THE TRIBUNAL RESUMED ON WEDNESDAY, JULY 18, 2001, AT 10:30 A.M. AS FOLLOWS:

THE CHAIRPERSON: Good morning.

MR. DURCAN: Good morning, Madam Chairperson. The next witness is Dr. Smith.

DR. JAMES SMITH, HAVING AFFIRMED, WAS EXAMINED AS FOLLOWS BY MR. DURCAN:
A. My name is James Kemp Smith.

THE CHAIRPERSON: Good morning, Dr. Smith.

Q. MR. DURCAN: Dr. Smith, could you tell us where were you employed from 1968 to 1975?
A. I was employed at the Protein Fractionation Centre in Edinburgh, part of the Scottish national blood transfusion centres.

Q. And in what capacity were you employed there?
A. I had several titles, but I ended up being called chief scientist.

Q. I see. And in 1975, where did you move on to at that time?
A. I moved to the Plasma Fractionation Laboratory situated in the Oxford Haemophilia Centre. This fractionation laboratory was part of the Blood Products Laboratory situated at Elstree, laboratory now called the Bioproducts Laboratory.

Q. I see. Did the Oxford centre have a particular speciality or knowledge?
A. The centre was concerned almost exclusively with the development of manufacture of coagulation factor concentrates.

Q. I see. You yourself, Doctor, in your capacity as chief scientist in firstly the Scottish centre and then later in the Oxford centre, would you have had a very specialist knowledge yourself in regard to the production of fractions?
A. Yes. In Edinburgh I had to contend with all the fractions, but I must say that Factor VIII and Factor IX began to be -- dominate my interests in the latter years of my time at Edinburgh.

Q. I see. And so we're clear, would your knowledge be what I would describe as a practical specialised knowledge of how these fractions are produced, what is involved in actually making them?
A. Indeed.

Q. I see. Now, during the time you were at the Protein Fractionation Centre in Edinburgh, did you yourself have contact with any personnel from the BTSB?
A. Yes. There was quite a lot of cooperation and sharing of information between the Irish centre and PFC.

Q. If we just take it up to 1975 for the moment. Can you recall who from the BTSB, who would you have been in contact with?

A. Apart from Dr. O'Riordan himself, the people with whom I had most contact would be John Cann, Sean Hanratty, Cecily Cunningham, Lee Chong. Dr. Walsh was -- also around during those years, but I didn't have much contact with him.

Q. From your contact with Dr. O'Riordan in particular, were you able to form any view as to what his attitude towards self-sufficiency in terms of fractionated products for Ireland, what view he had in regard to that?
A. My view would be that although he would be flexible about the means of achieving this, he was determined that the needs of Irish patients should be supplied, as far as he could make it, from the plasma of the Irish people.

Q. I see. And would that have been the case, that he was anxious that Ireland should be self-sufficient in regard to all requirements for fractionated products, including Factor VIII and Factor IX?
A. I believe that to be the case.

Q. I see. Did discussions take place between Dr. O'Riordan in particular and the authorities in Scotland in regard to how -- in regard to the issue of contract fractionation?
A. I was not a party to these discussions, but I believe that contract fractionation was one of the possibilities mentioned by which Scotland could assist Ireland in its quest for self-sufficiency in certain products.

Q. But perhaps if I ask you a more general question then: In terms of that assistance which you've just indicated, what was being contemplated at that time?
A. The main proposal, I believe, from Dr. O'Riordan's side, was that the Irish centre should recover certain high-value /low-volume products, but that perhaps there was a place for Scotland in fractionating the remainder of the plasma for IGG and albumin, for which the need was not terribly great in Ireland, as I understand, at the time.

Q. I see. Now, when you say high-value proteins, what are we talking about there, what was being -- what was being discussed?
A. The dominant ones would be Factor VIII and Factor IX concentrates.

Q. So am I right in thinking that what was being contemplated was that the fractionation for Factor VIII and Factor IX would take place in Ireland and that the balance of the product would then be sent on to Scotland so that other fractions could be obtained there?
A. Yes. And if I could just clarify a little: What I mean by high-value/low-volume; first of all, Factor VIII and Factor IX are only trace elements in plasma and have to be very highly concentrated before they can be infused into patients. As it happens, the early stages of, say, cryoprecipitation for Factor VIII or ion-exchange recovery for Factor IX immediately contains the valuable part of the plasma by at least a hundredfold. You can, therefore, cope with the demands of this scale of fractionation and produce a large amount of Factor VIII and Factor IX in a relatively small facility, but recovery of IGG and albumin requires a high-tech, high-volume facility's ability to handle ethanol and so on.

Q. So do I take it from your last answer that it would be possible for a small facility, in your view, to produce Factor VIII and Factor IX?

A. Yes.

Q. Again, lest we're mistaken about terminology here, when we're -- when I'm talking about Factor VIII and Factor IX, would it, in your view, be possible for a small facility to produce intermediate purity Factor VIII?
A. It might have to be slightly larger than a facility designed only for cryoprecipitate or freeze-dried cryoprecipitate. But that would not be a great undertaking, to extend into relatively low volume intermediate purity production; becoming more difficult but not impossible.

Q. I see. Well, perhaps, in fairness, I should ask you a more specific question: Let's just take ourselves back into the 1970s, mid-1970s, perhaps going on a little bit from there, early -- let's say 1980. Would the technology have been there in terms of producing an intermediate concentrate for -- to allow a relatively small facility to produce such a concentrate?
A. My difficulty is knowing what you mean by "relatively small". I think it would have to have been slightly larger than the laboratories I saw in Pelican House in the early '70s.

Q. I see. It would have to be somewhat larger than that?
A. Yes.

Q. I see. Now, if I can go back to the situation with Scotland, and again, you were only there up to 1975. Was there -- or could the Scottish centre have fractionated Irish plasma and produced Factor VIII and Factor IX for Ireland at that time?
A. In the technical sense, I think that could have been done, and was quite an attractive option for the Scottish centre. There would have been -- there may have been certain difficulties in that, however; in other cases what you might call contract fractionation would have been done, there was pressure from the regulatory authorities in
Ireland, the donor or the fractionating nation, to ensure that the streams of the two plasmas were kept separate, and that would have raised difficulties even in the new centre in Edinburgh.

Q. Perhaps we'll break it down into pieces. If the country which was sending the plasma insisted on separate streams in the sense of keeping their plasma separate from other plasma in the Scottish centre, that would have caused some difficulty?
A. It would have made it -- increased the difficulty of Factor VIII and Factor IX production quite a bit, but it would have been very, very difficult with the larger fractions, IGG and albumin, with the system that Scotland was running at the time.

Q. If we just deal with the Factor VIII and Factor IX. While it would have rendered it perhaps more difficult, would it have been an impossible situation?
A. Not impossible.

Q. I see. Now, the other possibility is what I might describe as a shared system, which I presume means that the Irish plasma would have gone in with other plasma and that the product would have been produced at the end, which represented a shared source?
A. Yes.

Q. Was that a possibility?
A. That would have been more practical, I believe, from the Scottish point of view.

Q. I see. I think you said that this would have had some attractions from the Scottish point of view. Why do you say that?
A. The Scottish centre was built with an eye on fractionating more plasma than was currently available from Scotland, although Scotland was one of the most prolific countries in getting plasma out of the transfusion service. Part of the idea at the time was that the English centre was becoming more elderly and that we might receive -- there were certainly proposals to receive English plasma from the north of England, more naturally, more nearly going into the Scottish centre. Nothing came of that. Another possibility might have been to seek plasma from other countries of a similar size to Scotland.

Q. In other words, did you in Scotland have capacity to deal with more plasma and were sort of looking around the place to see was there a possibility of getting plasma from other places?
A. Yes, it improves the economies of fractionation if you utilise your capacity to the fullest.

Q. I see. Were -- again, I gather from your answers that you were at least familiar with the discussions that were going on with the BTSB up to 1975. Were these issues of the possibility, or do you know whether the issue of possibility of having Factor VIII and Factor IX made in Scotland from Irish plasma, were those things ever canvassed, do you know?
A. I cannot actually recall at this time.

Q. I see. The -- you mentioned the fact that contract fractionation was at least discussed. Were there arrangements with any other countries or any other areas in regard to contract fractionation by the centre in Edinburgh?
A. I -- if there were any proposals to other countries, which got any distance at all, I did not know of them.

Q. I see. Do you know -- I think it's part of the history, and we know it here in the Tribunal, that nothing came out of the discussions with Scotland. Do you know why that -- why the discussions with Ireland never came to any actual arrangement about any form of agreed fractionation arrangements?
A. No, I do not.

Q. You obviously left in 1975, and clearly no arrangements or agreements had been reached at that stage?
A. As far as I knew.

Q. I see. Was the Scottish centre helpful to the BTSB in regard to the production of Factor IX and how it might be produced in Ireland?
A. Yes. I recall, in fact, that the first clinical use of Scotland's Factor IX was in Irish patients. And from time to time we did, in fact, send product to Ireland, but naturally, Dr. O'Riordan wanted to have the control of his own products, quite naturally. And the best idea, given the volume relationships I've already talked about,

was for Ireland to look at the possibility of using Scotland's methods, using the Irish plasma in Pelican House.

Q. Do I understand you correctly, then, that before the Irish began to produce their own Factor IX on occasion, Scottish Factor IX might have been sent to Ireland?
A. Yes.

Q. Then would it have been the case that the Scottish method of producing Factor IX was, in effect, taken up here in Ireland?
A. That was the idea that was done with -- I think welcomed with open arms in Ireland and given very freely from Scotland.

Q. I see. And as you understand it, in essence the Irish method would have been at least very similar to the method that was being used in Scotland?
A. Certainly up until 1975, that would be the case.

Q. I see. Now, in 1975 I think you moved over, as you've mentioned, to the Plasma Fractionation Laboratory in Oxford. And did you have contact there with personnel from the BTSB?
A. I had less contact than before, because already there were very friendly -- we had good technical, scientific relations between Dublin and Edinburgh. But I did have contact at times with Mr. Hanratty; and perhaps Dr. Lee Chong, I'm not sure about that; and certainly Cecily Cunningham.

Q. I see. Now, would those contacts - and I'll go into them in more detail in a moment - would they have involved questions concerning the production of, firstly, Factor VIII, and secondly, Factor IX?
A. When Factor VIII first -- although our methodology had diverged greatly, even between Edinburgh and Dublin, in the means which we were proposing to use to make Factor VIII, there was one possibility of mutual interest, and that was the proposal by Rock's group in Canada to greatly increase the yield of Factor VIII from what, for all of us, was a limited supply of plasma.

Q. Now, given that you have a particular expertise in this area, could you, as simply as possible, explain to us what was, in practice, involved in the Gail Rock method of attempting to produce intermediate purity concentrate. How did it work, just in general?
A. In its basic form, it required the collection of blood, not into the usual citrate anticoagulants but into a different anticoagulant called Heparin, which works in a different way; the separation of that plasma in the usual way, leaving cellular fractions in a residue of Heparin. The Heparin plasma was subjected to a modified cryoprecipitation which, it was claimed, gave a much higher yield - double the yield of the usual cryoprecipitation of citrated plasma.

Q. I see.
A. This was the claim.

Q. I see. When would this process first have come to your attention?
A. I would say the mid-'70s, probably after I had gone to Oxford.

Q. I see. And would it be fair to say that it was of interest to you and probably to many other agencies who were attempting to produce fractions?
A. Yes, especially those nations trying to achieve self-sufficiency.

Q. I see. Now, did the Plasma Fractionation Laboratory in Oxford, did it look into whether the Gail Rock method was a viable method of producing intermediate purity concentrate?
A. We put quite a large amount of effort into it. It was not the only thing we were looking at, but it was an idea which we wished to give the full benefit, especially with such a strenuous claim to double the yield.

Q. I see. Perhaps it would be helpful to the Tribunal if you could give us an idea as to what the -- as to what was the size of the organisation in the Plasma Fractionation Laboratory, let's say from the mid-1970s moving into the early 1980s. What size of an organisation are we talking about?
A. Mid-1970s, when I arrived, the laboratory was fractionating 100 litres of plasma per week derived solely from the Oxford transfusion service and returning the product to the Oxford Haemophilia Centre, which made unusual demands in England and Wales. The -- by -- by the mid-'80s that would have increased to, perhaps, 300 litres a week. So it was always what you might call 'a pilot scale'. But we did have a cold-room in which ethanol fractionation might be undertaken; in fact, as soon as I arrived in charge of fractionation, I got rid of that responsibility and we shipped the plasma supernatant to Elstree for the bulk tank fractionation. So we were concerned from 1975 onwards only with the pilot development and manufacture of coagulation factor concentrates on a -- let's call it a pilot scale, small pilot scale.

Q. And how many people would have been employed there, let's say mid-1970s going up to 1980?
A. In research, development, manufacture and control, I guess we would have had about 20, low 20s, people in '75; and ultimately have about 35.

Q. And did the Plasma Fractionation Laboratory have a particular interest in research in what I might describe as the cutting edge of the area as developments that might be coming?
A. Yes. The fractionation lab grew directly out of the Oxford Haemophilia Centre - the MRC laboratory - which, in fact, was one of the main centres which discovered and researched the clinical aspects of both Factor VIII and Factor IX. The -- some point in 1960s, the centre employed Dr. Ethel Bidwell to start actually making something which haemophiliacs could use other than just research. And in due course I think, in 1972, they -- we moved into an extended area of the haemophilia centre, which itself grew, at that time, competent to make pharmaceuticals. It was relatively clean conditions and with enough space to undertake the larger job of fractionation.

Q. Therefore, would the centre have had a particular interest in research and ongoing developments?
A. I'm sorry, I didn't answer your question. Yes, first of all, Dr. Bidwell had research personnel of her own; not many, but a few. But our -- my aim, in going to Oxford, was to have the resources to take the development of a concentrate from the test-tube through to the pilot scale, and even beyond, by taking -- scaling up the production into proper manufacturing equipment in our own premises and then to

carry that forward into Elstree, which had a much larger capacity for these concentrates. So we specialised in coagulation factor concentrates and we specialised in a particular view of how you develop -- how you shortcut the development of concentrates.

Q. Can I take it that it would, therefore, be the case that the Gail Rock method must have had a particular interest to the Plasma Fractionation Laboratory in Oxford?
A. Indeed, the promise of getting more from less in the same space was deeply attractive to us.

Q. Did the Plasma Fractionation Laboratory, did it have a research budget?
A. It would be very difficult for me to discuss budgeting arrangements. At that time we were part of the Lister Institute, and funding arrangements, administration arrangements were extremely difficult. They were what you might call government-led, highly bureaucratic. I don't think there was ever something which we would call an R and D budget.

Q. I suppose what we're trying to get at is this: Did much of the resources available in Oxford, was much resources put into the question of researching the Gail Rock method?
A. I would say, at least in practice -- in practice, amounting to as much as a year in all, we probably put between 30 and 50 percent of our Factor VIII development efforts into scrutinising the Rock procedure.

Q. Would that mean that there was a fair degree -- a fair degree of work being done in Oxford in regard to seeing whether the Gail Rock method worked or didn't work?
A. Yes, and there was a particular reason for that in that one of the -- the cruxes for whether the Gail Rock method would work or not was, in fact, the assay of what you got out as cryoprecipitate or purified concentrate. And Oxford had continued to use a particular assay method which was less likely to suffer from interference than the methods usually available elsewhere.

Q. I see. So in a sense it was of particular interest to Oxford as opposed to other centres?
A. Not just interest, but almost an obligation, because we had this particular assay method.

Q. I see. What was the outcome of the research that was carried out in Oxford in regard to the use or possible use of the Gail Rock method?
A. We concluded that there was no real increase in yield; that it was probably an artifact of the assay or resided in some unidentified procedure which Rock was using, we could not repeat it; and that the penalties to the transfusion centre envisaging taking a large fraction of all their blood into Heparin rather than citrated anticoagulants far outweighed any potential there was to tweak the method and perhaps find a five percent improvement.

Q. Was there, therefore, a viable method of producing intermediate purity Factor VIII?
A. As we found it, after our investigations, I would have said not.

Q. I see. When would those investigations have been completed; when would it have been clear that it was not a viable method?
A. It would be clear to us, I would say, at the latest, 1981. But other laboratories did continue, bravely, to try and clinch the matter by producing -- undertaking infusions of the concentrate, which is the ultimate test.

Q. But I just want to deal with your situation at the moment and your particular expertise. Would you have been involved in these experiments -- or this research in regard to the Gail Rock method yourself, or would you have been part of the team that did it?
A. Well, I was designing the experiments on the whole.

Q. I see. So if I put it this way: You're in a particular good position to tell us about this. Was it as clear to you as to somebody who was designing the experiments that this simply wouldn't work?
A. I would say at the latest 1981, but probably I was beginning to suspect earlier that the problem lay in the assays.

Q. I see. Now, was there any contact with personnel from the BTSB in Dublin in regard to the Gail Rock method?
A. Yes. Mr. Hanratty was one of the people in Europe who were keen to exploit the advantages held out for the Rock method, if it could be done.

Q. Would you have kept the BTSB, and in particular Mr. Hanratty, informed of the progress of your research in Oxford in regard to the Gail Rock method?
A. Yes. This might not be formal, but certainly there was a time when there were even meetings of the concerned laboratories; I remember one in Holland, probably in the early '80s. The Groeningen centre was also very interested in doing this and the main protagonists at these meetings would be Dublin centres, Oxford centre, Groeningen and the Canadians.

Q. I see. And would, again -- you've told us what your view would have been by 1981, that it wasn't a viable method. Would you have made your view clear at the sort of meetings we've been talking about?
A. I think it all ended with more of a whimper than that. I don't think there was a meeting to draw our conclusion. I think we let the different participants know that we would not be continuing our investigations, but with the best of luck to those who were still in the field.

Q. Well, among the people you would have let know or -- would the BTSB have been among the people you would have let know that you were not continuing your research?
A. Yes, formally or informally, and that would be without assuming that BTSB were not having success. They may very well have been having more success than we were.

Q. But would you have told them, at least in informal terms, why you were not continuing your research?
A. Certainly.

Q. And that since you've told us, that would have been -- you would have come to that view in -- by 1981, you would have told the BTSB by 1981 that you were not continuing?
A. That's the best of my recollection, yes.

Q. I see. Just out of interest, where did the Plasma Fractionation Laboratory, when it decided that Gail Rock was not a real possibility, where did it head off at that stage in terms of research?
A. We had several threads: One was to increase the -- just lightly increase the purity or solubility of our own Factor VIII, our own intermediate Factor VIII. This was with a view to making it more compact. It was not very -- it was not as concentrated, as potent as the commercial concentrates that came to be available in the UK. So we put some effort, first, into that. Along the way we got an impression of what would have to be done to increase the purity further. And we looked at our own ideas and every other idea in the literature to try and do that without losing too much Factor VIII yield. This was still the dominant consideration for us. One of the groups with whom we had contact, continuing contact, was, of course, the Edinburgh group; formally and informally, especially informally. And we tended to let each other know if we had any useful leads. And in 1983 we had contact with Scotland which suggested they were making progress on two fronts: One was a zinc precipitation, to remove fibrinogen from cryoprecipitate; and the other was to begin to have some success with pasteurisation of Factor VIII. So there were several threads coming together in the early '80s.

Q. I see. We've heard from Professor Van Aken, who indicated that he felt the Groeningen centre probably did produce some intermediate purity concentrate by the Gail Rock method. Do you know of anywhere other than Groeningen that would have produced concentrate by the Gail Rock method?
A. Groeningen not only produced, but did the crucial experiment, or thought to be crucial experiment, of infusing a certain number of units into patients. And that was published but it was not my understanding that they continued to use that as their routine method of producing cryoprecipitate or Factor VIII. And it was not too long after that that Rock's laboratory closed, I believe, came to an end.

Q. Do you know when that was?
A. I can't recall. I believe it was the mid-'80s. There was no longer any driving force from Canada to maintain interest among those who had not yet dropped out for other reasons.

Q. I see. In the end, it would appear it was something that appeared hopeful at the start but ended up that it did not work - the initial hope was not borne out; would that be a fair way to sum it up?
A. That is fair, yes.

Q. Now, could I move you on to another matter. I think in late '85 or early '85, I think you had some contact with Mrs. Cunningham, is that correct?
A. That's correct.

Q. And the Tribunal has I think already looked at correspondence which took place at the time. And I hope you may have, Dr. Smith, a copy of a letter from Mrs. Cunningham to you dated the 24th of December, 1984?
A. I have that.

Q. And we'll put it up on the screen, then. Now, firstly, Dr. Smith, it's a long time ago. Do you have any recollection of actually getting the letter or -- at the time, or do you just have a general recollection of contact at the time?
A. I have a general recollection and I have no -- I have no copy of this letter in my files. And I've -- I have no access to the files which might contain confirmation that I received this.

Q. I see. But you have a general recollection of the content?
A. Oh, yes.

Q. Well, we've already heard Mrs. Cunningham in regard to the letter. And then there is a reference, as you can see, to a letter to Dr. Snape as well. And that I think is also -- I think you have a copy of that as well?
A. Yes.

Q. And finally, I think there's a letter of a -- or sorry, a copy of a handwritten note of what would appear to be a telephone conversation with you?
A. Yes. I suspect from the evidence that it was, in fact, my reply, or it preluded my reply to the 24th December letter, if no reply can be found.

Q. Again, can I take it you have no specific recollection of the telephone conversation in question?
A. I can't say that I have.

Q. But having examined this note - and we've had the benefit of Mrs. Cunningham's evidence about this - having examined the note, would you believe that there is internal evidence in the note to suggest that it is probably your telephone reply to her letter?
A. I believe that to be so, although I can't judge the date very accurately. But I'm almost the only person with whom she could have had such a conversation.

Q. I see. And again, I think the terminology which is used in it, and the content, would suggest that it probably took place late '84 or certainly very early 1985?
A. The terminology used is very short-lived.

Q. I see. Now, well, having identified the documents in that way, perhaps we'll go back to your statement and just take what your recollection of what happened at the time was. There's a reference in the note of bringing in a new concentrate. And this is dealt with, I think, at the top of page two in your statement, coded 8Y. Could you tell us what was that, what was coming at that time?
A. 8Y was developed in the autumn of 1984 in PFL, Oxford. We'd been working for almost a year in cooperation with the Scottish centre on means of pasteurising and dry heating Factor VIII concentrates. One of the obstacles to dry heating, apart from losses of activity, was that the products would remain insoluble when you added water to the freeze-dried concentrate. And the indications we had, that we would

have to carry out some purification, or at least removal of two problem proteins, before we would succeed in producing a heated concentrate. So during 1983 and '84 we were pursuing essentially pasteurisation in solution, but with retaining an interest also in the possibility of dry heating. I think it's fair to say that during early '84, we would have seen dry heating as likely to be less successful in inactivating non-A non-B Hepatitis and pasteurisation. I should stress that this is all about attempts to do something about non-A non-B Hepatitis. Because before we were aware this -- this all started before we were aware of the AIDS phenomenon.

Q. And would it have been the case that even going into 1984, the thrust of the work would have -- still have been in regard to non-A non-B Hepatitis?
A. Yes, although there was some suggestive work coming through using not the AIDS virus itself, which was unavailable for study until very late in '84, but on various retroviruses which might have a similarity to HIV. There were suggestions coming through that even relatively mild heat treatment might be successful against a retrovirus.

Q. But the particular work that was being carried on in the Plasma Fractionation Laboratory, it was -- its main emphasis was in regard to non-A non-B?
A. Indeed, and continued to be so.

Q. I see. Now, if I could just take you back for a moment to the discussion with Mrs. Cunningham. I think it's clear that there was some discussion of Factor IX --
A. Yes.

Q. -- and about the possibility of thrombogenicity in Factor IX. Can you say, would that have been a concern at the end of 1984/beginning of 1985?
A. At that time I think it's fair to say, certainly going back into 1984, it's fair to say that with the apparent absence of HIV from UK concentrates at that time, that thrombogenicity was the dominant fear which treaters had in applying Factor IX concentrates, and envisaging any step which might perhaps disturb the protein from them.

Q. Again, dealing with the period at the end of 1984, was there any concern caused by in vitro tests which had taken place at that time?
A. Within our laboratory, we had found, in the later part of 1984, that the laboratory tests which we used to predict, however unsuccessfully, thrombogenicity in patients, laboratory tests were being perturbed by the heating conditions we were using. And we determined that at least we must fix that before moving on to the next stage.

Q. And again, so we're clear, what was the heating process that you were using which was causing this disturbance in the laboratory tests?
A. We were heating our normal concentrate without any additions to it. We were heating originally at 80 degrees for 72 hours, and this was the product in which we found that some activation -- very little activation, but enough to cause us a problem, was occurring.

Q. I see. All right. We'll take it now just slowly for the moment: So the treatment that was causing the activation, or the heat treatment which was causing the activation

was 80 degrees for 72 hours. What we term here, and I think is commonly called, sometimes, superheat-treated --
A. Yes.

Q. -- was it causing much activation or just a small amount of activation?
A. It only required one in a million of the molecules of prothrombin to be activated, but this was sufficient to produce enough thrombin to respond in our very limited tests.

Q. I see. So it was a small -- it was a small reaction, but nonetheless, one of some significance, from your point of view?
A. Yes.

Q. When that in vitro -- when that in vitro testing threw up that effect, what was the response of the centre, of the laboratory?
A. We had had an interest in thrombogenicity, of course, since the early '70s, and I had a particular interest in it. Because of that, I was skeptical of the moves, throughout the '70s and '80s, to add Heparin to Factor IX concentrates. Because Heparin acts through a protein called antithrombin-III, which is essentially absent from the Factor IX, it is therefore really not affecting the concentrates; may be affecting the patient but not the concentrate. And I proposed the ideal way back in the '70s; that one of the things we could do would be to add some antithrombin-III to the Factor IX, otherwise we are wasting our time then in adding Heparin. But we continued under various pressures to add simply Heparin to our existing unheated normal Factor IX concentrate. But one of the ideas which came out of the heating discoveries was that Heparin alone could not cope with this laboratory quirk, but that antithrombin-III alone or in conjunction with Heparin not only cured the laboratory problem, but would be expected to deal with the problem on ejection as well.

Q. So was the solution to the difficulty that had been thrown up by the in vitro testing, was it to add what's called, I think, AT3 --
A. Yes.

Q. -- with Heparin?
A. In any event we did not add Heparin as well. We had sufficient mopping up of the unwanted thrombin with antithrombin-III alone. Some companies used both, but we did not find it necessary.

Q. So the solution which was arrived at was to add AT3 to the Factor IX which then helped to deal with what you have described as the laboratory quirk that had been thrown up in the testing?
A. Not only that, but excellent grounds for believing that this would also be a safeguard when it was infused into the haemophiliac, as it mimicked the normal defensive mechanisms of the circulation against activated factors like thrombin.

Q. Did your laboratory produce AT3?
A. We did at that time, we were one of the few laboratories which had antithrombin-III on hand because we had an interest in the deficiency and were promoting it for the treatment of deficiency.

Q. But would it be fair to say that certainly not every facility would have that particular product available, AT3, or an equivalent product?
A. Indeed. We were just simply fortunate in having a combination of circumstances.

Q. When was that solution found; when did the problem -- when did you discover that adding AT3 solved the laboratory difficulty?
A. It would be sometime in the period late 1984 to early 1985. This would not be a sudden eureka, you understand, it would be a result of many factoral experiments. And I couldn't put a month on when we were convinced; I would guess somewhere about March, but wouldn't like to be held to that.

Q. It's a continuum from late '84 into early '85. Now, what was decided - once this solution had been arrived at, what was decided should happen then; should there be further testing?
A. Well, against a background of -- I think probably 1984 was probably the peak of concern about thrombogenicity. Against a background of great concern about thrombogenicity, not only in unheated concentrates but a fortiori in anything heated, we decided not simply to depend on our laboratory tests; which, although the concentrate passed it, passed all these tests, were not terribly closely related to what was happening to patients. It was the best we could do. We would not trust these in vitro tests; that we would take advantage of the in vivo model, the dog DIC model, which had been running -- Edinburgh BTS had been running since the early 1970s, and which, I believe, and many people believed, correlated much better with the safety of Factor IX concentrates on injection into haemophiliacs.

Q. I see. So was it decided to wait for dog infusion tests?
A. Yes. And both centres, both Scotland and England agreed that they would carry out their experiments in a certain order and that they would both stick to that principle of dog experiments before release of the product for general use.

Q. I see. What product are we talking about here now?
A. Talking about our conventional Factor IX concentrate, but with the addition of antithrombin and heated 80 degrees for three days.

Q. I see. And that was what was being tested or tried out in the dog infusion tests?
A. At Oxford we never had any interim products between our unheated product and our fully -- what you call superheated product.

Q. I see. Doctor, again, from your experience of this area, would it -- is it correct to say that the greater the level of heat treatment, the greater the potential problems with thrombogenicity?
A. In our experience, that was so.

Q. So --
A. This is laboratory thrombogenicity.

Q. Yes. Again, if one takes a practical example, there is a greater likelihood of problems with what might be termed superheat-treatment, 80 degrees for 72 hours, than heat treatment at a lower level, perhaps 60 or 68 degrees for 72 hours?

A. That is what one would expect, yes.

Q. And in -- in your -- with your expertise in the area, would it be possible or would it be advisable to carry over what was happening with the superheat-treatment, what was happening in the in vitro tests with that particular heat treatment, to carry it over and to say that it would apply in regard to a less severe heat treatment?
A. No. I think any modest fractionator would say that he can talk only about his own concentrate. If several people told you the same story, you might begin to believe it was a general phenomenon. But all concentrates are formulated in a particular way. They are freeze-dried in a particular way. And these are things which greatly affect the survivability of the proteins, as well as, of course, the viruses which might be present.

Q. So the fact that the in vitro tests for the superheat-treated product, 80 degrees for 72 hours, was throwing up activation or signs of activation, wouldn't necessarily mean that product which was heat-treated at a lesser level would have the effects of -- or would have -- would show activation?
A. It's not conclusive, any conclusive proof that it would, but I think one would be foolish to ignore the evidence of a severe heated concentrate. One would have to start to ask questions about what would happen at lower temperatures. It's not proof.

Q. Yes. Now, in the end of the day, the dog infusion tests were taking place. When did the results come out from those dog infusion tests?
A. Hanging on the dog's breath all through the summer of 1985, and it was -- we had to delay issue, we had to postpone our planned issue because the dogs could only be operated on in a certain sequence and it took a long time.

Q. And what was going on during that time; what product was being used, or do you know?
A. We were quite firm that we would not release any interim-heated product, potentially HIV safer. Some clinicians chose to use our unheated Factor IX concentrates. Others, possibly an increasing number of others as 1985 progressed, became more concerned about HIV, and purchased commercial concentrate, heated Factor IX from abroad.

Q. I see. Is it possible for you to, looking back at that period, to sum up what would have been the position looking from, say, the middle of 1984, going into 1985, and say to the middle of 1985; what was the knowledge or what would the view be in regard to the effect of heat treatment and the desirability of heat treatment on Factor IX?
A. Well, if we stick just to the perceived risks of thrombogenicity and HIV - and it was HIV in that year which was dominating perceptions - I think there would be a slow change from 1984 onwards, from a majority thinking that HIV has not been apparent from UK Factor IX, unheated Factor IX concentrates; should we be taking the leap into the dark on thrombogenicity by abusing the protein in this grotesque way, heating it to 80 degrees for 72 hours, when we know that damage to prothrombin complex can lead to problems in patients? I think during that year, the emphasis changed and more people thought that they did need to have a heated concentrate to combat the possibility of HIV being present in UK Factor IX, and hence the rise in importation of heated - mildly-heated Factor IX concentrate.

Q. And by, let's say, mid-1985, what would the position have been in regard to that balance of risk?
A. I don't think it was possible to get from Elstree, from BPL, any unheated Factor IX after a particular point, and I think it would be early summer, in 1985. So the option of unheated UK Factor IX did not exist.

Q. I see. In your own mind, looking at it again with your own expertise, you must have been trying to balance up in your own mind the balance of risks at that time. Did your view change between the year we've taken, mid-1984 and mid-1985?
A. I think the fact that we held out, despite the disadvantage of not meeting our deadline of our projected time for issue of the severely heated Factor IX, the fact that we held out and did not submit to pressure for issue until the dog experiments had been done, suggested at that time we would agree with the view that thrombogenicity was still a major consideration.

Q. Did the Plasma Fractionation Laboratory in Oxford, did you consider heat-treating the product, the Factor IX product, at a lesser level, a less severe level than 80 degrees for 72 hours?
A. Not immediately; in fact, our early experiments on the heat treatment of Factor VIII were followed by heat treatment of Factor IX. And we thought, in the middle of 1984, that Factor IX was, in fact, going to survive severe heat treatment better than Factor VIII; it almost fell into our laps. It was only later in 1984 when we applied different tests that we had this indication that 80 degrees was going to cause problems. I cannot recollect precisely, but I assume we then went back, and apart from applying our fixes of antithrombin-III and Heparin, I'm sure we would have looked at the temperature relationships in the formation of this thrombin. But I can't recall precisely how much effort we put into showing how much there was at 70 degrees or 60 degrees. We were determined, by that time, we were going to go for 80 degrees, we could solve it, and that we would hold out until we could prove with the dog experiments that that was safe from thrombogenicity.

Q. I see. When you say you were going to hold out for the more severe heat treatment, what was the logic of that, what was the benefit that came with the more severe heat treatment?
A. I think by the time of '84 and '85, it was clear that our heat treatment would probably kill HIV. But it would be far from certain. We had no evidence to offer that it would inactivate the non-A non-B Hepatitis. It might be more activation than you'd get at 60 or 70, but we were -- we had no evidence to suggest that it would do that. All along, the problem with Factor VIII and Factor IX -- Factor IX from the early years, was knowing that it was transmitting non-A non-B Hepatitis. This was still remaining.

Q. Was it, therefore, that it was felt that while there mightn't have been any hard evidence to support the view, that the superheat-treatment was more likely to kill non-A non-B Hepatitis than less severe regimes?
A. Sorry, would you repeat that, please?

Q. Was the logic behind opting for the more severe heat treatment, that it would -- it was more likely to kill non-A non-B Hepatitis than less severe regimes, even though there was no hard evidence to support that view at the time?
A. Yes, and although there was no hard evidence, because no-one could culture Hepatitis C at that time, there was beginning to be evidence from our friends in Scotland, from model virus experiments, surrogate virus experiments, that we were killing a lot more of surrogate viruses at 80 degrees than at 70 or 60. So it wasn't entirely -- wasn't just a lick and a promise and a hope. There was some laboratory evidence that we were getting a sizable, useful increase in kill. And we also say that the opportunity -- the possibility of heating at 60 or 70 was not real because we would still have had to test that concentrate, gone through all the laboratory and the dog experiments. It would not have led to a more rapid introduction of a heated Factor IX concentrate.

Q. I think at page six in your statement you mention that Dr. Lane, who was I think the director in the Oxford centre --
A. Excuse me, the BPL centre.

Q. -- sorry, the BPL centre -- he was anxious to go for the severe heat treatment, if I put it that way?
A. In the autumn of 1984, we decided that unless anything came up to put us off course, that it was -- on the evidence we had, it was worthwhile going for the 80 degrees treatment.

Q. Yes. Now --
A. May I also say that, in the interim, we did have mildly heated Factor VIII concentrates to offer. We had no mildly heated Factor IX to offer.

Q. And I'm going to deal with that in a moment. Just, what was the perception at the time of the risk of infection from hepatitis, and in particular non-A non-B Hepatitis, from anybody who used concentrates, commercial concentrates? Was it perceived that they were likely to get non-A non-B Hepatitis if they used any significant amount of concentrate?
A. By 1983, it was shown conclusively, in fact in the centre next door to me, that whatever the source of the Factor IX and the source of the donors of the plasma, there was an almost one -- chance of one in any new previously untreated haemophiliac acquiring non-A non-B Hepatitis from Factor IX concentrate, from whatever donors, from whatever company; whether from US plasma, paid plasma or from UK voluntary-donor plasma.

Q. And I think you've made it clear that that applied whether they were paid donors or unpaid donors --
A. Exactly.

Q. -- that had contributed the plasma?
A. Yes.

Q. Now, I think you set out at page four of your statement some obstacles to the adoption of heat treatment of Factor VIII and Factor IX concentrates in the early-to-mid-1980s. And I think it's perhaps worthwhile just looking at that for a moment,

even though I think we've covered some of the ground in the answers you've just given. Perhaps we could put it up on the screen.Firstly, I think there's the issue of the fear of reducing the activity of the coagulant proteins. And that there was a 10 to 50 percent loss in activity, which I think had implications in regard to the availability and the cost of the concentrates, is that correct?
A. That is correct. And small addition to that, that availability doesn't just mean how much they would -- there would be to treat haemophiliacs, but how much there would be of NHS concentrates, which some treaters wished to cleave to.

Q. So it was a yield problem?
A. Indeed.

Q. And then I think at two you set out "fear of increased immunogenicity". Could you tell us what you mean by that?
A. I can't really, I'm not an immunologist, but there were certainly many fears, using concepts which I don't wholly understand. But some immunologists were, during the early '80s and right into 1985, were saying that if you wished to increase the immunogenicity of a protein concentrate, the first thing you do is heat it. That's certainly true of IGG concentrates, for instance. I was never quite clear myself whether these immunologists meant to apply that general concept to the very particular concept of the antibodies which arise in treated haemophiliacs, which are called inhibitors - inhibitory antibodies. To me, the history of Factor VIII concentrates in particular had been that recipients of any concentrate had a certain risk of acquiring an inhibitor within a few years of treatment. Going right back to the very crudest preparations of Factor VIII, including cryoprecipitate and freeze-dried Cohn fractionation I, there seemed, through the years, to be, in what literature there was, to be no increase in inhibitor incidence, depending on how abused the Factor VIII was.

Q. But this was at least --
A. It was an active fear.

Q. An active fear, yes. We've dealt with I think number three in some detail, the fear of increasing the thrombogenicity of Factor IX concentrates. I think if you look there, the next item, was there some concern about the use of stabilisers in regard to heat treatment?
A. Yes. The origin of this goes right back to the 1940s when the first protein to be successfully pasteurised was albumin, relying on the discovery that a tiny concentration of physiologically-active fatty acid protected the albumin from coagulation. Now, many years were spent trying to repeat this experience with other proteins and to find a magic stabiliser, but in the end Factor VIII only succumbed to heat treatment if you added very high concentrations of additives like sugars and amino acids. And it's not just a matter of conjecture, it's a matter of fact that, while protecting the proteins, some viruses were also considerably protected for the presence of these additives. We suspected that the same might be happening in dry heat, although perhaps to a lesser extent. But it did make the choice of what we call excipients, or the stabilisers or additives which you put in to protect substances during freeze-drying and storage, it made the choice of these quite a thought.

Q. I see. So this was yet another difficulty that had to be at least addressed in the context of heat treatment?

A. Yes.

Q. I think then there was a problem in regard - and it's dealt with at paragraph five - of non-A non-B Hepatitis. There was difficulty simply because of the nonavailability, obviously, at the time, of the virus in terms of trying to work out ways of patterns of inactivation of that particular virus, isn't that correct?
A. Yes. We didn't even know what family the virus might belong to to choose a respectable surrogate.

Q. So that created a difficulty at least in regard to non-A non-B Hepatitis. Was there particular problems in the laboratory method of testing an inactivation by adding a particular dose of virus, if I can use that expression, and seeing what would happen by way of heat treatment?
A. Yes, because the only method available at that time to determine the amount of virus in the inoculum and the amount remaining in the, say, heat-treated concentrate, was to inject into chimpanzees.

Q. And what particular difficulty did that cause?
A. There were no chimpanzees. And those few laboratories who had cornered the market in chimpanzees and set up breeding colonies and so on were finding that the results of their -- some cases were perhaps a bit naive experiments, were not being extended to clinical findings. This was by 1985.

Q. I see. And I think you just mention that in perhaps paragraph seven, that the only convincing way really to sort out what the effect of heat treatment was through clinical trials, and the results of those certainly in regard to non-A non-B Hepatitis were really only becoming available at a later time or --
A. Exactly.

Q. -- or relatively late in the day. Now, I just want to ask you something about -- at page five of your statement, you mention just there in the first paragraph in that page that it wasn't until October 1984 that the McDougal group reported that HIV added to concentrates was inactivated by even the mildest heat treatment. Was that an important event, that particular piece of information becoming available?
A. I think that was a trigger for most laboratories to really believe that they could inactivate HIV with the kinds of heat treatment which their concentrates could currently stand. It was a false dawn, of course, to some extent, but it was crucial in certainly inciting the English centres to believe that HIV could be inactivated. Before that it was all indirect evidence from surrogate viruses.

Q. Did the McDougal report that you referred to, is that CDC data that was becoming available?
A. Yes, although when I mention October '84, that was an informal statement made in confidence in Groeningen by a CDC member of the audience, and it was released the previous day. And that's why I stated October; I think it was well into 1985 before it was published.

Q. It had obviously become public knowledge in October?
A. Yes.

Q. Really, in regard to HIV, would it be fair to say that doubts about heat treatment and the effectiveness of heat treatment in inactivating the HIV virus, that after October 1984 those doubts were greatly reduced?
A. That's correct.

Q. But up to then had there been at least some real element of doubt as to whether heat treatment was or was not effective?
A. Yes.

Q. Now, I think to some degree, Doctor, we may have dealt with this already, but perhaps if we move on to page six of your statement. Could I just ask you to look at paragraph two, where you make the point which you've already said; that until 1984, the heat treatments which were being used in the Oxford centre had non-A non-B Hepatitis as their main target?
A. Yes.

Q. But then you go on to say: "During 1984, we became convinced that AIDS was caused by a virus and that US heated concentrates were not transmitting it." Now, when was that knowledge, if I put it this way, complete, or when did you really feel that was the case?
A. Personally, I thought the Gallo paper in the spring of 1984 was fairly conclusive that -- to me, that this looked like a virus. Not everyone agreed that AIDS was being caused by a virus. I think during '84 clinical evidence, unpublished, was coming through. Clinical experience was being shared in the clinical community that the American concentrates which had been relatively mildly heated in the hope of killing non-A non-B Hepatitis, were leaving their patients free of HIV.

Q. I see. Now, I just want to -- I think we've dealt with most of what's in the balance of the page, but there's just one matter at the end of the page I want to ask you about. It's the very last sentence on page six where you say: "From December '84, all existing and new batches of 8 CRV and HL were heated under one of those optional conditions determined by test heating and made available to clinicians from February 1985." Could you explain what you mean by that, what was happening in practice?
A. Yes. Although by early November our director decided to go for 80 degrees. It was only in December 1984 that the UK Haemophilia Centre Directors concluded that yes, they did want the UK Factor VIII concentrates to be heat-treated. We could not immediately switch to 8Y. The bulk of the fractionation had to be done in the Elstree facility, which was coping with, by far, the bulk of the plasma for England and Wales. And with the best will in the world and given the enormous efforts which BPL made in those months, they could not immediately acquire all the equipment and expertise to make 8Y from December. Our fallback position, for which we had already fairly well prepared, was to offer the current concentrate, intermediate purity concentrate, mildly heated. Now, we believe that 70 degrees for 24 hours was probably more severe on the virus than 60 degrees for three days; couldn't be sure of that, but that was our preferred method of treatment. Some batches on test heating remained poorly soluble after that treatment, and those we found could accept 60 degrees for 72 hours.

Q. So how did you physically carry that out to the stock that was on hand?
A. All right. I don't think we ever recalled a product, as some commercial companies did, and heated it and sent it back. I think it was only batches which we

had in process or, having finished quality control, about to be -- in quarantine, about to be released, which we -- initially in fact in the early months, until BPL developed its own large ovens, all had to be brought into the Oxford laboratory where we had a precision oven which could heat-treat all Elstree's product and all our own product; and returned it for, again, repeat quality control and release as heated intermediate.

Q. So would it be fair to characterise it in this way: That the stock which was on hand was taken in and a milder heat treatment was applied to it as an interim measure?
A. Exactly.

Q. Until 8Y could come on stream?
A. Exactly.

Q. And -- but there was no effort to withdraw stock that was outside or had already been issued; it was only the stock that was on hand that this was done for?
A. I was not personally involved in this, but it is my impression that there was no callback of stocks which was out there in people's fridges.

Q. I see. And again, we should be clear: We're just dealing with Factor VIII here, not Factor IX?
A. Exactly.

Q. I think the -- when was the first heat-treated Factor IX made available in terms of English product?
A. With the exception of very little given for clinical trial under closer controlled circumstances, the first release would be in October 1985.

Q. I see. And when was the product made available for clinical trials?
A. I think that was June or July. I would have to consult the records for that.

Q. And finally, I suppose, do you know when, in regard to Factor IX, did nonheat-treated or unheated Factor IX cease to be issued?
A. I think in the spring -- late spring or early summer of 1985.

Q. I see. Do you know whether there was any recall of product in regard to nonheat-treated Factor IX?
A. I think recall would have been untypical at that time. I think BPL's policy was not to actively recall.

Q. And I think, just to continue on where we were on to page seven, I think you mentioned the fact that 8Y was finally launched as the only Factor VIII product in September 1985, is that correct?
A. That's correct, yes.

Q. Finally, Doctor, do you -- you mention there in the last paragraph of your statement the question of infection or possible infection by English Factor IX. Do you have anything to say about that? When you wrote the statement, were you aware of any infection that had been caused by unheated English Factor IX?

A. In making that statement, I was giving my impression of the perceptions of clinicians. And certainly at that time it was my impression that no - and their impression, I believe, say the end of 1984, that there had not yet been a problem with HIV in Factor IX concentrates. I would not myself have said that's anything except an accident waiting to happen, but that was a perception. Whether there actually were any really confirmed cases of HIV from Factor IX, I am not myself equipped to tell you.

Q. I see. When you say it was "an accident waiting to happen," what do you mean by that?
A. Eventually the donor base in the UK was going to pop up with a few HIV-positive donors, and I did not myself believe that the fractionation process for Factor IX was a sufficient safeguard against the expected increase in the load of HIV in plasma pools.

Q. Therefore, looking back at your view at that time, did you feel it was inevitable that somebody would, or was highly likely certainly, that somebody would be infected by way of unheated English Factor IX?
A. Eventually, yes.

Q. And that was the balance that then had to be drawn in regard to the use -- the use of -- possible use of heat-treated product and difficulties with thrombogenicity?
A. Yes. And may I say that some clinicians were concerned that in going for a heat-treated American concentrate, they might be saving their haemophiliacs from HIV at the expense of an increased risk of non-A non-B. It was not my own perception but that was a perception at the time.

Q. Did you have a view yourself at that time, or is that an impossible question?
A. By 1983 I believed our concentrates were as likely -- almost as likely to give non-A non-B as commercial concentrates.

Q. I see. Again, if you can't answer this question, just say this. By, let's say, early spring 1985, did you have a view in regard to what was the safest course of action in regard to Factor IX, as to what should be used?
A. I should make it clear I'm not a clinician and I would not like to have been a clinician treating haemophiliacs in that year.

Q. And you don't wish to take it any further?
A. I don't wish to.

Q. Again, Dr. Smith, I think Dr. Snape may have said that there was a recall of unheated Factor IX. Would you bow to him in that --
A. Oh, definitely. A lot involved.

Q. Thank you.

THE CHAIRPERSON: Mr. McCullough, please.

THE WITNESS WAS EXAMINED BY MR. McCULLOUGH AS FOLLOWS:

Q. MR. McCULLOUGH: Dr. Smith, my name is Jim McCullough. I represent the Irish Haemophilia Society. And I just want to ask you one thing to start off with: You're not a medical doctor, is that correct?
A. That's correct.

Q. You are a scientist?
A. Yes.

Q. And who would be, if there is such a thing, who would be your counterpart in this jurisdiction in terms of fractionation, or would you have a counterpart in this jurisdiction, to your knowledge?
A. You mean in the BTSB?

Q. In the BTSB, yes.
A. I would have found it difficult to locate an exact equivalent in the -- in which I had contact with in the BTSB.

Q. Yes. Dr. Smith, just looking at your statement, on the first page of your statement, just second paragraph, you say that, the BTSB adopted a method of Factor IX production developed by the Protein Fractionation Centre. How did that -- how did they actually go about doing that; what was the procedure for teaching the people from the BTSB?
A. I can't recall the details, but normally the transfer of technology would occur by - first of all on paper, so that the recipient laboratory would be able to think about how they could cope with the activities concerned. If they thought there was a chance of finding the space and equipment and personnel for -- to adopt a new method, it would be usual for the people who were going to adopt it, the technical and scientific people, to visit the original laboratory, observe it in action, come back perhaps and modify their proposals for equipping the laboratory, doing testing, et cetera. And then there would be a dialogue, say the Irish board would equip itself with space and people and testing facilities, and then there would be a dialogue as they tried to practice the production and troubleshooting by mutual visits to try and ensure that there was a true sharing of experience.

Q. And there would be some slight differences in the way the BTSB would eventually produce its Factor IX from those of the -- that they had picked up in Scotland?
A. Inevitably, if there was a difference in scale or local conditions of some kind, there would be small differences. But we would be able to locate, I think, which were the important ones and which were scaled independent.

Q. Fundamentally, it would be the same process that they had learned and were putting into practice?
A. Well, what we would be learning in Edinburgh would be very likely to be applicable to any problem which they had.

Q. You say also that Ms. Cunningham visited the PFL in October '83. That was the plant in Oxford?
A. Yes.

Q. And you discussed certain matters there. What would your discussions have been at that time during October 1983?
A. The main purpose of Mrs. Cunningham's visit at that time was to observe and practice the assays, which were not my responsibility at Oxford; and to observe the Factor IX process, which was different from the Edinburgh process, but had some things in common; and she also took the opportunity to observe our Factor VIII process at the same time. Naturally, she was there for -- in Oxford for several days, and we would inevitably have talked about the whole range of concerns of -- over Factor IX at that time. These would include thrombogenicity, for instance.

Q. And in looking at the processes that were then employed in Oxford, would that have been in anticipation of updating those in the BTSB; to your knowledge, would that have been in her mind?
A. No, I don't think so. My impression would be that while it was of interest for her to see our Factor IX process, I would not have held out any promise that anything she'll have there would be immediately applicable in Ireland, or in Edinburgh equally. I think the main thrust of her visit was to get up to speed on testing of coagulation factor concentrates, which was a bit of a fair amount at that time.

Q. Yes. And was the issue of hepatitis discussed at that time in October 1983?
A. I think in the course of general discussions it may well have. I can't recall as I sit here.

Q. I beg your pardon. Would that be non-A non-B Hepatitis or Hepatitis B?
A. It would be essentially non-A non-B Hepatitis; HBV having been thought to be solved by the end of the '70s.

Q. So would there have been any discussion about -- as regards Hepatitis B as a marker for what was then emerging as a -- the AIDS problem and the HTLV-III at the end of October 1983?
A. I would have had nothing in my mind for HBV being a marker for non-A non-B Hepatitis, so I don't think there was any discussion along those lines.

Q. So the topic would have been non-A non-B?
A. Indeed.

Q. And during that visit, as you say there was no anticipation of actually updating what the BTSB had been doing up until then; it was simply Mrs. Cunningham observing the assay methods and having discussions with you as to the topics that were coming up in the fractionation field?
A. I wouldn't like to leave any impression that there was updating going on here. We were following different concentrates, and nothing she would learn at Oxford would be scientifically updating her.

Q. Yes. And was AIDS, just on another -- that you mention in your statement you say you don't recall discussing AIDS, but was AIDS a topic of discussion in October 1983 among fractionators?
A. It was not -- it was still very much in the -- up in the air. It was thought to be an American problem. I think some of us thought that this looks like a virus.

Q. On the issue of thrombogenicity that you were discussing with Mr. Durcan, when you talked to Ms. Cunningham, as she records in her manuscript note of the telephone conversation that she had, when you talked to her, were you talking to her about what you were doing at the time, which was the 80 by 72 Factor IX heat treatment being applied to the Factor IX; was your discussion to her in the context of thrombogenicity arising with regards to that product?
A. I can't be sure it was limited to that. I may have talked or reminded her about the general question of thrombogenicity, even from unheated concentrates, and it is quite likely that I told her what we had found; that heating certainly to 80 seemed to exacerbate the problem and it has to be dealt with.

Q. Would you have been aware also at that time that -- that would have been in December 1984 or shortly thereafter, into 1985. I think you got the letter in December, letter is dated the 24th of December. The telephone conversation followed the letter, so it was in some -- early 1985 that you would have had that conversation?
A. It was sometime in that time period, I would say spanning a period of two months - December /January. I can't be sure.

Q. Which was a period of quite sort of hectic activity?
A. Yes.

Q. How was that arising in that busy period; why were you so busy at the time?
A. Well, as I've already discussed, at that time Oxford was heating retrospectively the entire Factor VIII output from Elstree and Oxford. It required a great deal of organisation. We were running essentially three different heat treatments for Factor VIII concentrates; we were investigating the problem of test-tube thrombogenicity in our Factor IX proposal. We were quite busy.

Q. And that test-tube thrombogenicity in the Factor IX, that was a laboratory experiment that you were engaging in?
A. It was putting the -- our proposed heated Factor IX through an extended series of tests, which -- prior to dog experiments, which raised the problem and required a solution.

Q. So that was something that was well-established in your mind at the time when you had your discussion with Ms. Cunningham?
A. That it was a problem. I don't know if I was in a position to offer Mrs. Cunningham a solution to her problem at that precise date.

Q. Would you have been aware at that time when you were having that discussion that heat-treated -- commercial heat-treated Factor IX was available and in circulation in the UK and in Ireland?
A. I would not have been aware -- I would not have been certain that there was heat-treated Factor IX in December '84.

Q. Perhaps going into January,February '85?
A. I would not have been certain of that. I did not have the kind of contact with people who prescribed to know what they were prescribing. I certainly accept that people were muttering about preferring the mildly heated US concentrate to unheated

UK concentrate. I would have found that quite reasonable. But I can't give you any factual assistance there.

Q. But when you were having that discussion, would you have been -- if you had known that such a -- that there was a heat-treated commercial Factor IX being used, would you have had concerns about that?
A. Can you explain what kind of concern, what area; for safety or --

Q. Given that you had -- you were obviously concerned about thrombogenicity in the product that you were dealing with in Oxford, would you have had similar concerns had you known that a heat-treated commercial product was in circulation?
A. Yes. I'd have been concerned about even unheated concentrates, but the -- especially without having seen evidence that these heated concentrates had passed the kinds of tests that we wanted, I would have been a little concerned.

Q. Well, would that seem to indicate then that there was a difference of opinion between the clinicians and fractionators, like yourself, as to -- regards the importance of dealing with that issue of thrombogenicity before using these products?
A. I was certainly aware there were -- was more than one view on the matter, but I -- I would be hard pushed to think there was a consensus in the country at any time in 1984.

Q. When you did conduct your experiments regarding the product that you were dealing with, the superheat-treated Factor IX, when did that actually -- when did that actually go into use in Britain?
A. October 1985.

Q. And had it been available prior to that in -- under the named patient basis?
A. I should clarify that it was always named patient basis. Even before release of products, it was on a named patient basis. But especially, the clinical trial batches would certainly have been released on that basis, a very explicit named patient basis, and the understanding of the conditions under which it would be used.

Q. When you say it was always on the named patient basis, the distribution of this product, therefore, was always on that --
A. Certainly for a time. Until it was regarded as the BPL, or the BPL product.

Q. Yes. But in July 1985 when it was used on a named patient basis, had your concerns about thrombogenicity been -- had they been satisfied to any degree?
A. Insofar as laboratory evidence could -- can affirm that we really had provided antithrombin-III to mop up thrombin; I myself had little doubt that the dog experiments would prove to be successful. But we had reached an agreement that we would not make general issue of this until we had that to offer, that proof or evidence to offer clinicians who might doubt the effect of heating on thrombogenicity.

Q. Thank you, Dr. Smith. Just with regard to the actual process of heat-treating Factor IX, and you say you added the antithrombin-III; that step allowed you to heat-treat it to that degree, to 80 degrees for 72 hours. That was the step that you were able to take that allowed that to happen, am I correct in that?

A. It reversed the laboratory evidence of thrombin having been produced by heating. It dealt with it. It did not prevent -- possibly did not prevent the production of thrombin from one molecule in a million, but it reversed its effect. It negated its effect.

Q. So it cancelled out the adverse effects of the heating?
A. Yes, and we believed this was also a physiologically-active principle. It wasn't simply curing -- fixing the problem in the vial, it was actually removing the thrombin from injection -- possibility of injection into the patient's vein.

Q. And was that a difficult procedure to employ in manufacturing that product, the addition of the antithrombin-III?
A. Not for us, in that we were fortunate for having antithrombin-III on our shelves.

Q. For other people it would have been a difficulty?
A. Difficulty in believing it would be sufficient to cure the problem. There were many false dawns in this issue.

Q. And the actual heat-treating process itself, what did that consist of; how did you actually heat-treat the finished material?
A. The actual heating is -- appears to be trivial, but the process involves both very specific ways of freeze-drying followed by very precise heating. The heating itself is a technical matter.

Q. And is there a degree of precision that has to be used in actually conducting those procedures?
A. In -- let's say right back to the '40s, we would pasteurise the albumin. The balance of damage to the protein against damage to the virus was, even then, quite tight. And I believe the tolerance allowed by the regulators would be plus or minus one degree. If you extend that into the 1980s when we're talking about heat-treating much more labile factors, you can imagine that we wanted to achieve at least that level of precision in order to be able to know what we were doing.

Q. Yes.
A. So it was quite hard to achieve that. With current equipment, it was quite hard to achieve even plus or minus one degree.

Q. But if you went about changing those heat treatment protocols between one and another, for whatever reason, would you have had to conduct any type of safety verification procedures in between those steps in order to use that product?
A. If the oven had been reset to a different temperature, it would have to be revalidated over a week with temperature sensors all over it to make sure that every vial that went in was in that bracket of 80 degrees plus or minus one.

Q. But if you decided to change it from 80 degrees by 72 hours to a different temperature and different time, would you have to conduct any experiments as regards the safety of using that finished product?
A. If you were going to really progress to a different product altogether, it would certainly be worthwhile revalidating the oven perhaps on a reduced -- if you had shown that at 80 degrees the mixing of air and temperature in the oven was good

enough, you might rely on a more cursory revalidation to be sure that the accuracy of the oven -- you would be getting -- your set point was 60 rather than 63, say.

Q. Would you be obliged, though, to look at the effect that a new product would have on the patients by conducting some sort of clinical trial, or conducting some sort of experiments to satisfy yourself that it wasn't going to cause harm?
A. In normal circumstances, yes, of course. 1984 and '85 were very unusual times and the usual procedures for preclinical and clinical testing were sometimes accelerated.

Q. So there was something of an emergency situation prevailing, to say the least, in '84 and '85?
A. Yes.

Q. When that period had passed and if you were considering changing your heat treatment protocol, would you then have conducted a more strenuous testing of the finished product and the effect it would have on patients who would use that product?
A. I think you would certainly give that a lot of thought, and the regulator would probably have had some input into whether it required that, the changeover from one product to another. What you actually did would depend on whether you were going up or down, you know.

Q. Yes. And the regulator being the -- in your case, who would the regulator be?
A. Medicines Control Authority.

Q. So you had a government agency that you were contemplating doing this in several degrees --
A. This would be the regular way of doing it.

Q. Just with regard to non-A non-B Hepatitis, Dr. Smith, and the risk of that, at page three in the third paragraph you say that opinion -- "Opinion has always been polarised between groups that think that infection leads to serious liver disease and increased mortality" and those who would hold a contrary view, that it's definitively "a few patients would acquire chronic active hepatitis or die from it." Can I take it, from what you were telling Mr. Durcan, that your organisation would have been of the view that this was a serious condition that had to be dealt with?
A. Yes.

Q. And in that sense you -- from -- if I understand what you said to Mr. Durcan, starting in 1983 you would have addressed the problem of non-A non-B Hepatitis in a very serious way?
A. Well, we were trying to address it before that, of course, but we didn't have many tools in our kit. And it was only breakthroughs by originals which encouraged us to move much more rapidly.

Q. So you would have been of the view that this was something that had to be addressed, and that was the purpose of the various work that you were carrying out in terms of different heat treatments and culminating in the factor -- the superheat-treated Factor VIII and Factor IX?

A. Yes. I was working next door to the haemophilia centre, which was one of the leaders in trying to run down the two incidences of non-A non-B Hepatitis following the use of Factor VIII and Factor IX concentrates. And therefore, although that was only published in 1983, there were certainly many warning signals, which we took very seriously, all through the late '70s.

Q. So you wouldn't have agreed then with the other half of that polarisation; that this was something that very few patients would -- would affect very few patients?
A. I'm not a clinician. I found the -- recognised that it wasn't up-to-date, particularly across the Atlantic, in just how serious the consequences of non-A non-B Hepatitis was. I could not begin to judge the rights and wrongs of that. But it was certainly my impression that there was no convergence on how serious it was. I knew what I thought, but that's -- I'm in no position to be on record in that respect since I was not required to.

Q. But just from the actions of your organisation and philosophy of it, it seemed to be that non-A non-B was something that they had to deal with?
A. Yes.

Q. And they said that to England?
A. Absolutely, yes.

Q. And eventually achieved some degree of success in that?
A. Yes.

Q. Just with respect to that, Dr. Smith, could I refer you to page four, please. And just at item six, you talk about, "Laboratory testing for the inactivation of viruses consisted of adding a concentrate," you talk about how the actual test would be carried out; you note that non-A non-B Hepatitis could not be cultured. And you say there that, "The selection of surrogate viruses for study was difficult and the relevance and results of non-A non-B was always contentious."And in the following paragraph, also discussing non-A non-B Hepatitis, you say, about two-thirds of the way down, that entry at item seven: "The first satisfactory trial for non-A non-B Hepatitis was not published until 1987." But prior to that, had it come to the knowledge of your organisation that the 80 by 72 Factor IX and Factor VIII were effective for non-A non-B; can you remember when you actually were able to say, this is going to work, or you thought it was going to work?
A. When I thought it would -- well, it's only what -- as far as the most recent infusion. Somebody could get 8Y tomorrow and get non-A non-B Hepatitis after it, but we'll take it just when I thought. We started clinical trials of a very informal nature in March or April 1985 for the first batches of 8Y. The accrual of patients was extremely slow, for two reasons: One, that the criteria for sampling the patients, the programme for sampling for ALT testing was -- there was no agreement on that, firm agreement at the time. There were no -- there was no real convergence on the absolute criteria to be applied to the aminotransferase measurements or to confirmation of raised transaminases. And by that time also, a great many clinicians were already committed to trials of other concentrates and it was very difficult to accrue previously untreated patients. We, therefore, accepted the view of some clinical advisors, that patients, who had had previous treatment but perhaps only a few doses of cryoprecipitate many years ago and had been in good health, might offer a

degree of information at least, even if not perfect. And also, it was some of our -- some of us thought that the testing regimen was perhaps too dogmatic, and that even some patients who had missed one or, at the most, two tests, might still be regarded as quite good evidence that they had no ALT rise or a significant rise, and might be adduced, at least as additional evidence, to the perfectly-followed previously untreated patients.

Q. Yes. Just with regard to that, could I refer you to a paper that -- I think that you delivered at Melbourne in 1986. Did you get a copy of that paper, Dr. Smith?
A. I got the one from the following year, which is perhaps even more relevant, but I can recall the Melbourne --

Q. Have you got the Melbourne paper in front of you?
A. Oh, yes, I have. I'm sorry.

Q. That paper, Doctor, you seem to say in that at page 325, I think it's in the discussion section of it, at the very end there, last paragraph, and you acknowledge that these are interim results on a limited number of batches, but you say: "We think we are justified in thinking that the severe heating has been more effective in preventing transmission of non-A non-B hepatitis than milder heating according to Hyland (1) and Armour (3)" -- and I think they're references to the footnotes at the bottom -- "products in the studies published last year." And you also refer -- you acknowledge that "it was too early to know whether non-A non-B Hepatitis transmission has been eliminated by severe dry heating or whether we may see transmission by only a few batches, as has occurred with Alpha's Factor VIII concentrate heated in heptane." At that point in 1986 would it be correct to say, Doctor, that you had a fair indication that your product was successful in dealing with non-A non-B Hepatitis in those patients that you had followed?
A. That was my impression. In those patients we had followed, there was reason to believe that we had not given them non-A non-B.

Q. And can you remember at that time how you then viewed the product; was that with some degree of confidence?
A. I wouldn't put it so highly, given that almost every other concentrate, every other treatment up to that time had failed at least some patients. I was confident enough to really be appealing there for more people to bring forward patients so that we could be said to have a higher degree of proof.

Q. But you were sufficiently confident to present this paper to your colleagues in Melbourne, is that correct?
A. In the context of other treatments which reminded people of the ones which had failed on -- after initial promise.

Q. And do you remember when in 1986 that would have been, that paper would have been delivered?
A. Does it not say? I think it was the -- our summer; would it be August or September? I think the summer, our summer.

Q. Summer of '86?
A. Yeah.

Q. Just when you got to that point, did you ever go back to the BTSB or did anybody else from your organisation go to the BTSB and inform them that they had something that looked like it was going to work with respect to both HIV and non-A non-B Hepatitis?
A. I can't remember anyone consciously doing that. We would assume that BTSB had -- was actively reading literature - especially the promising literature, might very well have been present in the Melbourne meeting - and taken from that what they would.

Q. This meeting in Melbourne, it's the international association of -- the IABS, what organisation is that? Just at the very top of the first page?
A. Yes. That's the association of blood society or blood -- I'm sorry.

Q. It's an international organisation anyway?
A. I thought it was ISBT, actually.

Q. Maybe it is. I thought it was ISBT as well.
A. The usual people were there, usual suspects; fractionators, transfusionists, haemophilia treaters.

Q. Listening to this type of information being disseminated?
A. (Nods head.)

Q. But you never went back to Ms. Cunningham and said to her, 'we have something here that looks like it's going to work'; you don't remember doing that?
A. No. I wouldn't have thought of Mrs. Cunningham as being the filter through which BTSB would have made the judgment.

Q. If there was such a filter in the BTSB, who would you have dealt with, do you think?
A. I wouldn't have thought it my place, as a fractionator, to try and convince a particular clinician or a particular organisation to go this way. Not at this stage. If I had, if I'd had the brainstorm I might have taken it upon myself to do so, I think, at that time; even Dr. O'Riordan himself or possibly Dr. Walsh.

Q. Dr. O'Riordan would have been gone at that stage. But thank you for that, Dr. Smith. On page seven of the -- of your statement, in the very last paragraph, you say there: "Many clinicians considered the risk of thrombogenicity to be even greater than that of AIDS." Have you any real basis for that statement, Dr. Smith?
A. Other than my casual contact with clinicians in the normal way during that time, I don't think there would be anything in print to support this. But I'll come back to the -- what they were doing; they were using NHS unheated concentrate in preference to heated US concentrates. There would be some, in fact quite a few.

Q. Would you agree that when, indeed, some people continued using unheated Factor IX, there were a fair proportion of them who started using heated Factor IX during those years?
A. Yes, but I couldn't tell you at any particular month what the proportions would be. I would think, going through '84 - quite a lot of '84 and into the middle of '85, the

proportion would move very much towards those who couldn't wait to get a heated concentrate.

Q. And that was because of the developing problem. And I think we see also, in July 1985, Dr. Craske reporting that two patients had on -- two Factor IX patients had seroconverted, recommending heat treatment, heat-treated product be used from there on. Just with regards to that, you say that, "unheated English Factor IX never transmitted HIV." And Mr. Durcan has raised this with you. Was that your impression up until you -- up until October of 2000?
A. If I put in had never transmitted HIV, it would have been an appropriate reflection of the times. I cannot recall, as I said here, a well-proven confirmed case of transmission, but please don't take my word for it. I'm not prepared for the -- to go through all the details of publications which may have claimed a seroconversion. I bow to those who have --

Q. To the fact that there might have been?
A. Yes.

Q. Yes. Thank you, Dr. Smith. Just one thing with regard to the discussion you had with Mr. Durcan on the Gail Rock method and the method of fractionation. When you concluded in 1981 that that method wasn't going to work, between 1981 and 1984 what product did you develop, what Factor VIII product did the -- your organisation actually develop during that period?
A. We provided an improved version of our original intermediate purity concentrate, which differed only in being rather more potent. That was about two-and-a-half times -- it could be dissolved in a smaller volume of water to compete with the UK -- US concentrates being imported at that time. We were asked to do that; we did that. That explained the -- in doing that, and also in trying to take on board possibilities of protecting patients from non-A non-B Hepatitis, we had to go in to look at many methods of purification, at least to some degree, of the Factor VIII, to make it more amenable to severe treatments which might be virucidal.

Q. And would I be correct in saying the -- obviously the Gail Rock contract fraction, that Heparin method wasn't the sole output of your efforts during, even, the time when you were looking at it; there was other things happening in parallel to it?
A. Yes.

Q. Just one other item, Dr. Smith, before we finish: The AT3, was that the only change required before you could apply the appropriate heat-treating method?

THE CHAIRPERSON: Sorry?
A. The only actual change which we instigated. But we did check, having become aware of the importance of the freeze-drying conditions to the success of dry heating, we did look - go back and look very carefully at the appropriateness of the -- the robustness of the freeze-dried conditions for that particular concentrate.

MR. McCULLOUGH: Thank you, Dr. Smith.

THE CHAIRPERSON: Thank you, Mr. McCullough. We'll resume again at 2:00 p.m.. thank you.

THE TRIBUNAL THEN ADJOURNED FOR LUNCH.

THE TRIBUNAL RESUMED AFTER LUNCH AS FOLLOWS:

THE CHAIRPERSON: Mr. McGovern, please.

MR. McGOVERN: Thank you, Madam Chairperson.

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

Q. Dr. Smith, my name is Brian McGovern and I appear on behalf of Professor Temperley and Dr. Daly and Dr. Jackson, who are three haematologists in Ireland. I have really just one question to ask you: You said in the course of your evidence that -- and I think you were referring to 1985, that you wouldn't like to have been a treating clinician at that time. And I'd just like to ask you why you said that?
A. Well, I felt they were between at least two stools all the time, efficacy versus safety. The state of knowledge was extremely fluid, and they were dealing with terrible issues of life -- literal life and death to their patients; and were, almost inevitably, not going to get everything right first time. My sympathy was very much with not only with the haemophiliacs in this tragedy, but also with the people who had to make the really difficult decisions, much greater than mine, in a technical sense.

Q. I see. Thank you very much.

THE CHAIRPERSON: Thanks, Mr. McGovern. Mr. O'Brolchain, have you any questions?

MR. O'BROLCHAIN: That was the one question I wished to ask the doctor myself, so we have the answer already. Thank you.

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

MR. ASTON: Two questions, Madam. Thank you very much indeed.

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

Q. Dr. Smith, my name is Tony Aston and I appear for the National Drugs Advisory Board. I have just one or two general questions I want to ask you. The first one is this: You have explained, in answer to Mr. McCullough, in great detail, you have explained how complicated the procedure was. You said a very specific method for freeze-drying the product; you said there is a very precise and technical method of heating the product. And you have given evidence also in relation to what I think was your input into it, which was the addition of AT-III, which was a breakthrough in making the superheat-treated method possible, is that correct?
A. For the Factor IX, yes.

Q. For the Factor IX. Sorry, for the Factor IX. So, to take the Factor VIII first: The particular methods that were involved in freeze-drying and in applying the high heat

treatment, were those generally available or were they ones that had been developed by you and were peculiar to you, as far as you were aware?
A. The situation was that we had been using a particular freeze-drying plant for many years, in Oxford. And the way in which it was controlled -- sorry, a little bit technical here: It was controlled from the temperature of the product, not, as is usual, the temperature of the shelves. Now, controlling the temperature of the product gave us tighter control over what was happening in the primary phase of drying. It was an accident almost that we had this equipment. We did not realise at the time that it was crucial to the success. We found out later that it was crucial.

Q. I see. So what I really want to know is: Did this method of super heat-treating Factor VIII become available to other fractionators; and if so, when and how?
A. It would be available in the technical sense as soon as we published, which I think was in 1985. They were -- there was a patent on aspects of that method. And at least two fractionation centres elsewhere took out a license on that patent. There was nothing to stop anyone repeating the method, in a development sense, but there would have been this patent obstacle to adopting it.

Q. Adopting that, absolutely. When was that, do you know, that they took out the patent license in style of manufacturing the superheat-treated --
A. I think it was substantially after 1985; I would think not before the promise of the method had really borne fruit. I would guess late '88, '89, even.

Q. I see. And in relation to Factor IX, was there a separate patent to cover the addition of the AT-III?
A. No. We regarded that as prior art and there would be no opportunity to patent that. The aspects of the Factor VIII concentrate which we patented referred to the purification enabling a soluble product to emerge from heating.

Q. I follow. So in summary really, it was -- provided that you got a patent license, it was open to others to avail of the procedure, but nobody did, as far as you are aware, until '88 or '89 at the earliest, is that right?
A. To the best of my recollection. Yes.

Q. Now, just on one other very brief thing I want to touch upon with you, and that is the publication of the results. I mean, you attended this conference in Melbourne in Australia - a conference of fractionators, as I understand it - in summer of '86?
A. And transfusionists in general, yes.

Q. I see. And Mr. McCullough has brought you through the discussion of that. I mean, the results were hopeful but tentative, at that stage, would that be --
A. Very well put. Yes, I agree.

Q. Thank you very much. And apart from being distributed to the persons who had taken part at that particular conference, was that paper published?
A. A version, slice of history was published first in 1987 -- 1988, in The Lancet, probably under Dr. Colvin's name as first author, on behalf of the participants.

Q. Yes. I think we were familiar with that, with that publication in The Lancet.

A. That was the only other -- I seem to recall in 1987 also speaking to the ISBT in Munich, but -- with just an extension of the data that we had.

Q. But even these tentative results wouldn't have become part of the public domain until the publication in The Lancet in '88, would that be fair to say?
A. I think the UK haemophilia centre directors were -- would distribute interim information among themselves. Most of them were participating in the trial. But in a formal sense, publication in a peer-reviewed publication, I think this would be the first.

Q. Yes. It would have been known among the treaters that this was the product that was being used in the UK?
A. Yes.

MR. ASTON: Thank you very much, Dr. Smith, indeed.

THE CHAIRPERSON: Mr. McGrath, please.

MR. McGRATH: Just one or two questions.

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

Q. Michael McGrath is my name and I represent the Blood Transfusion Service Board. Really I suppose it's a follow-up to the questions Mr. Aston has been asking you. You mentioned that you believed that two fractionators elsewhere used the super-dry-heat-treatment method for both I think Factor VIII and Factor IX, as I understand your answer. Do you know who they were?
A. First of all, not Factor IX. Factor IX was public domain -- the patent was only for part of the Factor VIII process, unrelated -- not directly related to the heating stage, just preparing it. The two that I can recall were South Africa, Netal Blood Transfusion Service; and Commonwealth Serum Laboratories in Melbourne, Australia.

Q. I see. And you are not -- you don't have specific dates on when they would have commenced using that method of fractionation?
A. It was in -- not in my sphere at all, and I can't recollect the dates.

Q. I see. I see. We acquired some information to the effect from the Australians that in 1989, they issued AHF made under license to BPM using that 8Y method, the super-dry-heat-treated method in 1989; would that accord generally with your recollection or your knowledge?
A. Yes, approximately. Yes.

Q. Yes. And again, the information which we received was that the process was extended to Prothrombinex in 1992. Again, would you have any knowledge of that?
A. That would be the dry heating, but in no sense the propriety knowledge.

Q. Yes. I see. I see. Just one other issue. You mentioned again, I think in answer to Mr. Aston, that you said it was an accident almost that you had the equipment at that time; and you didn't realise the importance of having that particular equipment

when you were developing the process. Were other fractionators within the UK in possession of that equipment that you were referring to?
A. I don't think anyone else had precisely that equipment. It was a French freeze-dryer designed to dry bottles, and we had adopted it that particular way to dry vials. In the '70s there may have been other freeze-dryers which recorded the temperature of the product. It was not the usual way -- I am not saying it's unique, but it was unusual.

Q. Yes.
A. There were also other kinds of equipment we happened -- having started quite early along dry heating, we had foreseen the need for a high-precision oven. And any other person -- any other laboratory would have taken at least a year to specify, build, develop and validate such an oven. We had a headstart because of our prior interest.

Q. Yes. When you say "at least a year," is that a year from the time when people were reasonably confident that this process was, as it were, the -- a better process than the other being used?
A. From deciding to use an oven, to heat concentrate in an oven with the kind of precision required, it would have taken approximately a year; and in fact did. Elstree had to specify freeze-dryers for their larger production and it took a long time to get these fully validated for production.

Q. Yes. And again, just finally, in relation to the Gail Rock method which we -- you mentioned this morning. I think from 1981 you were -- you were, I think, less than satisfied that it was going to produce the results which you would have desired; as I understand it that is the timeframe which you have given the Tribunal?
A. Yes.

Q. But that others were a little bit more optimistic and continued with the procedure for some time thereafter?
A. Particularly the Groeningen Laboratory in Holland.

MR. McGRATH: Thank you very much.

THE CHAIRPERSON: Mr. Bredin?

MR. BREDIN: No questions.

THE CHAIRPERSON: Have you questions --

THE WITNESS WAS EXAMINED AS FOLLOWS BY MS. McNALLY:

Q. MS. McNALLY: My name is Maura McNally. I appear with Mr. George Bermingham instructed by William Egan on behalf of Cecily Cunningham. I have two questions for you: In relation to the decision to heat-treat or not heat-treat, is that the type of decision that you would describe as a fundamental policy decision?
A. Yes.

Q. And as a fundamental policy decision, is that the type of decision that would be reached simpliciter by a fractionator alone?

A. No.

Q. Thank you.

THE CHAIRPERSON: Thanks. Mr. Durcan?

THE WITNESS WAS FURTHER EXAMINED AS FOLLOWS BY MR. DURCAN:

Q. MR. DURCAN: I think I have just two short questions. In your evidence in regard to the heat-treated Factor IX, I think on a number of occasions you used the expression "we reached an agreement that we would wait 'til the dog infusion trials had finished". Who were the parties to that agreement; who decided that, is what I'm getting at?
A. It would not be a meeting at which I sat down with two others or three others or four others, it would be a process of consensus in several stages, orchestrated by Dr. Lane, our medical director. And without any doubt, taking into consideration the views of our other medical advisors, especially in the realm of haemophilia. There was, to my knowledge, no single crunch meeting.

Q. When you say "reached an agreement," is what you are getting at is that this was decided within the Plasma Fractionation Laboratory, having regard to the views of quite a large number of people, including the treaters?
A. Taken essentially by Dr. Lane, the medical director of both BPL and PFL, sure that he had the backing of his medical advisors and presumably a large part of the critical
fraternity.

Q. I see. The only other thing I want to ask you, Doctor, is this: You had the contact with Mrs. Cunningham around the end of 1984 or beginning -- right into the beginning of 1985. Do you know or do you recall was there any further contract in particular in regard to Factor IX during 1985, or can you recall?
A. I simply can't recall either way.

MR. DURCAN: Thank you very much.

THE CHAIRPERSON: Thank you, Mr. Durcan. Mr. Smith, thank you very much indeed. The Tribunal is obliged to you for coming.

THE WITNESS THEN WITHDREW.

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

THE TRIBUNAL THEN ADJOURNED TO THURSDAY, 19TH OF JULY, 2001, AT 10:30 A.M..