Witness statement to the Penrose Inquiry

Karin Froebel, 13 June 2011

I can't remember the exact date, but I think it was in 1982, that I moved into the new Department of Medicine Research laboratory at Glasgow Royal Infirmary. It was an open plan laboratory, into which five research groups moved. I was a post-doctoral research fellow, working on the cellular immunology of rheumatoid arthritis. Soon after the move, Professor (then Dr) Forbes, Director of the Haemophilia Unit, spoke to me about a new syndrome of immune deficiency affecting, among others, haemophiliacs in California. I responded by saying that, apart from one assay (the natural killer or NK assay) which I thought I would be able to develop, I was able to apply all the tests that were used on the Californian patients. I suggested testing ten patients with severe haemophilia, to see if there were any similarities. In the end, I ran samples from 17 patients through a number of immunological tests, both numerical, for proportions of lymphocyte sub-populations, and functional, for their response to mitogens and for natural killer activity.

I am not medically qualified, therefore for all my work using blood samples, both prior to this time, during this period and subsequently, I have been dependent on physicians to liaise with patients, and to take their blood. I don't know what was said to the patient, but I believed that they were aware that some of their blood might be used for research. I would run control samples with every patient sample, and for these I would ask colleagues for a blood sample. The controls would be told what their blood was used for if they asked.

At this point, I was looking to see if Scottish haemophilia patients had any of the differences to controls shown by American haemophiliacs, and I fully expected not to find anything. However I did find some differences: I found that the proportion of T-helper (CD4) cells was reduced, and that of T-suppressor (CD8) cells was increased compared to the controls. At the time I didn't know how to interpret this, and said in the paper that I didn't know how different from normal the results needed to be to imply a functional abnormality.

I found that the response of patients to one mitogen (phytohaemagglutinin or PHA) was similar to controls, but to a second, (Concanavalin A) was reduced. Mitogens were thought to stimulate T-cells in a non-specific way, so a reduction was an indication that something was abnormal, but was not specific as to what it might be. I found the response of patients in the second functional assay, that of natural killer cells, was similar to the controls. This was the new assay I had developed for this work, and I didn't have any other experience of it.

At this point, a virus had not been isolated. I knew very little about viruses then, and thought that because Scotland was making its own factor VIII from Scottish blood donations, and also that the Glasgow haemophiliac patients had not received any of the commercial American product for the previous 2 years, that a viral infection from factor VIII was not the explanation. I did not understand then that viruses could be slow or long-acting, and we were looking for other possible

explanations. I wondered if the reduction in response to mitogen might be related to the constant exposure to factor VIII, and repeating the mitogen stimulation assays with added factor VIII seemed to bear this out. I expressed this view in the October 1983 BMJ paper.

The laboratory work was done over the winter of 1982-3. I had presented it at a meeting of the Scottish Medical Society, I think, in the Spring of 1983, and it was published soon after as an extended abstract in the Scottish Medical Journal. I think this SMJ paper was the first report in the UK of what was later understood to be HIV/AIDS.

Things were moving very quickly in the field. In Spring of 1984, two reports, from Montagnier in France, and Gallo in the US, claimed to have isolated a virus from patients with AIDS. Both were working on an antibody (ELISA) assay, a blood test that would show exposure to the virus. We were interested to know as soon as possible whether the Glasgow haemophiliac patients had antibody to the virus. In Glasgow there was a freezer-full of stored serum samples from an earlier study, which Dr Forbes suggested could be used. I wrote to both Montagnier and Gallo, and had a reply from Dr Gallo, directing me to send the samples to his research scientist. The samples (77) were located, I think by Dr Madhok, packed in dry ice, and Dr Forbes and I took them to Glasgow airport to be air-freighted to the laboratory in the US. At this point, I still thought the results would be negative; that we were dealing with something different in Scotland and I can still recall the shock when the news came back that 12 of our 77 samples, ie 16%, tested positive. Very soon after that, Mads Mellbye appeared, and suggested writing a joint paper, pooling our results with his 22 Danish samples, and this resulted in the Lancet paper in December 1984.

At this point I recall Dr Forbes saying that he would speak to all the haemophiliac patients and tell them that they were at risk of infection, and should take the necessary safe sex precautions, ie use condoms. The test carried out in the US had not yet been approved by the regulatory body; therefore we could not say for sure that the 12 were definitely infected or that the 65 were definitely not. I also recall Dr Forbes telling me soon after, that he had spoken to all the patients. I had no direct contact with patients at any time.

The newly isolated virus was at that time being called LAV by Montagnier, and HTLV-III by Gallo. It was towards the end of 1985 that the scientific community agreed on the name HIV.

I left Glasgow in March 1985 when my funding came to an end. My name was included on a subsequent study, which looked at longitudinal serum samples from the Glasgow group of patients. It found that some had turned positive while they were still receiving American factor VIII.
Ref: Madhok R, Melbye M, Lowe GD, Forbes CD, Froebel KS, Bodner AJ, Biggar RJ, HTLV-III antibody in sequential plasma samples: from haemophiliacs 1974-84, Lancet, 1(8427), 524-5, 1985

I returned to work full time in HIV research in Edinburgh in November 1989.

SCHEDULE

Matters to be included in the statement

The Inquiry team is aware that from 1983 various immunological studies of haemophilia patients attending the Glasgow Haemophilia Centre were carried out. We are also aware that the results of these studies were subsequently published in the BMJ and Lancet. We would be grateful if your clients could answer, so far as they are able, the following questions:

1. The enclosed BMJ article, published on 15 October 1983, and entitled "Immunological abnormalities in haemophilia: are they caused by American factor VIII concentrate?" reported a study of cellular immunity in a group of 19 haemophilia patients. When was the study of these patients commenced? Late 1982 When did the study end? spring 1983 Were the 19 patients all being treated at the Glasgow Haemophilia Centre? I believe so What was the purpose of the study? please see witness statement What were the findings of the study? please see witness statement Were the patients aware that they were being studied? I don't know, but I believe in general terms that they knew that research was being done Was their consent obtained to be included in the study? I don't know, Were the patients advised that their lymphocyte abnormalities were "consistent with those seen in acquired immune deficiency syndrome and in acute viral infection"? please see witness statement Was consent obtained from the patients before publishing their data in the BMJ? I don't know Are there any other publications in respect of this study? please see witness statement

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2. The enclosed Lancet article, published on 22 December 1984, and entitled "HTLV-III seropositivity in European haemophiliacs exposed to factor VIII concentrate imported from the USA" reported a study of 77 haemophilia patients between December 1983 and July 1984. Were the 77 patients

different from the 19 patients mentioned above? I understood they were from the same cohort Were the 77 patients all being treated at the Glasgow Haemophilia Centre? ? I believe so What was the purpose of the study? please see witness statement What were the findings of the study? please see witness statement Were the patients aware that they were being studied? Was their consent obtained to be included in the study? I don't know, but I believe in general terms that they knew that research was being done Were the patients advised of the results of the study? yes Was consent obtained from the patients before publishing their data in the Lancet? I don't know Are there any other publications in respect of this study?

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3. In addition to the two studies mentioned above, were any other studies carried out on patients at the Glasgow Haemophilia Centre at this time? If so, please provide as much information as possible about the nature and outcome of the study(s) and references to publications where applicable. A later study (after I had left Glasgow) showed that the samples became infected while patients were still receiving Factor VIII from the US. I don't know where this work was done. (Madhok R, Melbye M, Lowe GD, Forbes CD, Froebel KS, Bodner AJ, Biggar RJ, HTLV-III antibody in sequential plasma samples: from haemophiliacs 1974-84, Lancet, 1(8427), 524-5, 1985).

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4. We understand that early testing of blood samples (described by Professor Forbes in an earlier statement as "special samples") for anti-HTLVIII was carried out by Dr Mads Melbye at his laboratory in Denmark (and that subsequent testing was carried out by Dr Follett at Ruchill Hospital). Were the "special samples" referred to by Professor Forbes, samples from the patients in the two studies above? Are you able to confirm when the testing by Dr Melbye took place? This may refer to work done after I had left Glasgow (see para 3 above).

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5. Did you continue to study the patients once their anti-HTLVIII result was known? No, I left in March 1985. If so, please provide as much information as possible about the nature and outcome of the study(s) and references to

publications where applicable. Was consent obtained from the patients for follow up studies?

6. Other than the studies carried out by Professor Ludlam in Edinburgh, are you aware of any other similar studies that were undertaken in Scotland? No.