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The Penrose Inquiry
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Dear Lindsey,

Response to queries arising in the Penrose Inquiry

Thank you for sending me the Preliminary Report of the Penrose Inquiry and for contacting me about the issue of the development of HIV screening tests.

I regret that I have not kept records of the events leading to the development of HIV diagnostic tests during1984-1985, and my recall of the discussions and events may not be wholly accurate. However, I shall do my best to respond to your queries. I have also provided you with Dr Philip Mortimer's address because he was involved with the assessment of tests. Unlike Dr Mortimer and Prof Richard Tedder, I am not clinically qualified, and I have not been involved in routine clinical diagnostic assays, in contrast to research tests. Prof Tedder's laboratory and mine worked closely together during the period under inquiry, and I provided expertise on the basic virology and propagation of retroviruses.

Narrative in section B4, pages 221-229 of the Preliminary Inquiry

Paragraph 8.124. At that time I was Director of Research at the Institute of Cancer Research (ICR). My laboratory was located at the Chester Beatty Laboratories of the ICR, but the name Chester Beatty Research Institute was no longer its official name.

Prof Tedder and I had indeed developed a radio-immuno-assay (RIA) for the detection of antibodies specific to HIV antigens. The paper published by Cheingsong-Popov *et* al. in The Lancet at the beginning of September 1984 (cited in note 141 of the Preliminary Inquiry) described this assay and it represented the largest study yet performed worldwide on blood samples taken from over 950 'high risk' individuals and a similar number of healthy, volunteer blood donors in England. The high sensitivity and specificity of the test meant it was worthy of consideration as the basis for the development of a test for mass use, for which a commercial company was needed. As stated in the Preliminary Report, Wellcome Diagnostics Ltd appeared to be the most suitable company for this undertaking, according to advice that the ICR received from the British Technology Group.

Paragraph 8.126. When the problem of false positive results with US tests was raised, I reckoned that the test we had devised would prove to be more specific for three reasons: First, our tests on nearly 1000 English blood donors had yielded no positives, genuine or false; therefore a high rate of false positivity with our test appeared unlikely. Second, the cell line (CEM) in which we propagated HIV-1 to produce antigen for the test was different from the US cell line; specifically, it did not express cell proteins called Class-II Major Histocompatibility Complex (MHC-II) antigens, which were thought to be a major cause of false positive results in tests based on HIV antigens produced by H9 cells, distributed to US companies by Dr R C Gallo. Third, our test used a competition format, that is, the donor's blood sample was titrated against a known, positive antibody control which the sample had to displace in order to register as positive. Such a format is inherently much less likely to yield false positives, but that might conceivably be at the cost of yielding less sensitivity, that is, false negatives.

Therefore an independent comparison of tests coming on to the market seemed advisable because of their different formats and perceived potential weaknesses. I should add that we also provided our HIV-infected CEM cell line to the Institut Pasteur in Paris, which used a non-competition assay to make what became the ELAVIA commercial test. With hindsight, one can say that the low false positive rates in both the British Wellcozyme test and the French ELAVIA test showed that the use of CEM cells was crucial in guaranteeing specificity.

Paragraph 8.127. As stated, there would have been a conflict of interest for our laboratories to continue to be involved both in developing a test and to take up the evaluation of tests. In fact I dropped out of both activities once Wellcome Diagnostic Ltd had been passed the reagents. My focus in late 1984 and early 1985 was more on Africa than the NHS, because we had demonstrated using the same research test that 'Slim' disease in Uganda resembled AIDS as described in USA, and that HIV infection had a horrifyingly high prevalence.

However, I continued to be a member of the Department of Health's Expert Advisory Group on AIDS (EAGA) until the end of 1985. I was then dropped because, in the Chairman's (the Chief Medical Officer) ironic way of expressing things, "Robin, you are too expert!" What Sir Donald meant was that the EAGA was transforming from being an *ad hoc* group of experts to become a Committee of the Department of Health which needed representation from different 'stakeholder' bodies, such as the National Blood Transfusion Service, and I did not represent a stakeholder.

Paragraph 8.128. My recollection of the discussions at EAGA, at least during coffee breaks and perhaps not minuted, was that the US companies were struggling to expand a supply of tests sufficient for the US market, in addition to making modifications as they developed production. There was considerable concern that the companies might 'dump' sub-optimal tests on the European market, including the UK. Thus there was concern about tests which yielded both false positives and worse, false negatives. This perceived danger may have been a factor in seeking to evaluate tests and to include British tests.

Paragraph 8.129. If I remember correctly, the Wellcozyme test was not the only diagnostic test being developed in the UK. There was a test devised by Dr A Karpas in the Dept of Haematology at the University of Cambridge, called the Karpas Test. I do not know whether it was evaluated as I was not a member of the screening test sub-group of EAGA.

Paragraph 8.133. I recall that there was real anxiety over the point that persons suspecting that they might have acquired HIV infection would come forward to donate blood simply in order to get a test if it was not available elsewhere. This might increase the risk to the blood and blood product supply if they had recently acquired HIV infection but had not yet developed antibodies, which is the period when they would be most infectious to others.

Paragraph 8.139. I remain sceptical about bullet point 4, that reliable US tests were available for purchase by the UK in March 1985. I do not think that in March 1985 the US manufacturers were even able to supply all the blood banks in the USA, although the situation had improved by the end of May 1985.

Response to the specific questions addressed to me

a) With reference to footnote 196 on page 223, there were initial reservations about the UK using an ELISA test rather than an RIA and yet the Wellcome test as developed was an ELISA. What was the reason for the change of preference?

Response: I do not recall much discussion about switching from the RIA test to an enzyme (ELISA) test because there was, to my mind, a fairly obvious advantage to develop an enzyme test for commercial production. The RIA was useful for the laboratory research that Prof Tedder and I were conducting in 1984 because it could be rapidly developed, and because Prof Tedder was already highly experienced in devising RIA tests for other human viruses, including the other human retrovirus, HTLV-I. For commercial development and for routine use by staff in blood screening centres (who are, of course, meticulous but less highly qualified than research scientists with PhDs), an enzyme test would avoid the handling of radio-active isotopes and allow simple read-outs of tests by a plate reader which detects a colour (or absence of a colour in the Wellcozyme format). By 1985, several mass produced commercial tests had already switched from RIA to ELISA, for example, the pregnancy test.

In our early negotiations with Wellcome Diagnostics Ltd, I recall that the big discussion was not RIA versus ELISA. It was whether the company would retain our competition format, albeit adapted to an enzyme read-out, or go for a positive colour test, whilst still using our source of virus grown in CEM cells. The key differences between our test and the US tests were (a) the use of CEM cells as a substrate for producing HIV antigens, and (b) the competition format of the test irrespective of being RIA or ELISA.

b) Would it have been preferable (perhaps in hindsight) for the UK to introduce one of the commercially available tests early in 1985, even on a short term basis, rather than await the results of the evaluation programme?

Response: With the hindsight that no new cases of infection by HIV via blood and blood products were recorded in Scotland between May 1985 and October 1985, it probably was preferable to wait and introduce an extremely reliable, robust, easy to use, specific and sensitive test. Furthermore, I do not think that the US tests were genuinely available to the UK at the standard approved by the FDA because the US companies were experiencing difficulties in supplying the home market with a quality product.

However, the Inquiry should weight my answer with the knowledge that I was an interested party. Although I have not personally benefitted financially from the royalties paid by Wellcome Diagnostics Ltd for the Wellcozyme test, the institution where I was employed at the time, the Institute of Cancer Research, did receive royalties, in common with Prof Tedder's Middlesex Hospital Medical School.

Final comments: During 1984 and 1985, virological research into HIV was just getting into gear. My laboratory was the first in the UK to become involved in investigating HIV when we received the French HIV isolate, LAV, from Luc Montagnier in February 1984. We researched this threatening new disease HIV/AIDS under immense pressure of time, and we did not know how dangerous the virus was to handle in the laboratory. We diverted grants awarded for leukaemia research in order to find out what the prevalence and risks of HIV infection were, and whether Slim disease in Africa was actually HIV-associated AIDS. We were also doing our utmost to cooperate with blood centres, including with Dr C Ludlam in Edinburgh, to ascertain the risk of infection among persons with haemophilia and recipients of blood transfusions.

I wish to add that I have neither consulted Prof Tedder nor anyone else in formulating this response because I think that it is important that I put forward my own recollections and views, however faulty they may be after the passage of time. If the Penrose Inquiry thinks that it would be useful, I am willing to contribute further.

Yours sincerely,

Robin

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