that consideration could and should have been given to swapping a quantity of the then available Scottish factor VIII concentrate for an amount of English 8Y sufficient to meet the likely demands of patients in Scotland who required treatment who did not appear to be infected with NANB hepatitis in 1985.

16. The reasons why a supply of 8Y was made available to Scotland in the summer of 1986

Evidence

Professor Ludlam told the Inquiry in evidence that he was the person who had instigated the request from the supply of 8Y through Dr Perry.233 Dr Perry was of the view that the request had been instigated by the infection of a virgin patient in Edinburgh with NANB hepatitis.234 It appears clear that the immediate concern was to cater for the needs of patients who may present for treatment in Edinburgh.235 As is discussed above, it appears clear that no consideration as given to the possibility of patients outwith Edinburgh. In our submission, this was a mistake.

232 Transcript for 27/10/11 (day 57); 153 (Professor Cash)
233 Transcript for 14/10/11 (day 55); 90(3 to 5) (Professor Ludlam)
234 Transcript for 7/12/11 (day 74); 13 (12) to 14 (8) (Dr Perry)
235 SNB.007.5911 appended to SNB.007.5910
In SNB.006.0336 which refers to "haemophilia directors", Dr Perry said in evidence that he was making a request not just for Edinburgh but for use in the whole of Scotland. He stated in evidence that he was attempting to source a product for the whole of Scotland for the period until Z8 became available and that it was not his intention that any such supply should be conditional upon participation in a clinical trial. \(^\text{236}\) There seems to have been little effort made to calculate what the likely usage would be on this national basis.

**Conclusion**

Despite the fact that a need had been identified for the protection of virgin and minimally treated patients, no attempt appears to have been made to calculate what quantities might be needed. In our submission, this is suggestive of a lack of central control within the system. Whereas Professor Ludlam was, entirely understandably, concerned to secure a supply for patients in this category who might present for treatment at his centre (as had happened in May 1986), nobody paid regard to the similar likelihood of such patients presenting at other hospitals in Scotland. No attempt appears to have been made to calculate the likely need, based (for example) on the number of such patients who had presented for treatment in Scottish hospitals. Treatment records for patients with bleeding disorders in hospitals and by the UKHCDO would have assisted with such a calculation which, in our submission, could have been done simply. There was no system of dissemination of the availability of the product, the means by which one might get some or the proper circumstances for its use. No system of central control was devised. There appeared to exist a degree of confusion as to whose responsibility such matters would be as between Dr Perry and Professor Ludlam. In our submission, Professor Cash should also have been involved in that process.

**17. Steps taken to disseminate throughout Scotland the fact of its availability and the appropriate circumstances for its use and the extent to which those steps were appropriate in the interests of patient safety**

**Evidence**

Professor Ludlam gave evidence to the effect that, despite the fact that it had been he who had instigated the procurement of the 8Y, he felt that it was the responsibility of Dr Perry to disseminate

\(^{236}\) Transcript for 7/12/11 (day 74); 36 (15) to 37 917) (Dr Perry)
throughout Scotland that the product was available.\textsuperscript{237} Even within the Edinburgh centre, Professor Ludlam had no specific recollection of even telling his own staff about what it would be used for but thought that he would have done.\textsuperscript{238} This hardly seems convincing, given the background of the infection in May 1986 and the efforts which had been put in to secure the supply.

Dr Perry was clear that he took no steps to advertise the availability of the 8Y to centres outwith Edinburgh, or any other hospital for that matter and that he thought that Professor Ludlam would be best placed to spread that news to his colleagues.\textsuperscript{239} Professor Ludlam was, however, very aware of how precious the product was (as was reflected in his evidence about the fact that junior doctors in his hospital would not have free access to it).

Professor Lowe had no awareness of the availability of the 8Y product for use in Glasgow at any time, and certainly not in 1986.\textsuperscript{240}

\textbf{Conclusion}

In the summer of 1986, a decision was taken by Professor Ludlam to instigate a process whereby a supply of English 8Y would be secured. The Inquiry has heard no evidence that there were significant developments as regards the apparent safety of that product, when compared to the then available Scottish factor VIII concentrate between March 1986 and the summer of 1986. It was as a result of the infection of a virgin haemophiliac in Edinburgh in May 1986 that the order was made. In our submission, the presentation of virgin and/or other uninfected patients and the inevitability of their infection on exposure to Scottish concentrates could and should have been foreseen. The securing of a modest supply of English 8Y should have been achieved by March 1986 at the latest if not by September 1985 as identified by Deputy Chief Medical Officer Dr Aileen Keel in 1999. Appropriate measures should have been taken by the SNBTS, SHHD and the UKHDCD to publicise the availability of this product throughout Scotland and the fact that it should be used for virgin and other apparently uninfected patients from that time. Directions should have been given by the SNBTS for that supply to be controlled and distributed by a senior haemophilia clinician upon a request being made for it.

\textsuperscript{237} Transcript for 14/10/11 (day 55); 64(5 to6) (Professor Ludlam)
\textsuperscript{238} Transcript for 14/10/11 (day 55); 64(23 to 24) (Professor Ludlam)
\textsuperscript{239} Transcript for 7/12/11 (day 74); 42 to 44 (Dr Perry)
\textsuperscript{240} Transcript for 11/10/11 (day 52); 46 (5 to 6) (Professor Thomas
In answering questions about the failure to disseminate information throughout Scotland about the availability of the 50 vials of 8Y, Dr Perry was keen to emphasise the limitations on the role of PFC/SNBTS in the procurement of products not produced by them.\textsuperscript{241} In our submission, a distinction requires to be drawn between the general situation (which appears to have been that the PFC would not be responsible for the procurement of products from elsewhere) and the specific position with the 8Y in which they had undertaken the responsibility to become involved. We consider that steps should been taken by the PFC to advertise the availability of this product to hospitals throughout Scotland, in the limited sense contemplated in the questioning of Dr Perry in particular in light of the fact that the SNBTS and the haemophilia directors had met in March 1986 but were not scheduled to meet again for some time.\textsuperscript{242} We would also submit, however, that Professor Ludlam should have taken steps (both internally and nationally) to advertise to other haemophilia doctors the reasons why the product had been procured and the general circumstances in which it should be used. Some system of control of the supply by a responsible haemophilia clinician of the distribution of the product would also have been appropriate.

\textbf{18. What the supply of 8Y which was made available to Scotland in the summer of 1986 was actually used for}

Professor Ludlam gave evidence to the effect that the first 20 vials of 8Y were used on a patient who was allergic to the SNBTS factor VIII concentrate.\textsuperscript{243} A further supply was obtained from Newcastle. Dr Perry told the Inquiry that the other 30 vials were entered into the PFC stock system and they were eventually distributed to Professor Ludlam in Edinburgh.\textsuperscript{244} Professor Ludlam also implied that the further 30 vials were also used in Edinburgh but he was not sure what they were used for. Professor Lowe gave evidence (under reference to the Inquiry’s tables relating to product use) that no 8Y was used in the GRI.\textsuperscript{245}

The 8Y was obtained for a specific purpose (category 1 patients). As will be seen below, there were other patients treated for the first time in this period outside Edinburgh. The supply was not (it would appear) used for any of them.

\textsuperscript{241} Transcript for 7/12/11 (day 74); 54 (15 to 25) (Dr Perry)
\textsuperscript{242} Transcript for 7/12/11 (day 74); 55 (16) to 56 (16) (Dr Perry)
\textsuperscript{243} Transcript for 13/10/11 (day 54); 142 (1 to 12) (Professor Ludlam)
\textsuperscript{244} Transcript for 7/12/11 (day 74); 62 (10 to 23) (Dr Perry)
\textsuperscript{245} Transcript for 13/10/11 (day 54); 40 (16) to 41(1) (Professor Lowe)
The effects of actions and decisions taken over this period

19. The numbers of patients with bleeding disorders likely to have been infected with Hepatitis C through blood products in Scotland over this period and how they came to be so infected

Evidence

On 1 September 1999, Dr Aileen Keel (SHHD) asked Professor Ludlam and Professor Lowe to report on numbers of patients who received first time treatment between 1 September 1985 and 30 June 1987. This equates roughly with the period with which this topic is concerned. Dr Keel was trying to estimate the number of people who might fall into this category and so might be eligible for some form of no fault compensation. Profs Ludlum & Lowe undertook to provide Dr Keel with figures for numbers treated for first time between 01/09/85 (when 8Y became available) and 30/06/87 (when a safe factor VIII concentrate was made fully available in Scotland).

These figures eventually were reported in 2000. The number of people treated for the first time in Scotland with a blood product during the period from 1 September 1985 to 30 June 1987 was 18 in the East of Scotland and 13 in the West of Scotland. In the east of Scotland, eight were treated with cryoprecipitate (of whom four were known to be HCV negative and four whose HCV status was unknown) and 10 were treated with SNBTS Factor VIII or IX (of whom four were HCV positive, one HCV negative and the HCV status of five unknown). In the west of Scotland, two were treated with SNBTS Factor IX and were HCV negative, one was treated with SNBTS Factor VIII and Cryoprecipitate was known to be HCV positive, one was treated with a commercial Hepatitis C safe product and the remainder (nine) were treated with Cryoprecipitate of whom three were known to be HCV positive.

Evidence about the ways in which these patients were treated, their infection routes and the timing of their infections is clearly incomplete.

In his oral evidence, Professor Lowe added to the figure for 13 for the west of Scotland by indicating that he thought that 3 were from the GRI (adult patients) and 10 were children being treated for the

\[246\] SGF.001.2232
\[247\] PR, para 9.326
first time over this period at Yorkhill.\textsuperscript{248} Professor Ludlam clarified that the figure for the east of Scotland was the entire east of Scotland.\textsuperscript{249}

Further evidence about the patients first exposed to treatment over this period is also available in correspondence from Dr Cacchia.\textsuperscript{250} He identifies 29 patients treated (we assume for the first time) between September 1985 and December 1987. The paper reports 6 known HCV positive patients, who come from all across Scotland. 4 of them were treated with PFC factor VIII concentrates and two with cryoprecipitate only. No information is available about the treatment histories of the 9 patients who are reported to have tested negative for HCV. For 14 of the patients no information is available at all. The evidence about the ways in which these patients were treated, their infection routes and its timing are incomplete. The up to date position of these patients is not known. The tests applied or any evidence of follow up investigations are also unknown.

\textbf{Conclusion}

We represent two patients who were infected with NANB hepatitis transmitted on first infusion with an SNBTS concentrate over this period. We submit that both of their infections could and should have been avoided, had earlier and safer measures been put in place to recognise the need for treatment other than Scottish factor VIII concentrates to be given to those patients unless it was unavoidable. The patients identified above are potentially all ones whose infections could have been prevented by (a) 8Y being requested earlier and (b) more careful consideration being given to avoiding treatment with Scottish factor VIII concentrate. As far as (a) is concerned, later studies confirmed that the product was indeed non-infective for NANB hepatitis.\textsuperscript{251} Scotland went on to develop its own product heated under the same regime (80 degrees for 72 hours), namely Z8.

As far as (b) is concerned, there is the evidence of the Thomas paper detailed above in which everyone treated with only cryoprecipitate avoided infection. All got less than 70 units. The Inquiry has evidence from Dr Hay report in the C5 section which suggests that an uninfected patient might have been likely to become infected after an infusion of around 100 units of cryoprecipitate anyway.\textsuperscript{252} In his evidence, Professor Lowe told us that each bag of cryoprecipitate is from a single

\textsuperscript{248} Transcript for 13/10/11 (day 54); 60 (8 to 19) (Professor Lowe)
\textsuperscript{249} Transcript for 13/10/11 (day 54); 138 (7) (Professor Ludlam)
\textsuperscript{250} PEN.018.1483 (17 March 2000)
\textsuperscript{251} LIT.001.0330 and SNB.004.5996
\textsuperscript{252} PEN.018.0961 @ 0982/0983
donor but one required to pool together 20 bags for the average adult.\textsuperscript{253} Professor Ludlam told the Inquiry that the average adult dose was from 20 donors.\textsuperscript{254} The amount of product which would be required would vary from case to case. Professor Ludlam expressed the view in evidence that one would be infected with NANB hepatitis after exposure to between 100 to 200 donors based on an incidence of around 1 percent.\textsuperscript{255} On this basis it would take 5 days of treatment to become infected.\textsuperscript{256}

There will be likely to be emergency clinical situations in which the infusion of a concentrate is clinically unavoidable. There will be situations where even the administration of cryoprecipitate in sufficient quantities would have resulted in infection with NANB hepatitis. However, such situations would require a sufficient amount of that product to have been administered for the value of the small pool production system to be lost and the likelihood to become that the patient would be infected. Given that virgin and minimally treated patients would be likely to be at the milder end of the haemophiliac population and consequently have higher resting factor VIII levels, it would be likely, in our submission, that they would require lesser amounts of cryoprecipitate than others to achieve haemostasis. Evidence was given by Professor Lowe to the effect that the objective in the administration of treatment would be to get the levels up to "30, 40, 50 per cent which is approaching the levels required to achieve normal haemostasis".\textsuperscript{257} This would be more readily achievable, the higher the resting factor level. Other virgin patients are likely to include children, for whom smaller amounts of product would be likely to be required to achieve haemostasis anyway. In our submission, a significant number of infections could and should have been avoided over this period.

In particular, on the evidence available of which we are aware the earliest virgin infection within this period occurred in May 1986. It is, in our submission, it is likely that had proper measures (as detailed above) been taken in response to the fact of that infection, further infections over this period could and should have been avoided.

Further investigations

\textsuperscript{253} Transcript for 13/10/11 (day 54); 65 (18 to 19) (Professor Lowe)
\textsuperscript{254} Transcript for 13/10/11 (day 54); 136 (8) (Professor Ludlam)
\textsuperscript{255} Transcript for 13/10/11 (day 54); 133 (5 to 7) (Professor Ludlam)
\textsuperscript{256} Transcript for 13/10/11 (day 54); 136 (10 to 14) (Professor Ludlam)
\textsuperscript{257} Transcript for 13/10/11 (day 54); 26 (12 to 14) (Professor Lowe)
The Inquiry should investigate more fully the number of patients exposed to treatment for the first time who were actually infected by that treatment, as the information above is incomplete.

The Inquiry should also investigate other infections of patients over this period, even amongst patients who had been treated before but who were not already infected, as these patients are not included in the figures quoted above. The Inquiry should also investigate the treatment received by these patients and the way in which they became infected. As far as "minimally treated" patients are concerned, in the first place, one requires to consider what might be meant by this term. The medical records referred to during the evidence of "Alex" indicate that he was not a virgin patient in the true sense but that he had been treated with cryoprecipitate at Raigmore hospital. He was a virgin patient when treated locally with factor VIII concentrate in January 1987, as he had never been treated with a concentrate before. We would submit that the reason why the Inquiry requires to have regard to both virgin and minimally treated patients (ie patients not previously treated with a concentrate or treated with cryoprecipitate in relatively small quantities) was that these were the patients who were, on the basis of contemporaneous medical evidence, probably not infected. Medical witnesses like Professor Colvin seed to be comfortable with the concept of minimally treated patients in this sense. The phrase was used in contemporaneous correspondence. Given that the figure of 29 or 31 referred to above refers to patients who were treated for the first time over the period in question (which would actually include the witness "Alex" whose first treatment of any kind was within that period) there may be more people who were probably not infected but who had had minimal treatment outwith the period.

20. Whether the way in which the risk of contracting NANB hepatitis from NHS treatment was managed over this period was in the best interests of patients with bleeding disorders in Scotland

We submit that the strategic decisions of both the government, the UKHCDO and individual hospitals treating patients with bleeding disorders were not in the best interests of patients over this period, in particular patients who were not infected with NANB hepatitis at the start of the period and who required to receive treatment for their bleeding disorder in it. Our reasons for this are as outlined in detail above.

Recommendations for the future
21. What lessons can be learned from and what recommendations for the future arise out of the Inquiry's consideration of the evidence in the C3A section?

In our submission, the following lessons can be learned from the Inquiry's consideration of this topic:

- The need for better systems in primary care of picking up earlier patients particularly at risk of bleeding disorders.
- The need for clear information to be given to patients about their treatment and their involvement in treatment decisions, especially if there situation is unusual or presents medical difficulties.
- The need for better co-ordination between the roles of the government and the UKHCDO in making policy decisions and issuing guidance for the assistance of doctors treating patients with bleeding disorders. In our submission, it is not enough for the government to say that because clinical decisions are involved, they have no duty of care. By that logic, the government would have no responsibility for the treatment of patients within the NHS at all.
- The need for a better system of ensuring that information about developments regarding the safety of particular products is promulgated clearly. In particular, The need for UKHCDO guidance to be kept up to date to reflect all developments in attitudes to treatment.
- The need for a clear system for the dissemination of information beyond the major haemophilia treatment centres in Scotland in recognition of the fact that patients (in particular previously untreated patients) may present for treatment in any location.
- Closer co-ordination between the blood transfusion service and the haemophilia clinicians so that the clinical concerns of doctors could be met by the ability of the manufacturers to produce and procure products which address those clinical concerns.

JTD