THE TRIBUNAL RESUMED ON MONDAY 9TH OF JULY, 2001, AT 10:30 A.M., AS FOLLOWS:

THE CHAIRPERSON: Morning, Mr. Durcan.

MR. DURCAN: Morning, Madam Chairperson. The next witness is Professor Richard Tedder.

THE CHAIRPERSON: Good morning, Professor. If you wouldn't mind standing and take the oath, or if you wish to affirm, whichever you wish.

PROFESSOR RICHARD TEDDER WAS SWORN AND EXAMINED BY MR. DURCAN AS FOLLOWS:
A. Good morning. I am Richard Tedder. I don't know if you need anything further. That's my name.

Q. Don't worry. Morning, Professor. Professor, I think you are a Professor of Virology at The Royal Free and University College Hospital Medical School in London, is that correct?
A. That's correct.

Q. And when did you qualify as medical doctor? '73?
A. It is some time ago, yes. It would have been August '73. Or July.

Q. I think you have been involved in the Department of Virology in Middlesex Hospital since 1975?
A. Well, in fact, I did a placement there as medical student in '72, and I was involved with -- from the early part of '74 onwards and became a member of the faculty; it would have been January '75.

Q. I think you were part of the team of Dr. David Dane, is that correct?
A. Correct.

Q. And on Dr. Dane's retirement, did you take over in charge of the department?
A. Well, that is an interesting way of putting it. There was a vacuum and the medical school was in the process of being amalgamated, and somebody had to carry on. I suppose I acquired it really by just being there. But, yes, I carried on steering subsequently and became recognised head of department a few years later.

Q. Was that situation recognised and were you appointed head of the department in 1984?
A. Yes, it was -- it was a joint -- it was a rotate headship of Microbiology with a fellow microbiologist for the whole of Microbiology, and Virology was originally part of Microbiology and then became independent. And we have remained separate since.

Q. Up to 1984, what type of work were you involved in up to that time? Were you developing any form of tests or assays?
A. Of course that is the seminal year at which HTLV-III B burst on us, in May of that year. I suppose it's relevant to follow from 1980 when I was developing serology

initially for varicella chickenpox virus. That caused big problems on the radiotherapy ward. And that led me into a format of testing which was subsequently used with considerable effect for the leukaemia virus, which we worked on HTLV in 1982, '83. We were already aware of, from 1982 onwards, gay-related immune deficiency syndromes, GRIDS, subsequently called AIDS, and what we called ELS, Extended Lymphadenopathy Syndrome, in the GUM clinic. And we were developing ways of co-cultivation and trying to look for an aetiological agent. And when in 1984 access became -- we were given access to antigens derived from tissue culture from the early LAV-1 virus from Montaginier, we started developing in the early -- or mid part of summer '84 test.

Q. I will just stop you there. I will come back to where you are just at the moment in time - in the middle of 1984 - in a moment. I think prior to the development of a HTLV-III test, I think you might have been involved as well in tests or developing tests for Hepatitis B, is that correct?
A. Oh, sure. I mean, well, that goes back -- that is archival, truly archival. When I started with David Dane formally as a junior pathologist in '75, I was given an opportunity to be involved in some research work then. And I had a Wellcome fellowship for two years, which must have been '76 to '78 or '79, in which I was developing serological assays, first of all, for Hepatitis B antigen, these additional markers of Hepatitis B infection.

Q. When did a test for Hepatitis B first become available, approximately?
A. I think you would need to define which test you mean, because immunodiffusion tests were available in the early '70s; contrary immunodeficiency, probably '75. Those were used in the blood transfusion banks. Radioimmunoassay --

Q. I think the stenographer is having some difficulty.
A. If it helps, if I use the vernacular I can afterwards give you a glossary.

Q. I think that would be -- would be helpful. I think you were just taking us through the different forms of tests for Hepatitis B?
A. The history, I mean, I don't know how deeply you want to go into this, but the history started off with simple immunodiffusion tests and then developed into antibody/antigen interactions where you saw it in an electric field, and then where a reagent on a particle, which was red cells, so you have got what we call haemoglutination assays. I can remember in 1974 or '75 discussions with people developing a radioimmunoassay, and that was the assay which went into the transfusion service later on that decade as the blood products radioimmunoassay. And that actually held sway for quite some time up until the mid-'80s when there was both a desire to move away from home-built reagents and a desire to move away from radioimmunoassay, which led to the introduction of enzyme immunoassays.

Q. Would each of those -- what we see from what you have told us is a progression in terms of the form of tests that were available, and would they become more reliable over time?
A. Can I take that in two stages? You have asked two questions. Yes, there was an evolution of the technology, and that was designed to be more robust, easier to deal with, quicker functioning. So there was a technological aspect, operational aspect of the assays to make them more amenable to transfusion practice. The result of this was

two things: Firstly, on the whole, the tests became, with each step, more sensitive. And that, of course, when you are wanting to detect virus markers in the plasma of donors, is an important attribute; that you push sensitivity as far as you can. Whether they became more accurate is questionable, because the first introduction of the Abbott Radioimmunoassay Ausria-1 was associated with a four-fold increase in prevalence of reactivity amongst blood donors, which the manufacturer said was 'how marvellous the test is; for every one you are getting, we are getting four'. The trouble was that almost all of what they were getting was force reaction. You have to be rather careful when you say 'I am moving the technology forwards' because sometimes you get into problems of specificity. So on the whole, as tests evolve and the technology evolves, tests become more sensitive and usually more specific, but there can be creases, as a phrase that you use here; there can be wrinkles with the more specific assays, the more sensitive assays.

Q. Thank you. If I can take you back to what you were mentioning a few moments ago. Around about the middle of 1984, could you explain what -- your involvement in the development of tests for HTLV-III; what functions were you carrying out in the middle of 1984?
A. Yes. I can lead you through that. It's some time ago, and dates may not be absolutely precise. We had in the early part of May the back-to-back publication of Gallo and Montaginier in Science. That was followed a few days later by a press release from the Medical Research Council in London saying how important was this and what opportunities it gave for research. Some -- probably two or three weeks later, Robin Weiss, who was then the head of the virus unit at the Institute of Council Research in the Chester Beatty laboratories in Fulham in London, with whom I had been working on the issue of HTLV antibodies, was given access from Luke Montaginier, access to the LAV-1 virus isolate, and adapted that to grow along with HTLV-III B, which was a Gallo isolate, adapted those to grow in a variety of cell lines. We did not have the facilities in May '84 for growing the virus and were relying on Robin to produce an extract of tissue culture. It was a very crude style of antigen. And because of the experience I had had with initially the varicella antibody test and subsequently the HTLV-I or HTLV competitive test, it seems to me to be sensible to try and use that technology to develop assays, immunoassays for antibodies against whatever this was. Now, what's interesting, and it teaches one that you can do things from a cold start: We selected panels of sera on the apriori reasoning that if somebody was infected with this agent and it was a retrovirus, that they would have antibody and that the antibody would persist. So we took panels of sera, really on a blind basis; we made them into reagents and we tested those reagents as against themselves and against other panels of sera to see if we could differentiate between samples which came from young men with gay-related immune deficiencies, GRIDS - now we call it AIDS; young men in GUM clinics who had sexual partners with AIDS, because there were cases of AIDS in the UK in 1984 - against other perceived risk groups, taking sera from intravenous drug users, taking sera from UK donors, from donors giving blood in the UK who were not born in the UK, and made an experiment of trying to differentiate between reactivity - I have to say we didn't know what the reactivity was - and went into a series of reactive experiments where you took a panel of half a dozen -- we took panels of sera, made reagents from them - that's both immunoglobulin to coat the solid phase, to capture the virus, and the radiolabel to compete with -- and just set up blind tests. And then basically what happened was you got two populations of results; one on the right, one on the left.

And because of the format of the test, these were the ones that had the marker that we thought we were looking for. And we started with a differentiation of about three or four to one. We took the best reactants from that experiment, reiterated those into making more reagents and ended up with a differential of about four or five to one. Took the highest. We went through probably 100 reactor samples - titrated them; took the strongest reactive and made those into an assay form, and that was the assay form which we subsequently published on in September of that year but we had used from the middle of the first week in July onwards.

Q. Now, if I could stop you there.
A. Sorry, it's a difficult -- it's a difficult thing. As I said, it would have been nice to have a board and I could demonstrate.

Q. We have got you a board.
A. Good Lord. I will use it if you wish.

Q. We will keep going, Professor, and if need be, we will resort to the board in terms of the explanation. If I could take you to just where you have come to at the moment. You were doing various experiments and I think by July 1984, had you reached the stage whereby a test -- you, together with your team, had developed a test that could be used for finding antibodies for HTLV-III?
A. Well, I suppose the simple answer is yes, with all the caveats. It was entirely new. We did not know the significance from any scientific basis of the antibody that we were testing, but we knew it was intimately associated with HTLV-III/LAV I, and was at high prevalence in people with AIDS. 97 percent of individuals tested had reactivity in the assay and less than one in a thousand blood donors had reactivity within this assay. So it seemed to be sensitive, it seemed to be specific. It was repeatable and gave us good differential between reactive and nonreactive and that -- we presented within the department in the first week in July saying, look, chaps, we think we have something that's quite important here. And we developed the ability to grow larger volumes of the virus on-site and started providing this testing for people who wanted it through the laboratory networks in the United Kingdom, from I suppose probably August/September onwards.

Q. How long had it taken you to develop the test?
A. Well, about six weeks.

Q. Six weeks.
A. I mean, you are not often that lucky.

Q. I see.
A. Good reagents and prior experience enabled us to develop it very quickly. And then six months within starting, developed it into a competitive enzyme immunoassay format. It's an interesting history of how things can go well; not always.

Q. You just mentioned that I think by September you were in a situation, having announced it to your colleagues perhaps in July, I think by September you were in a situation to offer testing to various different groups?
A. Well, in September we published the -- probably what was equivalent to something like 75 or 80 percent of the global serology at the time came out in our

paper in September. And of course that followed -- was followed by a lot of people ringing up saying, if you are that clever, can you do it for us? And we tried to be as helpful as we could. It was difficult because it was radioimmunoassay, and we had very limited resources. We had no funding at that stage to do it and we just all clubbed together and got on with it.

Q. Among the groups who were anxious to have testing done, I think, were persons with haemophilia, is that correct, and persons with haemophilia I think in England, firstly?
A. I can't comment on the desire of the patients themselves, but I can comment on -- I can answer that in the sense that the haemophiliac directors and some of the clinical haematologists who had special responsibility for maintaining the welfare of haemophiliacs were particularly concerned to find out what the prevalence of this marker was in their patient populations.

Q. I see. And because of that wish, on their behalf did you begin to get specimens from the directors in England?
A. Yes.

Q. In regard to their patients?
A. Yes. I mean, I don't have my daybooks to hand, but certainly, my recollection is by the latter part of summer, early autumn, we were collaborating with a number of people, Professor Rizza, Eric Preston, Chris Ludlum, north of the border, to provide a basis for antibody testing.

Q. I see. And did that exercise extend at some stage to patients who were here in Ireland?
A. Sure. It did.

Q. I think we have heard evidence in regard to this, that our understanding is that that perhaps -- the exercise began to extend to Ireland around about December '84, January '85. Do you have any recollection of how those arrangements were made or what happened?
A. Well, I know that we had met with the UK haemophiliac directors and there had been discussions between Philip Mortimer, who was a close colleague of mine in the Central Public Health Service, who headed up the Virus Reference Laboratory at Colindale; and John Craske, who is well-known to this Tribunal, as a person with an interest in transfusion and blood component associated -- blood product associated hepatitis. So, the three of us - Philip Mortimer, John Craske and myself - had discussed how we were going to put in place testing using our competitive test. And Philip Mortimer had developed the same format of test initially on reagents we gave him at VRL; and that we stipulated that we needed to have a good quality serum sample; that we needed to have a knowledge of the therapeutic -- broad knowledge of the therapeutic regime of the patient; the type of deficiency they were being treated for, whether it was mild, moderate or severe; name and age, because this was being referred as a diagnostic, this wasn't as -- this wasn't a seroepidemiological survey. It required the same sort of accuracy of identificats on the samples from the patients; that we needed a name, date of birth and date -- certainly had a name and date of the sample, probably date of birth as well, just to make sure that we need -- that we had the appropriate identifiers for the patient. Samples would be referred to separated with

a work-nest. We could conduct the assays, stamp up a work-list and issue that back to the people who had sent us the samples, which would sometimes be a laboratory or sometimes come from the haemophiliac centre directly.

Q. In terms of results, I think you have indicated in your last answer they tended to be by way of list with the results stamped onto the list, is that correct?
A. As far as my memory serves me. I haven't seen them for a number of years, but yes, I remember stamping them.

Q. I see. Again, I don't wish to trouble with you the detail of what happened hereby, save for this: We have seen that lists that came back here and that were sent out to the treating doctors here. And in a number of cases, there was an entry of "negative, please repeat. AB below cut-off." Could you help us in regard to what that would mean?
A. Yes. It would be nice to see some of our original records and confirm this, but I think we were relatively secure with samples which fell within the normal population of sera negatives, and those would be negative. And we were secure with samples which were strongly reactive and fell in the population of positive samples. The difficulty arises with a specimen which falls between the two groups. If we had said "below cut-off," this means that our arbitrary level at which we consider something to be positive is below a certain level; it fell below that level and would be -- nowadays I think we would call it reactive. But because it was reactive at a very low level, one wanted to know whether that repeated in a subsequent bleed or follow-up from the patient.

Q. I see. Well, when it's -- when the request would be to "please repeat," would -- what would be intended? Would there be another sample, or what would happen?
A. I think in retrospect one was not as -- how can I put it? One was not strict as -- strict enough, perhaps, as we should have been. It would have been our belief that to "repeat" implies a resampling of the patient, not a resampling of the tube. Specimens which are weakly reactive in a tube that we have would remain equally reactive from the sending laboratory. And if the sending laboratory merely sent us a fertile sample, you would be -- it would not be contributory because it would be no better than retesting the sample and getting a weak reaction. In practice, what happens if you have a weak reaction -- we now know because tests are much more secure, but there is normally an evolution of that reactivity fairly quickly. And you see a patient's reactivity transiting from the distribution of negatives through the cut-off zones to the distribution of positives as you follow them up in time. That's why we would expect -- we would anticipate that you need to go back and rebleed.

Q. Sorry, just the last word there?
A. You need to go back and rebleed.

Q. Yes. That brings us up I think to around about the beginning of 1985, and you have been telling us about the testing arrangements which you were carrying out and your laboratory was carrying out. Had there been developments in terms of the introduction of other types of tests for HTLV-III?
A. There are two aspects to the answer of that. I'll take the simple one first, which is the commercial sector. NCI had licensed five manufacturers in the United States to develop serological assays, and they developed a very different format of assay, called

an antiglobulin test, based on a different principle from the one which I had worked with. These were becoming available in Europe early in 1985, probably March/April/May '85, something of that order. And at least three of the assays were becoming used in the clinical sector; certainly the Abbott test, the Dupont test and the Organon Technica (?) test.

Q. Yes. Could I just stop you there and ask you: In terms of those tests, when would they have first become available as tests that could be used by treating doctors or by -- or that could be used by blood banks?
A. Again, it's an awful long time ago. My memory would -- my memory is that the Abbott test was available probably in April '85. And that was probably the first one, but it's -- I can't guarantee that I'm correct on that.

Q. Yes.
A. But that is the sort of time that these became available.

Q. The -- these five tests, as I understand it, the technology which was used was different to the technology that was used in the form of tests that you had developed --
A. Correct.

Q. -- in 1984.
A. Yes.

Q. Was there a form of commercial test being developed which would have used the basic technology which you had developed in 1984?
A. Yes. Because we had discussions early in the year - the end of the previous year; end of '84, beginning of '85 - with the Blood Product BPLs; they then were Blood Products Laboratory. And BPL wanted to consider setting up the development in-house of an assay in the same way as we had collaborated in the previous decade on the development of the blood products RIAfor Hepatitis B. I talked at some length with BPL about this, whether it was feasible; and also, counselled views of my colleagues, including my then head of academic department - not of virology, but microbiology - who was Professor Patterson. And we elected, rather than hold it in-house, because of the need to move very quickly, elected to run with commercial -- well, not commercial outlets but commercial developers of immunodiagnostics. And actually approached, at the same time as I talked to Wellcome Diagnostics, I approached two or three of the big holders in the diagnostic fields in the States to see if either Abbott or NGI were interested in having access to the competitive technology that we had. And they all declined, partly on the basis that they said it will never work and partly on the basis that they were constrained by the NCI agreement. So the only people we could find who would run with this was the UK-based company, Wellcome Diagnostics, and we started that in probably February or March, a collaboration.

Q. And when did a commercial test become available from Wellcome?
A. It was field trialed in July or August, and was commercially available probably end of -- middle of August.

Q. I see. Let me --
A. It might have been earlier. I mean, sands of time...

Q. We are not tying you down here to an absolute date. But would I be correct in this general picture: That the five commercial tests we have been talking about, the other five commercial tests, perhaps would have been available from maybe April 1985; the Wellcome test would have been commercially available somewhat later, perhaps July/August?
A. Well, I think the first of the commercial assays was the Abbott, which was probably available in April -- April, beginning of May, '85. And the others started falling into place. We were -- it didn't impact on us because we were providing serological diagnostics on our own in-house assays. And the early noncommercial field-trial version of the Wellcozyme kit, we were developing that as we went and refining that and using that, coupled with limited confirmatory testing. So I can't comment on how widespread in the diagnostic field these other assays were. There is a run-off period; the big period is when the transfusion service in the UK was able -- able to go live with HIV, HTLV-III testing.

Q. It's exactly that I want to ask you about now: Was there discussion in England in regard to when the blood banks in England should introduce HTLV testing of donors?
A. Yes. There was a great deal of discussion, because we had actually wanted to run a pilot trial based on radioimmunoassays at the end of '84, beginning of '85, home-based in our local transfusion centre in north London. But the -- there was sufficient sensitivity to having one centre, even running an unofficial clinical trial, if you like, of HTLV-III antibody testing, that that was deemed to be an unsatisfactory way forwards. Extensive discussions must have occurred in early '85, defining the terms under which the NBS or - I forget what they called themselves - I think it was the National Blood Service, would go through to general screening. The main parties in the discussion would have fallen under the remit of the Expert Advisory Group On AIDS, or EAGA, as it was then known, and EAGA was chaired by the deputy CMO or the CMO, Chief Medical Officer, or his deputy, and had a subcommittee discussing the introduction of blood transfusion testing. This also raised very significant fears that in March or April time, that in order to have secure -- to secure the blood transfusion service, that the BTS could only introduce or only should introduce HTLV-III antibody screening at the same time - certainly not before - that there was confidential free counselled testing in the Genito-Urinary Medicine clinics in the UK as a whole. There was real anxiety of encouraging people to come forwards for HIV testing into a transfusion service which had yet to institute a secure HTLV-III antibody screening test. That led to the delay, deliberate delay of introduction of HIV screening, if I'm -- if I may use the word, HIV screening, but of course in those days it was HTLV-III B, but I think I will use HIV. So HIV screening would -- was not to be introduced on a piecemeal process; it had to come in across the country coherently, and dependent upon HIV screening under the Terms of Reference that I have mentioned for GUM clinics. This meant that the GUM clinics had to recruit staff, train them for counselling, and have those counsellors in place the same time as testing would start; that laboratories in the UK had to be developed who could produce HIV screening and confirmatory tests, because we already recognised, depending on the technology, a moderate to very high prevalence of force reactivity, or nonbiological reactivity, in screening tests. That had to be addressed and we had to have confirmation testing in the backup reference laboratories to enable the secure service for HIV testing to be undertaken in the GUM clinics.

Q. Do I take it from what you have just told us that, therefore, a deliberate decision was made to delay the introduction of testing in blood banks to allow alternative test sites to be available?
A. Yes, I think that is absolutely correct. I think the delay was actually regarded not so much as a delay, but the soonest safe time for the introduction of HIV testing in the transfusion service. That led to a temporal delay, yes, but a delay implies that you could have introduced HIV testing before; it was the firm belief of the transfusion service of the Department of Health and of the expert advisory group that it was not possible to introduce HIV screening in the transfusion service until one had parallel, secure, counselled, confidential testing in the GUM clinics.

Q. Yes. Was any consideration given to applying the solution that the Dutch authorities applied, which was to introduce testing in the blood service at the earliest possible time - which I think we know is not later than June - but not to report the result of the test to positive donors, thereby taking away the incentive for high-risk -- persons at high risk to attend at blood banks for the purposes of being tested?
A. I'm not aware of discussions particularly covering going with the Dutch approach. What I do know is that discussions were in place; should we tell people what is the significance of their findings? That was perceived to be absolutely necessary, that we could not have, on our books, identified donors whom we knew to be infective with a sexually transmitted dangerous agent, who had sexual partners and relatives who were at risk. It was not acceptable to any discussion that I'm aware of, had -- allowing those infections to remain covert in the transfusion service. That fell completely against the principle of openness and clinical responsibility which the BTS had for its donor population. It would also have been a very difficult point to get across to the - I use the phrase very advisedly, and it's not especially politically correct - it was one -- the risk groups. You would have had to get a complicated message through to the risk groups, "yes, we will test you but we are not going to give you the results for another two or three months." And I'm not sure how efficient that would have been.

Q. I see. When was HIV screening of -- in blood banks actually introduced in England?
A. Probably around about September the 14th or 15th.

Q. I see. Was there a period of time -- sorry, I will put the question a different way: Was that before the official date when such screening was introduced?
A. It was the longest shelf-life of blood components plus two or three days. So it was about 30 days prior to the October go-live date. The reason for this was to, A, have a little bit of a run-in period before we could have expected, had it happened, the recruiting risk donors into the donor panel; and more importantly, it was an attempt to defuse the situation of Mr. Jones ringing up and saying, 'my patient, Mr. Smith, is going under the knife tomorrow. You have started screening for AIDS today. I want my patient to have screened blood for tomorrow.' because the answer to that is, 'yes, it's all right, all the blood in your bank is now screened'.

Q. So --
A. Bit of a subterfuge. It was done for the best methods.

Q. And I understand. It allowed a situation after the go-live date that you could say -- or that the blood banks could say to people, no, you don't need to worry, the blood you are using --
A. Has already been screened. That's correct.

Q. Yes. So -- but therefore, the actual date of introduction was approximately just perhaps a little bit over a month before the official go-live date?
A. Correct.

Q. I see. Now, could I take you back to the testing which you were doing in late 1984 in regard to groups of persons with haemophilia. And perhaps if you look at paragraph 11 of your statement, this is the territory we are going to cover. What I'm interested in is this: What were the results in terms of percentages? What was the picture that was emerging in regard to the rate of infectivity in persons with haemophilia who were being tested in the autumn and the winter of 1984?
A. Can I just confirm, this is paragraph 11, page five, of my --

Q. Yes.
A. I think it's probably best encapsulated in the national pop -- you have a paper; what was the first -- the author of September '84, that for the figures in our particular study, it was 30 percent of recipients of Factor VIII concentrates were seropositive, about one in three.

Q. Were I think blood donors -- or a certain number of blood donors were also tested by way of the test you were using at the time; I think a thousand. And what was the result in regard to them?
A. They were seronegative. They were unreactive in the radioimmunoassay.

Q. I see. Now, you have just referred to a paper which was published in The Lancet in 1984. And I think it highlighted the fact that there was a large discrepancy between the number of haemophilia patients positive for the antibody and the numbers that had developed AIDS, is that correct?
A. That is correct.

Q. Now --
A. It was 34 percent actually on page 32 of my band, table two.

Q. Was there a view about the likelihood that persons with haemophilia who had antibodies or who showed antibodies on the test, their likelihood of going on to develop AIDS; I am talking about at that time, in the autumn/winter of '84?
A. Yes. There was considerable discussion, but this went beyond the question of haemophiliacs. It went to -- it started off with a discussion in any human infected with HIV, whether the antibody indicated antibody like the measles scenario - you have had the infection, you have got over it; or whether it's more like, for example, Hepatitis B anticore antibody in the Hepatitis B carrier where the antibody persists in the face of persistent virus. So the original discussions -- and we went -- it wasn't only in the UK, it was really globally. Some people were saying, well, antibody doesn't necessarily mean persistence. There were two datum points which argued against that: One was -- this is generally, this is not haemophiliacs specifically, because there is another wrinkle on that. Dealing just with the person whose serum

was reactive for HIV antibody, firstly, the evidence of animal virus infections with retrovirus - I worked closely with Robin Weiss at the time - would indicate that most -- not all, but most of those lead to persistent infection. So once the animal becomes seropositive, the animal is infected for the duration of its life with the retrovirus, which replicates and expresses and may or may not cause disease. So that was the apriori grounds from veterinarians, and the vets had quite a lot to teach us about retroviruses. The second datum which made this seem inherently unlikely to many of us: If you looked at the very simple parameter of how much antibody from the time that somebody converted, as long as you followed them the antibody would continue to rise. And there was more and more and more of it. This is very different from what happens in something like influenza, measles or rubella where your antibody is up very quickly and reaches a peak and gradually declines as you follow people in time. This hallmark of continually rising antibody suggests that you have got what we term antigen drive, and antigen drive you can only get because you have got persistent virus expression. So those were the apriori grounds for saying how long before we could culture the virus. But looking at the parameters of it within evolution in time, if you developed an antibody it was quite likely that it would be an indicator for persistent virus infection.

Q. I see.
A. So that -- that's the apriori ground. Now, if you want to reiterate the question with haemophiliacs, there is a difference.

Q. Yes. And that -- that is exactly what I wish to do: Again, I want to take you back to the article in September 1984 that was published in The Lancet, which is mentioned at paragraph 11 of your statement. At that stage, was there a view, a general view, that AIDS was not considered to be a likely outcome for the vast majority of haemophilia patients in particular?
A. Sorry, can -- I was just trying to find my position in the document. Can you just reiterate the question? Apologies.

Q. Yes. Certainly. I am asking you at the moment, or at the time the article was published in September 1984 in The Lancet, was there a general view among the medical and scientific community that the development of AIDS was not considered to be a likely outcome for the vast majority of haemophilia patients?
A. It's difficult to -- it's difficult to know, because if I just read you the last paragraph, last sentence, bar one in the paragraph.

Q. I think there is probably a number at the top of the page?
A. Page 33.

THE CHAIRPERSON: Yes.
A. And it's The Lancet, September 1, Lancet page 480. It comes down the left-hand side to the paragraph, last paragraph of text. I will just read the last two sentences because I remember we had a great deal of discussion of what we were going to put in the text here, because there was some considerable sensitivity. And you have it on the screen. If I can take you to the last two sentences: "Thus until the whole spectrum of host responses to HTLV-III is better defined, the conclusions that can be drawn from a test for antibodies to this virus are strictly limited. What is certain, however, is that a test for anti-HTLV-III is not the same as a test for AIDS." That was a very specific,

heavily-argued, multiply-discussed, rewritten-dozens-of-times last two sentences in this paper.

Q. Yes.
A. Robin and I would have probably put something slightly different.

Q. What would you have put?
A. We would have said that the evidence is that antibody is associated with persistent infection with this virus; persistent infection does not in itself mean AIDS. Because we were very aware of concerns about segments of the population in the UK who were infected with HIV but who had very little prevalence of disease in spite of a high prevalence of infection. We already, at this stage, were beginning to talk about index disease and nonindex infection, which led very quickly on to the concept of the iceberg - when you see that -- what you can see above the tide-line or the water-line, but what you actually founder on is what is beneath the water-line. These last two sentences were designed in a way to try and bring people to focus on the possibility that this really might be a very serious antibody marker and not indicate disease. But of course, there remains the possibility that all might be well, but probably not. It's very difficult in those days to write anything because whoever you wrote -- whatever you wrote, you were liable to do damage; the whole question of damage limitation.

Q. Yes. I can understand the sensitivity of the time, Professor. But the article -- you have read out the last two sentences. Was your view that perhaps the risks were somewhat greater, that people would go on to develop --
A. If -- yes, because I actually in my statement, the bottom of paragraph 11 on page 5, I actually say that -- referring to the view above of the large discrepancy between the number of haemophiliac patients positive for the antibody and the number who developed AIDS, ratio of about one in a 1,000. And I go on to say, "I should say that this was not a view held by myself or other virologists involved in these studies, given the animal data on retrovirus infections and the similarity of the antibody response in gay men and haemophiliacs."

Q. Yes. So your view at the time would have been perhaps that the risk of persons with haemophilia going on to develop AIDS was somewhat greater, but the article in the end was a compromise between all the authors, perhaps?
A. Yes. I mean, when you say "somewhat greater," somewhat greater than what? I would have said it's probably not dissimilar from that which you would have expected in a gay man or an intravenous drug abuser, that there would be an evolution to disease, but it evolves with time; whether it would evolve at the same rate in the haemophiliacs, reached the same proportion of disease in the fullness of time, it would be difficult to predict. But I certainly felt, and Robin Weiss would have felt, as we discussed it, with the balance of evidence, that it's not going to be very much different, although it might be later starting.

Q. I see.
A. Can I just, sorry, amplify one other question which may help: There was a strong body of opinion that the presence in Factor VIII concentrate of immunising virus antigen could be not dissimilar because from the -- some of the --

Q. Just for the stenographer, if you go back to the start.

A. There was a lobby amongst haemophiliac directors who, understandably, wanted to explore all avenues, and they believed that it was possible, and I would agree it was possible, that there could be, in the Factor VIII antigen, virus antigen, which in itself would lead to immunisation. And the antibody response in the haemophiliacs could be different from that which was seen in the gay man who was exposed to living virus, and that the haemophiliac, in the concentrate, had been exposed to material which was dead but immunogenic. And there is literature suggesting that this might have happened for Hepatitis B surface antigen, which is a very stable virus antigen, which could get through a Factor VIII concentrate in the presence of antibody at immunogen, and people were discussing and hoping that perhaps the antibody in the recipient of the clotting factor concentrate would fall into this immunised-but-not-infected group. So that was another discussion point which people had at the time.

Q. Again, that was a particular point of view held by some people at that time, is that correct?
A. Correct.

Q. Did you agree with it?
A. I thought it was inherently most unlikely.

Q. I see. Now, in fairness, I think it must be made clear: We are looking back at all of this. There were a number of different views of different types at that time, perhaps; the end of 1984, going into the beginning of 1985?
A. Yes. You must remember that for many, even virologists, retroviruses were right at the bottom of the list of doing anything relevant to the human species, so it was -- we were working in a very rarified atmosphere in an extremely politically sensitive field with interest groups already developing strong political lobbying. And trying to beat a path which would involve the least damage was sometimes very difficult, and one had a whole series of discussions. It was only in 1984 with the description by Gallo and Montaginier of the virus that people eventually generally accepted that this was an infection. Previous to that, people had thought it was a noninfection - there was a strong lobby suggesting it was of noninfectious aetiology, as late as 1983.

Q. I just want to move on to paragraph 13 in your statement. And in that paragraph, I think you are dealing with an outbreak of HIV which was associated with Scottish Factor VIII. And I think you were involved in the investigation of that outbreak, is that correct?
A. That is.

Q. I see. When did this first come to light, this outbreak, as a result of Scottish product; I think you give March '85?
A. I think it was earlier than that. I think it was -- I mean, March '85 was the description of one of the young men who developed glandular fever-like illness, but I think this was predated by a discussion with Christopher Ludlum; I think it must have been in late autumn '84 when we did the first testing for him, because it was -- it was certainly -- I will never forget. It was sitting in what used to be David Dane's room at the end of the corridor, looking out on an autumn sun which was a very hot sort of Indian evening, Indian summer evening, which should have been a lovely evening. It was about half past 7:00, 8:00, going through this litany of positive, positive, positive. And Christopher Ludlum obviously getting more and more pensive and me feeling

less and less kind, as this evolution of damage done to a cohort evolved. That was the very early testing when he had sent us cohorts of samples which he already had a clinical suspicion that something had occurred, and that was the beginning of the evolution of knowledge on the Edinburgh cohort.

Q. Could you explain to us what happened with the Edinburgh cohort; how had they become infected?
A. Well, it's still surmised, but one perceives that, I mean, as you have mentioned, the retrospective scope; it's a highly-clinically sharp instrument. So if we look through the telescope backwards in time, we now know that the virus burst in the acute infection of HIV can be very large indeed. You can get ten to the seven, ten to the eight, HCV -- different virus, HIV/RNA copiers (?) in the acute phase. We see this in the pre-glandular fever illness when the patient is asymptomatic or they are coming up to be tested just at the time post-exposure. And as they are going into that, the glandular fever syndrome, these people have vast quantities of HIV virion in their plasma - ten to six, ten to seven; rarely, but sometimes, ten to the eight. A donation of plasma taken at that time and put into a native Factor VIII concentrate will lead to potential contamination of any product from that starting pool. And one thinks or surmises that there was a single donor involved during the time, that Edinburgh was already suffering from HIV transmissions in the Fringe Scenes of the Edinburgh Festival, the drug-sharing which went on at that time in the early '80s. This material was contaminated with one donor and this led to a significant level of infection; in fact, it was, I think, the first point-source of infection which could be died down in a single concentrate. This was in the days we did not have genotypic sequences. I think nowadays if one was associating an outbreak like that, you would want to look at the genetic sequences of the virus and confirm they form a clustering in the genetic landscape. What we had in Edinburgh was a cluster in the time and geographical landscape of Scotland. And that's very good evidence of a point-source.

Q. How many people were infected from the particular batch of
A. I think in the first year it was 15, and there was one late seroconversion that is documented in some of the papers.

Q. Did the fact -- and I think there may be three additional seroconversions --
A. Takes it up to the figure of 18, I think.

Q. Yes. Did that have some significance in terms of showing the timescale during which a person might seroconvert?A. Well, yes, it would have done. Because seroconversion, when you are dealing with a sexually transmitted disease of which people may be a little bit coy, sometimes it's difficult to find out when exposure actually occurred because you didn't know, but you could relate it to this. And I mean, the shortest seroconversion they saw there was 31 days. This is moderately long by primary HIV seroconversion now; we reckon it's about 14 to 21 days. So it's very similar to most acute virus infections, particularly as tests have got better nowadays. And if one looks at the patients who present with glandular fever, it's probably about 14 days.

Q. I see. I think you have told us that the shortest time interval in regard to the Edinburgh cohort from exposure to seroconversion was 31 days. What was the longest?

A. Well, the longest one was this patient who I seem to remember actually left the United Kingdom and went to southeast -- went to Australasia, I am not sure whether he went to Australia. This was reported as being at least 160 days. Now, that is out with the normal distribution of that particular cohort. One has to wonder - this is why I say it would be generically nowadays; if you had an outlier like that, out with the normal distribution of a group of patients, you would say, well, I will only put him in now if I have genetic sequencing. It's shows it's the same virus as everybody else has, because, humans being humans, you don't always get the complete truth of what went on, but one mustn't criticise at the time. This was the outlier in that group.

Q. In any event, the results which were published at the time, I think would that have indicated that there could be a considerable delay between exposure and seroconversion?
A. Yes. I mean, one out of 18 being more than 160 days, yes. Occasionally you can get that. But I mean, nowadays there are some literature cases of people claiming much, much longer times. It's difficult to interpret, to make -- to rewrite one's serology; you need crucial scientific data and evidence which will stand up to very tight scrutiny, and that is really, essentially, genotyping and good sequential sampling. But yes, some people take a very long time to seroconvert. It's, fortunately, one virus where seroconversion does seem to be the order of the day; there are other agents, of course, as we know, where seroconversion is less proficient.

Q. Could I just ask you about the Edinburgh cohort again: The pool of plasma that was involved in the manufacture of Factor VIII, was the same pool of plasma used to manufacture Factor IX or did that become obvious or become clear at the time?
A. I have to say - unless you can take me to the paper and let me just have a look at it - I can't remember that. It's possible they could have made Factor IX from it. It was a small donor pool. I seem to remember it was -- it was less than 500 donors.

Q. I think it's dealt with at paragraph 14 in your statement.
A. From the same pool. Right. That shows you how long ago I wrote this. Apologies.

Q. What I'm getting at is this, Professor: Did the fact that the Factor IX from the same pool didn't infect people, did that give rise to a theory that in some way the process of manufacture of Factor IX might partition away the virus and, therefore, mean that your chances or -- of being infected with Factor IX were certainly less?
A. Almost a leading question, isn't it?

Q. Just bringing you back to your statement, Professor.
A. I don't know whether we have rules for this.

THE CHAIRPERSON: They are not quite as strict in the Tribunal.
A. Coming back to reality. I think the two aspects to that: The fact that not everybody in the cohort who was exposed to Factor VIII, that Factor VIII that became infected, suggests one of two things, two interpretations of that: Either you can't infect everybody, and half the people you couldn't infect, I think that's inherently unlikely; or, that the virus level, even in the native Factor VIII, was present at probably one infectious dose every half dozen vials, or something like that. Because if you look at the dosage of Factor VIII necessary to get -- or sorry, I'll start again: If

you look at the Factor VIII usage in the seropositives and seronegatives, there is a suggestion that the seropositives took more, both in terms of units and the number of ampules. So that in a biological system of transmissibility of infection, would suggest that you are pretty close to one or a small number of human infectious doses per ampule and that you probably -- you need multiple ampules given over a series -- passage of time to effectively infect individuals. So it's not -- I hate the -- it's not, every time, a coconut. There is not enough virus in each vial to infect everybody efficiently. So any changes in manufacture which may lead to partitioning or changes in virus degradation would mean if you are right on the edge of infectivity in a different blood fraction, fractionated into a concentrate in a different way, may lead to increasing loss of virus, so therefore, less infectivity. So partitioning of the virus, which means there is just less virus there, which also leads to loss of infectivity. Both of those scenarios are possible.

Q. And the second scenario you were talking about, was that at least, that view, put forward in regard to Factor IX at the time, that it might be less infective because of the method of production?
A. I would have to look at the transcripts of the meetings that I went to, but yes, it was -- there was a general discussion; I mean, exteriorising a bit further: Why had intramuscular immunoglobulin got such a safe record at that stage? We didn't know of any specific virus inactivation step in that. So within the discussions of blood fractions and concentrates, the whole discussion is centred around which one concentrate of the virus - which one lost the virus, which one inactivated the virus. This was early days for virus inactivation, as you realise, in the early 80's.

Q. All I'm trying to establish: It seems to have been a topic of discussion at the time, as to whether the particular form of production of that -- that if one made Factor IX, might have had an effect on the infectivity?
A. Right.

Q. To move on to something else: Was retrospective testing carried out in England in regard to blood samples from persons with haemophilia, did that take place at some stage?
A. Yes, because there was a question of trying to pin down when people had become infected. This was important from an auditive, when the infectivity was first introduced into the UK through Factor VIII concentrates, and also, patients who wanted to know when they themselves had become infected. We were involved in many series of lookback - what we now call lookback exercises; they weren't in those days, they were sort of historical archives - trying to find out when infection occurred. We were in receipt of funding from the UK Haemophiliac Society, and David Watters and I had talked about how we would make access available for this testing at a time when there was no funding from the Department of Health to do this. And we -- my department was in receipt of a grant for this. So we made as much testing available as was necessary and it was used by the directors of the haemophiliac centres.

Q. I see. Can you help us, and I think this is at paragraph 15 of your statement: What was the picture that emerged from that retrospective testing in England as to when infection may have occurred?
A. Well, as we are continually taught, human populations are diverse and come in different shapes and sizes, and that's -- the same is true for haemophiliacs. So a

haemophiliac is, by definition, somebody with Factor VIII deficiency, but they can be mild, moderate or severe; long-standing. They can be treated with a variety of blood products. Putting it into a general context: The recipients of commercial Factor VIII probably had infections arising from the early 80's - '81, '82, '83. But the time we did a contemporary survey at the end of '84 and -- samples, '84, '85, there was a disparity between the prevalence in recipients of Factor VIII concentrate from America as opposed to the recipient of native - in our case, UK - Factor VIII concentrates prepared at BPL.

Q. And what was that disparity?
A. The recipients of the highly -- the severely affected Factor VIII deficient haemophiliac who had received commercial Factor VIII concentrates had seroprevalence of somewhere around two-thirds, being seropositive, as opposed to under 10 percent, 5 percent, or less, depending on where you look, which group you looked at in the recipients of UK native Factor VIII.

Q. I see. And in the UK figures, would they have included the Edinburgh cohort, or do you know?
A. I can't remember whether we put that in or not, but that would clearly -- you are right in raising that because that would bring the prevalence up for the whole lot, it would have extended it, and I think the only way I could look at that would be the author list and perhaps going back into the archive files.

Q. Again, is it possible, in regard to the commercial concentrates, people who were treated with commercial concentrates - you have told us that the infection would have been in the early '80s; do the figures go any further than that, can you say from the retrospective testing, by the end of a particular year with the majority of infection have taken place?
A. In the UK or globally?

Q. In the UK, first?
A. One would have to refer to, I think, the Rizza publication we were involved in, which gives the time course. And I'm not sure which that is.

Q. I think perhaps --
A. The one, my reference 14 is probably not the best because that was -- that was fairly ad hoc.

Q. I think the one at 14, which is -- number 14, 53 in the book --
A. It's confusing having the references numerated and pages numerated independently. Yes, I mean, that I would have said is -- well, it's easy to be critical nowadays; the figures for the late '70s are very small, and by 1980 you have one-third of the commercial recipients being infected. But I would say, in comparison, if you look at the figures for the British recipients they are very small indeed.

Q. Yes.
A. Probably not relevant.

Q. Now, this is the table on page 54, is that correct?
A. Correct.

Q. And --
A. Sorry, table two is the important one.

Q. Yes.
A. And I think, in fact, if one looks at the acknowledgments, we are thanking Chris Ludlum for involvement, so I should think that would have included some of the Edinburgh cohort. I can't see why it wouldn't have done.

Q. I think that's clear from perhaps 53, where it says on the right-hand -- "Results and discussions: By contrast, only 18 patients among 166 who had received British Factor VIII exclusively were seropositive. At the time of study, 15 of these cases were accounted for by infections arising in a group of 33 Scottish haemophiliacs given a uniquely infectious batch of British concentrate." That would suggest that the figures include the Edinburgh cohort?
A. Well, 15 of the 18. So if you were to remove those from the discussion, you would be talking 3 out of 166, which would be approximately 2 percent.

Q. So without the Edinburgh cohort, the infection rate from British concentrate would have been very low indeed?
A. Yes.

Q. I see. And again, just -- perhaps you can just interpret the table there for us, as to what it means.
A. Sorry, could you say which table?

Q. Table 2 in -- on page 54?
A. I have it.

Q. In terms of commercial, I think the number tested in -- from 1978, samples, presumably, were ten, and the number positive were nil; 1979, 28 and nil; 1980, 70, and 23 samples I think were positive, and that's 33 percent. Was that -- does that suggest that is when the infection was starting, in 1980?
A. Yes, I mean, it clearly does. The questions I would have, looking at it now, is what was the selection of those samples and how representative were they of the centres from which they came. We were just taking whichever specimens we could gain access to, and epidemiologically, yes, that's what it suggests, but there is a slight caveat. I don't know the mix of the samples and --

Q. But subject to those reservations about where they might have come from, the samples, all I'm trying to interpret at the moment is what this says in -- then if one goes on to 1981, the number tested were 56 and the infections - the number found positive were 28, which was 50 percent?
A. Correct.

Q. And by 1982, the number tested were 72, and the number positive are 46, which is 64 percent. Is it possible to get any accurate picture from these figures as to when -- is it possible to say, by any date, when the majority of the infection had taken place?
A. Well, the difficulty with this is these are individual cross-sectional -- these are year cross-sectional surveys, so they are not actually -- it's not a longitudinal cohort,

which is a pity. These, as far as I understand from what we wrote - being an author I'm responsible for that as much as anybody else - these were individuals tested over the -- at each year. What I haven't -- what embarrasses me now, going back on this, is I don't know whether somebody tested in '83 also appears in '84. So I'm slightly nervous over this. What it suggests was that, on a cross-sectional survey in 1980, approximately one-third of the recipients identified and tested in 1980 were already seropositive. That would probably mean that the material which was used in 1979 /early 1980 was a period in which you had had a major influx of virus-contaminated material in the United Kingdom.

Q. I see. And --
A. I can't say -- I can't -- I can't say why it's only reached two-thirds, because, again, these are cross-sectionals and these might be relatively new patients coming into Factor VIII concentrate therapy, or they could be people who are reactant to infection. And it's just not possible, without going back and reanalysing this, to say which of those scenarios is true.

Q. Is there further data in regard to this - we have looked at this article, of which you were a co-author; is there more definitive information available, or do you know?
A. For the United Kingdom?

Q. For the United Kingdom?
A. Well, there was -- there is a series of publications from Rizza himself which we were involved with and also -- I think those are probably the important ones, is Charlie Rizza data on the longitudinal analysis. There are two datum sets: One is the Rizza data, which is the Oxford Haemophilia Centre; and the other is the - (inaudible) Medical School. Both attempted to follow longitudinal.

Q. Would you be aware of what the picture which emerges from that data is?
A. Very similar, as far as I can recall. I'm not sure if I -- I don't think I -- I don't think I actually referred to the Rizza paper or the Luzzatto paper. It's essentially similar. It's better characterised because it's longitudinal cohort studies, not cross-sectional studies which were our data, which was very early.

Q. I see. You don't think the fundamental picture is different from the other data which you have just referred to?
A. No. I mean, it's basically -- it all started to happen at the turn of that decade, beginning of the 1980s.

Q. Yes. Now, I want to bring you -- I want to bring you on to deal with the next topic in your statement, which is non-A non-B Hepatitis and infectivity of concentrates. And I think you will find that at paragraph 18 in your statement. Would you have a view, Professor, in regard to recipients of clotting factor concentrates made from pools, multiple pool donors or multiple -- pools of multiple donors, what is the likelihood of somebody receiving such clotting factors, what is their chances of becoming infected with non-A non-B Hepatitis?
A. Of course, non-A non-B is a phrase which includes both Hepatitis C and possibly other agents. And a previously untreated patient given Factor VIII concentrate, native Factor VIII concentrate, would almost invariably have a degree of transaminitis, 30, 40 days after exposure to the Factor VIII concentrate. So it's almost always you will

get some disease. Now, whether that is invariably associated with virus infection; if so, which virus? One can only tell with virological testing. But it's a very common outcome.

Q. I see. And if the plasma pools are from voluntary donors as opposed to paid donors, would that affect the situation?
A. You are asking me a contemporary question; at the beginning of the 21st Century or retrospectively?

Q. I'm asking you -- perhaps if you take it back at the late 1970s, beginning of 1980s.
A. Well, in practice, Hepatitis C, which is a predominant principal cause of non-A non-B Hepatitis, is relatively common in the donor populations anyway. I think what would happen is that you would find that there is a higher virus inoculum in a commercial donor, but the noncommercial donor would still have the pool -- the pool would still be contaminated with HCV.

Q. Is the picture fundamentally different for voluntary donors as opposed to paid donors?
A. Depends on the pool size, because you have to work at the -- you have to work at the mathematical probability of getting an infectious donor in a pool. And once you start going into the processing of 1,000, 2,000, 3,000, 4,000 donors, every pool is going to be contaminated with Hepatitis C virus --

Q. Whether it's made --
A. -- whether it's commercial or not.

Q. Once we are into those kind of figures of pools, thousands of donors as opposed to hundreds of donors?
A. Yes, that is using the biological endpoint of intravenous inoculation of a susceptible human with a blood product. When you start defining the blood product and considering that you may get virus partitioning or virus kill, particularly if your virus killing is only partially effective - let's say would remove 99.9 percent of the virus instead of 99.999 percent of the virus, sounds big figures - you will find that the commercial product has probably got a higher virus level than the noncommercial product.

Q. I see. And if I can contrast that situation with somebody who would be using cryoprecipitate; again, would you have a view in what -- somebody who would be, over time, on a regular basis, using cryoprecipitate, what their chances - and again I'm talking now in late '70s, early 80's - their chances of getting non-A non-B Hepatitis?
A. Well, you have -- there are a number of parameters which effect the transmission of an agent through cryo. The first thing is that you have to consider what is the donor exposure, and are you better -- that is a valued judgement -- how swiftly do you become infected with Hepatitis C if your exposure to the donor panel is limited to the occasional use of cryoprecipitate. How many years can you run without being exposed to cryoprecipitate from 5,000 donors. It probably takes you a longer time -- if the prevalence is low in the population, it probably takes you a longer time to become infected with Hepatitis C if you receive cryoprecipitate, because you don't have what I term the nonbiological amplification. By this I mean if you take -- if you

take a pool of plasma and you put one infectious donor in - it doesn't matter what the agent is - but you put an infectious donor in that, that infection in infected material virus can partition into all components from that panel, from that pool. And that is nonbiological amplification, because you then transmit that to all the recipients of that product and they become infected. In contrast, the recipient of the cryo is really a statistical game; what are the chances if you are having an exposure to 5,000 haemophiliacs over -- 5,000 cryoprecipitates over a period of ten years? So you are a mildly affected haemophiliac, what is your chance of receiving the material from a HCV-infected donor? It becomes a prevalence and purely a risk exercise with a chance of getting an infected donation rather than running the exposure which is inherent in the blood product.

Q. Therefore, if one has multiple exposures to cryo over time, was it likely that the person -- you have told us it's a matter of risk, it's calculating the risk; but if somebody had multiple exposures over time to cryoprecipitate in the late '70s, early '80s --
A. It really -- I am sorry -- but it becomes a question of what is the prevalence of the infected donor in the donor panel, and that's very important; and are you, for example, removing the intragenic donors because they have caused non-A non-B in a recipient of the blood and, therefore, you pull them out because you know they have been associated with post-transfusion hepatitis, because it's all part of the audit and control of donors. Because if you get an adverse result to a donor, you pull that donor out. The multiple exposure, you have to specify how many exposures, over what length of time; if -- what is the usualisation of cryo in a particular patient; how long does it take them to have an odds-on chance of being exposed to an HCV-infected donor? Really it's a measure of the utilisation rate and the prevalence of infection in the donor panel.

Q. So there are a number of parameters which you need to know before the question can really make any sense?
A. Yes.

Q. Okay.

THE TRIBUNAL THEN ADJOURNED FOR LUNCH.

THE TRIBUNAL RESUMED AFTER LUNCH AS FOLLOWS:

CONTINUATION OF EXAMINATION OF PROFESSOR RICHARD TEDDER AS FOLLOWS BY MR. DURCAN:

Q. MR. DURCAN: Good afternoon, Professor. Perhaps just a few items, perhaps, we could usefully deal with. If you go to page 54 in the book, and I think there was a table there that we were looking at this morning. Have you had a chance to consider that at lunchtime in terms of the information in it?
A. Yes. I was embarrassed at not being able to recognise my own data this morning. The -- there are, in fact, two cohorts of patients, up until and including 1983. If you take both the column of number tested under "Commercial" and the column listed under "Number Tested" on the British, that gives you the total number of patients who were followed in that particular cohort, and that's 204 patients. Followed from 1978 through to 1983, a single sample; or, if there were more than one

sample available on each year, the most recent sample for each year on one patient only is attested to in those two columns. And that means that the data shows the seroprevalence longitudinally by year for 1978 of only 12 patients followed, up to and including 1983; of 204 patients is a sum and total of the cohort. That is, in fact, a point prevalence over six years of a cohort of a maximum number of 204 patients. So the datum points up to and including 1983 are annual prevalences in this cohort of individuals treated variously with commercial or British. And you will see that the deficiencies -- that there were few samples stored on the patients who were recipients of British Factor VIII up until 1983. 1984 is a cross-sectional study of somewhere in the region of 481-odd patients, and that is a cross-sectional study in 1984 of a different set of patients covering 315 recipients of commercial, 166 recipients of British. And if you interpret that, there is a one percent sera prevalence of antiHTLV-III or HIV antibody in recipients of British Factor VIII in 1983 as opposed to a 66 percent prevalence in recipients of commercial Factor VIII in the same year, 1983. And the figures are also similar for the year 1984, although, as we discussed this morning, they are skewed by the inclusion of 15 seropositive individuals in the -- in amongst 166 recipients of British Factor VIII. And those are -- as we said this morning, 15 of those are the haemophiliac recipients of the Scottish Factor VIII concentrate.

Q. If they weren't there, obviously the figures would be relatively similar?
A. It would be -- it would be 3 out of 166 in 1984, as opposed to 1 out of 99 in 1983.

Q. Thank you very much for looking over that again. If I could just refer you back to page nine of your statement again, paragraph 18. Have you found that, Professor?
A. Yes.

Q. Now, just in the middle of the paragraph you refer to studies which were undertaken on a number of Factor VIII concentrates derived from voluntary donors for evidence of HCV. And I think this testing was done by PCR. Could you tell us what the outcome of that testing was and what it shows?
A. This is work which was published in 1993 and is page 55 in my band of papers - Hepatitis C Viral RNA clotting factors, Mike Makris, Jeremy Goss and Chris Ring, with myself and Eric Preston bringing up the back end of the team. This was an opportunity to use relatively new technology in the early 1990s of reverse transcription RNA rescue from Factor VIII concentrates. And then looking for the presence of HCV virus genom -- sorry, yes, HCV virus genom -- changing viruses again - HCV virus genom in Factor VIII concentrates.

Q. And what was the outcome of the studies, what was --
A. Essentially that if you had native Factor VIII - that's not heat-treated or nowadays would be not virus inactivated - the prevalence of HCV RNA was much higher; and also, that it was higher in the Factor VIIIs made from commercial as opposed to volunteer donors. So two spins on that.

Q. And did those studies look at what the effect of heat treatment was, the different forms of heat treatment?
A. Well, inasmuch as one was privy to the manufacturing procedures that the -- that were in the public sector, yes. And that's on page 56 of the article -- sorry, some of

you may have got an inverted page. It's 1899 of the article itself, the paper. And tables two and tables three -- well, tables one, two and three talk about the -- table one talks about the prevalence in concentrates without virus inactivation, and it tries to relate it to the time of manufacture of the concentrate, showing that the products which expired '75 through '79 had a -- one out of five were RNA positive; and '80 to '85, eight out of eleven were RNA positive. The virus inactivation mentions briefly in table two -- tries to relate to the prevalence of HCV RNA detection in Factor VIII and Factor IX. The figures are very small, obviously, and the Factor IX is only 4. -- four datum points as opposed to 20 for the Factor VIII. I'm not sure whether four out of 20 versus nought out of four is actually statistically significant. There's actually a trend there. It's very small.

Q. What was found about dry heat treatment at 60 degrees, I think it's for 32 hours? What was the effect --
A. In this very small group, as you can see from the virus inactivation that we have there dry heat at 60 appeared not to, in two out of two, affect viral genome stability. But, you know, this goes back to the discussions we were having this morning. It depends how much virus you put in. That might just be a quirk of fate or it might be a genuine phenomenon and you would need to do much larger studies.

Q. It's a very small amount of material you were dealing with here?
A. Yes, these were archival materials held in people's deep freezers and we were lucky to get that.

Q. The dry heat treatment, 80 degrees for 72 hours, I think is this called superheat-treatment. What was the effect?
A. Well, it -- I mean, it ostensibly shows that you were unable to detect HCV RNA in any 12 ampules of Factor VIII concentrate treated under those prolonged and hot conditions. But unless one knew what went in at the front end, it's a bit dangerous to say that it's absolutely because of the heat treatment; although obviously the simplest explanation is that, well, we know now that 80 degrees /72 hours does prevent infectivity. What I would say is that unless one looks at table three, the data in table two on the prevalence of HCV RNA does not actually tell one anything about infectivity because that is virus genom, and the only way you can assess it is by actually putting material treated with one of these protocols into previously untreated patients and determining whether there is evolution of post-product hepatitis. And that becomes an objective marker of infectivity.

Q. And this would be set out in table three, is that right?
A. Well, effectively, yes, because these are details of the concentrates given to patients. This was -- as I say, in patients three to seven concentrate was heptane-treated; eight and nine it was pasteurised. And I'm not sure what one and two were -- yes, dry heat -- short dry heat treatment. So not knowing the input virus, and as a virologist looking at infectivity studies, you always want to know how much virus was present in the start material. If you just take it on face value, these data would show that wet heat at -- wet heat at 60 degrees for 20 hours is not very efficient at preventing transmission of Hepatitis C.

Q. And dry heat --

A. Dry heat at 60 -- dry heat at 60 - well, out of the two they show you detect HCV RNA in both; you get a non-A non-B Hepatitis in the recipient but you know they're terribly small figures.

Q. In regard to -- I don't think they're there, but the other two -- or the other possibility then moves on is superheat-treatment. From your knowledge of the studies that have taken place, how effective is it, superheat-treatment?
A. Well, if you're talking about 80 degrees Centigrade for a protracted period, it's very efficient.

Q. And equally, solvent/detergent?
A. Yes, I mean, solvent/detergent for an envelope virus is very effective. It has one concern, that it is not -- it would not be effective against nonenveloped viruses. Heat treatment against nonenveloped viruses is, in itself, not terribly effective. But it's all we have.

Q. That's fine. Thank you, Professor. There's only one other question I want to ask you and it deals with the introduction of the commercial test for HIV which we were discussing this morning. If you -- I think you were involved with the committee which was looking at this and which was making the various decisions. Can you recall in the spring - perhaps if we take the months of May, June, July 1985, can you recall whether the five tests which were coming from abroad, the commercial kits, were they available in the sense -- I don't just mean available in small amounts, but were they available in sufficient amounts that blood testing or testing of blood samples or blood donors could have been introduced; whatever about for all the reasons you've told us, the advisability of doing it, was there enough commercial kits available?
A. I'm not certain. What I do remember was Abbotts were first into the market and they would have made a strong play and presumably would have come into the market with a view to capturing the donor screening. We would have had to have, in any case, undertaken sensitivity and specificity trials both in the Public Health Laboratory Service and in the Blood Transfusion Service. I think you would only be able to find this out by looking back at the expert advisory group papers, and probably there was then a committee which was the Advisory Committee on Virological Safety of Blood, ACVSB. And both of those committees would probably have the availability of kits at the time. Certainly they came in in late spring, early summer; whether or not the manufacturers would have been in a position with equipment, training and were free agents to serve the BTS in the UK, I'm not certain.

Q. One final thing: On page 13 at the end of paragraph 25, you've been -- you're talking about the, again, the commercial kits. And you mention in the final sentence: "Following satisfactory trials, all blood donations bled in regional transfusion centres throughout England and Wales were tested from the 15th of October, 1985." Would you happen to know when those satisfactory trials ended or when they were --
A. Can you just identify which text we're in? We're now in the --

Q. In the statement, page 13. Page 13 bottom of 25, end of
25. It's the first paragraph on the page there, last sentence: "Following satisfactory trials, all blood donations bled in regional transfusion centres throughout England and Wales were tested from the 15th October, 1985." What I was wondering is, would you

happen to know the trials which you referred to, when did they end, when were they concluded?
A. Well, if we work back in time, that's the only way I can do it. We have the 15th of October is the start date. As I said, it was probably 14th or 15th of September was the initiation date. Prior to that you're going to have to have at least a month or so procurement of equipment, placing it in the laboratories and training. So that takes one back to middle of August. The committee would have wanted to have seen field-trial data on sensitivity and specificity, I would have thought certainly no later than the end of July - end of July, beginning of August, something like that. Because if it was the end of August -- beginning of August, that only gave one six weeks to enter into negotiation with companies, set up contracts, introduce testing and training.

Q. And who carried out the trials that are referred to there?
A. There would have been -- two groups principally would have carried out the trials. One would have been the Virus Reference Laboratory at Colindale, which Dr. Mortimer was then the director, and John Perry was his deputy. They would have looked at the proficiency with which the various kits performed in terms of detection, sensitivity. In those days we were constrained by HIV acute seroconversion samples being extremely rare, and the protocol at that time was to use a dilution of a positive sample diluted in a negative to give you a weak reactive test specimen. Those would have been set up and examined by Philip Mortimer's team at Colindale. At the same time, probably running contemporaneously because of the pressure to commit the BTS to choose manufacturers, there would have been studies hosted in a number of the transfusion centres running the tests to look at the initial reactive rate and repeat reactive rate and determine what these tests were seeing. Since HIV was really quite a very low prevalence in the United Kingdom - it was something, in those days, of about 0.01 or 0.02 percent - the chances of finding a genuine seropositive donor during these field-trials for specificity in the transfusion service would have been negligible.

Q. I see. And were both of those sets of tests finished prior to the introduction of --
A. Sorry.

Q. -- prior to the introduction of the commercial test into blood banks?
A. If you're asking me can I remember that, no, I can't, but I can surmise we would not have introduced testing unless those two datum sets had been available for analysis and for making an informed choice.

Q. Thank you very much.

THE CHAIRPERSON: Thank you, Mr. Durcan.

Mr. Bradley, please.

MR. BRADLEY: Thank you, Madam Chairperson.

THE WITNESS WAS EXAMINED AS FOLLOWS BY MR. BRADLEY:

Q. MR. BRADLEY: Good afternoon, Professor Tedder. I appear on behalf of the Irish Haemophilia Society and my name is Raymond Bradley.

A. I can't see you from here, Mr. Bradley, but -- there you are. Hello. Yes.

Q. Go back in time again to the early 1970s. The documentation I'm going to use during the course of my examination is your statement, the articles that you've attached to your statement and certain other additional documentation that --
A. In the other two bands that I have?

Q. Yes. I'll try to use as little medical articles as possible. Now, in the early 1970s -- you've included an article by Dr. John Craske from Manchester. And I think he's also a virologist, isn't that correct?
A. Correct.

Q. If we look at page three of the booklet, I'll be looking at the first column, we can see what is the -- last two paragraphs: "What is required is a freeze-dried Factor VIII concentrate"?
A. Can I just stop you there. Which band are we looking at, because --

Q. The first column, page three, last two paragraphs?
A. Of mine, not your first one?

Q. Yes, yours.
A. Okay. Right. This is a paper in The Lancet, August 2,1975?

Q. That's correct.
A. Can you take me to the text again, please.

Q. I can. I can take you to the test -- first column, last two paragraphs. It starts as follows: "What is required is a freeze-dried Factor VIII concentrate prepared from volunteer donors in the United Kingdom, prepared according to an approved protocol of testing. A small quantity is available but it is likely that some reliance will have to be placed on commercial sources for some time to come."In the meantime, some or all of the following measures might help to lessen the frequency of jaundice: "1. Commercial Factor VIII concentrates should be reserved for the treatment of life-threatening bleeds in all haemophiliacs and for covering major operations."2. If used for treatment, commercial concentrates should be reserved for severely affected haemophiliacs, since they are more likely to be immune to Hepatitis A and B. Treatment should be carried out by experienced staff who are aware of the risks of using large pool concentrates." And it goes on about a trial. And final paragraph: "A more general study is now in the process to determine the true frequency of jaundice in haemophiliacs in British haemophilia centres associated with the use of commercial Factor VIII and UK-manufactured concentrates and to find additional cases associated with the batches implicated in this outbreak." So it appears in the early 1970s the -- late 1970s, in or around 1975, the treatment options that would have been considered in order to minimise exposure to hepatitis were cryoprecipitate in preference to concentrates. From a virologist's perspective, what was the reason for Dr. Craske giving that opinion?
A. It's difficult for me to know what John Craske was thinking, but you're asking me to interpret the --

Q. To interpret --

A. -- the meanings behind this. I think it's a recognition that there is an inherent hazard in using blood where you increase the donor exposure of the recipient by using a pool rather than individual donations. For example, a European-size plasma pool may have plasma from 2,000, 3,000, sometimes more, donors. So your donor exposure through a single vial of product made from that plasma is 2,000 to 3,000. The similar therapeutic option may -- sorry, different therapeutic option but with the same therapeutic outcome might be the exposure for an instance, say, to 10 or 15 cryo packs, which, for the same amount of Factor VIII that you would get, you might expose the recipient to 20 donors rather than 2,000 to 3,000 donors. And if you're dealing with an agent which is relatively uncommon, clearly you would get a safer outcome in terms of exposure to whatever the agent is by going through the cryoprecipitate rather than the concentrate. I'm assuming that that is -- that is how I interpret what John Craske has said there; that you reserve the exposure to high donor numbers; you reserve that for expose -- you reserve that exposure to patients who really need acute reconstitution of the Factor VIII procoagulant levels.

Q. And that experience, I presume, was gleaned from the Hepatitis B and Hepatitis non-A non-B infections in the mid-1970s, a particular lesson was learned at that time?
A. Yes, essentially. I mean, it's -- the difficulty with Factor VIII concentrates and non-A non-Bs, I think many people now recognise, is that you are using a clinical outcome which involves not only a clinical disease but abnormalities; elevation of liver function tests, which are often perturbed by administration of intravenous material without infection. And you're using that to define the clinical outcome as a result of exposure to a blood product. Nowadays the criteria would be much stricter in terms of we're dealing with non-A non-B, known as Hepatitis C; we would want virus markers, antibody markers and longitudinal follow-up on patients.

Q. But at that time that was the only method of ascertaining whether somebody had suffered a consequence arising from receipt of a concentrate?
A. I accept that. But even then, one realises that it is all that was available, but it is by current questioning that -- but I accept --

Q. But at the time that was the option available for testing. And if you saw abnormal LFTs, it was an indication of liver biochemistry reaction and, therefore, an indication of consequences potentially occurring; would that be a fair synopsis at the time?
A. Yes. I mean, one of the difficulties is with post-transfusion or post-blood product or postanesthetic, people's liver function tests can change. And it's difficult to work out what is the aetiology of the change in liver function tests. But in principle, if you have an elevation of liver function tests, which means leakage of liver enzymes into the plasma, the implication is that you have liver damage for one of any number of reasons.

Q. Okay. And if you have a cohort of patients such as patients with haemophilia who, in general, have abnormal liver function tests after receipt of a concentrate, that would suggest the possibility of liver damage, even at that time?
A. Yes. It would be nice to have a temporal relationship; that the exposure leads to a period of transaminitis at a -- at a reliably predictable time.

Q. But a temporal relationship can only -- a temporal evaluation can only occur once a sufficient period of time has elapsed to allow the study to be undertaken, maybe such as a liver biopsy or damage to occur, actual clinical damage?
A. Yes. I think what you're putting is what we, in virology, would call an incubation period. At the end of the incubation period, if nothing's happened, nothing's happened. Within the incubation period, things occur or phenotypic expression of virus exposure occurs - illness if you want to call it, or post-transfusion hepatitis, or whatever.

Q. In relation to concentrates, and we'll talk about commercial concentrates more in this jurisdiction, it was known at the time that the donor pools were large?
A. Okay.

Q. It was known that they were incapable of screening for every virus?
A. Yes.

Q. Would you accept that, because --
A. We still are.

Q. And also, every virus hadn't been discovered at that time?
A. Yes.

Q. So consequently, if a virus did hit the donor pool or the blood supply system, these products, because of the nature of the size of the donor pool, were highly potentially infectious?
A. Yes. I think that is -- I mean, that is implicit in paragraphs one and two which you've pulled out from John Craske's paper. He doesn't actually quite put it in this way, but a native, nonheat-inactivated -- what we would now call a nonvirally inactivated Factor VIII concentrate bears with it the virological imprint of its donor panel.

Q. And that particular lesson had been learned from the experience with Hepatitis B in the period 19 -- before the introduction of Hepatitis B screening?
A. Yes. I'm just -- you're throwing back another virus. A number of things were learned from Hepatitis B but yes --

Q. That was one of the things that was learned?
A. The contamination of a pool -- the contamination of pooled blood and pooled blood products or plasma pools, ectrogenic plasma, was well-known from the Second World War.

Q. And that was the reason why certain companies endeavoured to develop the heat treatment process to eliminate Hepatitis non-A non-B in the late '70s, early '80s?
A. Well, a bit -- well, it was later than that when they actually developed anything which was regarded as being safe and appropriate for use other than small clinical trials, yes. But I mean, it's a principle --

Q. As a principle -- I suppose the date of introduction of heat treatment, as a principle, that was the logic behind the introduction of heat treatment, that the pooled nature of these products made them susceptible to viral contamination?

A. I think that's logical. I'm not sure that the manufacturers would have put it in those terms. They might have said, 'well, we're getting bad press because we're causing non-A non-B, let's try and find a way of inactivating non-A non-B'. That is probably a narrow view of the broad comment, which I agree with; that plasma -- a native fractionated plasma pool has the virological imprint of its donor panel. It's as simple as that and it depends on all things between your donor at the front end and your product at the back end.

Q. When you mention the bad press, I presume you're talking about medical articles and you're talking about the fact that from 1978 onwards, the medical journals seem to indicate there was histopathological damage ascertainable on liver biopsy in respect of patients who had contracted non-A non-B Hepatitis?
A. Correct.

Q. And that was the motivation that led towards the introduction of heat treatment initially; it subsequently became discovered?
A. I can't comment on the motivation of commercial companies in relation to why they want to introduce a safer blood product. I mean, your philanthropic point, I agree.

Q. Would you accept also that because the products weren't virally inactivated at the time, that any viral contaminant that came along could potentially infect the recipients of those products?
A. Yes, I think that is a very fair comment.

Q. So therefore, these products from the early 1980s, even before the advent of AIDS, were potentially infectious?
A. They remained as they were in the 1970s, yes.

Q. You indicate in your statement that individual plasma donation testing by most sensitive RIA methods was a recommendation of Dr. John Craske. Do you know whether that was brought in and introduced by the pharmaceutical companies in relation to --
A. Can you take me to where I said that.

Q. Sorry, paragraph 7.
A. What period do you want me to comment on?

Q. Period, I presume, 1974 to 1980. And it would have been after the discovery of the Australia antigen test?
A. The Australia antigen was first described in 1968 by Barrett Bloomberg, and -- or '67, '68 then was linked with acute hepatitis of the long incubation type in 1968 or '69, and they vary on the 42 nanometer. Article was identified in 1970 by David Dane and bears his eponymic title. Surface antigen would have been variously screened for during that period, and, unless I have data from the manufacturers, it's as difficult to know which assays they were using. They would have been initially using counter immunoelectropheresis in the late '60s and probably early '70s, and would have, shortly into the '70s, have been using Ausria, Ausria I and then Ausria II, which was the Abbott sandwich radioimmunoassay. I can't comment on -- because I don't know; if you have the data then I can look at it and comment on it -- when the manufacturers

introduced changes from CIE to radioimmunoassay but it would have been somewhere in the early 1970s.

Q. Well, even changes to radioimmunoassay would not have eliminated Hepatitis B from the products because of the window period concept?
A. Yes. There are -- many windows are there, front window and the back window. I don't think we really want to get into this, but these are -- would you like to tell me what you mean and see if we agree, or would you like me to hazard a guess what you mean? I'm not trying to be devious.

Q. What I'm basically trying to indicate is that even after the introduction of Hepatitis B screening, the safety of the products in terms of Hepatitis B couldn't be guaranteed because of the concept of the window period; the fact that certain people wouldn't have seroconverted at the time of testing?
A. Yes and no. In fact, the majority of cases of Hepatitis B antigen present in the stock pools were not due to deficiency and sensitivity of detection, which are the window cases, but were due to technical failure to identify a hooching positive surface antigen plasma donation. So in fact, if one -- if manufacturers, and as we have to do in the BTS, tightened up very, very carefully on information technology and information transfer, you would have actually saved a lot more contamination of your stock pools than if you'd strived to get the extra 10 nanograms or 20 nanograms of sensitivity. Now, if you assume that you correctly identify every plasma pool -- every plasma donation which goes into a pool that contains surface antigen, and you remove those, there will still be a very low level of HBs -- sorry, of HBV DNA present in that stock pool. But it would be much smaller than most of the contaminations which we saw, which we were fairly convinced were due to a deficiency in operational practice rather than a deficiency in sensitivity. You see what I mean? The bulk of the contamination occurred through failure to correctly identify the seropositive sample. The residual infectivity which occurred, even if you pull all the surface antigen positives out, is due to these people who have HBV, have Hepatitis B virus in their plasma, but cannot be identified by surface antigen. And this occurs at the upswing of the infection before they become antigenaemic very early after exposure and infection, and occurs in the downswing when the case -- the cases of infection resolve. And they have yet to produce high levels of neutralising antibodies. So both of those types and stages of infection can lead to a low level, but I would emphasise low level contamination of plasma pools.

Q. But you, I presume, accept that the larger the plasma pool, the greater the risk?
A. Well, not necessarily in the context of once you started screening blood, because there is actually, for Hepatitis B, as you probably know, there is a protective effect of having anti-HBs, and the interesting corollary is that if you have a very small donor pool and you get one of these low level, without-antigen, carriers and you have no anti-HBs from the other donors in there or not a high level of anti-HBs from the other donors, that pool, although it's a very small pool, might be infectious. If you made the pool ten times as large and got in three or four really good anti-HBs plasmas into there, it might render it noninfectious. So it's not quite as simple as 'the larger pool's more dangerous'.

Q. Okay. Let's turn it around: If you saw recipients or factor concentrates becoming Hepatitis B positive after the introduction of screening, would that be a matter of concern to you?
A. Of course, yes. I mean, you're quite right. You need to -- you have to have a surveillance mechanism of looking for adverse outcomes of any therapy, and that's an adverse outcome of a blood product therapy.

Q. And in that regard, during the course of the period 1980 to '84, if you saw people with haemophilia starting to develop Hepatitis B in circumstances where they hadn't been vaccinated for Hepatitis B, that would be an issue of significant concern, as a virologist?
A. Well, I think -- yes, I mean, obviously, because it becomes a post-transfusion hepatitis event in this case, what I would call a PTHB, post-transfusion Hepatitis B. I know this is not transfusion, but it's post-blood product B. One would want to know whether this is becoming more frequent or it's the same frequency or is related to unique blood products or is it a result of changes in -- sorry, we're having to do a little bit of boxing. Don't worry, ma'am. I'm sorry -- in relation to exposure to a new blood product made from a different donor panel. These are all questions that you rightly ask.

Q. Would it be a concern that would lead one to consider the withdrawal of a product?
A. That -- well, of course. When you have an adverse outcome of any therapeutic intervention, you have to do -- I mean, nowadays we're so politically correct we call it a 'risk analysis,' as you know; you have to weigh the advantages versus disadvantages, and certainly there was an opinion that, well, Hepatitis B is relatively trivial. We can immunise against it, we have a vaccine we can give people, schedules of immunisation which might protect them. That's a relatively small price to pay in relation to the change in lifestyle associated with Factor VIII concentrate. And the -- not only the change in lifestyle, but the protection against very serious adverse bleeding incidents. But those are not my words, those are other people's words and I'm not sure what I would do in that situation. But clearly you have to look at both aspects, harm and good.

Q. But in relation to Hepatitis B, if the incidence of Hepatitis B increased in the recipients of a blood product, would that indicate that it was a high-risk donor pool, when screening had been introduced?
A. Let me just think about that. What you're saying is if -- when you say increased incidence, do you mean that the incidence had previously been low in the recipients and now was going up?

Q. Take that as a theoretical exercise?
A. Well, it is a -- it's a situation which you could be in. You would need to know whether the -- do you see, it depends a little bit about the product, if the product has a propensity for concentrating virus into the product, the method of manufacture. Or, for example, you're removing neutralising antibody for one reason or another. All of these can perturb the rates of infectivity. It is relatively difficult in that situation to infer a biological correlate on the donor panel. You can say, yes, they are probably at higher risk than another donor panel which is treated -- whose blood products are garnered in the same way, treated and manufactured in the same way, who were not

associated with post-blood product B. But it's -- that is slightly different -- or slightly bridled the point of saying it's a dangerous donor panel. Because I know what you mean, but that's a value judgment which you can only put on objective data.

Q. Okay. But bringing yourself back in time to the period 19 -- before 1983, before the Montaginier discovery of HTLV-III. At that time, if you saw an increasing incidence of Hepatitis B and in circumstances where you knew this particular phenomenon mirrored Hepatitis B in terms of impact upon the recipients, would that be an issue which you'd take into account in relation to the risk assessment pertaining to the continued use of concentrates?
A. Well, I think that -- yes, I think without a shadow of doubt, because you've already made the point, I think quite fairly, and I would agree with you; that a natural blood product made from a large number of donors which is able to transmit either non-A non-B or Hepatitis B has to be a vehicle through which other infectious agents can pass. That is one of the concerns that one always had in making a pooled blood product. But then you have to say, what are the other agents; are they viruses or are they, nowadays, prions, or whatever? And you've got to remember, back in 1983 - you'll probably ask me - people's perceptions were very less precise than they are nowadays.

Q. One of the things we're discussing was limiting the donor pool size to minimise the risk of transmission of viral agents. And we talked about cryoprecipitate. When in the UK you discussed cryoprecipitate as an alternative treatment option, is it wet cryoprecipitate or freeze-dried cryoprecipitate?
A. Cryoprecipitate is a wet, frozen fraction of plasma.

Q. So that's the perception in terms of the United Kingdom in relation to references to cryoprecipitate?
A. Yes, to my understanding.

Q. Okay. And when you make comparisons in your statement, that's -- the comparative factor is that you're using wet cryo versus concentrate?
A. It would be the cryoprecipitate fraction from a single -- usually from a single donation. So each cryo pack which one used to have to pool, and I used to have to do this as a duty pathologist, it was never a very pleasant procedure, especially if there were 40 or 50 of them. Each of them was from an individual donation, so hence an individual donor.

Q. So if there was a more convenient product between wet cryoprecipitate and concentrate, then that would be a -- and had a limited number of donors into that product, that would be a preferable product?
A. Well, you're introducing three or four changes in that phrase. Can we take them in order?

Q. Yes?
A. A more convenient form of therapy which is more amenable to home use and self-administration surely is a great advantage. A more controlled product which has a standard amount of procoagulant activity per unit of protein is also an advantage. I wouldn't want to link those advantages with big or small pools, particularly as small pools are operationally very difficult to manufacture.

Q. Okay. There would be certain -- would you accept that there were certain advantages in relation to small pooled products in terms of safety in that you can monitor the donors and - if they're regular and consistent donors - for adverse reactions?
A. Possibly. Can we dissect -- sorry, we need to dissect this because you're -- what you're striking at, quite rightly, is decreasing donor exposure in the recipient. I've already mentioned the hazards of small pools; that when you start getting down to hundreds of donors, your ability to say that the plasma is truly representative of inverted commas, 'normal human plasma', becomes difficult because you've become susceptible to chaotic statistical events. And that's particularly relevant to anti-HBs, which the prevalence in the UK donor panel is probably one percent or so and only one in ten of those really matters and has a good level. So you need 1,000 donors at least to get a reasonable level of anti-HBs. You talk about audit and valid -- what was the phrase you used, sorry, validation of donors? Accreditation of donors, was it? Should have been accreditation of donors. Accreditation of donors; you can have donors whom you know absolutely everything about. And I have to say that one of the central planks of transfusion microbiology in the United Kingdom has been, where at all possible, we get to know our donors extremely well. And we use the information of the outcome of their red cells or plasma going into patients in a way to validate the regular donor because the regular donor is somebody against whom no black marker's been raised by an adverse outcome. This is something which we used to have the luxury of in the United Kingdom.

Q. In terms of discovery of HTLV-III as being a retrovirus and Montaginier's preliminary assertions in that regard from your perspective as a virologist, did that result in you considering how this particular retrovirus could be eliminated, based upon comparative analysis of other blood products such as albumin or looking at what had occurred elsewhere with retroviruses?
A. When are you talking about, 1983?

Q. Period '83 to '84.
A. Well, Montaginier first described it as ATLV in 1983, nine months before the Gallo /Montaginier back-to-back in 'Science'. I think at that time - it is a long time ago - one didn't know enough about the mechanism of transmission of that agent in blood and blood products to do anything other than guess. We knew that they earlier the described retrovirus in 1980 by Henoma (?) and Gallo of the HTLV-I, HTLV-II, the HTLV family, human T-cell lymphoma leukaemia family, we knew that was associated with blood transfusion, but was intensely so associated, and that infected people had a very high level of neutralising antibody present in their plasma. If we worked on those parameters for HIV, we would have been wrong, because we would have failed to recognise the fact that this had a very strong cell-free feature about its persistent -- well, we now know about its acute infection as well as its persistent infection, but that was a very important feature of the persistent infection with HIV. I think, you see, you also have to recognise that, even in 1983, in the Washington -- the March Washington meeting, CDC-sponsored meeting, there was a very strong lobby who said, "look, this is not an infectious agent. We know it sounds like Hepatitis B, but those of you working with Hepatitis B are being too liberal with the facts." This is due to antigen overload -- antigen overload in the haemophiliacs because they're getting all the allotypes of seroproteins; antigen overloads in gay men because all the

STDs which they are getting and material retained in the rectum after intercourse. All of that means you have plenty of assaults on the immune system; why do you have to look for a new agent? New agents don't happen. And there was a very strong lobby for that led by David Patillo in that March meeting. And it was only the beginning of the indication of cases in haemophiliacs who had had relatively limited exposure - not all of them; some of them had relatively limited exposure that led one to believe that we virologists -- or led us to believe we virologists were right. But we were very much in the minority in 1983.

Q. But that would have been, I presume, from December '82; it was known that AIDS had been transmitted to a child with no other risk factors from a blood transfusion, so therefore, the opinion of virologists --
A. Well, you see, a single blood transfusion in an infant is quite a replacement of the body fluid with alloantigens and you -- you were -- you would be right, and I would have been right to sympathise with you, but there would have been people who said 'For God's sake, you're dealing with a young child with an immature immune system. You're putting a whole lot of adult blood in there. Are you surprised that the immune system becomes dysfunctional?' that would have been the argument. It would not have been, this has to be a transmissible agent. Those of us who believed would have said this is an -- this is a transmissible agent. Viruses hunt in packs.

Q. But at that time, the view of virologists, would it have been that this particular condition was caused by a virus?
A. Some, but not all, virologists would have believed that. I certainly did because I was working closely with Robin Weiss, who was a retrovirologist and had a massive experience in animal retroviruses. And well, this was -- we were working with veterinarians and they were all sorts of things which -- I put it very simply and very easily: It felt awfully like Hepatitis B with another name. And that's all I can say. But as I pointed out, that was my view. I managed to persuade Robin that that was the correct view and that there had to be a transmissible agent there, but in 1982 we did not have a transmissible agent. The French had not talked about this either and many of us were having to culture from biopsies of lymph nodes and from peripheral blood an agent, but we couldn't find one. But we thought that one was there.

Q. Then when Montaginier discovered NANB and said that it was a retrovirus, and subsequently confirmed by Gallo, did that lead to the belief that this particular virus or retrovirus could be killed by heat treatment?
A. Well, if one had known -- one would have to postulate that there was plasma -- it was free in the plasma, and not necessarily complex with neutralising antibody. It would be, if you look at all the previous retroviruses, it would be relatively friable and enveloped, and you can make whatever conjecture you want from that. You would expect it to be soluble, to be sensitive to lipid solvents, to detergents; you would expect it to be sensitive to nucleic acid like beta-propiolactone; you would expect it to be sensitive to heat.

Q. When you say "friable," sensitive to heat treatment in terms of the elimination of the virus; when you say "soluble," you mean beta-propiolactone or tri(n-butyl) phosphate in terms of elimination of the virus?
A. Beta-propiolactone it doesn't -- beta-propiolactone chelates, C-H-E-L-A-T-E, chelates nucleic acid and destroys its infectivity, but it doesn't get rid of the virus but

it's incapacitated. The solvent/detergents which disrupt the membrane allow the nucleic acid to be accessed by nucleases in the plasma, and that destroys the virus.

Q. But in essence, from the date that the condition was discovered to be caused by a retrovirus, was it reasonable to assume, as a virologist, that it could be eliminated using these methods?
A. Might being. I'll be -- I'd like to be a little bit less precise than could or would, as it might well be.

Q. Would it be a reasonable scientific approach in terms of the fact that there was no other method of eliminating the virus available at that time?
A. To use heat treatment?

Q. To use heat treatment.
A. Yes, it would have been, but again, you have to undergo the risk analysis. What is the risk of using a heat-treated Factor VIII product in widespread clinical usage? If it turned out -- one of the arguments which was discussed -- or one of the issues which was discussed extensively in '84, beginning of '85, was whether you could, through using heat-treated -- heat treatment, render the Factor VIII procoagulant much more likely to generate inhibitors. And there was real anxiety, because Factor VIII inhibitors can be clinically terribly difficult to work with in a patient whose got a high inhibitor. And a number of -- a number of haematologists in the haemophiliac field were very nervous about using a Factor VIII concentrate which might contain what we would call a neoantigen.

Q. I accept the other issues, and those were issues from haemophilia treaters; but from the perspective of a virologist in terms of minimising the risk of transmission of this particular condition, once it was discovered that AIDS was caused by a retrovirus, heat treatment seemed a reasonable scientific option?
A. It seemed a reasonable scientific option with the riders of yield of Factor VIII and the potential for serious adverse sequelae of inhibitor induction. I mean, you know, we were virologists, we were meeting with everybody. And it was round-table discussions; it wasn't just virologists saying, "go forth and heat-treat."

Q. But if you consider that in the United States the FDA licensed heat-treated product in March 1983, surely, if there was difficulties with inhibitors, there would have become -- they would have become apparent within a certain period of time of that date?
A. You might care to believe that. I could not comment.

Q. Okay. You have delivered statistics in relation to the incidence of HIV infectivity in the United Kingdom. And we talked -- discussed the longitudinal study and that article at page 54?
A. That's annual point prevalence, page 54.

Q. 54.
A. I have it.

Q. Factors -- is it safe to transfer statistics from one jurisdiction to another jurisdiction or other issues that should be taken into account in relation to viewing

those statistics, such as: A, the prevalence of use of cryoprecipitate in a different jurisdiction; or B, the date of commencement of concentrate treatment for particular patients?
A. I think both of those could be relevant. I'm not quite sure -- you use the term transfer from one jurisdiction to another jurisdiction; can you lead me to what that means.

Q. If there were differences in those particular two caveats that I've mentioned, would it be safe to apply those UK statistics to another country?
A. It might be safe, but it might be unsafe because they -- they carry with them all the caveats of prevalence of infection within the donor base, and all one is doing in these data set in table two is comparing the outcome of two blood products - one made from American donors, which are the commercial sector concentrates; and the other made from British donors, which is the British Factor VIII concentrate. So in sense, in one sense you are looking at the outcome, in a coherent set of patients, of exposure to two different products. Now, you talk about cryo. If one perceived that the incident rate -- sorry, not the incident -- the prevalence rate of HTLV-III infection in 1982 or '83 was less than 1 in 50,000 blood donors in the UK, you would have to use an awful lot of cryoprecipitate to get more than one or two hits in the total number of patients included in table two. So I think cryoprecipitate is probably irrelevant. Date of onset of Factor VIII treatment, yes. I mean, it would be appropriate to know the -- as I've said, '78 through '83, 204 patients were divided into those who had commercial versus those who had NHS Factor VIII. And you'll find the patients' details mentioned on page 53 under "Patients and Methods," which is the bottom paragraph on that left-hand column and the paragraphs at the top of the next page.

Q. Were patients who are in receipt of commercial concentrate solely in receipt of that commercial concentrate or were they in receipt of two products such as cryoprecipitate and commercial concentrates?
A. Well, the answer is neither to both questions, both options, because they were patients with inherited Factor VIII deficiency; were divided according to their treatment, since 1978, into those who had received any commercial Factor VIII concentrate and those receiving British-prepared factor concentrate only. So according to the information that we have at the time, this was the -- I'm not sure where these -- whether these were the Rizza patients or whether they were the Luzzatto patients. Seroconversion began in this group in 1980. Those must be Professor Luzzatto's patients. Because if you come down to the results in discussion on the same page, the second paragraph, it refers to -- take you down; contrasts - two, three, four, five lines down from there -- seroconversion began in this group as early as 1980 and continued through '81 and '82, previously noted by Professor Luzzatto. So that must be in the sense that that refers to the 204 longitudinally-followed patients. Those are the criteria which had been used by Professor Luzzatto, which we then report there. Does that answer your question?

Q. In essence, if a patient didn't commence on a concentrate until 1982, obviously that patient or patient group, that patient group couldn't be infected prior to that date, or it would be unlikely to be infected from a commercial concentrate?
A. Well, they wouldn't --

Q. They wouldn't?
A. They wouldn't have been exposed to commercial concentrate. What, I don't know; I mean, all I can tell you is what we were told and what we reported in the paper.

Q. So therefore, if there's difference in treatment options between one particular cohort of people with haemophilia and commercial concentrates and another cohort of people with haemophilia in commercial concentrates, it could affect the transmissibility of the data from one group to another group; it just can't rely -- the only way to determine when a group of patients became infected is to do a proper epidemiological study; do you accept that?
A. Of course. And, as I said this morning, this database is complex and confounded because it was all we had available at the time. It does -- up until 1983 and including the 1983 figures are based on a cohort of 204 patients. What you see is that for the -- every year up until 1983, we are missing a considerable number of patients. So although at the end of the -- at the end of the 1983 period of follow-up, it's 105 on the left and 99 on the right, which gives you the 204 patients in the status cohort. We start in 1978 with a much smaller number and there are only ten patients bled -- 12 patients bled in 1978 who we then follow through to -- and are included in the 1983 census point. I mean, clearly, yes, going back on it, it would have been nice to have a sample from every patient enrolled in 1978 and followed through, but you must remember, this was very -- you know, we were only a-year-and-a-half into, two years into serological census, and an awful lot of questions to be answered.

Q. Would you consider it would be appropriate to apply those statistics to an Irish situation?
A. You could not get better safety in Ireland through using that commercial concentrate in your naive patients. Your -- that's a double negative. The situation would have to be as bad, if you were using the same commercial concentrates in this country, as it would have been in the United Kingdom on the commercial concentrate.

Q. But it would also need to be the same frequency of treatment?
A. Oh, yes, sure.

Q. And it would also need to be the same proportion of people with severe haemophilia and people with mild haemophilia in both studies?
A. You would have to -- taking this in terms of predicting what was the outcome in this country, you would need to know duration of exposure and exposure to what quantity of blood component. I mean, clearly you would have to harmonise it for those two parameters.

Q. So in essence, what would need to be done is to do an epidemiological investigation in relation to our situation to ascertain, with exactitude, what is the prevalence of HIV infectivity on a yearly basis in the haemophilia community?
A. Yes, but that doesn't invalidate making a broad estimate of the damage which could have been expected to have been done if you'd used the same amount of -- broadly the same amount of Factor VIII concentrate in broadly the same number of patients. I can't believe that it would be -- it might be imprecise, but it's going to be in the same sort of order of magnitude of infection as we saw in the United Kingdom.

Q. But you made a number of assumptions there: You said broadly the same number of patients and broadly the same number of Factor VIII concentrate. If you had a situation where patients were being prescribed both freeze-dried cryoprecipitate, which was product we didn't -- we were discussing earlier on, we didn't mention -- and concentrate, therefore the situation would be radically different to the statistics in that particular study; should be?
A. I think you can -- if you're talking about Irish-produced, locally-produced freeze-dried cryoprecipitate, an interesting concept to me, not one I've come across before, but I think your prevalence of infection in your donor panel is unlikely to have been much different from the UK. I mean, it might have been different; I would say you'd have to show me it would be different. I'd say it would be the same, but, either way around, it comes down to the amount of donor exposure that your recipients have had to the same donors that our recipients were exposed to.

Q. I'm not comparing the Irish freeze-dried cryoprecipitate to the concentrate, I'm comparing the commercial concentrate used in the UK versus the mixture of commercial concentrate and freeze-dried cryo used here?
A. On the basis that the freeze-dried concentrate -- sorry, the freeze-dried cryo will spare some exposure.

Q. Yes.
A. Yes, but that is controlled -- that is controlled in -- for what I've said. But I say it depends on the donor exposure that your recipients have had to American donors, and you can work that out. You can make an estimate of that on the basis of the number of vials, the number of -- the amount of Factor VIII that's been used. It's --

Q. But that's also dependent on the category of patients; whether they have mild haemophilia and require regular treatment, et cetera, et cetera, and the proportion?
A. But, at the end of the day, it comes down to how much commercial Factor VIII concentrate did you use in this country --

Q. And at the end of the day --
A. -- and which year you used it.

Q. It does. And also it depends upon the date of commencement of usage of concentrates as well?
A. Or when did the exposure start, how long did it last and how intense was the exposure.

Q. So in order to do a proper assessment in relation to the circumstances in any individual location, it is necessary to do a proper epidemiological study?
A. If -- if by "proper epidemiological study" you mean a study which takes into account when they started on Factor VIII, how much Factor VIII they got and what the level they got was, then yes, I agree entirely with you.

Q. Okay. No discrepancy. You -- there was a meeting in late 1984; there's an AIDS Advisory document to be found at page 34 of your booklet. Maybe we can have a look at it. What was the purpose of that meeting on December 14, 1984, with various parties in attendance?

A. It was to -- I mean, this is -- I can only interpret what I see. We had so many meetings and they're rather lost in the saucerisation of time. Judging by this, was essentially to develop secure serological testing for HTLV antibody, which involved my colleague Philip Mortimer at the CPHL, and my laboratory or my department which I was working in at the Middlesex Hospital Medical School. And this was essentially a meeting designed to put forward protocols for testing. It also involved recommendations of utilisation of Factor VIII concentrates. We were, I think at that particular stage, we were present as virologists, but our principal reason for being present was to talk about how to make secure testing available to haemophiliacs in the broad sense.

Q. If you look at page 35, and bottom of the page, it refers to "Options in probable decreasing order of safety from AIDS for Haemophilia A." Would you, as a virologist, and the other virologist in attendance, have had an input in relation to the advancement of that particular policy?
A. Clearly we would have done, judging by the people who were present: Richard Lane from BPL, John Cash from Immuno, Harold Gunson from BTS, Philip Mortimer from CPHL and John Craske, as virologists we would have been involved in that. It would have been a consensus of opinion; not necessarily unanimously held by everybody that was there. It was worked out as a consensus opinion of everybody present.

Q. And the preference, it appears to be in relation to Haemophilia A heated UK concentrate, then single donor cryo, heated imported concentrate, unheated UK concentrate, unheated imported concentrate. As a virologist who was in attendance at that meeting, would that particular order, or decreasing order, have been advanced on the basis of safety issues?
A. It would have been advanced through the -- it would have been advanced by discussion of the interested parties present. It is -- there would have been little data, been very little data -- virtually no data on which to support that ranking, but broadly speaking, a heated UK concentrate would have been predicted to have been safe, relatively safe. Whether that should have ranked above single donor cryo is a matter of debate. Virologists are always nervous about nonbiological amplification; that's putting a lot of small aliquots of donations together into a pool and then injecting that into something. That's always raising a degree of anxiety on virologists, and still does. Whether the absolute ranking of those is absolutely correct and supported by everybody, I can't remember, but it would have been a synthesis of, okay, who thinks what is the safest and who thinks what's the most dangerous, and we rank things in between there. And I can't be more precise than that. But we would have certainly been involved.

Q. If you look at page 36, this may have -- "In general, heated concentrate appears to be the recommendation of virologists consulted but individual directors wish to make up their own minds." So would the representation of virologists at the time have been based upon assessment undertaken in relation to the efficacy of heat treatment?
A. I don't think there would have been any data available for HTLV -- HTLV-III transmissibility or ablation of infectivity of heat treatment at the time.

Q. I think there was something the CDC published in October '84 and Spiral (?) published in September '84?

A. Yes, but that's not UK manufactured.

Q. No, but in relation to the effectiveness of heat treatment?
A. Yes, I mean, broadly speaking, heat treatment would be a sensible idea if you wanted to get rid of a virus, but, you know, you're asking for justification of what was more of a wish-list rather than anything founded on -- certainly founded on UK data in 1984, and if we had been able to -- I can't comment, but the question would be would we have been in a position to license in the manufacturing protocols which were reported by CDC. And that I don't know. Other people can answer that question.

Q. But assuming that products were available, both heat-treated and nonheat-treated, the preferable option would be heat-treated products arising out of that particular meeting, whether from a UK source or a commercial source?
A. Okay. Well, you have to consider how much is available and we've already been over the question of inhibitors and, of course, then there's the question of finite physical resources -- financial resources of health services in any country. And your yield of Factor VIII in heat treatment is lower and the cost is, therefore, higher. That's not a decision that would have influenced us as virologists, but I'm just saying it's a decision -- it is a feature which bears on medical practice.

Q. But as a virologist, the recommendation coming from that meeting was to use heat-treated product for safety reasons?
A. Well, I wouldn't actually agree with you. The outcome of that meeting was a ranking of safe to unsafe, which the haemophiliac directors had the choice -- had an informed choice of which option they would use.

Q. I accept that.
A. We don't say 'thou shalt not use native Factor VIII', we rank it. Options in probable decreasing order of safety. Now, if you have a bleeding patient and you have no heat-treated NHS Factor VIII, and you're out of cryo and you have a patient who is presenting with a severe bleed, you might have to elect to use unheat-treated imported Factor VIII concentrate, because you have no other way of saving that patient's life. So I mean, you can't put me in the position of saying, yes, I mandate only the thing on the top of the list because that's safe.

Q. I'm not; I'm just saying that in general the recommendation from virologists was to use heat-treated concentrate because of safety reasons.
A. Yes, but not to the exclusion of everything else.

Q. And the balancing exercise would have to be made by a haemophilia treater, dependent on the seriousness of the particular bleed?
A. Yes, I think broadly, but with the knowledge that virologists would have preferred it to have been heat inactivated.

Q. In relation to the use of the superheat-treated method in the United Kingdom, did you undertake any studies for BPL in respect of this effectiveness in relation to the elimination of non-A non-B?
A. No, we did not.

Q. Did not. You indicate in your statement that you've undertaken certain work for the Blood Transfusion Service Board here in Ireland. Is that because there isn't a virologist attached to the BTSB, or are you doing confirmatory testing, or what's the circumstances that that occurs?
A. Can you tell me, is that in my statement, because I need to see what it's in relation to. Can you take me to the page?

Q. Paragraph number two. "I have carried out testing of samples provided by the Blood Transfusion Service Board in Pelican House, Dublin."
A. This relates to the HCV infection resulting from the intravenous rhesus D immunoglobulin. I'm not saying that we haven't done things inter alia between the late 1970s and the late 1980s, 1990s. We've probably tested some samples. We tested samples from reference work from almost every transfusion service -- I should say every transfusion centre in the UK but principally this relates to the Hepatitis C problem.

Q. Would it be normal for a Blood Transfusion Service to have a virologist attached to it to do the preliminary testing?
A. I can't comment for this country; in the United Kingdom there has been -- it's been usual to have a transfusion microbiologist, either clinical or nonclinical, in close concert with testing laboratories. It may be somebody who occupies a post that is not formally trained as a microbiologist or it may be somebody who's followed a degree in microbiology and then becomes a virologist in the sort of -- either a clinical one like myself or nonclinical one like John Barbara. I'm sure you know. But we have some used to transfusion practice.

Q. Do you feel that a virologist as part of a Blood Transfusion Service team would bring something to the table that would otherwise be missing.
A. That's a leading question if ever I heard one. I would like to believe that we are useful, yes. I think that in transfusion microbiology, we tend to forget John Barbara and myself, other people have noted the feat of David Dane, who I think is without doubt one of the greatest microbiologists and transfusion virologists that's graced the last century. I think we do bring -- we bring a particular patina and the particular care and a particular hysteria about transmissible reagents, which is sometimes useful.

Q. And sometimes necessary?
A. Maybe. I'd like to believe it's necessary, but yes, I think we have a role to play.

Q. Two very short questions: One is in relation to plasma quarantine?
A. Quarantining.

Q. Quarantine of plasma. Do you think that's good process in terms of viral safety? Is it -- it's a very general question but...
A. I think it could make a very safe material, but it might break the bank in the cost of it and the amount of plasma that you could not use. I think operationally, although it makes cogent virological sense, it makes virtually no sense operationally. And it's -- again, it's a question of swings and roundabouts. If you're going to quarantine plasma, you have to know how long you're going to quarantine it for and what criteria you use for release of it. And you also have to be able to predict what proportion of

those donations you can release on fulfilling those criteria. Very, very similar problem we have with some organ -- well, tissue transplantation.

Q. But is it, as a concept or as a process, advisable to implement for a limited time span?
A. The only quarantining which I've seen used on a routine basis goes back many years to when we were preparing in the UK clotting diagnostics and we wanted highly purified, highly clean fibrinogen. And those were accredited donors whose material was actually taken and only released on a subsequent test for whatever virus markers we were using and the physical examination. So that was a very limited use of quarantining.

Q. You were using quarantining in --
A. In a very narrow sense.

Q. Very narrow sense, but it was where you had a very specific cohort of donors you are specifically using for a particular product?
A. For highly selected, highly conserved donors, but it would have been almost impossible -- I'm led to believe it would have been extremely difficult to allow that for the throughput of plasma that we require in the UK for fractionation.

Q. But if you were using a small donor pooled product and you wished to continuously monitor your donors, would plasma quarantine have been an additional safety method that could have been introduced in such circumstances?
A. Within the limited discussion which we're having on a very small donor panel, a very small specialised utilisation of the product - in this case a product which had no therapeutic implications but was being used as a diagnostic - yes, it could have. But I'm very loath to expand that and extend that into quarantining in the general sense for plasma procurement.

Q. But quarantining in terms of manufacture of cryoprecipitate, very specific now, do you think that would have been a good process to introduce in combination with ALT testing?
A. You are having two bites at the cherry now. Now you would have to separate those two questions.

Q. Quarantining as a concept pertaining to the manufacture of cryoprecipitate; do you think from a viral safety perspective that would be advantageous?
A. I would need to know on what criteria you release material from quarantine. Because that defines how safe -- what the impact of quarantining is. If quarantining is just waiting until the donor redonates, I'm not sure how much value that's going to have. But if it redonates and is tested for and perhaps red cells have already gone into somebody else from the first donation, and that patient is being followed up and that patient does not have an adverse outcome, then it could have an impact. But the operational coherence of that, on plasma procurement, when the shelf-life -- the shelf-life in terms of product -- in terms of plasma in fractionation product release is so short, I'm not sure how you could get adequate quarantining to impact on safety.

Q. But if you were dealing with regular donors for a particular product, in those circumstances would it not make sense that before they return for the next donation, which would be set, you should quarantine the product?
A. What you're talking is essentially using regular repeat donors rather than first-time donors. I don't actually consider the differentiation between first-time donor and repeat donors as a matter of quarantine. I consider that a matter for transfusion microbiology practice, not to fractionate first-time donors. But that can impact on -- would have impacted -- could have impacted on safety back in the 1980s, because nowadays as you know we have plasma inactivation and product inactivation, all of which renders materials essentially virus inactivated. So the loss of the first-time donor has less impact now than it would have had with native blood products. Then it would have been significant, but I'm not sure if that's what you wanted from me, is quarantining. I don't consider that quarantining -- that to me is prudent plasma procurement practices.

Q. I think we've clarified the differentiation. Next issue is Hepatitis B core antibody as a surrogate marker for HTLV-III. Would you accept that if that particular surrogate marker was used for a high-risk donor population, that it would eliminate 80 percent of the potentially infectious donors?
A. This sounds awfully like transferring from one jurisdiction to another jurisdiction.

Q. It is.
A. I'll just pull your leg on that. Can you define which infection you're thinking of?

Q. HTLV-III.
A. No, I don't think it would do. At least all I can do is talk to data derived in the United Kingdom; both in the two big countries, geographical countries, in Scotland and England. In both situations HTL -- anti-HBc is not a marker for high-risk lifestyles within our constituency and within our blood donors. In the United States, the seroprevalence of anti-HBc in the patients of AIDS is probably 70, 75 percent. But those are a skewed population from the person who might be infected with HIV in a blood donor setting.

Q. Very simple concept: If Hepatitis B core antibody had have been applied as a marker in or around 1983 to a high-risk donor population, it would have eliminated a significant proportion of those persons who were -- who went on to develop AIDS. I can show you an article if you wish?
A. Take me to the article. Take me to the article, if you wish to put me on the spot like that, and let's have a look at it.

Q. It's in the larger booklet of --
A. Band one or band two?

Q. Folder -- it's actually three, the article you received this morning. I'm looking at the --

THE CHAIRPERSON: Can you give the name of it, Mr. Bradley, the title?

MR. BRADLEY: Title of the article is Transfusion-associated AIDS. It's an article by Herbert A. Perkins of the Irwin Memorial Blood Bank, San Francisco, California. Very simple point. Table two.

THE CHAIRPERSON: Sorry. Just what was the page, please?

MR. BRADLEY: It has page 101 at the top.
A. Table 10 -- page ten, I beg your pardon.

Q. MR. BRADLEY: Page six of the second booklet.
A. That is based on CDC data in 1983.

Q. CDC data. And the reason I'm asking the question is that the products that were used here derived to a large extent from the United States, or a significant extent. So therefore I'm looking at potential surrogate markers that could have eliminated the infectivity of those particular products.
A. I have to ask you, do you know the donor panel on which this data is based? Because it's my suspicion this would be Bay Area, San Francisco.

Q. It would be -- it would be a high-risk donor panel?
A. And that is an extremely anomalous -- or it's a panel which is unique in the sense that it was preferentially enriched by gay men, partly because of the Hepatitis B immunisation programme set in place by Wolf Smuzness and Merck, Sharp & Dhome; and also partly because of the ethnicity - ethos, if you like, rather than ethnicity - the ethos of the people who live in the Bay Area who are very -- who would be perceived to be seemingly socially responsible and very good and reliable donors. So if you're asking me whether anti-HBc testing would have helped in essentially a gay donor panel in San Francisco Bay Area, yes I think it might have. But again, I would point you to constituencies and jurisdictions; to a jurisdiction here within the country the size of the United States, I'm not sure that you can extrapolate from Bay Area to the rest of the American commercial donor panel that were -- the noncommercial American Red Cross donor panel.

Q. Exclude the noncommercial Red Cross donors and look at the commercial donors, and look at the pharmaceutical companies, and look at the sources of their donor pools. In such circumstances would Hepatitis B core antibody have been a useful surrogate marker to introduce?
A. It would have identified -- if you're -- again, if you're talking about the Bay Area, it would have identified the significant proportion of people who were at risk but it would have taken away -- I dread to think what the proportion of donors would have been removed from the donor panel. You might have removed -- say you remove 20 or 30 percent of the donor panel; a reduction of available blood by 30 percent would have catastrophic knock-on effects. It's not without its risk. The -- elsewhere in this band of papers there are data from the Cladd Stevens paper on the TTV study, and that's page 132. It's interesting, if you go to page 135, they talk about if they combined ALT and anti-HBc, which would have been probably the most effective bilateral -- sorry, testing a loss of 8 percent of the donor panel. And that -- I mean, a loss of a few percent of a donor panel in western allopathic medicine is dangerous. That's 8 percent, and that's not in the Bay Area. So I would just predict that you would get a very significant loss of blood.

Q. You would if you continued to collect from that particular source?
A. Sure. Well, then surely the best thing is not to collect from that source.

Q. It is. Thank you very much.

THE CHAIRPERSON: Are you finished, Mr. Bradley?

MR. BRADLEY: I am, yeah.

THE CHAIRPERSON: Mr. Connolly?

MR. CONNOLLY: Thank you, Madam Chairperson. I have no questions.

THE CHAIRPERSON: Mr. McGovern, have you any questions?

MR. McGOVERN: No questions.

THE CHAIRPERSON: Ms. Murphy?

MS. MURPHY: No questions.

THE CHAIRPERSON: Mr. O'Brolchain?

MR. O'BROLCHAIN: Two questions, Madam Chairperson.

THE WITNESS WAS THEN EXAMINED AS FOLLOWS BY MR. O'BROLCHAIN:

Q. Professor?
A. I see you, sir.

Q. I'm hiding here behind Mr. Bradley.
A. I have you in sight.

Q. I appear for Dr. Cotter, a haematologist in Cork; and the Southern Health Board. And I wonder if I could ask you to turn to page 7 of your statement, end of page 6 and top of page 7.
A. Statement, sorry. This is paragraph 13?

Q. That's right, end of paragraph 13 on page 6 and the top of page 7. You're dealing with the cohort in Scotland?
A. Yes.

Q. And in that you indicate at the top of page 7, that some of the patients seroconverted on samples taken some time afterwards. Do you see at the top of page 7?
A. Correct.

Q. Then you go on to say: This may have reflected the relative insensitivity of the earlier testing methods or a delayed seroconversion. Can I take it from that that -- first of all, was it known then that the testing at the early stages were somewhat insensitive, that they weren't as accurate as they subsequently became?
A. I think you have to take this as -- in the paper, we said it's one or the other.

Q. Yes.
A. In practice, we were using a competitive radioimmunoassay which used the same components, differently manufactured and differently labelled, as were used in the Wellcozyme commercial assay. The commercial assay proved to be very -- really quite sensitive, as if you like -- I don't like the phrase, but 'the first generation assay,' something which came out within the first year or so of serological tests being commercially available. It has essentially remained unchanged in the last 15 years and is still a very sensitive and highly specific test. This was put in really as a discussion point, but we don't know why these people take some time to seroconvert. I mean, their alternative -- there's an alternative explanation which seemed -- crossed our minds but we didn't put in the discussion, which is, well, maybe they have been infected from something else. And this comes back to what I was saying this morning: If you really want to have proof of -- proof of infection, you need to have the genomic studies to confirm that the virus present in your index material is the same, or very similar, to the viruses which are present in your infected individuals. Because you rely on people not having other risk factors. You rely on people not sharing somebody else's Factor VIII concentrate when they're on holiday or something like that. And there are opportunities for other transmissions. But having said that, certainly one of them, one of the people took a long time to seroconvert. And I don't know whether that was seroconversion related -- or delayed seroconversion from the SNBTS material, or a virus which got in by some other means.

Q. Some other means, yes. Well, in the last sentence of that paragraph 13, you say that "the shortest time interval from exposure to seroconversion was 31 days, but another of the 18 patients who eventually seroconverted was negative when tested at least 160 days after exposure." What's the longest period of time between testing and seroconverting?
A. Well, the longest that I know of is in the Danish cohort where they claim something like 18 months on post-sexual exposure.

Q. I see.
A. What I -- when we wrote up the first needle-stick transmission, that occurred -- seroconversion happened at 14 days from exposure. Certainly our experience nowadays with close surveillance in the GUM clinic is something like 14 to 21 days, from exposure to presenting with an illness and seroconversion. So it's not really a slow virus in the sense that the virus replication starts very quickly and seroconversion follows. Having said that, there have been isolated incidences of people remaining P24 Antigen for a month or even two months before producing a seroconversion. But, you know, these weigh out outliers in the scientific literature. They're all right, but they have to be seen within the general caucuses of what we describe as normal. Normal, I would say, is say 14 to 28 days, 14 to 21 days. I prefer 14 to 28 days, I could live with, if you wanted to get the first good confirmed seropositive reaction.

Q. I suppose the effect of what you're saying is there are exceptions, or there appear to be exceptions?
A. There appear to be exceptions. How many of those are genuine biological situations or how many of those are human endeavour obfuscating reality, I really wouldn't like to comment on.

Q. The last matter I wanted to ask you is the question of two people taking the same batch, one being infected and the other not being infected. How often did that happen?
A. Well, clearly that happened in about 50/50 of the Scottish outbreak. There were 13 or 14 -- 15 infections in the first instance and late infections occurring in the 18 -- 15 and 18 in the first instance, and then it became -- I think it reversed as we got the two or three late seroconverters in the cohort. So those figures may not be absolutely right, but it's not uncommon in that situation, particularly with the SNBTS material only to infect half the people. We know that there's a correlation with the dose; the more you got -- or the people who became infected had a higher risk of acquiring infection. The implications are that -- there are two implications from that: One is that you can't infect all of the people all of the time. There may be periods of refractories maybe, or the post-lymphocytes are not in a state whereby they will support early virus replication, so people may be refractory for a short or long time. There is good data to support that in female sex workers in at least two countries in Africa. Or that the amount of virus in the concentrate was approaching say half a dozen vials, was approaching one or two or three human infectious doses. So you needed to have quite a dose of Factor VIII in order for you to be exposed to infectious virus. Now, if you combine those and mix any proportion of those two explanations, you can run from being able to infect everybody most of the time with a high inoculum - for example, a blood donation from a seropositive individual - or almost invariably will kick off the recipient to getting to a very small dose of virus in the Factor VIII, Factor VIII which would kick off some of the people some of the time. So you've got a whole range of almost absolute infectivity to very low infectivity.

Q. Now, the article that you're referring to is a 1988 article, Simmons, et al. This is the one that you referred to at the top of the page, in your paragraph 13.
A. Yes. I mean, that was a description in more detail, virological detail and serological detail of the Edinburgh cohort.

MR. O'BROLCHAIN: Thank you very much, Professor.

THE CHAIRPERSON: Thank you, Mr. O'Brolchain.

Mr. Murphy, have you any questions?

MR. MURPHY: No.

THE CHAIRPERSON: Mr. McGrath?

THE WITNESS WAS THEN EXAMINED AS FOLLOWS BY MR. McGRATH:

Q. MR. McGRATH: Just two very short matters, Professor Tedder. Just for the purposes of clarification, in relation to the study of the 15 haemophiliac Scottish patients who had seroconverted, I think you mentioned that the results started to come through from mid-1984 or thereabouts?
A. End of -- sort of late summer, early autumn '84.

Q. Autumn 1984. And the findings were published in The Lancet in August of 1985. But just for clarification purposes, I think that those patients -- according to the article, that almost all the patients attending the Edinburgh Haemophilia Centre had received -- who had received Factor VIII and Factor IX concentrate, that that concentrate was prepared exclusively from locally collected plasma in Scotland, is that correct?
A. My understanding, yes.

Q. Yes. And just one final point: Now, I don't have the precise page number, but I'm working from the booklet of articles that I think you might be familiar with. There was a booklet of articles with 17 I think different articles, and these were subsequently paginated and it was article number nine, a document that Mr. Bradley referred to. The AIDS advisory document. I'm afraid I don't have that pagination.

Page 34 apparently.

THE CHAIRPERSON: Page 34, thank you.
A. I think that's -- page 34 is Intellectual Celebrity Syndrome. I think it must be the other book.

MR. NOLAN: Your own book.
A. My own book, yes. Depending which book we're working in. I have it.

Q. MR. McGRATH: Yes. And I think that document in fact is dated the 14th of December, 1984. It's on the final page of that document at the bottom of the page.
A. Yes.

Q. And I believe that Mr. Bradley brought you through a section of that document dealing with the Options in Probable Decreasing Order of Safety from AIDS for Haemophilia A. That obviously concerned Factor VIII and not Factor IX; that's what he was dealing with, isn't that so?
A. That's my understanding, yes.

Q. Whereas we see insofar as Haemophilia B is concerned, we can see the options as it were set out there: Mild; Christmas; fresh frozen plasma, if possible; virgin patients; and those not previously exposed to concentrate, use fresh frozen plasma or NHS Factor IX concentrate, if essential; and severe and moderate Christmas Disease previously exposed to Factor IX concentrate continued to use NHS Factor IX.There's no suggestion of heat treatment, heat-treated Factor IX at that stage?
A. Correct.

MR. McGRATH: Thank you, Professor Tedder.

THE CHAIRPERSON: Thank you Mr. McGrath.

Mr. Durcan, do you wish to re-examine?

MR. DURCAN: No, thank you, Madam Chairperson.

THE CHAIRPERSON: Professor, that concludes your evidence for today, and thank you very much indeed for coming. You've been most helpful.

THE WITNESS THEN WITHDREW.

THE CHAIRPERSON: We'll adjourn now until 10:30 tomorrow. Thank you very much.

THE TRIBUNAL THEN ADJOURNED TO TUESDAY, JULY 10, 2001, AT 10:30 a.m.