THE TRIBUNAL RESUMED ON THE 19TH OF JULY, 2001, AT 10:30 A.M., AS FOLLOWS:

THE CHAIRPERSON: Good morning.

MR. FINLAY: Morning, Madam Chairperson. Dr. Foster, please.

THE CHAIRPERSON: Good morning, Doctor.
A. Morning.

THE CHAIRPERSON: Would you stand, please, and take the oath, or if you prefer to be affirmed.

DR. PETER FOSTER, HAVING AFFIRMED, WAS EXAMINED BY MR. FINLAY AS FOLLOWS:
A. Peter Foster.

Q. Dr. Foster, I think your present position is development manager at the SMBTS Protein Fractionation Centre in Edinburgh?
A. That's correct.

Q. And I think did you get your primary degree in 1968 from Edinburgh University in chemical engineering?
A. It was the Heriot-Watt University in Edinburgh, but it was chemical engineering.

Q. I see. In I think 1969 you got an MSc in biochemical engineering from the University College in London?
A. That's correct.

Q. And in 1972, PhD in the department of chemical and biochemical engineering, again in University College London?
A. That's correct.

Q. Yes. Now, I think then did you join the PFC in Edinburgh in 1973?
A. I did. It was January '73.

Q. Yes. And I think you joined there as a research scientist?
A. I did.

Q. And you have been at the fractionation centre in Edinburgh since then?
A. That's correct.

Q. Yes. Now, I think in that period, Dr. Foster, I think that you have published a significant number of articles, isn't that correct?
A. I have published some work, yes.

Q. Yes. And I think you have been involved in essentially the practical and scientific work in connection with the fractionation of Factor VIII and Factor IX?
A. That's correct.

Q. Yes. And I think you have given papers at various conferences on what one would expect from a scientist publishing in that field?
A. That's correct.

Q. Yes. Now, I think you may be aware, Dr. Foster, that Dr. James Smith gave evidence to the Tribunal yesterday?
A. Yes.

Q. And of course, I think he was at the fractionation centre in Edinburgh until 1975?
A. That's right. He left in August '75.

Q. Yes. So you would have overlapped with him for a period of two years?
A. Yes. We worked closely together for that period.

Q. Yes. And then I think when he left, I think did you become, in fact, the head of the Research and Development department?
A. I was made head of Research and Development in April 1974.

Q. I see. I see.
A. Dr. Smith was the deputy director.

Q. I see. I see. Now, I think Dr. Smith gave evidence yesterday about his awareness of some contact that there was between the fractionation centre in Edinburgh and the BTSB; I think in particular with Dr. O'Riordan of the BTSB in the early 1970s.
A. Yes, that's the case.

Q. Yes. Would you yourself have had any direct involvement in that contact?
A. No, I wasn't involved in it. I was aware that the director of the centre, Mr. Watt, did have a relationship with Dr. O'Riordan, and there was correspondence that we have in our files that illustrates that.

Q. Yes. And I think you have provided to the Tribunal, Dr. Foster, an exchange of letters which took place in October and November of 1975, isn't that correct?
A. That's correct.

Q. I think if we look in the book, they are contained at pages two and three of the book. Isn't that correct?
A. That's correct.

Q. Yes. The first letter in October of 1975 was from Dr. O'Riordan to -- addressed to Dr. Watt saying: "The board is presently formulating plans for construction of a custom-built transfusion centre. Bearing in mind the facilities provided at your centre and the population served, it would be most advantageous to us if you could arrange for the completion of the enclosed questionnaire. A copy has also been sent to John Cash in respect of the routine facilities provided by the regional transfusion centre. Thanking you in anticipation and with every good wish." John Cash would have been where, Dr. Foster?
A. At that time he would have been director of the Edinburgh Transfusion Centre.

Q. Yes. And that would have been a blood transfusion centre as distinct from your centre, which was a fractionation centre, purpose-built fractionation centre?
A. That's correct. We had been in the same facility; both at the Edinburgh Royal Infirmary until 1975, and then our new centre opened in '75, so at that point we had split into two different sites. And the transfusion centre remained in the Royal Infirmary, and we were in our new fractionation centre. Cash was the director at the Royal Infirmary and Watt was the director in the fractionation centre.

Q. I see. And in Dr. Watt's reply to Dr. O'Riordan of the 11th of November of 1975, he sets out -- Dr. Watt set out an account of the situation which then obtained in the fractionation centre in Edinburgh, isn't that correct?
A. That's correct.

Q. And in particular, in the third paragraph: "The PFC was designed to handle a minimum of 1,500 litres of plasma per week working on a 46-week year, with capacity to increase to at least 3,000 litres per week. Of this plasma, it was expected that the 1,500 litre level to process 200 litres of fresh plasma with the remainder as outdated or partly aged plasma. At the level of 3,000 litres per week, it was expected that 1,000 litres would be provided as fresh plasma. The plasma was expected to come from Scotland and from the English Blood Transfusion Service on a contract basis. At the minimum level of working, it was expected that 1,000 litres of plasma would come from Scotland each week and the remaining 500 litres would come from England. How this will work in practice is difficult to define at the present time since there is no plasma available in England to send to Scotland. Elstree is, for the present, able to absorb all available plasma from the English Blood Transfusion Service. this is a matter for some concern since it affects the economic viability of this centre." And he goes on then to deal with the situation in the centre. And in the next paragraph he mentions that the centre had a stockpile of product which would in effect keep them going for the moment. And then about five lines into the paragraph he said: "It had been in my mind that sometime in December I would write to suggest to you that you might like to reconsider a reintroduction of the ad hoc scheme we operated jointly a few years ago but on the basis that we could undertake to fractionate your plasma and return all fractions to Dublin. I have discussed such an arrangement in principle without specifying source of plasma with the Scottish Home and Health Department and discovered they are receptive to this idea, provided the plasma does not come from a commercial source. I had intended to make this proposal because I believed there would be mutual benefit in such an arrangement since the increase in plasma volume would reduce our costs per litre processed, and I thought we could offer you the fractions at fairly low cost for processing. I believe this to be possible, even, although, we would remain at the low end of our efficiency scale. However, if the Blood Transfusion Service Board is planning to incorporate large-scale fractionation within the proposed new transfusion centre, it may be that you would not wish to consider such a proposal." Now, Dr. Smith in evidence said that although he wasn't directly involved in any of these contacts, his understanding was that -- what Dr. O'Riordan was interested in would have been the notion that Factor VIII and Factor IX would have been fractionated by the BTSB in Dublin, and the remaining plasma would have been sent off to Scotland for further processing by the centre at Edinburgh. Were you aware of that situation?
A. No, I can't really comment on that. All I am aware of is what you have got in front of you, which is the correspondence that we have on file.

Q. Yes. Now, I think you don't have any further correspondence on file that would be relevant to that issue?
A. That's correct. I have looked through the file and could find nothing else relevant to this issue.

Q. Yes. Now, what was the situation in terms of the use of the capacity of the fractionation centre in Edinburgh between this time in 1975 and, say, 1985, if we take that period?
A. Well, the centre had really only just opened in '75. We took possession of the building at the end of -- end of '74, and we were commissioned in the centre in June in '75. So when Watt wrote this letter, it was very early days in what was possible. The centre had been planned jointly with our colleagues in England, who were undertaking an expansion at Elstree, and the arrangement was that the expansion at Elstree was sized in a predictive way to handle about two-thirds of the plasma that was expected in England; and the Scottish centre was sized to handle Scotland and one-third of the plasma from England. That was the arrangement.

Q. Yes.
A. The extension of Elstree was completed in the early 1970s, and as Watt says, was able to absorb all of the surplus plasma that was at that time available in England. In Scotland, the decision was taken to begin to operate the centre with Scottish plasma and the centres were staffed and equipped to operate at that level, which was up to about 1,000 litres a week. The building and all of the arrangements were there with some extra equipment to go up to 3,000 litres a week, as Watt suggested.

Q. Yes.
A. Plasma from England did not come to Scotland. That arrangement did not proceed. And however, I think the planning that had taken place earlier did not fully predict the increase in demand for blood products. And so more and more plasma became available from Scotland. And so, the capacity began to be increased just to handle Scotland. And in the early 1980s, we also received plasma from Northern Ireland. So by the mid-1980s, we were processing at about the level of 60,000 litres a year, which is getting close to the 1,500 mark. So we still had surplus capacity even in 1985.

Q. Yes. And clearly from Dr. Watt's letter -- and perhaps obviously there would have been an economy of scale if the fractionation centre had been operating at full capacity?
A. Yes.

Q. Or it was thought there would be?
A. Watt was very concerned about this. He was aware that the costs of a fractionation facility are not insignificant and a lot of the costs are fixed costs - the cost of quality, the cost of researching, the cost of whatever. And therefore, the more plasma you can process, the more economic it becomes. And he was very concerned that the Scottish centre might be uneconomic. It was necessary that you had a reasonable capacity.

Q. You mentioned you began to fractionate plasma from Northern Ireland in the early 1980s.
A. That's correct.

Q. Can you just explain what the arrangement was in relation to that plasma?
A. Could you explain your question a little bit better.

Q. Certainly. What happened in concrete terms; first of all, was the plasma from Northern Ireland fractionated separately from the plasma from Scotland?
A. Yes. When we first received the plasma from Northern Ireland, we processed it discretely. And we were also doing that with plasma from Edinburgh and Glasgow, as far as Factor VIII manufacture was concerned, because we were interested in gaining information on how the plasma -- the blood was being processed back when it was being collected, to understand if there were any differences in collection that would affect the Factor VIII yield. We carried out almost, if you like, discrete experiments, in fact, on the different --

Q. If you just take it more slowly for the stenographer?
A. We did process this plasma separately for some time for Factor VIII manufacture.

Q. And the reason for that was that there might have been some differences in the way in which plasma was collected in Northern Ireland in Edinburgh and in Glasgow?
A. That was our -- that was what we wanted to examine.

Q. Yes. And to see whether or not -- if there were differences in the method in which plasma was collected, to see whether that would have any impact on yield, is that --
A. That's correct.

Q. Yes. And so for how long would you have fractionated the plasma from Northern Ireland, from Edinburgh and Glasgow separately?
A. I can't give an exact answer for that. It was sometime in the mid-'80s, I think, that we stopped doing that, because we had heard all the information that we needed and it was no longer of interest to us. And it was not something that anyone required us to do, and so it -- thereafter, we pooled all of the plasmas.

Q. I see. Did it impose any enormous difficulty to do that, Dr. Foster, to fractionate the plasma separately?
A. It wasn't enormously difficult. It was slightly more difficult and it required more careful scheduling, but it wasn't -- it wasn't impossible, no.

Q. Yes. Now, I think one of the documents which you have made available to the Tribunal, Dr. Foster, is a document which you -- of which you were the principal author, which was a submission by the Scottish National Blood Transfusion Service to an inquiry which was carried out by the Scottish Executive, is that correct?
A. That's correct.

Q. And I think in the book of documents, that starts at page 30, isn't that correct?
A. That's correct.

Q. And there are a number of matters in this that I want to refer to, because it contains a very comprehensive history and survey of a lot of the matters that the Tribunal would be concerned with. But if I could just ask you, first of all, I think you give a history starting at page 30 of the production of Factor VIII protein at the fractionation centre in Edinburgh, is that correct?
A. That's correct.

Q. And I think the basic fractionation process was based on the method of Johnson, which was developed in New York; I think that is referred to at paragraph 2.7, is that correct?
A. That's correct. That would be the product that we introduced in 1974.

Q. Yes. And that was similar to the work that was done at Elstree and Oxford?
A. That's correct.

Q. Yes. Now, I think from 1974 until the mid-1980s, were you working on the question of yield, Dr. Foster?
A. I was working on a number of aspects and yield was one of the primary aspects.

Q. Yes. And can you just explain to us, in general terms, what the problem was; what the problem was about yield? If we start, say, in the mid-1970s, what was your problem with yield?
A. Our objective was to achieve self-sufficiency, and yield is one of the components of achieving self-sufficiency. And the process that we had established in 1974, firstly we had difficulty with that process operating in production. At the scale that we were operating, even though this was a modest scale, it was still a difficult process to carry out. And as a consequence of that difficulty, meant that there was a concern about the yield of the process. And obviously the higher the yield, then the easier it's going to be to achieve self-sufficiency. And I began to examine the process. We did some work in the laboratory under Jim Smith and under myself, which wasn't very productive, and so I began to look more and more at the manufacturing process itself to try to learn what was happening and to make what measurements we could, bearing in mind that the analytical methods that were available at that time were quite limited. But it was quite obvious we were losing a lot of Factor VIII at the first step in the process, which was the cryoprecipitation step.

Q. I see. And so did you decide to look at that process closely, the cryoprecipitation?
A. I was looking at every step in the process, but in particular, the cryoprecipitation was the one that seemed to me to need the most attention, was the most productive place to start with. And it was also important to start at the beginning because if you make changes there, it's logical to do that first and then make changes subsequently downstream; rather than make changes downstream and change the process upstream. You go around in circles if you do it that way. So you had to start at the beginning.

Q. Yes. Now, at that time, in a general way, Dr. Foster, can you describe what the cryoprecipitation process was; I mean, how was it done?

A. The principal of cryoprecipitation is you are separating a material which remains insoluble after the plasma has been thawed. The plasma comes to us frozen, we thaw it in a semi --

Q. Again, just for the stenographer.
A. Plasma is received frozen. And when the plasma is thawed, when it's melted, there is a residue which remains insoluble. And that residue is called cryoprecipitate, and it contains Factor VIII.

Q. Yes.
A. The procedure that we were carrying out at that time involved a batch process where we would have about 150 litres of plasma that had been crushed into a kind of a snow consistency, and then melted in this vessel that was 150 litres in volume. And melting that snow in this vessel would take about an hour to an hour-and-a-half. And at the end of that process, the melted material, which had the suspended cryoprecipitate contained in it, would be passed through a centrifuge in which the solids could be checked and separated from the supernatant.

Q. Yes. And did you examine the yield which was obtained from a cryoprecipitation process of a large batch of that kind, or relatively large batch as compared with the yield from -- similar process of a much smaller batch?
A. Our batch size was fairly constant at that time, so I was looking simply at our manufacturing process. But the yields that we were achieving there at the cryoprecipitation step were much lower than would be possible in the laboratory if you were doing small-scale laboratory experiments where you were preparing cryo at a very small scale. And so there was obviously a difference there between one -- what one could achieve in the laboratory compared to what one could achieve at full scale.

Q. Yes. And did you then, Dr. Foster, devise a system for carrying out the cryoprecipitation, which instead of -- essentially, instead of dealing with an entire batch at once, involved a continuous thawing process?
A. That's correct. It seemed to me at that time there were two possibilities: One is that because of the length of the process, the Factor VIII was being degraded over that period of time. The second possibility was that the Factor VIII was going into the solution phase rather than staying in the precipitate, because the solution might be getting too warm. And you have to control temperature at this point to achieve an accurate precipitation. Which of those were taking place, I didn't know; and it was possible that both were taking place.

Q. Yes.
A. It seemed to me to address both of those issues; one could move from a batch process to a continuous process, because in a continuous process you can carry out the procedure much more quickly so you reduce the time available for degradation, if it is taking place and you can achieve a much higher degree of temperature control.

Q. Yes. Did you develop such a procedure, Dr. Foster, and did you find that it was successful?
A. Yes, I did. I developed a process -- procedure which was installed in our production operation at a pilot scale in 1979, and the results were very dramatic. And

we replaced our previous batch procedure with this continuous procedure during 1979. And I then went on and scaled up the process further following that pilot design, and put in it what became a substantive design at the beginning of 1981.

Q. Yes. And would you have published the information relating to that procedure? I think you refer to the references here in the reports in the appropriate scientific journals at that time?
A. Yes, I did.

Q. Yes. And did you also look at some of the other aspects of the actual production process with a view to seeing whether you could increase yield?
A. Yes, I did. We were monitoring the whole production process. And during the late '70s, some new analytical methods became available where it was possible to detect the Factor VIII protein independently from its activity. And by measuring both the activity and the presence of the Factor VIII protein, we got more information about what was happening. And I discovered that there was a lot of Factor VIII taking place, and we knew it was taking place near the end of the process but we didn't know why. And this helped us to understand why that loss was taking place, and to then begin a programme of work to try to correct that.

Q. Yes. So apart from the continuous thaw method, were you able to fine-tune other aspects of your production process to improve yield?
A. Yes. The later aspects were not put into production until the mid-1980s --

Q. Yes.
A. -- because it was more difficult to make those changes. But ultimately, yes, we made further changes which made it an important contribution to yield.

Q. Yes. Now, were you aware of what I think is referred to as the Rock method, or the Gail Rock method of taking plasma into Heparin?
A. Yes, I'm familiar with that.

Q. Yes. Did you do work on that in Edinburgh?
A. No, we didn't. I read the papers, but we were already well advanced with our own work that was going on with a similar objective. And so I didn't work on that myself. But I maintained an awareness of what was going on and was aware of other people working on that method.

Q. Yes. I think Dr. Smith told us about the work that was done at Oxford yesterday; and I think he said that that work continued up until 1981 when they didn't pursue it any further. They came to the view that it wasn't going to be of assistance to them.
A. Yes, I was aware of that and I was familiar with the work that they were doing there and the reasons why they stopped.

Q. Yes. Now, do you know, Dr. Foster, whether other people carried on attempting to get benefit from the Rock method after that, after 1981?
A. Yes. I think that the method -- further work was carried on in the Netherlands, in the centre run by Dr. Smit Sibinga, and also in Denmark. I'm not too sure what happened in Smit Sibinga's laboratory, but I think the method eventually was abandoned in Denmark. The method continued to be used until the mid-1980s, and it

was abandoned because at that point they wanted to introduce the solvent/detergent treatment to inactivate viruses. And they found it wasn't compatible with the procedure, and so it was abandoned at that point.

Q. Yes. Did you see difficulties about that procedure from your own point of view?
A. Yes. There were two things that struck me as not being particularly attractive about the procedure: One is that the -- various steps seemed difficult to perform and may not be robust on a scale up; but more importantly, Rock was making a change in the anticoagulant, and from our point of view, we make a wide range of products from plasma, as -- and the blood components as well. And in changing the anticoagulant, you would have to validate anew every product, not just Factor VIII. So you couldn't just change the plasma for Factor VIII, you would have to change the plasma in the blood for everything. And it seemed to me that was -- that would require a lot of work.

Q. Yes.
A. And you would -- instead of focusing on Factor VIII, you would be solving problems with other products that didn't have a problem in order to get the whole package completed. You would go at the speed of the slowest rather than focussing on Factor VIII. It seemed to me to be tactically the wrong thing to do.

Q. Now. I think, Dr. Foster, if we return to your report and page 31, the pagination at the top right-hand corner of page 31. You deal -- under the heading of "hepatitis and Factor VIII," you set out in paragraph three the history of the risk of hepatitis in connection with the use of Factor VIII, isn't that correct?
A. That's correct.

Q. And I think if we just look at the first three paragraphs, and paragraph three in general, and refers to general scientific papers. If we turn to paragraph 3.4, you say: "Scottish National Blood Transfusion Service worked throughout the 1970s to try and remove the risk of hepatitis from coagulation factor products, collaborating on research into methods for removing viruses from Factor VIII and Factor IX concentrates," and you refer to a number of references there. I think were the methods of attempting to remove viruses referred to there, they didn't involve heat treatment, is that correct?
A. That's correct.

Q. Did they essentially involve an effort at physically separating the virus from the concentrate?
A. That's correct. One method involved a method of precipitation, separation by solubility differential, and another was a method of absorption.

Q. Yes. And did they come to a practical result?
A. No. Neither of these processes were ultimately successful.

Q. Yes. And I think you say, you go on to say in paragraph 3.5 that work was superseded in the early 1980s by research into heat treatment as soon as you became aware of developments in that area?
A. That's correct.

Q. Yes. I think you then list the -- you go on to deal then in your report with the heat treatment of Factor VIII, and you first of all deal with the heat treatment for albumin. And you go on then in paragraph 4.2 to deal with the question of heat-treating of Factor VIII concentrates. What was the view in relation to the general proposition of heat-treating Factor VIII, Dr. Foster? What would have been your approach and what was the approach of fractionators generally to that proposition that one could heat-treat Factor VIII or Factor IX?
A. I think when it was first suggested, it was something that we found quite astonishing.

Q. Why was that?
A. Factor VIII was regarded as a very labile protein. In our hands we had problems with the -- with the material. Even at room temperature it didn't survive for long periods of time. General teaching was to avoid damaging proteins as much as possible, try to use gentle methods. And so the notion that one could take the protein that seemed to be the most sensitive of all and labile of all, and to heat that, was quite a revolutionary idea, as far as I was concerned.

Q. Yes. Now, I think you go on to deal with then -- did you become aware of the research in Germany by Behringwerke?
A. That's correct.

Q. Into what I think was the pasteurisation at 60 degrees Centigrade in a liquid for I think 10 hours?
A. That's right.

Q. Yes. And was there a problem with that process, Dr. Foster?
A. There were a number of problems with that process, from our point of view: Our objective, as I said earlier, was to achieve self-sufficiency; and in that, yield was a critical parameter. The process that was being carried out in Germany had an extremely low yield.

Q. Yes.
A. And it just wasn't a viable process from our point of view because of that. And so -- we were very interested in the fact that they were -- had made that -- so much progress in heat treatment. And they had some data from chimpanzees that was encouraging, and we felt it was very well worth pursuing. And so our research programme aimed to learn from that and see if we could achieve a similar process but with a higher yield.

Q. Yes. And when would that research work have started?
A. That started in 1981.

Q. Yes. And then I think do you mention at paragraph 4.7, did you become aware in August of 1982 of an -- another approach to heat-treating; I think heat-treating in the lyophilised stated?
A. That's correct. Yes.

Q. And what was the report that you heard about that, Dr. Foster?

A. The -- this was at the International Society of Blood Transfusion Congress in Budapest, and there was some abstracts in the - book from a Dr. Rubenstein. When I went to look at the posters which were meant to describe the work, there was nothing there. So Rubinstein did not attend the conference, but his abstracts were published.

Q. Yes.
A. And so that information, at least in the abstract form, was available.

Q. And I think was that in August of 1982?
A. That's correct.

Q. And what was the information that --
A. There were a number of abstracts which described the concept of dry heat treatment - or heating the freeze-dried product - and demonstrating that, in certain conditions, the Factor VIII activity could survive the heat treatment. When the heating got to temperatures of 80 degrees, the material appeared to be not soluble, not sufficiently soluble to be clinically useful. But at a lower temperature, such as, 60 degrees, the product appeared to survive that. We didn't provide any information on whether there was any inactivation of viruses, and he said that that was work that was planned to be done.

Q. Yes. Now, I think -- in your report you go on to deal with the general development in relation to dry heat treatment designed to try and provide protection against the risk of non-A non-B infection. And you refer to a number of papers that I think the Tribunal is already familiar with, so perhaps we don't need to go into those. If we could go to paragraph 5.3, Dr. Foster. I think did you continue with the research into pasteurisation of Factor VIII?
A. We did. We carried on doing our research in pasteurisation. But also, because we were aware of the work on dry heat treatment, we did a small amount of work in that area also, in the -- at the same time.

Q. Yes. And in relation to the pasteurisation, did you reach a stage in -- during 1983 when you were able to prepare a pilot batch of pasteurised Factor VIII?
A. Yes, we did. We'd made sufficient progress in our research to increase the yield with modifications to the process that we felt were justified in operating -- preparing a pilot batch in production. And there was great interest in having this evaluated clinically because many of our colleagues found it difficult to believe that you could heat Factor VIII and it would still work. They thought this -- they didn't believe what was happening in Germany. They thought something must be wrong here, that it wouldn't possibly work. There was great interest in some kind of clinical evaluation.

Q. Yes. And I think did you arrange for a clinical evaluation of your pasteurised product?
A. We did. We prepared this and submitted it to one of our -- the clinicians and arranged for a clinical evaluation. And the product was infused to -- intention was that a number of patients would be treated in this evaluation; but the first patient who was treated had what was judged to be an adverse reaction. This patient was treated on three separate occasions. On each occasion they were judged to have had an adverse reaction which the clinician regarded as sufficiently serious not to proceed.

Q. Yes. And so was the whole project of the clinical study abandoned then at that stage?
A. Yes, the clinical study didn't proceed. We were informed of this information in January 1984, and we then reviewed our position. And one of the differences -- we hadn't heard from Germany that there had been any adverse reports like this. And one of the differences between our material to increase yield over the German material was it is less pure. And we believed perhaps this was the reason why we were getting these sorts of reactions in this individual. And we decided that we would embark on a programme of increasing the purity of this material to address that issue.

Q. Yes. I think did you subsequently discover that in fact the people in Germany had experienced a similar difficulty to yourselves?
A. They had difficulties with yield. I don't know if they had any reactions in patients, but their yield was low and I'm not sure that that was sustainable in the long-term for them. And so they wanted to improve their process and they -- they subsequently changed the way that they carried out a large part of their process in removing some of their stabilisers and that was -- turned out to have been very similar to the direction that we took in treating the purity of the product.

Q. Yes. Yes. Now, I think you then deal in your paper, Dr. Foster, with the emergence of AIDS and the risk of AIDS in relation to Factor VIII. Is that correct?
A. That's correct.

Q. And apart from general matters that you refer to in the opening paragraphs, I think there was a very particular event which you referred to at paragraph 6.5 in Edinburgh, is that correct?
A. That's correct.

Q. What happened in October of 1984, can you just explain to us?
A. In October '84 we learned for the first time that there were patients in Edinburgh who were found to be HIV-positive; and these were people who were -- one of the early uses of HIV screening tests that had become available. And these individuals had only ever been treated with products manufactured by SMBTS, and so this told us that our blood supply was contaminated, and we didn't know that until this point.

Q. Yes. And obviously I presume that was a very disquieting piece of information?
A. It was disquieting. I mean, I think we knew it was just a matter of time.

Q. Yes.
A. But when that was going to happen, we didn't know. And it had happened.

Q. Yes. Now, I think in the following month, in November of 1984, did you obtain information about heat treatment in connection with the HIV virus?
A. Yes, we did.

Q. And can you just explain that to us, what that communication was?
A. Okay. I was attending a conference in the Netherlands in Groeningen centre which was directed by Dr. Smit Sibinga. And Dr. Smit Sibinga organises a conference every year in this centre and in November -- October/November 1984, the topic was plasma fractionation. And I was an invited speaker, and I might not have

gone to the conference if I hadn't been invited. But one of the other speakers was there, a Dr. Jason from the Centre for Disease Control in the United States.

Q. Yes.
A. And she gave a presentation where she gave very up-to-the-minute data concerning results which showed that HIV was significantly inactivated by dry heat treatment at 68 degrees.

Q. Yes. And was that -- was that presentation she gave, was that part of the papers for the conference?
A. The proceedings of the conference were published, but it didn't contain that data. Because the way the conference was organised, the speakers would have handed in their manuscripts when they arrived. And Dr. Jason only received this information by telephone just before her presentation. So she altered her presentation to give us to the up-to-date data, and that didn't go into the conference proceedings.

Q. Yes. Yes. I think did the CDC publish that information in an MMWR bulletin?
A. There was a bulletin published. It was on 26 October where there was some general information. More detailed data were published in the paper with McDougal that didn't get into print for a number of months.

Q. Yes. But prior to that, Dr. Foster, had there been any evidence to the effect that heat treatment would inactivate -- dry heat treatment would inactivate the HTLV-III virus or LAV virus, as it then was called?
A. There was some information I think from Cutter Laboratories that was published in The Lancet using a similar type of virus that showed some possibility that this might be effective, but there was nothing on -- to my knowledge on HIV itself.

Q. Yes. And I think you refer in your paper to the article by Colombo, which was published in The Lancet in 1985, which showed this process not to be effective, the dry heat treatment process not to be effective against the risk of transmission of non-A non-B Hepatitis?
A. That's correct.

Q. Would you have been aware of the information that that was the case before the publication in The Lancet?
A. Yes. We'd heard of that, of that data beforehand, yes.

Q. Yes. Now, I think at this time, Dr. Foster - in fact, I mean nothing to do with any of this - was there -- in
October/December of 1984, was there a planned upgrade of the facility in Edinburgh?
A. Yes. We had stopped manufacture of all of our products at the end of September. And we had a basically three-month shutdown in order to upgrade the facility. And we had taken the opportunity to do that because we had very healthy stocks of Factor VIII and so were able to take some time out to upgrade the facility.

Q. Yes. And as a result of this communication, did you then set about dry heat-treating your product; firstly, I think at 68 degrees Centigrade for two hours?
A. That's correct. We had already established that the product that we were manufacturing could tolerate that degree of heat treatment. And we -- because we had

about a year's supply of Factor VIII in stock, we decided to apply that degree of heating to that material immediately, and we were able to distribute heated Factor VIII throughout Scotland and to Northern Ireland on the 10th of December.

Q. Yes. And I think did you subsequently progress from two hours to 24 hours?
A. Yes, we had. At the same time we had been undertaking further research to see if we could extend that heat treatment, and we discovered that there was a way that we could modify the way the product was formulated to extend that to 24 hours. We couldn't apply that retrospectively to the material that had been already processed, but we could apply it to newly prepared material. And so as soon as we started manufacturing in January '85, we made that revision to the process that allowed us to heat the product at 68 degrees for 24 hours.

Q. Yes. Now, I think at paragraph 6.11 of your report, Dr. Foster, did you deal with the question of the Prothrombin complex, Factor IX complex?
A. Yes, that's correct.

Q. I mean, obviously Scotland -- Edinburgh had been fractionating a Factor IX complex as well as a Factor VIII?
A. That's right.

Q. And what was the -- what was the general method used to fractionate the Factor IX?
A. The method that was used was an ion-exchange absorption of cryosupernatant and the desorption of the Factor IX. And it was virtually identical to the process used at BPL.

Q. Yes.
A. The product wasn't heat-treated until '85.

Q. Yes. Now, what method of heat treatment did you apply to that product?
A. We found we were able to heat this to 80 degrees for 72 hours. In order to do that, we had to make a change to product formulation. Without that, there was some evidence from our laboratory studies that the product might be thrombogenic, it could cause a thrombosis in patients. And we had to revise the way the product was formulated to correct that laboratory measure. That led to concerns over the possibility of a risk with this product, and so we did more extensive studies in animals before we were able to release it for use in patients.

Q. Yes. I think Dr. Smith described that they had added a substance to the Factor IX in Oxford in order to deal with this possible problem?
A. We were working on it together and we both really did the same thing: We added some antithrombin-III to correct that problem.

Q. It was the same process that was being used?
A. Essentially the same process, yes.

Q. Yes. And I think the -- again, the study to see whether there was any thrombogenetic effect was a joint study between yourselves and the people in Oxford?
A. That's correct. We did that together.

Q. Yes. And I think you refer to the reports of that study, the study that was done in dogs, I think, there at pages 348 and 350 of your references that you have given us?
A. They are in there, yes.

Q. Yes. What happened in practice in Scotland about this, Dr. Foster? First of all, when did the Factor IX heat-treated at 80 degrees Centigrade for 72 hours, when did that first become available?
A. We made the first material available for clinical trial in July '85. Following satisfactory clinical evaluation, we started to make material available I think it was the 12th of August, '85, to the Edinburgh centre. And we were able to supply material to all of Scotland and Northern Ireland by the 1st of October.

Q. Yes. Now, what had happened during the course of 1985 in relation to the unheat-treated Factor IX?
A. We were aware that there were commercial products becoming available that had been heat-treated. SMBTS doesn't distribute commercial products; that is up to the individual clinician to do that themselves.

Q. Yes.
A. But we were aware that individual clinicians were purchasing the heat-treated material in the United States. We learned of this I think certainly in April -- by April '85, that was happening. We had regular meetings with the haemophilia doctors; and in discussion, we agreed that we would cease to issue our product, meanwhile, until we had completed our own development, and that they would purchase commercial material in the interim period.

Q. Yes. Now, when was that agreement reached?
A. I think that we ceased to issue our product in May '85.

Q. Yes. And was it then known, had you agreed or arranged with the treating doctors as to when it would be possible for you to produce Scottish heat-treated product?
A. We were having continuing discussions with them and keeping them up-to-date with our progress.

Q. Yes.
A. And so they were fully informed of our developments.

Q. Yes. And when you ceased issuing them the unheat-treated Factor IX, was it your understanding that the treating doctors intended to purchase commercial heat-treated Factor IX until Scottish heat-treated Factor IX would become available?
A. That was our understanding, yes.

Q. And so far as you are aware, is that what happened?
A. As far as I'm aware that is what happened, yes.

Q. Yes. When you ceased issuing the nonheat-treated Scottish Factor IX in I think -- did you say May of 1985?
A. That's correct.

Q. -- was there any recall at that time of the unheat-treated product?
A. We recalled the unheated product in October after we had been able to restock with the heated product.

Q. I see. So, there wouldn't have been a recall in May of 1985?
A. No, we didn't do the recall then; because we had no knowledge of the supply situation, and we felt it was safer to have some material available in case there was a difficulty with supply, rather than have patients left with no treatment whatsoever. But once we were confident that we could supply material, then we did our recall.

Q. I see. Were you continuing to issue Factor IX to the treating doctors, unheat-treated Scottish Factor IX up until the issue ceased in May of 1985?
A. Yes, we were.

Q. And again, so far as you are aware, Dr. Foster, would that have been used by haemophilia treating doctors up until May of 1985?
A. It's possible, but when we did our recall, we did get material returned. So it couldn't all have been used. So, I think there was this transitional period when people were moving to heat-treated, in the April/May period.

Q. Yes. Now, I think you mention, Dr. Foster, at paragraph 6.12, that as a result of a lookback study which took place long after the event, you ascertained that, in fact, two of the first batches of heat-treated product, which had been - Factor VIII I think we are talking about now - which had been heated in November of 1984, had, in fact, received a donation from somebody who was HIV-positive, is that correct?
A. That's correct. And it was confirmed that the material that went into those pools was HIV-positive.

Q. Yes. But the heat treatment protocol that you had used, the 68 degrees protocol, was effective to inactivate that HIV virus?
A. That's correct. The recipients were all followed up very carefully and none of those who were susceptible had seroconverted to HIV.

Q. Yes. So -- perhaps in a rather unfortunate way, you were able to, after the event, ascertain that that heat treatment protocol was effective against HIV?
A. That was our interpretation.

Q. Yes. Now, Dr. Foster, I think you go on then to deal in some detail with the development of the Scottish Factor VIII heated at 80 degrees Centigrade for 72 hours.
A. That's correct.

Q. And obviously, that is what you were being asked to deal with by the committee, so it's dealt with in some detail in your report. That was precisely what the committee were inquiring into?
A. That was the situation, yes.

Q. Yes. But it's not something that this Tribunal is directly concerned with, I'm sure you understand. So, perhaps we can just look at the summary of what occurred. I think did -- when did that product become generally available, Doctor?

A. It was into general use in April 1987.

Q. Yes. Now, can I just ask you to go to page 37, Dr. Foster. At paragraph 7.10, where you report that "In September 1986, preliminary clinical data were reported by PFL /BPL providing evidence that their 80 degrees Centigrade dry heat-treated 8Y product had a reduced risk of hepatitis transmission, and recommending that this pilot study be followed by a formal prospective clinical trial with a stricter protocol." And the paper that you are referring to there, Dr. Foster, is at page 374, and perhaps we might just identify that for a moment, of the documents. And I think -- this is an interim report, described as an interim report, "Surveillance of previously untreated patients for possible virus transmission by BPL Factor VIII and Factor IX concentrates, 8Y and 9A: Interim report." And I think the report was in fact to the UK haemophilia treatment centre directors, is that correct?
A. That's my understanding, yes.

Q. And would that have come to -- would that report have come to your notice at the time, Dr. Foster?
A. I was sent a copy by Jim Smith. We weren't formally involved with that group who were doing the study, but Jim kept us informed and sent us a copy of this report.

Q. Oh, I see. And essentially, I think that this -- this report reported that there had been no evidence of -- firstly no evidence of HIV infection; but secondly, no evidence of non-A non-B infection in the persons who had been using the 80 degrees Centigrade product?
A. That's correct.

Q. And as you say there, it recommended that their pilot study"should be followed by a formal prospective clinical trial with a stricter protocol"?
A. That's correct.

Q. Because I think -- I think you mention in your paper, Dr. Foster, there had been a protocol established by the Committee on Haemostasis and Thrombosis for these clinical trials in respect of non-A non-B Hepatitis?
A. That's correct. That was under Professor Mannucci.

Q. Yes. And Professor Mannucci has described that to us. And I think the information supplied here in this interim report in 1986 would not have conformed with the requirements of that protocol?
A. That's correct.

Q. And what the authors of the report are saying is that the study should be pursued and indeed expanded so that it would conform to those requirements?
A. That was my understanding, yes.

Q. Yes. Can I just ask you, Dr. Foster, in relation to the Factor IX, the super -- or the Factor IX heated to 80 degrees Centigrade, that was available in Scotland from the autumn of 1985; isn't that correct?
A. That's correct. Generally available from the 1st of October to all centres.

Q. Yes. And what was the supply situation in relation to that; was there ever any shortage or problem about supply?
A. No. It wasn't a difficult product in the sense that the demand was relatively small, and we only recovered Factor IX from about 30 percent of the plasma at most. And so, there was, if you like, spare capacity Factor IX available if required.

Q. And at that time, Dr. Foster, did you receive any requests for that product from treating doctors outside of Scotland?
A. I'm not aware of any, no.

Q. And if there had been, what would the situation have been?
A. I think that would have been considered sympathetically, but it would have been a decision I wouldn't have been involved in. It would have been an executive decision.

Q. But do you see any reason in principal why such a request couldn't have been met?
A. No.

Q. And did that continue to be the situation in respect of Factor IX from that time onwards?
A. Yes, that has always been the situation with Factor IX.

Q. Yes. Have you in fact subsequently supplied - I mean in more recent times - supplied some product outside of Scotland?
A. We are currently looking at distributing surplus products outside Scotland, and we are getting permission for this from the Scottish executive.

Q. Now, if we turn to Factor VIII. I think you mentioned to us that the Factor VIII heated at 80 degrees Centigrade was available for routine clinical use from April of 1987, is that correct?
A. That's correct.

Q. And what was the situation in respect of supply of that product; what was the availability of supply?
A. Once we had moved to the new process, we were able to prepare reasonably good quantities, and we had good stocks of that product.

Q. Yes. And again, Dr. Foster, if there had been a request from outside of Scotland for a supply of that product, of the Factor VIII product, what would the position have been?
A. We wouldn't have had a lot of material to supply, but I think, depending on the nature of the requests, I'm sure that would have been considered as sympathetically as possible.

Q. If it was a request for a limited quantity of Factor VIII, for instance, for treating previously untreated patients, what would the situation have been?
A. I think that would have been looked at very sympathetically, but again, it would have depended on the quantities; but it might have been feasible.

Q. Yes. Now, I think in your concluding remarks, Dr. Foster, if we go to page 39 of your statement, you made some observations, and I think mostly by reference to published material in respect of the situation outside of Scotland, is that correct?
A. That's correct.

Q. Presumably for the purpose of comparison?
A. That was the intention, yes.

Q. Yes, I can understand. First of all though, at paragraph 10.3, you mention that you believed that the fractionation centre in Edinburgh was the first manufacturer, other than the English, the PFL/BPL, to have been able to achieve dry heat treatment of Factor VIII at the 80 degrees Centigrade, is that correct?
A. That's correct.

Q. And I think you say that you were aware of two other manufacturers who attempted and failed to achieve 80 degrees Centigrade heating of Factor VIII before the method of -- that you devised for freezing and freeze-drying of the solution was reported?
A. That's correct.

Q. Were they commercial manufacturers?
A. One of them was commercial, yes.

Q. Yes. And so far as you are aware, Dr. Foster, have other fractionators adopted that heat treatment protocol of 80 degrees Centigrade for 72 hours, apart from yourselves and Elstree and Oxford?
A. It's now becoming, obviously, back into use. There was a period when people moved to solvent/detergent treatment, but heating at 80 degrees is now coming back into favour in combination with solvent/detergent treatment. So there is quite a use of this approach now. Is that --

Q. Yes. That was what I was wondering about. Now, you go on then in paragraph 10.4, Doctor, to refer to the experience of other countries in using 60 to 68 degrees Centigrade heated Factor VIII concentrates. And what you say, "up to the early 1990s," is that correct?
A. That's correct.

Q. And then you analyse patient data. You say that: "Analysis of patient data suggests that the use of such products reduce the incidence of HCV or NANBH in haemophilia patients by about 75 percent in France." And there is a paper which you refer to, perhaps we will just look at it briefly. It's at page 425. It's a paper of "Clinical and biological survey of Haemophilia A and B patients infused with French heat-treated concentrates." Isn't that correct, published in 1988?
A. That's the one.

Q. Yes. And what are you referring to, to get your figure of 75 percent reduction?
A. Okay. If you look at table one --

Q. I think at page 426?

A. -- on page 426, the heating method, the different centres are described. So, for example, at the Lille centre, that was a dry heat treatment at 68 degrees C.

Q. Yes.
A. And Strasbourg, it was a dry heat treatment of 60 degrees. So I was using that information, combined with the information in table two, to try to link the patients with the product that they had been treated with, and then interpret the data in that way.

Q. Yes. The -- of course the number of patients that are involved that are being looked at are very small, isn't that right?
A. That's true.

Q. So therefore, I mean, it wouldn't be -- it wouldn't be correct to say that one could talk about the result for France as a whole based on this very limited study?
A. No. I wasn't intending to mean this was the situation in that country.

Q. Yes.
A. I was simply illustrating, if you like, the country where the work had taken place.

Q. Yes.
A. And then focusing in on the particular method that had be used to treat that particular product where that information was available.

Q. Yes. I understand. So what is shown in table two is that there was some non-A non-B Hepatitis infection, because it's under -- it's the second column, undernumber of patients: Patients with Alanine aminotransferase elevation; taking that as the then marker for non-A non-B infection, isn't that correct?
A. That's correct.

Q. What this paper shows; if you take the first in Lille, in Factor VIII, two out of seven patients had elevated transaminase?
A. That's correct.

Q. And if we take the same for Lille for Haemophilia B patients, it was one out of two patients?
A. That's correct.

Q. Yes. So the -- that's what you are referring to in this paragraph?
A. Yes. And if you look at the Strasbourg centre, where the product is heated at 60 degrees for 72 hours, you also see evidence of infection, but it was a reduced level.

Q. Yes. Yes. And then in terms of even the moist heat-treated at Paris, also involved some, though less infection; one out of six Haemophilia B patients and none out of four Haemophilia A patients?
A. That's correct. I was focusing really on dry heat treatment because that was related to what we had been doing.

Q. Yes. I understand. I think you similarly analysed particular figures at page 428, an article from Finland. And again, I mean, it's a very limited study. It analyses six patients in total, isn't that correct?
A. That's correct.

Q. And it was found that one of the six patients seroconverted to antiHCV positivity over a three-year period. Isn't that correct?
A. That's correct.

Q. And so, on that basis, at the bottom of the first column, they say "the incidence of HCV seroconversion among these patients was six percent per year or 17 percent for three years." Isn't that correct?
A. That's correct.

Q. Yes. And then you refer to a study that the Tribunal has already been referred to by Professor Mannucci at page 429, the paper by Morfini and Professor Mannucci and others. And I think in that paper, Dr. Foster, what you were I think particularly looking at was page 431, and the report from Florence in table two, is that correct?
A. That's correct.

Q. Where, of a total of 22 patients, 22 (sic) were negative for antiHCV and one was positive, using Koate HT dry heat-treated 68 degrees Centigrade for 72 hours.
A. Yes. It was 21 negative and one positive --

Q. Sorry, I beg your pardon.
A. -- for Haemophilia A. And that was using the dry-heated 68 degrees for 72 hours.

Q. It's like the others; it's not a large survey, it's a very small number of people, in fact?
A. That's right. That was all the information I could find.

Q. Yes. I follow. Now, I think you also refer then, Dr. Foster, in the next paragraph at -- in your statement to treating practices in the USA. And the -- again, perhaps we can stay with the book of documents. You are referring to an article which is at page 434, "the use of purified clotting factor concentrates in haemophilia." Isn't that correct?
A. That's correct.

Q. And I think the particular passage that you were referring to is at page 436 under the heading of "supply and cost considerations," the second paragraph under that?
A. That's correct.

Q. So, "In 1987 dry-heated products constituted approximately 90 percent of the total Factor VIII consumption in the United States (about 532 million units)" and there is a reference there to table 3 -- sorry, can we just stay with that. "Since the 1988 demand for dry heat-treated products was as high as 350 million units" -- there is a reference to unpublished observations -- "a significant supply shortage exists." So, what that paper seems to say, that in 1898 -- 1987, the dry heat-treated products still accounted for 90 percent of the total Factor VIII consumption of the United States?

A. That's my understanding.

Q. And that in 1987, there was a demand for -- sorry, 1988, there was a demand for dry heat-treated products which couldn't be met, is that correct?
A. That seems to be correct, yes.

Q. And if we look at the table then on the next page, on page 437, there is a reference to the price of different forms of concentrate, isn't that correct?
A. That's correct.

Q. Price per unit. And again, a price is given for the dry heat-treated product in I think the -- the third column across is -- is it winter 1989?
A. I think it is, yes.

Q. So what inference would you draw from that?
A. -- it's the winter of 1988. My inference is if there was a price on the product, that it was still being marketed at that period.

Q. Yes. Perhaps also, Dr. Foster, just to refer to something you don't refer to in your report but nonetheless perhaps may be relevant in this published article; at page 436. Near the end of the first column -- the authors have been dealing with some of the newer methods of viral inactivation, but then they say: "Unfortunately most of these newer methods of viral inactivation are not yet approved for use in Factor IX concentrates. Available Factor IX products are dry-heated for 72 hours at 68 degrees C(Konyne); dry-heated for 144 hours at 60 degrees Centigrade (Proplex); or heated in n-heptane for 20 hours at 60 degrees Centigrade, (Profilnine HT (wet) Alpha). Although to our knowledge no HIV seroconversions have been reported in patients using these products, NANB hepatitis transmission remains a significant problem."And there is a reference give for that observation. So it seemed what the authors were reporting, certainly at that time in the United States, that availability of the newer forms of viral inactivation in Factor IX lagged behind Factor VIII?
A. That seems to be the case, yes.

Q. Yes. Whereas of course in Scotland, it was actually the exact reverse?
A. That's the case, yes.

Q. Yes. Now, I think you also mention, Dr. Foster, at paragraph 10.6 -- sorry, going back to page 39 of your report, you say that "In 1986/'87, commercial imports (which were predominantly heated at 60 degrees to 68 degrees Centigrade) accounted for about 70 percent of the Factor VIII used in England and Wales. By contrast, there was little or no imported Factor VIII used in Scotland." Where did you get that figure of approximately 70 percent imported commercial dry heat-treated product for England and Scotland?
A. Okay --

Q. Sorry, England and Wales.
A. In the UK the haemophilia directors collect data on Factor VIII usage, which is provided to the Oxford Haemophilia Centre.

Q. Yes.

A. And you will actually find in the current issue of the Journal of Haemophilia in a paper by Rizza and Spooner, they actually give the usage of Factor VIII from 1969 up to the mid-1990s, I think. And they describe it according to different types of concentrate. They give a total quantity of Factor VIII used and they give the quantity that is commercial and the quantity from the National Health Service.

Q. Yes.
A. And we knew how much we produced, and we knew how much BPL produced, and therefore we were able to calculate how much was coming from the commercial sources.

Q. Yes. Yes. And I think did you in fact for the benefit of the committee, Dr. Foster, did you prepare a graph that showed in a graphic form that consumption of product?
A. I did that, yes, for a presentation that we gave to the Haemophilia Society in Scotland.

Q. I'm sorry. I beg your pardon. I'm sorry. But I think that is in a small supplemental book of documents that have been furnished for your evidence. If we look behind the divider, I think it's the third page in. Is there a document "Factor VIII concentrate used in the UK, estimated"?
A. That's correct.

Q. And is this a document which was prepared for the purpose of the presentation to the Haemophilia Society?
A. Yes, it was.

Q. And can you just explain the graph to us.
A. Okay. Taking the data that I have mentioned already that is provided by the UK Haemophilia Directors and knowing how much Factor VIII we manufactured and of what type and when we made the changes, and also having got information from the BPL, it was possible to calculate how much of the 80 degree heated Factor VIII that the BPL product 8Y, or our product that we called Z8, what proportion of the Factor VIII was represented by that type of product. And in 1985, that was only 13 percent of the Factor VIII used in the UK. And that is the BPL 8Y product that came into use in September '85. And so that 87 percent of the product that was used in the UK, either from ourselves or from commercial sources, was heated not at 80 degrees. And it was either in the range 60 to 68 degrees, if it was heated at all. And it might have been early '85, some products weren't even heat-treated. In late 1986, the proportion that was heated at 80 degrees, which was the 8Y product, rose to 28 percent of the total in the UK. And that shows the increasing output from BPL once it got into full production. But there was still 72 percent of the Factor VIII in the UK that was not heated under those conditions that was -- we believed were still -- had a risk of transmitting non-A non-B Hepatitis.

Q. Yes.
A. And you can see how those figures changed up until 1988. And even in 1988, when both ourselves and BPL were producing Factor VIII heated at 80 degrees, 55 percent of the total consumption in the UK was of products that weren't heated under those conditions; they were heated either in the range 60 to 68 degrees.

Q. Yes. Would that have included any product which would have been heated in solution?
A. Yes. I have included that in these tables because we don't know, having subtracted what BPL produce and having subtracted what we produce, we don't know the makeup of the rest of the material. And the Behringwerke product, the 60 degrees in solution, I think was licensed in the UK; how many was used, we don't know. I have seen figures of exports from Germany that are extremely low, so I doubt if there was any -- much used at all.

Q. What about the Alpha product, the Alpha pasteurised or steam-heat-treated?
A. I think that was -- Immuno was steam-heated. That was also licensed and that would be in this category, yes.

Q. Yes.
A. But that, I think, was associated with some transmissions of hepatitis.

Q. If I could just refer to one further article, Dr. Foster. If we go to page 468 of the book of documents. This is an article published by yourself and three other authors in 1997 in Haemophilia. Is that correct?
A. That's correct, it's a textbook.

Q. A textbook, sorry. I beg your pardon. A chapter in the textbook. And you might just go to page 479. I think it collects together there a table of "Hepatitis C virus and non-A non-B Hepatitis infection associated with coagulation factor concentrates which had been treated to inactivate or remove viruses." And I think these are all published works; I mean, published articles or letters, isn't that correct?
A. That's correct.

Q. And in fact, I think the Tribunal probably at this stage would be familiar with most of them, Dr. Foster, but it's nonetheless a very useful summary of the reported incidences of non-A non-B transmission by product which had been subjected to some form of viral inactivation, isn't that correct?
A. Yes, that's correct. Although since I wrote this I have discovered one or two other publications.

Q. I suppose that's an inevitability, Dr. Foster, that that will happen?
A. They were hidden away.

Q. Yes. Yes.

MR. FINLAY: Thank you very much, Doctor.

THE CHAIRPERSON: Thank you, Mr. Finlay. Mr. Bradley, please.

MR. BRADLEY: Thank you, Madam Chairperson.

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

Q. Good afternoon. My name is Raymond Bradley and I appear on behalf of the Irish Haemophilia Society. I have a number of brief questions for you. In relation to the early 1970s, from a safety perspective, what was the reason for the introduction of self-sufficiency in Scotland?
A. I think there was a general interest in, if you like, the ethical dimension of countries taking care of themselves, in terms of their own blood supply. And I think there was also, during the 1970s, a concern that the commercial products might carry a higher risk of infection than locally-produced products.

Q. Was that the genesis for the efforts to attain self-sufficiency in Scotland?
A. Both of those things were the driving forces.

Q. Okay. In relation to the advent of the AIDS epidemic, when as a blood transfusion service did you become aware of the risks attached to blood and blood products?
A. I'm not sure I can speak for the service as a whole.

THE CHAIRPERSON: Not a blood transfusion service.

Q. As a fractionation unit.
A. I became aware of the illness that became known as AIDS, I think, in late 1981, after it had been reported in the United States. I became aware that two -- a number of haemophilia patients had been diagnosed with this disease in the middle of 1982. And I heard a presentation by a Dr. Ericsson from the FDA where he described these cases. The notion that this was a result of blood transfusion wasn't something that seemed to be appreciated at that point in time; and it was only later in 1982 that there was evidence of a similarity in the way that this disease was spreading compared with hepatitis. And it was putting those two things together that suggested the possibility to us that this was probably a viral infection that may well be transmitted through the blood supply. That was confirmed for me in the middle of 1983 when I heard Bruce Evatt from the CDC give a presentation at the Royal Federation of Haemophilia where he gave a very thorough description of what was happening in the United States, and looked at the epidemiology of the illness and the -- if you like, the lifestyle of the haemophiliacs and the other people who had developed this disease. And the connection seemed, at that point, to me, to be very clear.

Q. Would that be what is known colloquially as the Stockholm Congress?
A. That's right. It was a World Federation of Haemophilia -- there was two meetings in Stockholm at that period: World Federation meeting, and also International Committee of Thrombosis and Haemostasis. I forget at which meeting he made that presentation.

Q. Yes. In relation to the operation of the service in Scotland, the logo that you use as the Scottish National Blood Transfusion Service, is there a differentiation between the two perhaps, fractionation and blood collection?
A. No, we are all part of the same organisation.

Q. And in terms of knowledge and information in relation to scientific and medical matters, that presumably is shared?
A. That's correct.

Q. You have seen the correspondence from Dr. Watt. Is Dr. Watt alive today?
A. To the best of my knowledge he is.

Q. And did he continue to work with the Scottish National Blood Transfusion Service up to what date, approximately?
A. He left at the end of '83.

Q. And would he have held those views in relation to spare capacity at the Scottish National Blood Transfusion Service up to that period?
A. I think he would, yes.

Q. In terms of the research that was undertaken in respect of viral inactivation, what was the motivation for that research; what was the reason that it was undertaken initially?
A. We were concerned about the transmission of hepatitis, particularly non-A non-B Hepatitis, and that was the motivation.

Q. And was that a serious concern for you as a blood transfusion service, or Scottish National Blood Transfusion Service?
A. Yes, it was a very serious concern, although there was a belief that the commercial products carried a higher risk. We had evidence from our own population that became available to us in the late '70s that hepatitis was being transmitted to patients in Scotland, even those being treated with cryoprecipitate. And so there was a very strong motivation for us to deal with that.

Q. And in the late 1970s, would you have had evidence of the consequences of Hepatitis non-A non-B, such as the development of cirrhosis or chronic active hepatitis?
A. No, we didn't have that knowledge at that time.

Q. And in relation to ongoing knowledge, would you have interaction or discussion with haemophilia treaters pertaining to the consequences of blood products?
A. Yes. We met regularly with the treaters to plan, to meet their needs, whatever they might be; and that included product quality as well as quantity.

Q. During the course of your direct evidence you mentioned to Mr. Finlay that plasma was contract fractionated in Northern Ireland. Were there any difficulties in introducing that particular process?
A. No, not that I'm aware of.

Q. In terms of maximising yield from the plasma collected, what are the necessary matters that need to be taken into account in order to achieve that particular objective?
A. First you need a high quality of plasma, and you need great care in the way the plasma is collected and how it's anticoagulated and how it's handled. You need to take great care in how it is frozen and how it's transported and kept in a frozen state. You need to take great care at every step in the manufacturing process, and that has to be very carefully defined. And the key steps, as I have alluded to, were the cryoprecipitation process, which is a difficult step to manage. And it's important to keep Factor VIII in a stable state, and we have learned over the years how to do that.

Q. So, for example, if there was any difficulties with freezing the plasma or transporting the plasma, that would have an impact on yield?
A. Yes, it would.

Q. Was there a serious impact?
A. It could be very serious; the product could be seen as failing to be acceptably manufactured.

Q. In terms of the yield achieved from plasma collected, as an average, what would you expect it to retain, the Scottish National Blood Transfusion Service?
A. Which period?

Q. 1980 to '85; and a difference during that period, would you tell us, as well.
A. Okay. By 1980, we were achieving a yield of the order of 280 units of Factor VIII per litre of plasma. When we introduced heat treatment at 68 degrees, there was a loss of yield as a consequence of the heat treatment, which was of the order of 20 percent. So you reduced that figure from 280 by 20 percent, multiplied by 0.8, and that is where we would have been at in 1985.

Q. And in that regard, it was obviously a necessity for attaining increased number of donors. Was there any difficulty on the other side of the service, for the other side of the service in providing such donors?
A. We didn't have to increase the number of donors greatly. In 19 -- going between 1975 and 1983, when we became self-sufficient, the number of donations was only increased by 15 percent. What took place was a change in medical practice; instead of blood being used as whole blood or provided as whole blood, we changed to component therapy, so that people were treated with red cells. And that allowed us to recover the plasma at the beginning when it was still -- when the Factor VIII was still active, rather than have plasma that was time-expired where Factor VIII had been damaged. And so there was really a change in medical practice that was most important, and that allowed us to increase the quantity of fresh frozen plasma fivefold in that period. And so it wasn't so much getting extra donors, it was a change in medical practice.

Q. What you are saying: As the increased requirement for plasma became apparent, you improved the methodology to achieve the objectives?
A. We had to change medical practice, and that's not always easy. And so our medical colleagues were very involved in doing that.

Q. The ratio of use of red cell concentrates to whole blood, have you any idea what the ratio of use is in Scotland?
A. No, I'm sorry, I don't have those figures.

Q. In terms of the usage of red cell concentrates, were you achieving 40 percent usage?
A. Eventually we moved to virtually 100 percent usage.

Q. Virtually 100 percent. Did you introduce a method of maximising yield called SAG-M?

A. I think that was investigated. I don't think it went into routine use.

Q. Okay. Would it have had any impact upon increase in yield?
A. It wouldn't have increased the yield of Factor VIII, no.

Q. In terms of the introduction of the 80 degrees by 72 hours heat treatment method, what was the motivation for increasing the heat treatment process over the norm?
A. We were still uncertain about the effectiveness of 68 degrees heat treatment against HIV. The knowledge that we had was based on the experiments that I described earlier carried out at CDC; and that, although that was evidence to do something, it was still rather flimsy. And so we wanted to see if we could take the heat treatment further, and we were aware that our colleagues in England were going down that route. And in it was around about October '85, we made a key discovery ourselves which helped to us understand how to do that. And it was at that point that we took a decision to move to 80 degrees heat treatment.

Q. In relation to the period around May 1985, you indicated that you ceased to issue your own product. Why did you make such a decision?
A. That was the Factor IX concentrate?

Q. Yes.
A. That decision was taken collectively between SMBTS and the haemophilia treaters and the Scottish Department of Health. And we were aware that heat-treated product was available commercially, that could be purchased; and given the knowledge that we -- that HIV was in the Scottish blood supply already, it was felt that it would be preferable to have patients treated with a heated product rather than an unheated product as soon as possible. And that was the earliest possible way of achieving that.

Q. Was it widely appreciated or published at the time that the Scottish blood supply had become infected with HIV? Would that have been known?
A. Yes. That was published quite quickly by -- I think Dr. Ludlum had a letter in The Lancet as quickly as he could do so.

Q. Mr. Finlay referred you to a number of articles in relation to the incidence of Hepatitis C infectivity in both Italy and France. The studies that were referred to were quite small studies. Would they have complied with the ICTH protocol of 1984?
A. I must say I very much doubt it, but I can't answer that definitively.

Q. If you had six patients in the study, would the confidence interval in relation to that study be seriously affected?
A. I think it would; it's not enough patients.

Q. Yes. In relation to the period after 1988, and the evolving state of viral inactivation processes, would you have been aware of alternative processes that were coming on the market around that time?
A. We were aware of the work at New York Blood Centre in the solvent/detergent treatment, which I guess that is what you are referring to.

Q. Yes.

A. We were aware of that in 1985, that that work was taking place. And we did consider that at the time. But there were two concerns about the process at that point: One was that we -- because the virus that caused non-A non-B had not been identified, we didn't know if it was enveloped or unenveloped. And of course the solvent/detergent method is only effective against enveloped viruses; and there was some data that suggested that non-A non-B might be nonenveloped. And therefore, that procedure wouldn't be effective. And the second concern was that because these are toxic chemicals, they have to be removed from the product. And the technology wasn't really available in 1985 to do that. And so, although we were very interested in that approach, and we had done some work along similar lines ourselves, we deferred that approach at that point in time and focussed more on heat treatment.

Q. When would you have become aware as person involved in fractionation that the solvent/detergent method was equally as efficacious in relation to the removal of Hepatitis non-A non-B?
A. I think the first studies that showed that quite clearly were probably about 1988. I think it's a paper by Horowitz, where he did some clinical studies.

Q. There's a paper in 1987 in the Journal of Epidemiology as well?
A. Okay.

Q. We discussed the market availability of alternative safer products, and that in the United States 90 percent of the products were heat-treated. Would the market considerations in Europe be different to the market considerations that would be applicable in the United States?
A. I have no idea, sorry.

Q. All right.

MR. BRADLEY: Thank you very much, Dr. Foster.

THE CHAIRPERSON: Thank you, Mr. Bradley.

THE CHAIRPERSON: Mr. Butler, please.

MR. BUTLER: Thank you, Madam Chairperson.

THE WITNESS WAS EXAMINED AS FOLLOWS BY MR. BUTLER:

Q. Dr. Foster, Nicholas Butler is my name and I represent three haematologists: Professor Temperley, Dr. Daly and Dr. Jackson. I just have one or two things I'm going to ask you to clarify. You have said in response to Mr. Bradley that you had meetings with practitioners and treaters in respect of their needs, isn't that the position?
A. That's correct.

Q. And is that throughout the period we are discussing?
A. Yes, that we had regular annual meetings that were tripartite with the haemophilia directors, the Scottish Health Department and the SMBTS. And in between there was annual meetings; there was a working group that would meet as

necessary to deal with the business. So we had quite frequent meetings to discuss matters of common interest.

Q. Yes. Could I refer you to paragraph 7.8 of your statement, at page 36 I think. Do you have that?
A. Yes, I have got that.

Q. Here you are describing the movement towards achieving the introduction of the 80-degree, dry heat-treated product, isn't that right?
A. That's correct.

Q. And you say there in the second sentence: "We therefore shelved our work on increasing purity and concentrated instead in adapting our existing technology to be able to introduce 80-degree Centigrade dry heat-treatment to Factor VIII, to increase the margin of safety with regard to HIV, as this remained the overriding concern at this point in time," first of all. And then you say, "this change in strategy was endorsed by the SMBTS management in February 1986." Can I just ask you to clarify what -- whose overriding concern and how widespread that was, in relation to HIV?
A. I am talking about the overriding concern within SMBTS, that we were heating at 68 for 24. We knew that other manufacturers were heating at 68 for 72 hours; BPL were heating at 80 degrees. There was evidence that HIV might still be being transmitted by some products heated at only 60 degrees, and that knowledge made us still nervous about the position we were in. And we wanted to advance beyond that as quickly as possible.

Q. Yes. And was that sort of view consistent with the view of clinicians, as you heard them, at the time?
A. I'm not sure I can speak for the clinicians.

Q. Very well. Very well. Well, could I ask you this then: In terms of dealing with the HIV virus and the non-A non-B virus at this period in time, do I understand your statement to be to the effect that the HIV virus was considered a far greater threat and more urgent need of being dealt with than the non-A non-B virus?
A. Yes. That would be the case, yes.

Q. And did that general relative concern continue for a time subsequently?
A. Yes, I think that probably is true. Looking back over the records, there is much more work and concern, obvious concern about HIV. And that continues right through beyond '85 into '86, even into '87. There is still considerable concern about HIV because people were still not sure just how safe the products were even as late as that.

MR. BUTLER: Thanks, Dr. Foster.

THE CHAIRPERSON: Mr. O'Brolchain?

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

Q. Dr. Foster, Angus O'Brolchain, acting for Dr. Cotter and the Southern Health Board. I have just one matter I want to clarify in my mind. In October 1984, you learned that the local supply in Scotland was contaminated, isn't that correct?
A. That's correct.

Q. And do I understand that a Factor IX continued to be supplied until May of 1985?
A. That's correct.

Q. And then, in October of 1985, the product that was, if you like, out there was recalled and replaced with the heat-treated product?
A. That's correct.

Q. So does that mean that for one year, there was unheated Factor IX coming from the local blood supply in Scotland?
A. We stopped issuing the product in May --

Q. Yes.
A. -- '85. And we did that as soon as we were -- we were sure, in consultation with the clinical colleagues, that alternative supplies could be made available that were heat-treated that were purchased from commercial suppliers. And it was our understanding that it was the heat-treated product that would be used. But because we were not ourselves clear on the supply situation, we did not want to leave patients with no treatment whatsoever, and so we didn't recall our material until we could be sure that there were supplies of Factor IX from us that were going to be adequate.

Q. So I take it from that that you are of the view, therefore, that it was preferable to allow the product which might be contaminated to be out there rather than to have no product at all?
A. We don't treat patients, and so it's essentially up to a clinician to decide in -- given the circumstances how the patient should be treated. We were -- we did not want to leave clinicians with no product whatever whatsoever; we wanted to have -- them to have at least a choice; that there would be something there if a circumstance arose where they needed something. So we didn't want to withdraw the unheated material and leave the doctors and the patients with no treatment whatsoever, but it was up to the judgement of the clinician as to what would be the appropriate treatment in whatever circumstances arose.

MR. O'BROLCHAIN: I see. Thank you, Doctor.

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

Mr. McGrath, please.

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

Q. Dr. Foster, Michael McGrath is my name and I represent the Blood Transfusion Service Board. I just a have few questions for you. As I understand the situation, the fractionation method which you developed yourself in Scotland, that you commenced developing that sometime in the mid- to late-'70s, is that so?

A. Are you referring to the Factor VIII manufacturing process?

Q. Factor VIII manufacturing process.
A. We were modifying the procedure that had already been established in 1974 and trying to improve that.

Q. Yes. So the -- as it were, your objective during that period, from 1974, '75 onwards, was to bring to fruition what had been commenced in Scotland in 1974?
A. That is correct. And it was to -- also to better understand these processes so we could make further improvements.

Q. When did you first become aware of the Gail Rock method?
A. I was aware of it when it was probably first published, which was the late '70s.

Q. The late '70s. So is it the case that you had already commenced on your own particular procedure or process prior to learning of this, the Gail Rock method?
A. That's correct.

Q. And now, in -- and obviously you have told the Tribunal that you kept abreast of developments as to what was happening, in so far as the Gail Rock method was concerned. Do you know was it -- it was hoped that the Gail Rock method would produce a higher yield?
A. That was my understanding of the purpose of that work, was to produce a higher yield.

Q. Yes. And therefore -- I take it, therefore, that the higher the yield, the less plasma you would require?
A. That's correct.

Q. So in terms of the Gail Rock method, had it been brought to a successful conclusion, it would have meant processing less plasma?
A. Either processing less plasma or making Factor VIII from the quantity of plasma that you have available.

Q. I see. I think you have indicated to the Tribunal that whilst the matter wasn't considered any further after about 1981 or thereabouts in Scotland, there were other countries who continued to look at the project, isn't that so?
A. Yes. We didn't do any work on it ourselves at all, but it did continue in the Netherlands and in Denmark. And Rock herself published further, I think, in New England Journal of Medicine in 1984, they published results of some clinical studies in which the half-life of the material did appear to me to be lower than what one would expect from a concentrate.

Q. I see. In any event, the -- insofar as the period '81, '82, '83 and into '84, was concerned, the process was still developing and other countries were still, as it were, pursuing the Gail Rock method?
A. Yes. People were still working on that because people -- obviously people were very, very interested in trying to find some way to increase Factor VIII yield, and so they were working on whatever they could. Countries continued to try and work on this to make it work.

Q. Now, so far as Factor IX is concerned, I would just like to direct your attention to one of the paragraphs in your paper, your submission. And it's on page 35. It's paragraph 6.11. At the same time, I think the reference there was January 1985. "Studies were being undertaken on the dry heat treatment of Factor II, IX and X concentrate, namely DEFIX, which was used to treat Haemophilia B. Changes to the DEFIX process were discovered which enabled the product to be modified to withstand heating at 80 degrees for 72 hours. However, as factor IX concentrates were known to carry a risk of causing thrombosis, it was necessary to carry out suitable safety studies in animals prior to infusing the new heat-treated concentrate into humans. This precaution delayed the clinical trial and introduction of heat-treated DEFIX, or DEFIX until October 1985." Now, I wonder, are you aware of publication in The Lancet in August of 1985, which is in the small black folder at page 11. This was the report of seroconversions in a population of haemophiliacs in Scotland, and it dealt with both Factor VIII and Factor IX. I just ask you to note at the summary, the last sentence in the summary which is on page 11: "Ten other patients received a batch of Factor IX concentrate from the same donor plasma; none of these patients seroconverted." Now, it appears that 15 haemophiliacs acquired the antibodies insofar as Factor VIII was concerned. And if I could ask to you look at the conclusion, which is on -- again, going somewhat forward, that is on page 236 of the article. I don't know whether it's actually paginated within the book. I think it should be on page 14 of the book, if it's paginated. And -- do you see that, Doctor?
A. Sorry. Could you just repeat?

Q. It's on page 236 of the article itself; I'm not quite sure of the page itself. The top left-hand column: "The Factor IX batch prepared from the same pool of plasma had been given to eight patients with Haemophilia B and two with Haemophilia A with antiFactor-VIII inhibitors. None of these individuals showed seroconversion when tested up to four months after infusion of this batch. Patients with Haemophilia B have fewer lymphocyte subset abnormalities and lower prevalence of antibody to HTLV-III, and are less likely to develop AIDS than those with Haemophilia A. It is possible that the HTLV-III virus is preferentially excluded from the factor IX concentrate during its manufacture."And indeed, reference number 10 to -- reference is made, reference number 10, I think it's a publication from the MMWR, from the Centres for Disease Control. At that time in 1985, were you aware of that, were you aware of that phenomenon that there was a feeling that perhaps seroconversions were not certainly occurring quite as readily in Factor IX patients as in Factor VIII patients?
A. There did seem to be more concern about Factor VIII than Factor IX. But maybe my interpretation of this paper would be a little bit different today.

Q. Yes. It might be different today, but casting your mind back to that time in 1985, I'm just wondering, were you personally aware of that view that seems to have been there and reflected in that article?
A. Yes, I was.

Q. In relation to the diagram and the graph which Mr. Finlay went through with you, I think this was a talk that was given to the -- by the SMBTS to the Haemophilia Society in November of 1999, isn't that correct?
A. That's correct.

Q. These were slides that were used?
A. I gave the talk.

Q. You gave the talk. I see. And insofar as the -- insofar as the graph that Mr. Finlay has referred you to, the Factor VIII concentrates used in the UK estimated between 1985 and 1988 is concerned, would you have been aware -- are you aware of roughly what the figures would have been in 1988 and 1989?
A. The figures are here for 1988.

Q. Yes, I beg your pardon; 1989 and 1990.
A. No, I think that -- I don't have that information.

Q. You don't have that information. I see. Just one or two other minor matters: In terms of -- are you familiar with Proplex and Autoplex, those products?
A. Generally familiar.

Q. Generally familiar. Were you aware of any report back in 1988, 1989 or thereafter, any reports of HCV in these products?
A. I don't think so.

Q. Do you know what the protocol is for those products?
A. You mean the manufacturing method?

Q. Heating protocol.
A. Heating is of the order of 60 degrees for 144 hours.

Q. Yes. And finally, in terms of heat-treating Factor IX, was the moisture content different in Factor IX than in Factor VIII?
A. Moisture content is a very important parameter, and certainly in our hands we find the products are very different. And if you dry them with a similar type of freeze-drying cycle, you could end up with very different moisture contents. Factor IX tends to be -- come out more dry than Factor VIII. But it depends on the product formulation. So you can't necessarily apply that across the board, but that would be our experience.

Q. I see. So that as I understand that, would that effectively mean that your experience is that the moisture content of Factor IX is lower, or was lower than in Factor VIII?
A. It's possible to adjust the moisture content by adjusting the freeze-drying cycle. But it is easier to get a lower moisture content in Factor IX than it is in Factor VIII, and that is something that might occur if someone isn't aware of all of the need to control these aspects very closely.

Q. Yes. And does that have any implications in the context of heat-treating Factor IX as opposed to Factor VIII?
A. The lower the moisture content in the product, then the more -- the degree of virus inactivation will change; it may change. And certainly with regard to HIV and Hepatitis C, if -- the lower the moisture content, the less virus is inactivated.

Q. Yes. Are you aware of the moisture content in the Armour Factor IX product; would you be aware of that?
A. No.

MR. McGRATH: Thank you very much, Dr. Foster.

THE CHAIRPERSON: Thanks, Mr. McGrath. Mr. Murphy?

MR. MURPHY: No, My Lord.

THE CHAIRPERSON: Mr. Finlay, do you wish to re-examine?

MR. FINLAY: No, thank you.

THE CHAIRPERSON: Very well. Dr. Foster, your evidence is completed. Thank you very much indeed for coming.

THE WITNESS THEN WITHDREW.

THE CHAIRPERSON: We will adjourn now to tomorrow morning at 10:30.

THE TRIBUNAL THEN ADJOURNED TO FRIDAY, 20TH OF JULY, 2001, AT 10:30 A.M..