Microbiology Services Division - Colindale

Margaret Fraser
Witness Liaison Manager
The Penrose Inquiry
44 Drumsheugh Gardens
Edinburgh
EH3 7SW

**Health Protection Agency,
Microbiology Services
Division, Colindale**

**Virus Reference
Department**

61 Colindale Avenue
London NW9 5HT

Tel [redacted]
Fax [redacted]
www.hpa.org.uk

26th September 2011

Dear Margaret,

I am responding, albeit lately to the letter of 22 June from Gemma Lovell. Please convey my apologies to Lord Penrose, I have simply been unable through pressure of work to deal with this previously. I hope the responses below, taken in order from Gemma's letter, will provide a framework for Wednesday's discussions.

1. At the end of April 1984 Bob Gallo announced ahead of publication in the May journal of Science that he had isolated a novel retrovirus from patients who were suffering the newly described immunosuppressive disease associated with Kaposi's sarcoma and pneumocystis pneumonia. He named this virus HTLV-III. The article was back-to-back with a similar description of the isolation of a virus IDAV/LAV1 by the Pasteur Institute group led by Luc Montagnier. The characterisation of IDAV had been described in the previous year by the French group.

2. In May 1984 Gallo made available HTLV-III to my colleague Robin Weiss at the Chester Beatty laboratories (CBL) in London. I and my colleagues at the Middlesex Hospital Medical School (MHMS) had already undertaken the development of a serological assay for the detection of antibody to HTLV-I which had been proposed by the Gallo group as a cause of the immunosuppressive disease now called AIDS. It was therefore natural for us to collaborate again with Robin and attempt to undertake the same development for this new virus.

Interestingly, and in retrospect how unfortunately, Luc Montagnier had already offered CBL access to IDAV and arranged for a courier to bring the material to London in the autumn of 1983. A ferry and trains were delayed, the contact was not met as anticipated and the cell culture was left over the weekend with the result that the culture had died. Things might have been different had we had access to this culture...

I cannot comment on the refusal of the National Cancer Institute (NCI) to grant commercial access to HTLV-III as I was more concerned with the need to develop the antibody assay. During this period antigen was initially prepared from lysed cells grown at CBL and subsequently through expansion on cell cultures in spinner flasks at MHMS. We had developed methods for generating high levels of antigen suitable for our assay and were not constrained by lack of antigen in our research work. Similarly studies were being undertaken at CBL to isolate a British strain of HTLV-III and subsequently once developed we had access to this virus, CBL 1. In the early part of the work we were not constrained by antigen availability.

3. In paragraph 3, reference is made to having a prototype test for research use in August 1984, in fact the assay was considered to be working by the end of the first week in July. Initially this would have been conducted using a lysis of the cell line H9 infected with HTLV-III. Subsequently we were able to pass the virus into a more favourable human lymphoblastoid cell line, CEM and eventually by autumn were growing CBL 1 in CEM cells to support our work.

There are a number of other issues which have not been addressed in this description. Firstly there was a requirement to have highly selected plasma from infected individuals to use both as a capture antibody for pulling viral antigen on to the solid phase and also for the production of initially a radio labelled and subsequently enzyme labelled antibody. The use of a competitive assay for a virus is complex as the HTLV-III family was novel and unexpected. This was the hallmark for the success of the assay. Also, conditions for lysis and inactivation of the viral antigens were critical to allow these materials to be handled on the open bench.

I have clarified the offer by the French group. In terms of finding a commercial partner, I had made contact with the five diagnostic firms licensed by NCI to develop tests, none of whom were prepared to work with us. This was particularly irritating since these companies were using the supernatant of infected cells whereas our assay was based on lysing the infected cells. As a result for example Abbott were discarding each week enough antigen to supply the whole of the UK for six months. In order to work with individual companies outside the NCI franchise it was necessary to have an independent UK-based isolate.

4. I suspect that the UK isolate may have been made before this time but do not have a date for this. Robin Weiss may well be able to provide this. The radio immuno assay (RIA) was running at the Middlesex Hospital from July 1984 onwards, it was not used in anger until the end of summer 1984. At that time we would have been using the RIA test for screening for antibody to HTLV-III (anti-HTLV –III) and confirming reactivity by indirect immuno fluorescence on virus infected cells. We felt that this would be as secure in defining serological reactivity as would be the use of a western blot which is every bit as subjective as immunofluorescence. Reference is made also to the Centre for Applied Microbiology and Research. This was not an easy collaboration and in practice I had to undertake stirrer cultures for much of the scale up undertaken by our colleagues in Wellcome Diagnostics.

There was an interesting unwillingness of CAMR to follow the precise protocol we had for engendering maximal antigen retention in the cell component. It was not until late spring 1985 as far as I can recall that the CAMR antigen came online.

It is difficult at this time to recall exactly when we started our collaboration with Charles Corker and his colleagues at Wellcome Diagnostics. Further on in the letter reference is made by John Cash to comments from Richard Lane, director of the Central blood laboratory authority (CBLA). It would have been natural to expand the existing collaboration between CBLA and MHMS since both had worked together to develop the very successful blood products laboratory (BPL) RIA for the detection of HBsAg (a marker for hepatitis B infection). Certainly Richard Lane was prepared to undertake this but overall there was a need to have those who were already skilled with the production of enzyme-linked immunoassay (Elisa) involved and for this reason, and in light of current collaboration pre-existing with Wellcome Diagnostics, it was felt better to run with Wellcome.

I realised in retrospect this was a disappointment to colleagues in BPL but even at that stage there was a general diagnostic move away from RIA to Elisa. Given also that there was a need to move rapidly with any test, on balance a commercial concern versed in the manufacture of diagnostic assays was to be preferred. This was discussed by myself with the Dean of the medical school before any eventual decision was made.

5. In the September Lancet paper we described the serological testing of a total 2000 blood donors without detecting any seropositive donor. We believed that we needed a much larger number of donors to be tested in order to define the seroprevalance of HTLV-III and in order to deliver this we would have had to have involved other centres in addition to the North London blood transfusion Centre (NL BTC). One very important issue appears unrecognised in this letter.

Given that there was no generalised screening for blood donors at the end of 1984 there was an understandable reluctance in the National Blood Service to institute screening in part of the service, even if only for a sero-prevalence survey and for a limited time, since this could be anticipated to draw in to donation individuals who were curious to know their own status. I believe that instances of donors seeking access to "aids tests" were documented by others. For this reason no attempt was made to introduce part screening for any purpose in the NBS until such time as the NHS had free access and confidential screening available in the GUM clinics.

I am not in a position to explain the statement "we would therefore be in a strong position...... companies". My recollection is that any test considered fit for purpose would be subjected to scrutiny in the UK, on the UK plasma/serum and panels of positive and negative samples and that all tests suitable and available would undergo investigation. This would have been simultaneous for all assays and not sequential as suggested in the letter. There was no intention to delay in order to favour the Wellcome assay kit. I was particularly concerned as an independent scientist that no favours should be given to my assay in view of the very real potential conflict of interest since both my institution and myself stood to benefit from inventors' rights. That said, as a person who worked with the transfusion service, also as a clinical virologist providing a diagnostic service, I was concerned that the assay should be sensitive, specific and technologically easy to use. I believe these attributes more than anything else were responsible for making this a successful exercise, in support of my views you may be interested to look at the letter in the New Scientist from Dr. Barbara and Dr. Hewitt on 29 August 1985.

6. I suspect there would have been much discussion in autumn and early winter of 1984 relating to the need to screen donors for this infection. I cannot recall this meeting, at the time an awful lot of work was ongoing.

7. At this point in 1984 no formal funding had been obtained for the serological development work being undertaken at MHMS although around this time we were involved with an MRC funded study of STD patients co-ordinated by Prof Michael Adler. In order to move from a hand to mouth production of reagents to a more secure supply and provision of reagents for diagnostic use we had to improve the production of antigen, define the optima for production of all reagents and develop alternative strategies for confirming serological reactivity.

By the time I wrote to seek funding it was already becoming apparent that we would not be able to conduct a large-scale serological assay in donors for the reasons stated above. Parallel studies of sexual networks and other risk groups would be undertaken to expand upon the data presented in the September paper. In particular the development of confirmatory algorithms was essential both for the betterment of individual patients and for the potential investigation of sero-reactive blood donors.

Most serological reactivity apparent with the American assays, formatted as antiglobulin and not competitive assays, was likely to be non-specific and in order to do no harm with antibody testing, protocols had to be developed to confirm specificity.

8. With the introduction of any new tests, particularly when dealing with an infection by a virus which we had not previously had any experience in the UK (notwithstanding that we ourselves have experience with testing for antibody to HTLV) there has to be very careful monitoring and investigation of all reactive sera. This is essential in order to define whether the very large number of weakly reactive samples expected do in fact harbour real low level specific signals. Part of this can only be conducted in STD clinics since it is in that environment that we expected to find new infections. This required an investment in staff and equipment. This also was a time at which we were considering switching from an RIA to an Elisa but maintaining the 96 well microplate lay-out.

9. I do not recall any specific meetings to clarify the proposals laid out in my December letter. All I can say is that as a group at that time we were extremely strung out and any resourcing would have been welcome. We were also one end of a joint collaboration with Chester Beatty laboratories. I have said above that any commercial product deemed fit for purpose would have been put forward for assessment. The development of the competitive assay, either in RIA or Elisa format was an integral part of developing an assay for epidemiological studies, clinical use and blood donor screening. The mechanism of introducing this into the transfusion service was clearly outside my remit and was a major operational issue for the NBS. It is correct to say that we would not have introduced an RIA version of the competitive assay, although this would have been exceptionally easy, because we were working to evolve the assay into an Elisa format and little would have been gained in timing because the principal constraint on testing donors was the need to have parallel free access testing within the GUM clinics. This latter component for the NHS was in inextricably linked to the introduction of donor testing. There would have been no intention to grant any special favours for the Wellcozyme sign assay as it became known, the exclusion of the RIA format was for operational reasons.

10. I currently only have the last page of this document and therefore am not in a position to comment. Given the anxieties over the specificity of many tests I can understand the reason to have a properly funded investigation of both sensitivity and specificity. I suspect it would have involved all manufacturers' assays judged as fit for purpose. It was entirely natural that the Central Public Health Laboratory of the PHLS should undertake this work.

11. I am uncertain as to the identity of X. From my letter just before Christmas it is possible that it might have been referring to myself. Alternatively it could have been Philip Mortimer. Looking back I'm relieved that we were not asked to undertake such an evaluation, it would have been a massive deflection. It would have also constituted ammunition for the comment of conflicts of interest. I see no discrepancy between the two responses, more the potential for a conflict of interest had we been asked to conduct an evaluation of commercially available assays while working with an industrial collaborator at the same time. To be in such a position would have rendered it extremely difficult for us to have meaningful conversations with the diagnostic firms concerned.

12. I also find it strange that Alison might have considered not accepting kits unless they had FDA approval, it is not practice now nor was it then to rely purely on third-party data for the introduction of an assay, particularly not one of this importance.

13. I do not agree with the interpretation laid out in the letter relating to the response from Wellcome Diagnostics. My understanding is that, with the speed at which assays were developing, including the migration of the competitive assay from the RIA to the Elisa, the normal extensive investigation

undertaken by a manufacturer to justify the claims for its assay would not be forthcoming. Since the letter states that they would be happy to submit their products for evaluation I do not believe that Wellcome regarded the evaluation as secondary, they were to my knowledge extremely focused on delivering a working assay based on the competitive format.

14. I do not understand anything other than what is written. I think it would be appropriate to consider the issue of commercialisation of a test by a UK manufacturer as being entirely separate from an evaluation program that is being set up to investigate the performance of a number of kits, including that of the UK manufacturer. This would avoid any potential conflict-of-interest and in my view would be appropriate. I am not aware of any relationship between Wellcome and the DHSS in respect of either commercialisation or the evaluation.

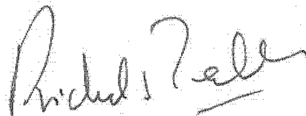
15. Philip Mortimer and I were colleagues in a number of fields. We exchanged material at this time on a regular basis and were involved in many discussions relating to the development of testing algorithms.

16. I have explained earlier the decision to run with Wellcome Diagnostics and explained how this may well have bruised the aspirations of Richard Lane. I have no recollection of any "secret meeting". It is clear however that following the decision by CBL and MHMS to run with Wellcome Diagnostics a number of meetings must have occurred but I have no recollection of a covert one involving members from DHSS and our collaborators.

17. The migration of the competitive assay from RIA to an Elisa test would have occurred in spring 1985. This would have coincided with a general move in the diagnostic community from RIA to Elisa with a reduction in the biological hazard associated with exposure to radioactivity.

18 I joined the Department of Virology in 1973 and worked under Dr. David Dane who regularly provided advice to NLB TC. MHMS also provided support to the development and manufacture of the BPL RIA for HBsAg. The Department of Virology also provided the diagnostic reference testing for donors who were found to be infected with hepatitis B. When Dr. Dane retired in 1980 I took over headship of the Department and this involved also providing the same reference and diagnostic service to NLBTC. This work continued up until the 90s when I became an official external adviser to the NBA.

Yours sincerely,



Prof Richard Tedder
Consultant Medical Virologist