PENROSE INQUIRY – C4 – QUERIES DR BRIAN C DOW RESPONSE

This is a response to a request to Susan Murray from Janet Marsh (A38705) dated 19 August and received by myself on 25 August 2011. I have cut and pasted the schedule paragraphs in blue, with **my responses in black**.

Schedule of Questions (A38112)

Introduction: In preparing statements, witnesses are asked to refer to pages 272 to 320 of the Preliminary Report. It should be noted that, due to the recovery and processing of further documents since the publication of the Report, there is additional material referred to in these questions. In addition, as referred to in paragraph 31 below, part of the narrative in Chapter 9 has been extended.

1. The Inquiry Team now has the correspondence referred to at paragraph 9.93. The letter of 5 July to Chiron is SNB.008.3584, SNB.008.3585 was a letter to Ortho asking if they were to market the test and SNB.008.3586 is the reply from Ortho dated 19 July.

2. The Inquiry team has minutes of the meetings of two groups which considered developments in the testing for hepatitis C over the period 1988 to 1991: the ACTTD and the ACVSB. **Why was it necessary to have both the ACVSB and the ACTTD? What lay behind the raising of the roles of the two groups at the meeting of 24 April 1990[1] – had it come to seem that there was unhelpful overlap?**

The ACVSB was a group set up by the Department of Health, whilst the ACTTD was a group (mainly blood service orientated with the exception of Drs Follett and Mortimer (virologists)) specifically to discuss means of reducing transfusion-transmitted diseases.

3. **How was the membership of each body determined, in particular the Scottish representation? We have a copy of the letter inviting Dr Perry to serve on ACVSB[2] – was he in fact nominated by SHHD? How did Dr Mitchell end up on both groups?**

Both Drs Mitchell and Perry should be able to answer better than I.

4. The first meeting of ACTTD was on 21 February 1989. Further papers are now available, at SNB.006.1920, 1921, 1922 and 1923. SNB.006.1923 is the draft terms of reference, which were agreed at the meeting as the terms of reference of the committee.

[1] Minutes SNB.001.9761
[2] SNF.001.1263

5. Each group met in May 1989: the ACTTD had its second meeting on 19 May and the ACVSB its second meeting on 22 May. The minutes of the former meeting are now available at MIS.001.0009. At that meeting, Professor Cash expressed a desire to proceed with testing the Ortho assay. The minutes of the latter meeting may reflect a different attitude. Reservations appear to have been expressed about the benefits of the Ortho test, and the possibility of proceeding in due course without resort to the Ortho/Chiron test was mentioned. A figure of 50% was given as the sensitivity of the test – **what was the source of that figure? What further data from Chiron additional to the information in the article in Science in April 1989 (LIT.001.0629) was being anticipated?**
   I cannot comment, other than it would appear (from MIS.001.0009) that the English blood service had already started evaluating the Ortho 1st generation HCV ELISA by using samples that had exhibited abnormal ALT levels.
6. Professor Cash duly proceeded with his intention to arrange testing of the Ortho assay, as set out in paragraph 9.123. From the report of this study referred to in paragraph 9.148 (SNB.006.1596) it is evident that one objective was
   "to determine the efficiency of the test in the examination of sera from patients with alleged post-transfusion non-A non-B hepatitis along with the implicated donations."
   Was this the Scottish equivalent of the assessment discussed in paragraph 9.126?
   What was the particular function of these studies – were they seen at the time they were initiated as potentially sufficient to inform a decision as to whether or not to proceed to introduce the Ortho test or were they in some way preliminary to a further assessment?

The English assessment dated 23 June 1989 (SNB.001.9545) only reported on the incidence of anti-HCV reactivity at 3 different English centres. The Scottish evaluation did encompass a similar study within it (first objective) but also had 8 other objectives (SNB.006.1599) including objective 3 "to determine the efficiency of the test in the examination of sera from patients with alleged post-transfusion non-A non-B hepatitis along with the implicated donations." The function of the studies were to evaluate the only commercial serological tests for the detection of anti-HCV to try and answer the listed objectives. The conclusions (SNB.006.1625) were as stated. The report was then sent by Dr Mitchell to ACTTD for discussion.

7. **What was the relationship between that assessment process and the exercise referred to at paragraph 9.124 (the assessment of samples of special interest using 1000 Ortho tests)?**
   I presume Dr Mitchell on 13 June 1989 at the SNBTS Directors meeting was referring to the proposed study (SNB.006.1596) conducted at BTS Law.

8. At the meeting of ACVSB on 3 July 1989, Dr Mortimer reported a view that the Ortho tests were reliable. The Chairman asked for all the data to be given to the committee at its next meeting. On the face of it, this does not appear to reveal a sense of urgency. **Was there a sense of timescale within which**

testing might be introduced? Why did ACVSB not consider it necessary to commission its own evaluation of the test?

In mid 1989, the Ortho HCV ELISA was about to be launched globally. The test kits used in the SNBTS evaluation comprised two lot numbers, DEV89038 and HCV101. The DEV kit was probably meant to be a Developmental kit (produced in smaller volumes) whilst HCV101 would have been one of the first production lot numbers. I cannot comment on any proposed timescale of introduction at this point. The ACVSB was a DoH committee that took advice from various transfusionists and virologists for the minister to consider. I cannot comment on the action of ACVSB.

9. Paragraph 9.128 narrates a letter from Professor Cash of 28 July 1989, concerning the fact that the decision on testing was to be taken by SHHD not SNBTS. **Did Professor Cash ask for this letter to relieve pressure from Ortho representatives?**

   The letter would appear to clearly state that SNBTS personnel could not discuss the introduction of routine donor HCV testing with any commercial company until SHHD had approved.

10. Dr McIntyre replied to Professor Cash on 2 August 1989. His reference to introduction of a further test was conditional, suggesting that the principle of introducing a further test designed to reduce the incidence of post-transfusion hepatitis had not yet been determined. **Is this a correct impression**? He also mentioned his understanding that any new test would be introduced simultaneously throughout the UK. **What was the source of his understanding?**

    I cannot comment on this correspondence.

11. At this time there was also correspondence between Professor Cash and Dr Gunson regarding the timing of screening and the desirability of Scotland and England moving together on the matter. We now have the letter of 26 July from Dr Gunson (SNB.006.1574) to which the letter referred to in paragraph 9.129 is the reply. In his letter of 3 August 1989 to SNBTS Directors Professor Cash referred to its being only a matter of time before the new testing programme would be commenced. **At this point, was he envisaging a shorter time period than in fact eventuated?**

    I have never seen this correspondence before the Inquiry. However, it would appear from both letters (SNB 006.1574 and SNB 008.2606) that it was likely that the UK would introduce HCV testing in unison and probably around the same time as other European blood services.

12. Dr Mitchell and Dr Follett attended a meeting with Ortho representatives and also Drs Gunson, Contreras and Barbara in London on 23 August 1989. Dr Mitchell's report of the meeting is SNF.001.1449. It is clear from that report that the next meeting of ACVSB was scheduled for 17 October 1989, which would be after the Rome meeting on the virus, organised by Ortho. **Was there a view that the meeting of 17 October (subsequently postponed – see paragraph 15 below) was likely to take the decision to recommend the introduction of screening? What is the "turn-key" system referred to in**

paragraph 4? Were the figures presented by Dr Mitchell (paragraph 5) those from the ongoing studies referred to in paragraphs 9.123 and 9.148?

I cannot comment on the first two questions. The latter question relates to the ongoing studies that were eventually reported as in paragraph 9.148.

13. A Civil Servant, G W Tucker, sent a memo to Michael Forsyth, (at the time a Minister rather than Secretary of State), on 23 August 1989 (as discussed in paragraphs 9.134-6). The memo was prompted by an article in the Guardian regarding the hepatitis C test. At the end of the memo, it is stated that "this (was) a UK issue" and that the Department of Health were "taking the lead". This appears slightly different from a position that the health departments were working together to appraise and, if appropriate, introduce the tests simultaneously. There is also the penultimate paragraph of page 3 of SNB.002.4627, which seems to suggest that the Scottish decision would be taken in its own right, on a recommendation from ACVSB. **What was the position – were the health departments for Scotland, England/Wales and Northern Ireland working jointly on the decision or was it an issue on which Scotland would follow whatever decision was taken in England? Was the formal position that the decision for Scotland would be taken in Scotland, independently from the decision for England?**
I cannot comment.

14. From the letter discussed in paragraph 9.140 (and from other statements made around this time) it appears that there was no question of introducing screening until a satisfactory confirmatory test became available. Our understanding of the thrust of this particular letter is that it was possible simply to repeat a positive test, using another kit the same as the first, or to carry out a further test using the same antigen but a different set of reagents and that the latter was preferable and should be facilitated by Ortho as soon as possible. **Is this correct?**
What Ortho was planning as a confirmatory test involved a recombinant immunoblot assay with the c-100 and 5-1-1 recombinant HCV proteins painted onto a nitrocellulose strip together with control bands. These reagents (c100 and 5-1-1) were also the basis of the solid phase coating on the first generation Ortho HCV ELISA test and therefore were far from ideal as an independent source for confirmation. The worry was that false positives would occur because of cross-reacting antibodies that would be reactive by both ELISA and RIBA.

15. The Rome symposium in September 1989 was clearly an important meeting. We have reports of this meeting prepared by Dr Mitchell (SNB.001.8678) and Dr Gunson (SNB.006.1456), and the sequence of events from and after the meeting is set out in paragraphs 9.143 to 9.159. Dr Gunson's report of the Rome meeting was amended after the meeting of ACTTD on 9 October; his recommendation remained that introduction of testing be approved in principle by ACVSB. The meeting of ACVSB on 6 November did not accede to this recommendation. Evidence about this period and about the proceedings of the two committees at this time was given to Mr Justice Burton in A v NBA, and an extract from his judgement is provided. Unfortunately, it is not possible for this Inquiry to hear from Dr Gunson, he having died on 15 October 2005. **It**

would assist the Inquiry if those who were members of either group and who can recall this period could provide any further comments or recollections of events at that time, including the discussions at the meetings. Similarly, those who were not members of one of the two committees but who recall the atmosphere of the time may wish to provide their comments or recollections.

I was not a member of either group at that time.

16. Para 3 e ii of the minutes of the SNBTS Directors' meeting on 29 September 1989 says Scotland had not been invited to participate in UK evaluation but SHHD had asked that they should and so the West and SE regions had obtained kits for evaluation. This must have been a different exercise from the evaluation conducted by Dr Dow and his colleagues,[3] who looked at samples from Aberdeen, Dundee and Glasgow. We are able to follow the latter study but are unaware of how the participation of the West and South East regions in the former was organised. **Is it possible for any of those involved to recollect this information? It also appears from this set of minutes that Dr Mitchell was not particularly enthusiastic about the Ortho test ("not robust") – is this an accurate impression?**

This was the same exercise as reported in SNB 006.1596 – see tables 3, 5 and 6 which includes materials from the SE (Edinburgh) region.

17. Ortho were pressing ahead with their confirmatory test – see para 9.163. **Was this (RIBA) the one that was thought unsatisfactory at the autumn meetings? At that time, what were seen as the defining characteristics of a satisfactory confirmatory test?**

As mentioned above (para 14), the first generation RIBA was based on only two specific HCV recombinant proteins which were both products of the same area of the genome (the non-structural (NS) 4 region). As both these recombinant proteins were the coating materials for the solid phase ELISA microwell, it was predicted that the same cross-reacting antibodies would produce (false positive) reactives in both ELISA and RIBA systems.

The experience with HIV of a HIV viral lysate used in a Western blot technique gave a much more confident confirmation with several specific bands with known HIV positives (see figure 1). Alternatively, the use of specific neutralisation tests in HBsAg confirmation had also proven to be very reliable.

[3] As narrated in paragraphs 9.123 and 9.148 of the Preliminary Report

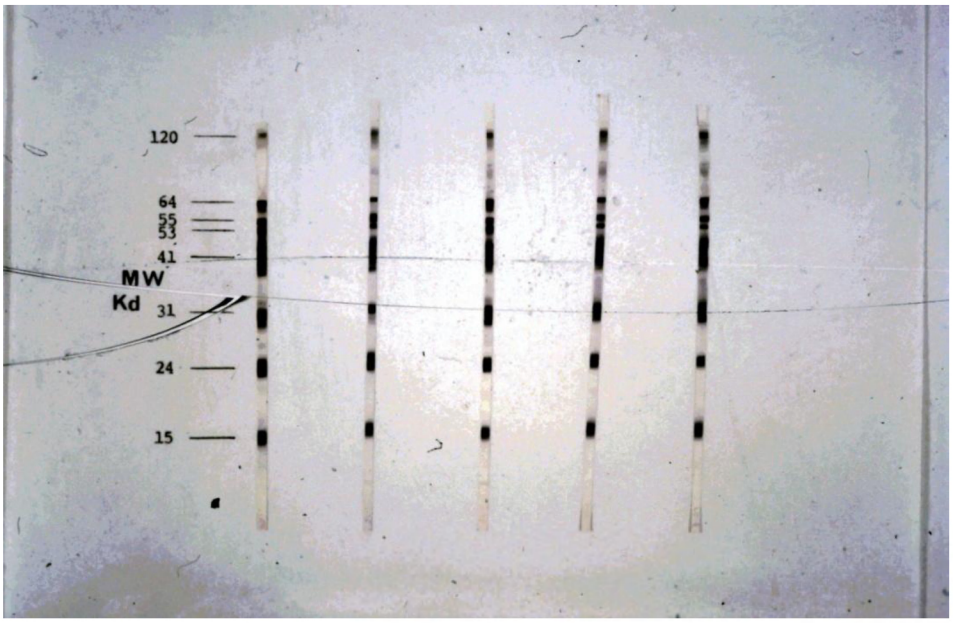

Figure 1 Early HIV western blot strips showing several HIV specific bands with 5 known confirmed HIV positive samples

18. We now have letters referred to in 9.162 and 9.163 (SNB.006.1560 and SNB.006.1561).
19. Dr Barbara's editorial in the December 1989 edition of Transfusion Today (LIT.001.3786) indicates that Ortho were developing confirmatory Western Blot assays. **Is it correct that they were simultaneously developing tests using both RIBA techniques and Western Blot? If so, was it considered that Western Blot would be superior?**
It would be incorrect to assume that they were simultaneously developing tests for both RIBA and Western Blot – as far as I am aware, they had only developed a recombinant immunoblot assay (RIBA).

20. In December 1989, the final report of the SNBTS evaluation of the Ortho kits was produced (paragraph 9.168). There was a concern, mentioned also in the October report, about the reduced sensitivity compared with "the dev kit". **"Dev" may stand for development, but what was the "dev kit"?**
The "Dev kit" and "dev" both refer to the early developmental lot numbers (same lot possibly) that were provided by Ortho prior to them launching the production lots (latter all prefixed by HCV XXX).

21. Over this period, there are repeated references at meetings to the need for the Ortho test kit to be approved by the FDA for use in screening in the USA. Yet a number of evaluations of the kits were being carried out in the UK. Moreover, there does not appear to have been any legal requirement for licensing of the kits in the UK. **Why, therefore, was it necessary to tie introduction of the test in the UK to approval by the FDA?**
The FDA were notoriously strict controllers of the quality of test kit systems. To be informed that a kit was FDA-approved meant that the manufacturers were expected to keep the same sensitivity and specificity over all lots that were produced, thus ensuring that the kits were robust

quality products. I cannot comment on the reasons that others may have insisted on FDA approval.

22. Paragraph 9.187 of the Preliminary Report narrates the transmission in February 1990 of a Press Statement from the USA to Dr McIntyre and to the DoH. **Can any present or former civil servants shed light on the handwritten notes on the letter from Professor Cash, in particular the comment that the statement had "stirred up a hornet's nest"?**
This is not for me to comment.

23. The meeting of ACVSB on 24 April 1990 again stopped short of recommending the introduction of testing. According to a note Dr Perry sent to Professor Cash about this meeting on 2 May, (SNF.001.1710) he and Dr Gunson had both felt that there was sufficient data to justify testing now. **Can Dr Perry now recall his sentiments at the meeting? What did he consider to be the answers to the negative points made in paragraph 29 of the minutes of the meeting (SNB.001.9761 at 9764)?**
This is not for me to comment.

24. The memo from Dr Young dated 23 May 1990 (paragraph 9.207) appears to suggest some concern about progress on the issue of hepatitis C screening. **Can Dr Young recall anything further about the CSA management committee meeting, and what in the discussion there prompted the memo? After Dr McIntyre attended each meeting of ACVSB, to whom within SHHD would he report its proceedings? It would also be helpful if all the "hieroglyphics" on this letter could be translated – who are all the individuals writing or referred to and what was the role of each in dealing with the memo?**
This is not for me to comment.

25. Dr McIntyre responded to this memo on 6 June (SGF.001.2034). Mr Panton then wrote on it on 7 June. **What is the background to his reference to the need to "dip" into the contingency fund? There is another (handwritten) memo from someone to Mr Hogg and Mr. Panton dated 6 June 1990 (SGH.002.7935) but this does not appear to add anything to the narrative of events – is this correct?**
This is not for me to comment.

26. The letter from Dr Metters to Dr Perry of 5 June 1990 (SNB.002.0245) suggested that the study to investigate the significance of a positive reaction to the antibody test might not now proceed; the subgroup comprising Drs Gunson, Mitchell, Mortimer and Tedder had taken the view on 23 May that an extended study of RIBA and PCR techniques might not be appropriate. **If the study had been considered important at the ACVSB meeting on 24 April, why was it no longer considered so? It appears that the grant of FDA approval of the test may be the explanation – was this so?**
I cannot comment other than the RIBA test mentioned was still RIBA-1 and this had limited value (see also paras 14 and 17).

27. In his letter of 21 June 1990 to Dr Gillon (SNB.005.5023) Dr Cash said "now that we know we will have access to confirmation testing". At the ACVSB meeting of 24 April Professor Zuckerman remarked that the RIBA test was not good enough to use routinely as a confirmatory test (explained in A v NBA as meaning not good enough because it also tested for the antibody). Dr Tedder commented that the PCR test was not yet suitable for the mass screening needs of RTC laboratories. **Can Professor Cash recall what testing he was thinking of in his reference to access to confirmatory testing being available?**

I cannot comment, other than the SNBTS Microbiology Reference Unit was the planned portal for eventual confirmatory testing.

28. Paragraph 9.215 refers to a bid for funds to introduce testing. It appears to the Inquiry team that, given the information in SNB.013.4871, had screening been introduced before the financial year 1991 – 92, it could only have been paid for from the reserve (the contingency referred to in SGH.002.7930). **Is this correct?**

I cannot comment.

29. The ACVSB meeting of 2 July did recommend that screening be introduced, but not before the results of a comparative study of the Ortho and Abbott tests, (the latter only having become available at the beginning of July**). Why was it considered necessary to have a UK wide comparison of the two tests, and selection of one of them?** The alternative would have been to allow each centre to decide individually which test to use – as was ultimately the outcome (see paragraph 9.241). **Does the fact that this was ultimately the route followed (see for example letters SNB.005.2555 and SNB.004.7202) mean that the time taken for this study was, in retrospect, wasted?**

I was involved in performing confirmatory tests on the comparative study of Ortho and Abbott tests, as confirmatory laboratories throughout the UK had been involved. It should be remembered that the Ortho and Abbott test systems identified different reactive populations but with some commonality (particularly with true HCV positives). The date of possible introduction (1 April 1991) is based solely on using either first generation HCV test.

30. We have not found any memo by Dr McIntyre reporting the decision of 2 July 1990 to others in SHHD. **Was there such a report or note of the meeting**? The minutes record that a submission would be put to Ministers and the minutes of the next meeting (21 November) record that "a note had gone to ministers" after the July meeting. We have located some documentation from the Department of Health but have not found any memorandum or submission to the Scottish Health Minister and would be grateful if any such document could be identified to us.

I cannot comment.

31. As is recorded in the Preliminary Report (paragraph 9.241), the meeting of ACVSB on 21 November 1990 decided that hepatitis C screening should be introduced as soon as practicable. At that meeting, Dr Gunson thought that a six month period to set up testing would be excessive (paragraph 21 of minutes). In his note of the meeting, Dr McIntyre records that the chairman

had suggested 1 April 1991 as a realistic start date. We have not found it easy to determine why, given those views, testing was not introduced until 1 September 1991. We have amplified this section of the Preliminary Report with additional material now available to us, and enclose a copy of this enhanced narrative for reference. The following questions address this period.

The announcement by both Ortho and Abbott that second generation HCV assays were to be launched meant that any proposed introduction of the first generation HCV test on 1 April 1991 had to be reconsidered by those who had made this proposal.

32. It appears from Dr McIntyre's note of the meeting of ACVSB on 21 November 1990 (SGH.002.8501) that any submission to the Scottish Health Minister was to await sight of the draft of the English submission. The memo from Mr Tucker to Mr Panton dated 21 January 1991 (SGH.002.7890) asks for preparation of a submission; a later memo apparently dated 19 March 1991 (SGH.002.7880) indicates that the Scottish submission was based on the English one but shorter. It appears that the submission did not go to the Scottish Minister until 24 July 1991 – SGH.002.7828. **Is it possible for those involved within SHHD to explain why the submission was not sent more quickly?**

I cannot comment.

33. **The correspondence at the end of January 1991 now referred to in paragraphs 9.251 and 252 suggests that both in Scotland and England there was difficulty in moving the issue forward in the early part of 1991 – is this correct?**

It should be remembered that this was when both Ortho and Abbott were proposing to launch second generation HCV tests.

34. **Why was SNBTS not to be told that there was an unofficial start date of 1 July 1991 (SGH.002.7886)? Why would this be confidential to the extent of not informing the transfusion service?**

I cannot comment.

35. As is recorded in the Preliminary Report, Newcastle unilaterally commenced testing in April 1991. It is evident that Professor Cash and other transfusion Directors were opposed to this action, although it is also evident that Dr McClelland became increasingly uneasy at the delay (SNB.002.7902). **Is it the case that there was no consideration of Scotland similarly going ahead more quickly? If ministerial approval had been granted in Scotland around the same time as such approval was granted for England and Wales (January 1991), could this have happened, albeit with a second generation kit which was still being evaluated?**

Glasgow BTS actually started routine donor HCV testing using the second generation Abbott HCV ELISA test towards the end of May 1991 and continued until the official start date of 1 September 1991. The repeat reactive donations were isolated and confirmatory tests (RIBA-2) performed on all referrals. Any specimens exhibiting reactivity on RIBA-2 (be they indeterminate [1 band reactive] or positive) were individually tested for the presence of HCV RNA by

polymerase chain reaction (PCR). Thus, this extended pilot allowed sufficient confidence to be built up in HCV confirmation.

36. What was the "near disaster" referred to in Professor Cash's letter of 17 June 1991 (SNB.011.8178)?

I do not know what the "near disaster" was.

37. SNB.005.4822 appears to be a recognition that there had been failings in the process leading to the introduction of screening. Do those now providing statements agree with Mr McIntosh's views?

During the period of 1989-1991, I was actively involved in the evaluations of the first and second generation HCV test systems and various means of confirmation e.g. using 8M Urea for avidity testing of reactive samples [the use of avidity tests helps in ascertaining how recently an antibody has been produced and how good a reaction it has with its corresponding antigen, with poor avidity associated with recent production, and good avidity associated with extended production], using the Abbott neutralisation confirmatory test; as well as the first generation RIBA (RIBA-1) and the eventual "gold standard" second generation RIBA (RIBA-2). I realise that there was considerable concern over the lack of adequate confirmatory HCV tests and it was only with the latter RIBA-2 test that confidence was established. Looking back now, I would accept that first generation HCV testing could have been introduced earlier than September 1991 but wonder if, had that happened, whether the introduction of second generation HCV testing would have been delayed. Such a delay would have allowed the 30% of HCV positives (mainly genotypes 2 and 3) missed by first generation HCV testing to be transfused and potentially infect recipients. I realise that SNBTS moved onto third generation HCV tests fairly rapidly and years in advance of the United States who required our data to help obtain FDA approval.

The extended pilot study conducted at Glasgow BTS ensured that around 50% of the Scottish blood supply was being routinely tested with second generation HCV tests by the end of May 1991. It also provided a period to establish the RIBA-2 confirmatory procedure in conjunction with PCR testing of RIBA reactive samples. In addition, in this period from May to September 1991 excellent collaborations were established particularly with Professor Peter Simmonds of Edinburgh University. Through this collaboration, HCV genotype 3 was discovered and patented.

I was not personally involved in making any of the political decisions in the introduction of HCV testing.

Brian C Dow
5 October 2011