PENROSE INQUIRY – DR BRIAN DOW - TOPIC B4

"The decision not to use kits from the United States of America for testing donated blood for the virus [HTLV-III] as soon as they became available but, instead, to follow a process of evaluation of the kits before any such use"

This is a response to a request to Susan Murray from Gemma Lovell (A38958) dated 24 August and received by myself on 30 August 2011. I have responded only to the questions in the schedule where I am able to make a comment. Thereafter I have attempted to address the specific areas delineated within paragraphs 1 and 2 in the letter. I can only comment on my experience following completion of my part-time secondment to Ruchill hospital in 1985, when I returned to West BTS to supervise the running of the routine blood donor HTLV-III testing section until 1989.

I have cut and pasted the schedule paragraphs in blue, with related questions in red and kept my responses in black.

Schedule:

12. On 25 January 1985, Dr Cash wrote to Dr Ruthven Mitchell (SNBTS Director Glasgow) [SNB.005.9713]. Dr Cash advised that WBTS should undertake, on behalf of the SNBTS, initial evaluation studies of commercial HTLV-III antibody kits.

What particular steps had the SNBTS taken with regard to the introduction of HTLV-III screening in Scotland as at 24 January 1985? When the SNBTS was considering its own evaluation, would this have occurred at the same time as the introduction of a commercial test or would a test have been introduced only after the evaluation had been completed?

Response:

To my knowledge, there was no commercial test available for blood donor evaluation purposes prior to 24 January 1985. I realise that around March/April 1985 an Abbott HTLV-III test system had become available (from its use in Ruchill) but there were apparent problems with numbers of false positives (poor specificity – see also paragraph 25). A national evaluation (funded by DHSS) had not approved this test for use on blood donors. It had only approved two commercial anti-HTLV III tests (Wellcome Diagnostics Wellcozyme assay and Organon Diagnostics Vironostika assay). Around July 1985, SNBTS were in the position to perform a mini-evaluation of these two proposed commercial anti-HTLV-III tests. This was a mini-evaluation as, from recollection, supplies of these test materials were extremely limited. I was not involved in the procurement process, but would have expected that these tests for evaluation would have been provided free of charge. The outcome of the West evaluation was that the Wellcozyme test from Wellcome Diagnostics was the favoured test system (it was British, appeared to be more robust, and was user-friendly). SNBTS would not introduce a commercial test without having performed a satisfactory evaluation.

13. At the SNBTS Co-ordinating Group meeting on 19 February 1985 [SNB.003.9171] it was decided that Dr Cash's letter should not be pursued at the present time.

Did the SNBTS abandon its own evaluations altogether and await the DHSS evaluations and, if so, why? Was the decision to await the results of the DHSS evaluations made by the SNBTS or the SHHD? What discussions took place between the SNBTS and SHHD regarding this matter?

Response:
From recollection, there were insufficient supplies of any (other than the Abbott test) commercial HTLV-III test kit in early 1985 for a significant evaluation for blood donor screening purposes - to allow proper specificity studies to be conducted normally needs around 2000 tests. I realise a national (DHSS) evaluation had been performed at PHLS Colindale around May-July 1985. Following this evaluation, there was a recommendation to use either of only two assays (Wellcome or Organon) and small amounts were provided presumably to all Regional Transfusion centres for preliminary assessment/evaluation (see paragraph 12). I am not aware of the decision processes or discussions between SNBTS and SHHD.

16. We know that by July 1985 (when the first stage of the DHSS evaluation programme was completed) that Wellcome had switched from a radioimmunoassay to an ELISA test.

Does Professor Cash know when the switch occurred and/or why? What implications, if any, did the switch have for the NBTS and SNBTS? What, if anything, had changed between January/February 1985 and the date of the switch which made it acceptable for an ELISA test to be used within the blood transfusion services when it had not been acceptable beforehand?

Response:
I am not aware of the Wellcome RIA test or any switch from that to EIA.
SNBTS had experienced the use of radioimmunoassay for the detection of HBsAg through its use of the Abbott Diagnostics Ausria-II test since 1975. No commercial company developed a radioimmunoassay for the detection of anti-HTLV-III.

The Abbott HBsAg test entailed usually a delivery of fresh batches on either a fortnightly or a monthly basis with fairly short shelf life (max 6 weeks). The use of enzyme-immunoassay tests allowed for bigger batches to be produced with shelf lives of 3- 6 months initially (when kits are launched), with kits (in 2011) sometimes having expiry dates over 1 year in advance. This allowed for a more robust test and less need for fortnightly quality control (QC) assessments on new batches.

From a Health & Safety angle, the use of isotopes (for radioimmunoassay tests) were also under strict control by Radiological Protection Boards, entailing laboratory staff that were potentially exposed to wear monitoring badges. Thus it was necessary for transfusion

services to accept the use of ELISA techniques that resulted in completely new equipment being used. In the case of Wellcome, washing and reading equipment were delivered to Regional Transfusion centres at the time of the first delivery of kits for routine use (end September /start October 1985). The attached figure (Figure 1) shows the equipment necessary for the Wellcome Diagnostics anti-HTLV-III assay – Wellcome provided the Skatron washers and also a spectrophotometer (not shown in the figure). Trained staff, space together with pipetting equipment, timers and incubators were also required to perform the tests.

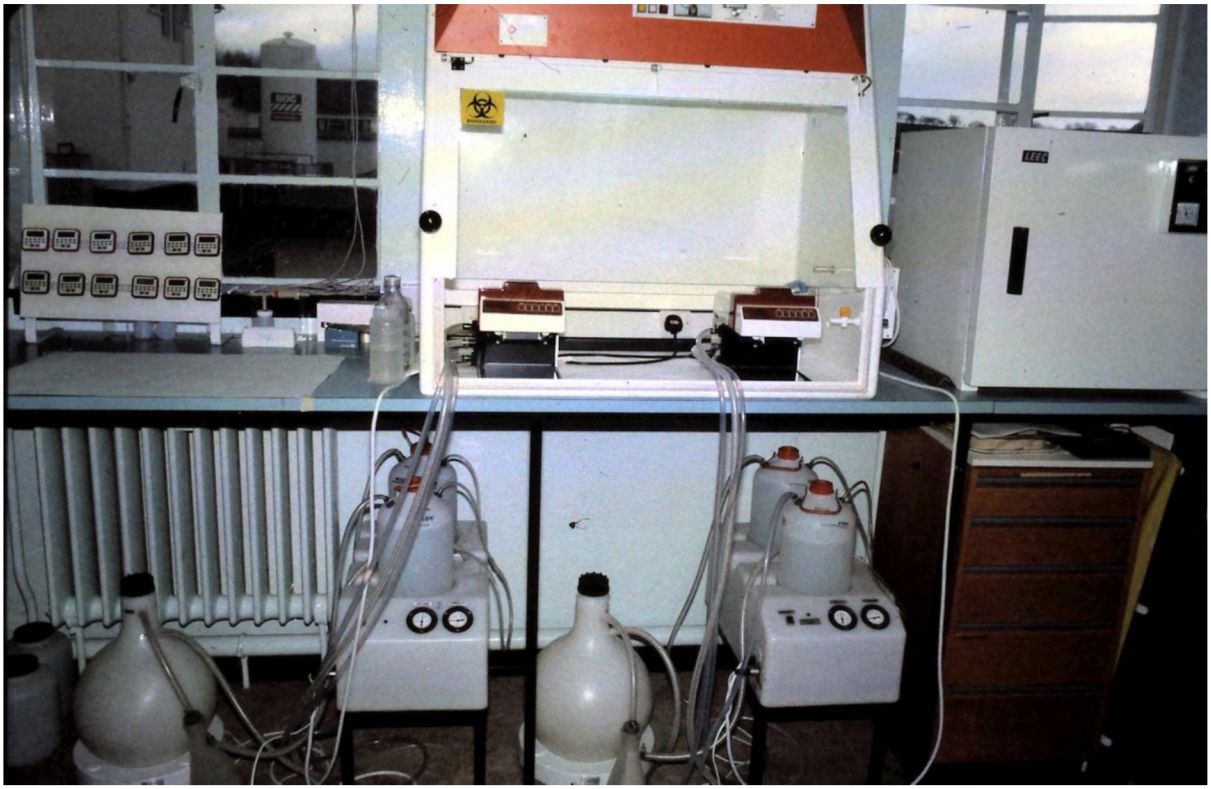

Figure 1 Equipment necessary for performing the Wellcome anti-HTLV-III ELISA test

22. HTLV-III screening of blood donors was introduced in Scotland (and the rest of the UK) on 14 October 1985.

Why did the working party amend the report and recommend that screening tests be introduced prior to the completion of the second stage of the evaluation?

Why was HTLV-III screening not introduced in Scotland until 14 October 1985 given that the first stage of the evaluation was completed on 30 July 1985?

How long did it take to make arrangements for alternative testing venues in Scotland for non blood donors to obtain testing? Who was responsible for arranging alternative testing?

Response:
I am unaware of a second stage to this evaluation or any amended report. The West of Scotland mini-evaluation of the 2 potential screening kits, favoured the Wellcome Diagnostics Wellcozyme assay over the Organon Diagnostics Vironostika assay. Wellcome were not in the position to provide sufficient kits to allow the commencement of routine donor testing until mid September, and even then we in the West had horrendous problems with plate validation failures as it was apparent that the test kit was less sensitive than the original (developmental) batch tested in July 1985. Wellcome had indicated that they only had limited supplies of HTLV antigen from Porton Down to satisfy the almost total demand from the UK blood services. The West Centre managed to overcome these validation difficulties (together with sensitivity issues). Some specificity problems did arise in attempting to identify very weak positive samples.
I cannot comment on alternative testing sites or who was responsible for their arrangement.

23. The corrigendum recommended that long term contracts be avoided until the results of the NBTS evaluation were available. The minutes of the SNBTS Directors meeting on 2 October 1985 [SGH.001.6412] note that the South East and North regions had only purchased a 3 month supply.
With this in mind, could a short term supply contract have been entered into at an earlier date (ie. whilst the first stage of the evaluation was being undertaken)?

Response:
It would have been extremely unwise to have signed a contract before completion of an evaluation. Purchase of 3 month supply does not equate to a contract for 3 months. As mentioned above, the kits would have had expiry dates of less than 6 months. Kits had to be refrigerated and 3 months supply would have filled several shelves of our laboratory refrigerators. The supplies were bought only when the company (in most RTCs this would have been Wellcome Diagnostics) could provide enough to furnish the demand for all the RTCs in the UK (excluding Sheffield who had chosen the Organon test).

24. The Inquiry team is aware that by the time that HIV screening commenced in the UK (14 October 1985), Ruchill Hospital (Glasgow) and the Clinical Virology Laboratory (Edinburgh) had been established as reference centres to carry out confirmatory testing.

When exactly were these centres established and able to start carrying out confirmatory testing? Who was responsible for establishing them?

Response:
The EAGA 5th meeting minute of 30 July 1985 states at 4.1 "The Chairman said that since the Group had last met (29 May 1985), the Department (of Health) had provided £750,000 to the PHLS for its programme to provide facilities for HTLVIII antibody tests and reference Centres for confirmatory tests, plus £58,000 for the evaluation of the test in this financial year." From this I would have presumed that SHHD would have then established the Scottish HIV reference centres based at Ruchill hospital (under the direction of Dr Eddie Follett) and the Clinical Virology Laboratory, based in the Bacteriology Dept, Edinburgh University Medical School (under the direction of Dr John Peutherer).

25. The minutes of the SNBTS Directors meeting on 2 October 1985 record that the East, South East, North and North East regions had all chosen the Wellcome test by that date.

Which test was chosen for the West?

Response:
Dr Ruthven Mitchell, West Director, was not in attendance at the SNBTS Directors meeting on 2 October 1985. This may be the reason that the West was not mentioned. However, as indicated above at 16, the West used the Wellcome test for routine anti-HTLV-III donor testing.
For information, a table for the number of referrals for confirmatory purposes for the first 176,149 tests (on W Scotland donations) with the Wellcome HTLV-III assay is shown:

Number of donations tested	176,149	(Oct 1985-?end 1986)
Initial screen positive (Manufacturer's protocol)	73	0.040%
Repeat reactive	31	0.017%
Confirmed HIV positive	6	0.003%

From the table it is seen that 25 of the 31 repeat reactives were false positive. Data on use of the HIV tests on blood donors during the last 20 years showed that around 99% of repeat reactives are false positive.

In addition in the first few months of testing, the Abbott HTLV-III test was sporadically used in parallel (<5,000 tests). Abbott Diagnostics provided kits free of charge for this evaluation, hoping that the poor specificity found in earlier studies had been resolved. In our hands, the Abbott test proved less specific (around 30 repeat reactive samples [all false] were referred after testing for a short period of time) than the Wellcome test and as a result this was not considered suitable as a replacement for the Wellcome test (see para 12).

Response to the specific matters in the letter of 24 August 2011 to Susan Murray from Gemma Lovell. Items in red have been cut and pasted from the letter, items in black indicate my response:

1. In his statement, Dr Mitchell suggested that Dr Dow might be able to give the Inquiry "more information concerning the papers on false positive dates (?data) for various tests reported by Dr Mortimer and reviewed by Dr Gunson and Dr Rowlinson". Is Dr Dow able to assist in this respect? Does he have copies of these papers?

Response:
Miss Vi Rawlinson worked for Dr Harold Gunson in the National Directorate of the NBTS (based in Manchester). Vi Rawlinson produced a monthly collation of Centre HIV testing data to allow centres to compare their data. Within this confidential data were comparisons with Centres using other tests (e.g. Sheffield commenced testing using the Organon assay when the rest of the country used Wellcome), and also quality control data – example of the latter for West of Scotland BTS was as in this table:

Panel member	Number of tests	Failures
DMRQC Low Positive 1	246	0
DMRQC High Positive 1	245	0
DMRQC panel 2 (6 members)	317	0
DMRQC panel 3 (6 members)	72	0
DMRQC panel 4 (6 members)	522	0
DMRQC panel 5 (6 members)	60	0
Ruchill Weak positive	1286	10*
Ruchill Strong positive	1177	0

*= every failure resulted in the entire team associated with this control being repeat tested

Regional Centres were expected to test the Division of Microbiology Reagents and Quality Control Low Positive 1 and High Positive 1 together with a panel, consisting of 6 samples at least once per day. Any failure to detect would have resulted in consideration to retest the entire days HTLV-III test runs. The Ruchill samples were used only locally in the West Centre and were used with every session team (approximately 4 to 6 donor sessions were held each day).
These data gave the testing staff at all UK RTCs the confidence that their testing procedures would identify known positives on a daily basis when some could go an entire year without finding a real HTLV-III positive donation. As the results were published on a monthly basis, RTCs could view how they performed against other centres using the same or different batches or different manufacturers kits.
These monthly HIV testing data were stored in files at Gartnavel BTS.

2. Professor Cash also suggested that Dr Dow might be able to assist the Inquiry in respect of the technical issues regarding the introduction of any form of donation screening. In his statement, Professor Cash states:

"I believe it would be helpful to the Inquiry Team if there was an understanding of the several technical issues regarding the introduction of any form of donation screening. It is my belief that while there seems to be sufficient understanding of the importance of test specificity and sensitivity it

may not be appreciated that there is a lot of associated and dedicated/specific equipment which comes with use of the kits.

I am unsure that the substantial challenges of data pick up and handling have yet been fully appreciated by the Inquiry Team. I make these comments because Ms Lovell has rightly referred to satisfactory 'systems'. I am least qualified to comment further on this topic, and if further expertise is required then Dr Brian Dow and/or Mr Archie Barr would be of much assistance. But I think I can advise that a particular kit manufacturer might have an excellent assay in terms of specificity and sensitivity but the associated instruments/devices and data handling systems were less than optimal – examples of which were published".

Response:
See Item 16 above plus my co-authored and related papers -Barr et al (Lancet May 3 1986 page 1032); Houston & Barr (Medical Laboratory Sciences 1986: 43: 340-3); Barr et al (Medical Laboratory Sciences 1987, 44, 97-99); Mitchell et al (Lancet Feb 6 1988 page 298); Challis et al (Vox Sanguinis 1988, 55, 244-245). These papers show the problems associated with the introductory use of the Wellcome HTLV-III kit with regard to sensitivity and address the problems of false positive tests (specificity). The paper by Houston and Barr shows how the data was handled.

With regard to availability to attend the hearings, I am unavailable on Tuesday 27 September 2011 but would be able to attend on one of the other days (28, 29 or 30) that week.

Brian C Dow
12 September 2011