Thursday, 3 November 2011

(9.30 am)

DR RONALD MCINTOSH (affirmed)

Questions by MR MACKENZIE

THE CHAIRMAN: Good morning. I understand you wish to affirm.

Yes, Mr Mackenzie?

MR MACKENZIE: Thank you, sir.

Good morning, Dr McIntosh.

A. Good morning.

Q. Could we start by looking at your CV, please? That is PEN0171199. I'll take you briefly through it. We see you graduated with a Bachelor of Science (Honours) in genetics. You then, I think, undertook a PhD in immunoglobulin matters. Then, Health Professions Council, clinical scientist. Is that some official registration?

A. Yes, since comparatively recently, I think, the last ten, 20 years, scientists working in the health service are required to be registered with the Health Professions Council.

Q. If we scroll to the very bottom of the page, please, we see under "Publications and Presentations", you have published over 50 items, both as the first author and co-author but you have spared us a long list of them,

thank you.

If we could then look at your career history and deal with it chronologically, we can see that between 1979 and 1982 you were a scientist at the Medical Research Council at the Western General Hospital and then in 1982, I think, you joined SNBTS Protein Fractionation Centre. Is that correct?

A. That's correct.

Q. And between 1982 and 1987, you were a senior biochemist there in the research and development department. Just to complete your CV, we see that between 1987 and 1990, you were a principal biochemist in the same department, and then between 1990 and 2001, you were a principal development scientist, I think in the same department. And then 2001 to 2007, you were operations manager at the PFC. Was that a move out of the research and development department?

A. Yes, it was, although, being a relatively small centre -- and one of the strong features of the PFC is that production, research and development, engineering, QC, all departments were on one site, we still kept, obviously, in close touch with colleagues in research and development.

Q. As operations manager, were you responsible for the manufacture of products?

A. Yes, I was the named person with responsibility for product manufacture at that time.

Q. Thank you.

Then we see between 2007 and 2009, you were director of the Protein Fractionation Centre and then 2009 to present, a consultant in biologics specialising in human blood plasma products and you are self-employed. So you have left the NHS?

A. That's correct. PFC was closed down and I took voluntary early severance from the service.

Q. Thank you. I would like to go back, please, to 1984 and to ask, please, what your first involvement was in development work of Factor VIII concentrate.

A. In 1984 -- I joined the PFC in 1982 to work originally with Dr Anne Welsh on the development of immunoglobulin for intravenous infusion. That product was successfully produced in 1982 and went on to become one of the major projects in the plasma fractionation industry. By 1984 I had experienced a number of other projects on troubleshooting projects. It was also a role of the R&D department to take on the solving of production problems if they arose. So in August 1984, I think it was, Peter Foster asked me if I would take on the project to develop the method which had been devised by Professor Alan Johnson in his lab at New York University

medical centre, to develop it into a manufacturing process.

Q. Thank you. I would like to ask you a few questions in turn, firstly about the ZHT project and then secondly the Alan Johnson project. I should say we have covered much of this ground previously. So I'm not going on ask you questions in detail but I think, given you are here, it is helpful just to make use of your knowledge and expertise in these matters.

So dealing firstly with ZHT, when Dr Foster spoke with you in about August 1984, what did you understand to be the stage or state of the ZHT project and what, if any, problems did you understand there to be with that project at the time?

A. Fine. I should say I wasn't directly involved in the ZHT project but because I was taking over on what was the successor project to that, or a project that was intended to facilitate pasteurisation, I did understand what the issues were.

Those were firstly that in order to achieve satisfactory recovery of Factor VIII across the pasteurisation process, it was necessary to add very high concentrations of stabiliser, and stabilisers were carbohydrates. So these were of the order of 20, 30, 40 per cent. This gave an extremely large volume

solution and also a solution that was exceptionally -- that was very, very viscous. So this made the processing time long and it also was difficult. For example, a very viscous solution is difficult to mix, it's difficult to pump. So the idea was that if a purer Factor VIII preparation could be prepared, then if the key feature in stabilisation was the ratio of the product to the stabiliser, then the concentration of stabiliser would fall and it would make it much easier to handle. If it was that the concentration of stabiliser was still needed, then with a much purer product, you would have a much smaller volume. So that in itself would be beneficial in making the process stages fit into the working day and also fit the equipment that was available at PFC.

There were other issues also, I think. It was commented, certainly to me, that the precipitation step, where the Factor VIII was recovered from the high concentration of stabiliser, was a difficult one to control and it was possible perhaps to look at alternative technology for that, instead of precipitation, ultra-filtration, which we adopted in the successor process, the NYU process, and there had also been of course an adverse reaction to ZHT, which I think has been commented earlier in the evidence to the

Inquiry. So to make changes to the process, if changes were required to make the product more acceptable on infusion, then we would need a process that we were flexible with to make changes to.

Q. Were there any difficulties in yields of the ZHT process?

A. Yes, I think so. The NY process, the original PFC intermediate Factor VIII concentrate, was a very elegant process that gave, in a relatively simple processing method, a very high yield. So that had been the basis of the success in PFC in providing the quantities of Factor VIII that allowed it to become self-sufficient and allowed it, for example, to transfer over to dry heat treatment so successfully. So it was necessary to maintain a yield in any new process that would allow us to have a similar output.

Q. Now, just before we leave ZHT, when you spoke with Dr Foster in August 1984, at that time what was your understanding as to whether it would have been feasible to ramp up the ZHT process to full production at PFC?

A. It would not have been feasible. The difficulties in processing such a large volume of viscous solution and also adding additional processing steps to fit into the available working schedule and production, would have made it very difficult to do.

Q. Thank you. I'm now going to leave ZHT and move on to the NYU Professor Johnson project, doctor. Again, I think we have gone over this in some detail but are you able to help us in relatively simple terms what it was that the Professor Johnson project brought to the table, and perhaps give us some indication of the initial work on that project?

A. Certainly. What Professor Alan Johnson's process, developed by him in his laboratory at New York University medical centre, offered us was a method for the purification of Factor VIII using materials that were already available and developed. So what it offered us was a purification of Factor VIII using ion exchange, chromatography technology. In fact, the process involved an ion exchange step and a subsequent purification step on a different chromatography media that didn't work entirely on ion exchange technology.

This provided a product that was, after the second step, maybe over 1,000 units per milligramme. So this is a very, very, very good product. After the first step, between 100 and 200 units per milligramme. The key feature of the Alan Johnson process was that he had developed a way of formulating the material prior to separation that allowed you to use existing separating materials. So you didn't require to invent any new ion

exchange material or any new separation technology.

The caveat to that was that the ion exchanger that Alan Johnson was using, had a very low binding capacity and the process that he was using, he was taking a direct extract and applying it to the first ion exchange chromatography step. So this would not have given us the processing capacity we would have required with the many more complex steps in order to meet the requirements for Factor VIII production at PFC.

A further feature, however, that made the process attractive and worth tackling these issues, in addition to giving us a means of purifying Factor VIII much further, was that according to Alan Johnson's results, this was a high yield process. So this would allow us to get the purification that was needed to aid pasteurisation, without compromising yield which already had become an issue in the development of the pasteurisation process.

Q. Thank you. Just to recap a little, am I correct in my understanding that with Professor Johnson's ion exchange chromatography step, the intention was that there would be a prior step of zinc precipitation on the cryoprecipitate extract?

A. Yes. As I say, one of -- in taking a look initially -- in fact, Peter had already seen this, he had observed it

because he was familiar with the work on ZHT -- one of the ways of improving the capacity of the Johnson process was to load less material into the process. So if we could carry out a partial purification before beginning the ion exchange chromatography, that would then of itself give the process a much more needed capacity. And to do that, we used the front end of the ZHT process.

Q. Okay, and the front end of the ZHT process was?

A. Was zinc heparin precipitation and alhydrogel adsorption.

Q. Zinc heparin precipitation. This may be an oversimplification but in short, during the zinc heparin precipitation step, zinc and heparin are added and they precipitate out the unwanted fibrinogen and fibronectin?

A. That's correct.

Q. Whereas with the Johnson ion exchange chromatography, what is happening in simple terms at that step?

A. Okay. In the ion exchange step, ion exchangers are solid phase gels or resins -- a convenient way to think of them as beads that carry a constant charge. So proteins, because they are made up of amino acids, will also carry a charge and you can influence the charge on the proteins by the way in which you formulate them, the pH that you have them at. So the idea of ion exchange

chromatography is if you have anion exchanger, such as we were working with here, one that carries a positive charge, if you can arrange the conditions such that the protein you are interested in carries a negative charge, then it will bind to the ion exchanger. You either can wash the other proteins off, then you can alter the condition inside the ion exchanger by coming on with a second buffer that will either alter the pH or alter the ionic strength and you can elute the Factor VIII from the ion exchanger.

Q. This may well be an oversimplification but very broadly speaking, is it right to think of things this way, that at the zinc heparin precipitation step, one is taking out what one doesn't want, the fibrinogen and fibronectin, and leaving in what one does want, the Factor VIII, whereas with the ion exchange chromatography step, one is extracting what one wants, ie the Factor VIII?

A. Yes, there would still be some proteins other than Factor VIII left in the supernatant from the zinc precipitation process. So you would bind them to the ion exchanger, and then typically you would have a wash step where you change the conditions to elute some of the proteins you don't want that have bound, but leave the Factor VIII on. The second elution step to remove

the Factor VIII.

Q. Yes, thank you.

A. But it is as you describe, you are adsorbing the Factor VIII and some other proteins, then washing off the other proteins and eluting the Factor VIII.

Q. I think I'm going to quit while I'm ahead on this matter, unless the chairman would like to ask any further questions at this stage?

THE CHAIRMAN: I think what we have to envisage is what we have been told about before, a columnar arrangement.

A. That's correct.

THE CHAIRMAN: In that, at your stage, you have introduced positively charged particles of some kind.

A. Beads.

THE CHAIRMAN: And anything that has got a negative charge that is then introduced is likely to be adsorbed on to the column of beads.

A. Yes, to different degrees of affinity that's right, yes.

THE CHAIRMAN: So the next stage is to distinguish the FVIII among that by eluting out anything that's different.

A. That's correct.

THE CHAIRMAN: So you get a better concentration of FVIII at the end.

A. And a purer product.

THE CHAIRMAN: And a purer product. If that's sufficient

for general understanding, let's go on.

MR MACKENZIE: Before returning to your statement, I should just complete this by asking what work was undertaken on the NYU projects between you starting and roughly August 1984, up until, let's say, the summer of 1985.

A. 1984 to the summer of 1985. I carried out a great deal of work on the process. The first objective was to give it a higher capacity and as we have discussed, that was done by using the zinc precipitation step to reduce the amount of material that had to be processed. The next stage was to replace the ion exchange gel, which Alan Johnson was using, which had a low binding capacity, with an ion exchange gel that had a higher binding capacity, and we worked with a company called Pharmacia who were experts in the manufacture of ion exchangers, in order to obtain a gel of this type.

By this time, I think recognising that this was much more -- we were adding several more complex steps, by this time I think I had agreed with Peter that we should for the moment leave out the second chromatography step, the aminohexyl step, because Jim Smith in his group at Oxford had been working on the use of aminohexyl for the separation of Factor VIII, and it was in discussing that with Jim and his group and Peter suggesting I contact them that introduced me to Jim and his group.

So having talked to them and realising the difficulties of it, we agreed that 100 or 200 units per milligramme was sufficient purity for what we needed. We would assume it would have been sufficient purity. In fact, too high a purity of product does bring problems, but we can go into that detail if you wish.

The other major advance was that in order to prepare a higher purity Factor VIII, the Factor VIII was required to be eluted from the ion exchanger in a very high ionic strength, and to do this Alan Johnson used very high levels of calcium. It is not possible, in a physiologically acceptable formulation, to have very high levels of calcium, so we had to substitute the high levels of calcium for high levels of other salt combinations which we worked on, in order to be able to elute the Factor VIII. And this required a combination of high levels of salt and wetting agents to prevent non-specific binding, levels of alcohol, surfactants that can act as emulsifiers to prevent the Factor VIII binding to the column. And the last problem was to develop a formulation in which the very high purity product was stable. Proteins will bind to surfaces and so when your protein is present -- when your activity, the product you are after, is present in a very, very small amount of protein, if that small amount of protein

sticks to the side of the vial or sticks to the side of the tube or sticks to the piping, then you have lost all your activity.

So it was important to develop a formulation in which it was stable. Then from then on it was a matter of scaling the process up. So we did a lot of work to try to simplify the Johnson process and to combine a number of manufacturing steps in the Johnson process, such that it would make it simpler and easier to introduce them to production.

Q. If we could now turn to your statement and I will take you through the questions we asked there, it's PEN0171234.

A. Yes.

Q. It should come up on the screen. If you have a hard copy, please feel free to use it.

A. The screen copy is fine, thank you.

Q. We asked you, along with the other witnesses, a number of standard questions. The first question relates on 8Y. Could I ask, doctor, do you remember when you personally first became aware of PFL's work on 8Y?

A. I think I say -- can you scroll up? It would be, I think, late 1984, because August 1984 I started work in the NYU process. As I say, the NYU process as well as the ion exchange chromatography, had a second

chromatographic step using aminohexyl sepharose, and Jim Smith's group had been working on the purification of Factor VIII using aminohexyl sepharose, and Peter suggested I contact Jim's group to discuss that step. And it was through those discussions with the scientists in Jim's group at Oxford, Lowell Winkelman and Peter Feldman and Dave Evans, that I would have learned of the 8Y process.

Q. So that was probably in late 1984?

A. Yes, late 1984, I would imagine.

Q. Just on the question of your contact with scientists at PFL, between 1984 and 1987, how much contact, if any, did you have with scientists at PFL and BPL and how was that relationship?

A. Lots of contact as and when needed, really. It tended to be more that Jim and Lowell would visit us than we would visit them. I don't know why that was. Perhaps so Jim could see his sister in Edinburgh. That tended to be more the case. But they were never more than a phone call or a letter away, as were other staff at BPL. When I first started work with Anne Welch on immunoglobulin, one of our problems was anti-complementary activity. So within weeks of being at the PFC, I was on the phone to the person at BPL, Mike Kavanagh, who was working on that. There was never

a problem with collaboration.

THE CHAIRMAN: Can I interrupt you just a little bit. You are displaying the sort of problem that my daughter displayed after she went to Glasgow. She began to speak so quickly that the rest of the family found it difficult to keep up, and I think at the moment you are stretching the capacity of the stenographer beyond --

A. I apologise.

THE CHAIRMAN: It's all right. It's a perfectly natural phenomenon but we all have to speak more slowly to make sure that we are picked up. Especially when there are technical terms around, which are challenging anyway.

A. Thank you.

MR MACKENZIE: Thank you, doctor.

We have your answer there. I don't think your written answer adds a lot to that perhaps. If we look at the written answer, you essentially say that matters are correctly set out in two SNBTS briefing papers which were sent to the Inquiry, and your final comment is:

"One comment I would add is that we were aware of some of the major features of the 8Y process, such as using high concentrations of heparin as a precipitating agent ... prior to receiving a more detailed description of the method of manufacture in a copy of the patent application received after its publication in

March 1985."

So again, when you say, "I would add ... we were aware of some of the major features of the 8Y process", is that a reference to late 1984?

A. Yes, I'm sure it would have been.

Q. Thank you. Over the page, please, the second question we asked was:

"When did it seem likely from evidence of its clinical use that 8Y ... did not transmit NANBH?"

You refer in your response to:

"... the development of evidence that the heat treatment of 8Y at 80 degrees for 72 hours could prevent the transmission of NANBH. From the initial report, the UK haemophilia directors ..."

That's in September/October 1986 to the later published findings. It's described also in the briefing papers referred to above, and you explain:

"I would first have learned of these clinical results from Peter Foster ahead of them being reported or published, as Jim Smith at the PFL kept the PFC up-to-date on these matters through Dr Foster."

Dr McIntosh, we have heard that clinical trials, phase 2 trials of 8Y started in April 1985 and that there would be a period -- I think a number of months -- before one could really place any weight on the results,

given one is looking out for elevations and transaminase in recipients. Do you remember in 1985 -- perhaps towards the end of 1985 -- whether you received any communication of preliminary results of the 8Y trial?

A. No, not directly. Any information I would have received on the progress of 8Y trials would have been from Peter or Bruce Cuthbertson who, as head of quality, would have had an interest in these things. No, I received nothing directly from Jim or his team.

Q. I think the first reference we have found in the PFC documentation to knowledge of the initial 8Y clinical trial results is a reference in an addendum to a report by Dr Perry in January 1986, referring to a personal communication with Dr Smith. So do you think it's unlikely you would have been aware of the initial 8Y results before then?

A. Very unlikely.

Q. Yes. Moving on to question 3, please, we say that:

"In October 1985 PFC discovered that their existing intermediate NY Factor VIII product withstood heating at 80 degrees centigrade."

We asked:

"Why was such heating of the existing ... product not introduced immediately?"

Am I right in thinking, doctor, you made that

discovery, albeit with the qualification you give in your written answer, you conducted that experiment?

A. Yes.

Q. In your written answer, you explain:

"The discovery to which the question refers did not, in fact, demonstrate that the existing intermediate NY Factor VIII product withstood heating at 80°C but rather that small samples of NY Factor VIII material could withstand 80°C heat treatment when freeze-dried in a particular way."

I will come back shortly, doctor, to ask you questions about this experiment but just to complete your answer, you say:

"This observation was made initially during the experiments being carried out to design a new freeze-drying cycle for the high purity, high potency Factor VIII product that would have resulted from the NYU project."

We have heard about that:

"Freeze-drying of the high purity material had completely failed using a model cycle based on the standard production cycle of that time. Experimental samples were in small volumes, eg 2 to 3 millilitres, dispensed into relatively small, eg 10 ml vials, because this was the dose form in which we anticipated a high

purity/high potency product would be presented. The control samples of intermediate purity Factor VIII were prepared in the same way."

A. Yes.

Q. Why did you include a control sample of the intermediate purity Factor VIII?

A. The freeze dryer being used in these experiments is called the "SMGR". It's a steam sterilisable dryer, so it's capable of producing clinical grade sterile material. That was located in our pilot plant. It's much smaller than the production dryers. I think the size of freeze dryers is normally annotated by the shelf area. The shelf area in this dryer would be half a square metre. Our production dryers at the time -- SM200, the "2" stands for 2 square metres; and the SM600 for 6 square metres. So it's much smaller.

So when we had prepared sufficient Factor VIII material to freeze-dry, because freeze-drying would be a part of any of the Factor VIII process that emerged from the NYU project, it's initially to determine what its freeze-drying characteristics were. So in the first experiments, we used the existing production cycle for the production freeze dryers. Because the pilot dryer is different from the production dryer, you have to run a model of the cycle. I see in my written reply I do

say it's a model cycle.

The analogy I used to use to people is like, if you are in a family saloon and you are doing 2,000 revs in third gear, you are not doing the same speed as if you are in an articulated lorry in third gear doing 2,000 revs. So it's a different machine and an entirely different design and internal layout. So you need to put different inputs in to get hopefully the same output. You are modelling what the production output would be.

When you conduct that kind of experiment, it's necessary to have a control of the material that would behave normally under those conditions, so that you can distinguish, at the end of the experiment, if the experiment has not been a success, is it because the freeze-drying conditions are not correct or is it because the model has run inappropriately? So the purpose of the control is to determine whether or not the model cycle has operated correctly.

Q. Thank you.

A. And you would include a similar control in order to determine what the effect of the cycle was on the normal product for which the cycle had originally been designed.

Q. I understand. That's fine, thanks. I may come back to

ask you some questions about freeze-drying later but I'll simply continue with your statement just now, if I may. You go on to say:

"The observation that the control samples withstood heating at 80 degrees was important in suggesting that intermediate purity Factor VIII material could be successfully heated at that temperature when freeze-dried in a particular way."

A. Yes.

Q. Over the page, you say:

"However, even if these new freeze-drying conditions would have been applied to the normal NY dose form, 35 to 40 ml in a 65 ml vial, the time taken to complete the new cycle with this amount of material in each vial of a batch would have vastly exceeded the available production capacity."

Can you just explain that sentence, please?

A. Yes. The freeze-drying cycle that was required for the high purity material used a much slower primary drying phase. The temperatures were lower and the length of time taken to remove the water in the first phase of freeze-drying, which is done by sublimation, was much, much longer than the cycle that had been operating for the NY intermediate purity product in production.

Q. Reading on:

"What was required, therefore, was a more concentrated Factor VIII solution so that the height of the filled product in the vial was much lower than NY, to give better freezing conditions and an acceptable cycle time. To prepare a more concentrated Factor VIII solution, some additional purification was needed and this could be achieved using the cryoprecipitate processing conditions employed in an NYU project, which had been derived from the ZHT process. This was the basis of the Z8 project, ie to prepare a Factor VIII solution of sufficient purity, such that it could be concentrated into a formulation that would allow the Factor VIII solution to be freeze-dried in a manner that would enable the product to be heated at 80°C."

I'll pause here, doctor and perhaps just ask you a few questions about the freeze-drying cycle used at PFC.

Now, it might be helpful perhaps to have a picture before us while we do this. We looked yesterday, I think, at a photograph PEN0121695 at page 1712. It's at page 18 of the document, 1712. Here we go.

A. Okay.

Q. We don't, I think, have a date for these photographs, doctor, but --

A. The one on the right-hand side is certainly

contemporaneous with the Z8 development. It's the SM200, which I referred to earlier. The one on the left-hand side is a much later picture of a larger dryer, when the dryers have been moved to be integrated with the aseptic dispensing area.

Q. So he can ignore the one on the left and stick with the one on the right-hand side of the page?

A. The principles of the way they operate is the same, but the one on the right-hand side, as you suggest, gives us a clearer picture.

Q. I should start by asking: this is a photograph, I think, of the type of freeze-drying unit, the freeze dryer used in the Z8 process. Was that same unit also used in the NY process?

A. Yes.

Q. I see.

A. The intermediate purity Factor VIII process, yes. Although, we did in the Z8 development have to make some adjustments to the way that freeze dryers operated, largely in control of heating and cooling.

But perhaps should I -- are you suggesting I should describe how freeze-drying and the freeze dryer works?

Q. Yes, I think in general terms, if you could explain how freeze-drying and the freeze dryer works.

A. Fine. What you see is the front of the freeze dryer.

It's a cylindrical steam-sterilisable pressure vessel, although the 200 was sterilised by freeze steaming, it wasn't entirely steam sterilisable and was replaced later other. So as well as this chamber, which is a large tube, there would be a second chamber containing what is called a "condenser", and a valve between the two.

So it's convenient to think of freeze-drying in three distinct phases: freezing, where, obviously, you set the structure of the product, and I think you have seen from earlier evidence how important that is in influencing how freeze-drying is carried out; also, the depth of the freezing, the temperature to which you freeze, because of the different chemical properties of products, then they will have different final freezing points when the product is totally frozen, and the product must be totally frozen because the next stage, primary drying, is when you are removing the water by sublimation.

So you are arranging conditions of temperature in a vacuum, such that the water moves directly from the solid phase of ice to the gaseous phase. When it does that, it moves to the other chamber, which contains the condenser and the condenser runs at a very low temperature, lower than the temperature of the product.

So there is a pressure gradient from the vapour pressure of the water leaving the product, to the pressure inside the first chamber, to the vapour pressure at the temperature that the condenser runs at. So you will sometimes see this perhaps in your freezer at home, things will dehydrate, the ice will move to the coldest part of the freezer.

So having set the freezing conditions, you enter the first phase, which I have just described, which is lyophilisation -- the first phase of lyophilisation, which is sublimation. At the end of that primary drying phase, you should be left with something that contains a relatively small amount of water, typically 5, 6, 7 per cent. The level of water is then so low that you can safely evaporate the remaining water, you can drive it off.

So in the secondary drying phase, the temperature is increased in the chamber and typically vacuum control runs to maximum vacuum so you drive off residual water to leave you with, in general, residual water contents of less than 2 per cent. Although, in terminally dry heat-treated products, you have to have fine control over residual water content; give a maximum and minimum residual water content, so you are controlling the amount of water left in the product for terminal dry

heat-treating.

So these shelves you see here and the tubes you see going into them can either be heated or cooled. So here the product is being loaded onto the dryer perhaps -- no, I think it's being unloaded. But initially, the product is loaded onto the dryer and shelves will be cooled to give freezing and then a vacuum is pulled inside the chamber and the temperature is increased. And the pressure inside the chamber and the temperature of the shelves need to be designed such that the product stays below what is sometimes called the temperature of insipient melting, so it remains solid. So you do not get any evaporation.

Then in our later cycle designs, a key feature of that stage is that the product temperature stays constant, so that the heat you put in is taken up by the sublimation of the water. So if this balances, the product stays constant in temperature. If you keep those conditions constant, when the product begins to rise of its own accord, it's because there is no more ice left to sublimate, so you know that primary drying is completed. You then add a period to ensure all the vials have caught up with one another, because in bigger freeze dryers you have large batches, and then apply the secondary drying conditions.

The secondary drying conditions can vary from 20 to as high as 40 degrees, sometimes reached in different stages depending upon the residual water that's required to be driven off. And the final residual water content you want to leave in the product.

I hope that was clear.

Q. I think that's probably sufficient on freeze-drying at present.

THE CHAIRMAN: In general, are you going to come back to ask freeze-drying in a particular way, the particular factors that are introduced in this paragraph that either reflect what we have just heard or distinguish the generality in some way, and I'm not sure what one should understand?

A. What I was describing there was -- if you like -- in general terms, the way we designed the freeze-drying cycle that we used for Z8, for use with that dryer. But if you want, I can point out the features of that cycle that were important in making Z8 able to be heated at 80 degrees.

THE CHAIRMAN: I'll leave it to Mr Mackenzie to deal with it when it suits him in his preparation and so on, but I just do not want the point to be lost. The particular factors are quite important to understand.

MR MACKENZIE: I think what I may do, sir, is stick with the

generality now and then I'll come back to look at what happened in October 1985, and then what changes were made later in 1986.

THE CHAIRMAN: Thank you.

MR MACKENZIE: Returning, please, doctor, to your written statement, if I may, we had then, I think, reached the next part of the question, where we had asked in the middle of the page:

"Why did it take until May 1987 before intermediate Factor VIII, manufactured by PFC and dry-heated at 80 degrees for 72 hours, was available for clinical use?"

In your written answer you give us a summary, a precis of what happened. I'll read that first and then take you through various documents, but in your written response you tell us that:

"The decision to develop an intermediate purity Factor VIII concentrate that could be heated at 80 degrees was made in late December 1985 and the product (Z8) was available for clinical evaluation in early December the following year.

"Albeit that part of the strategy was to retain as much of the existing manufacturing methodology as possible, this development required new purification, concentration, formulation, freeze-drying and heat

treatment procedures to be introduced and adapted to production scale operation under conditions suitable for the preparation of clinical grade material.

"Standard operating procedures for production and quality control needed to be prepared and approved for use together with batch record documentation.

"The finished product would have to complete the necessary quality control testing and batch release procedures before being made available for clinical use.

"To take this project from R&D laboratory scale work to production scale clinical grade product inside a year would normally be considered a rapid rate of development."

I would like to pause now, doctor, and take you through a chain of documents to really chart what happened between late 1985 and the product being issued for clinical use.

Is the best starting point your experiments in October 1985, we touched upon earlier, when you discovered that the intermediate purity NY Factor VIII withstood heating at 80 degrees in the adapted freeze-drying process? Is that the best place to start?

A. No, I don't think so. Having established that it would be possible to use that type of material to prepare a product that could be freeze-dried in such a way as to

make it heat-treated at 75 or 80°C, severe heat treatment, the key step then was to design for production a way of preparing material of that type.

Q. Yes. So when did that work start? Presumably in a laboratory.

A. That work started in the laboratory. I think in part of the documents you gave me to look at before the evidence, there is one of the early --

Q. Is this in late 1985?

A. Yes. 21/11/85.

Q. I see. Perhaps then we could go to two laboratory notes. Firstly, please, PEN0171378. This is a handwritten note dated 11 November 1985 relating to NY776. Do you recognise the handwriting in this note?

A. It's Peter's writing; it's Peter Foster's writing.

Q. Do you know what this note relates to?

A. I had to think hard about that. I didn't instantly recognise it. First of all, it's obviously about heating and then there are unheated products. NY776 is the product code and batch number for the previous intermediate purity product. And NYU195 is the code and the run number for the high purity material we had been preparing in the laboratory.

So then I couldn't work out what the word is beside the date, and I think that's "photo". I think this is

Peter taking photographs of vials that we had heat-treated that had been prepared in this -- in different ways. As a way of recording -- because the first thing you looked for, having heat-treated products under different freeze-drying cycles, was simply their appearance. You could tell if it had not been a success. But the NY776s are either intermediate purity material filled at smaller volumes that would represent as a model what we were aiming for in the Z8 process, or they may well be very small volumes as a model for further experiments on the freeze-drying of very high purity material. I suspect they are model materials for the freeze-drying of very high purity material because of the formulations, because they contain lysine. I don't think we worked on lysine formulations for Z8.

Q. So in terms of the chronology, we have in October 1985 the discovery that the intermediate purity Factor VIII can survive high heating in the adopted freeze-drying conditions. Is that right?

A. Yes.

Q. And then in November 1985, does this document suggest that some further work was undertaken in respect of heating the intermediate purity product?

A. I'm not sure about that. It could either be the

intermediate purity product or using small aliquots of the intermediate purity product as a model for the freeze-drying conditions required for the high purity product. Could be either. I can't tell from that sheet.

Q. I understand.

A. But certainly the next phase, having established that it was possible -- that the NY-like material could survive heating at 80°C, when freeze-dried in a particular way, the next phase was then to take larger aliquots of that material in order to be able to demonstrate that we could also do that in a volume of product that would be compatible with making a clinical product.

Q. Yes. I think you will recognise the next document. It is PEN0171379.

A. Yes.

Q. We can see these notes are dated 21 November 1985 and if we then go to the third page, we can see another sheet, dated 2 December 1985. If we then go back to the first sheet, please, can I ask you what is happening in this document? What does this document refer to?

A. Because we were using the front end of the ZHT process --

Q. What do you mean by that?

A. The zinc precipitation step -- well, it's actually the

TRIS extraction, zinc heparin precipitation step and alhydrogel adsorption. Because we were using that as the feed stock material for the first NYU purification step, this was a step that had been used in ZHT -- then we used the laboratory worksheets that had been developed for ZHT.

So this is the -- if we scroll down. Adjust pH filter, yes. So you can see that instead of carrying on into the pasteurisation stage of the process, by adding glycine and sorbitol, we are adjusting the pH to 7.4, filtering and dispensing.

So this is one of the early experiments where taking the -- as I call, front end of the ZHT process and not carrying on into pasteurisation but freeze-drying that material, preparing that material for freeze-drying in such a way that it could be terminally dry heat-treated. So these are the fist laboratory scale experiments on the preparation of Z8.

Q. And in particular these experiments are looking at increased purification of the intermediate product using zinc heparin precipitation and also, presumably, including the new freeze-drying process, developed as part of the NYU project and also looking at dry heating at 80 degrees rather than pasteurisation?

A. Yes, yes. The material from this laboratory scale

processing would have gone into freeze-drying experiments.

Q. Thank you. Can we then look at another document, please? PEN0171376. This is a memo from Dr Foster to yourself, dated 22 October 1985 on the question of heat treatment of Factor VIII, and I think in short, setting out the difficulties in seeking to heat the NYU product at 80 degrees and suggesting a number of options?

A. Yes.

Q. I couldn't see, Dr McIntosh, a reference in this memorandum to the NY intermediate control having survived severe heating. Is there an explanation for that?

A. Sorry, can you scroll down the document?

Q. Yes. Take a second just to look at the memo, and over the page as well.

A. And can we keep going?

Q. We should go over to page 2 as well, please.

A. No, it just seems to concern freeze-drying experiments on high purity Factor VIII, NYU Factor VIII.

Q. Yes. Do you remember, Dr McIntosh, we looked just two minutes ago at the experiment conducted on 21 November 1985, which was the start of what became known as the "Z8 process"?

A. Yes.

Q. Do you remember, at that time did you conduct this experiment on your own initiative or had you first discussed what you proposed to do with Dr Foster?
A. I'm sure I would have first discussed it with Peter. I mean, before we turned all of our full attention to the Z8 process, then we would have continued on with -- with the initial development of the Z8 process and the freeze-drying experiments. We would have continued on with our attempts to freeze-dry the high purity material, since the freeze-drying work and the processing work could go on independently.
Q. Yes.
A. So there would be a period in which the two are -- a short period in which the two would still be being worked on, until we had obviously established that we were clear and confident that we could prepare an intermediate purity product that would be capable of being processed in production from the initial observation that the intermediate purity-style material could be freeze-dried in such a way. So there would be a period while we would be working on that but still continuing to work on the high purity Factor VIII, because we were clear that the Z8 option was feasible.
Q. Doctor, I apologise for jumping around a little.
A. No.

Q. While it's in my mind, you told us about the freeze-drying process in general. In October 1985 a change had been made to the existing freeze-drying process to enable the NYU product to be freeze-dried. Can you just tell us what that change was, please?

A. Yes. Some of this, I think, is covered in earlier briefing material that Peter may have provided you with, where he contrasts the previous production cycle for the NY intermediate material and the Z8 cycle.

What I'll do is I'll just explain the salient features of the Z8 cycle. That might be easier than trying to compare them.

The key features --

Q. When you say the "salient features" of the Z8 cycle --

A. Sorry, that were required to freeze-dry high purity material which we then observed would also give us intermediate purity material that could be heated at a higher temperature.

Q. So what time are you talking about when you are about to go on to describe a particular freeze-drying cycle? What date?

A. This is contemporaneous with this. So this is late 1985, isn't it?

Q. Sorry, it's my confusion but are you about to tell us the freeze-drying cycle that had been revised in the NYU

process or are you telling us the freeze-drying cycle employed to manufacture NY in late 1985?

A. No -- well, I'm about to describe the changes that needed to be made to freeze-drying practice at PFC in order to be able to dry -- in order to be able to freeze-dry the high purity product, and it's those changes or the features of those changes that also gave Z8 the improved purity -- intermediate purity product, the characteristics that allowed it to be heated at severe temperatures.

Q. I understand.

A. Just briefly, the existing intermediate purity process -- freeze-drying process was a recipe that was applied to all products without necessarily being based in what were the characteristics of the product. This recipe operated in a number of freeze-drying plants. I saw it operate at a number of freeze-drying plants. And it was that the product would be loaded on to the freeze dryer, the shelf would be cooled, I think to minus 40, then, after a short time, primary drying would be initiated.

Primary drying would be carried out by pulling -- by reducing the pressure in the chamber to give a vacuum of -- I think I recall correctly -- of about 200 millibar, and the shelf temperature would be increased

to plus 10°C. These conditions were maintained for one hour for every millimetre of plug height. Then, after that time, the shelf temperature was raised to initiate secondary drying to 20°C and vacuum control, as it's called, was then switched off. So the dryer pulled a maximum vacuum and these conditions were maintained until what was called an "acceptable pressure hold test" was completed.

Pressure hold test involved closing the valve between the freeze-drying chamber and the condenser chamber. Remember, I described to you earlier that freeze dryers had two chambers. So if there was still residual water being, at this stage in secondary drying, evaporated from the product, then the water comes in to the atmosphere in the condenser chamber and the pressure drops. So when you close the valve, if there is no change in pressure, it was judged that the product had dried sufficiently.

This kind of turn-handle approach to freeze-drying was what was applied in many plants.

So when we -- and if you looked at the profile of this cycle, it drove the sublimation very fast in primary drying. And also, using a plus 10°C shelf temperature and a fixed vacuum would take no account of the conditions required to remain below a critical

temperature for products of different chemical or physical compositions.

So I think what we did empirically was begin to reduce the primary drying temperature. I'm not sure if it was at that time or soon afterwards, we actually began to do more fundamental work on the low temperature characteristics of the products using a technique called resistivity. It doesn't matter about the detail of the technique but it allows you to determine when the product is fully frozen, what the phases of freezing are.

So this then told us that for the high purity Factor VIII, we needed to maintain a very low product temperature of, I think, minus 35°C. So we had to arrange conditions in primary drying such that we would put in heat -- that's to say the shelf temperature was warmer than the product temperature but the product still stayed at a much lower temperature than we would normally have used for freeze-drying in the PFC at that time.

THE CHAIRMAN: Can we just pin down what it was that failed, as you say, on page 2 of your statement. You say:

"Freeze-drying of the high purity material had completely failed using a model cycle."

Based on the standard production cycle you have just

described?

A. Yes, the primary drying conditions were much too warm, so the product literally boiled instead of sublimation occurring. You were still at a temperature above which the product -- there were still liquid components in the frozen material. I know it's difficult to think of liquid components in a frozen material but, depending upon the chemical composition, you know, true freezing, complete freezing doesn't happen until very low temperatures.

THE CHAIRMAN: So you understood at that stage why the freeze-drying cycle was unsuccessful?

A. Yes, we only -- I think we had just run that experiment once because when it happened -- I think Peter has somewhere in his submissions, it seems obvious -- it is obvious, because the chemical make-up of this material is so different from what we have handled before. So we will need to go away and design a different cycle from first principles, which is what we did.

THE CHAIRMAN: That's the next stage. When you were setting out to do that, you had a set of first principles to apply, temperature and variation and things of that kind.

A. Correct.

THE CHAIRMAN: And then was it just a case of progressively

changing individual factors to see whether you were making progress?

A. Yes, that's right. At laboratory and large laboratory and pilot scale. This is the work that went on from late 1985 into early 1986, and the freeze-drying work would have gone on in parallel with the processing work which you have just seen the laboratory sheet of.

THE CHAIRMAN: Could I bring in the standard product control just to see what's happening there? So far as the standard product is concerned, you had plenty of experience by that stage of using your ordinary freeze-drying cycle and getting a result?

A. In production, yes.

THE CHAIRMAN: When you introduce the control into the pilot scale, the equipment that you are going on use to test these various factors, do you try to see whether you get the same result with the control first or what? Why is it coming in first?

A. The control is not coming in first. It's freeze-dried at the same time.

THE CHAIRMAN: I see. So you didn't actually test the new system with --

A. No, it's a control sample included in the experimental run at the same time.

THE CHAIRMAN: So you are doing the progression, as it were,

towards a solution with the whole material in?
A. That's correct.
THE CHAIRMAN: A true control, as Professor James says, and you were getting satisfactory results on it?
A. Yes.
THE CHAIRMAN: So that would demonstrate -- is this right? -- that the ordinary product would perform in your new situation to the same level of satisfaction as in the standard?
A. Correct.
THE CHAIRMAN: But also you are moving towards a better result overall?
A. That's right.
THE CHAIRMAN: And that all happened in October for the first time, did it?
A. It happened, as you saw from the earlier one, October and -- I'm not sure -- actually, I would need to look back to determine when the exact first freeze-drying runs were completed, the fist freeze-drying runs for NYU, but they were certainly late 1985.
THE CHAIRMAN: I think our assumption from other information has been that it was October 1985.
A. It would be about then because we needed first of all to resolve the issues I talked about earlier in the NYU process and then, remember, the process we received from

Alan Johnson ran in a 10 ml column. It was very small. So the next stage was to scale that up to get enough material.

THE CHAIRMAN: Yes --

A. And also the problem is to physically get enough material. With a high purity product, you need to consume quite a large amount of starting material. So we had a build a relatively large-scale process operating in the research and development laboratory.

THE CHAIRMAN: So really one shouldn't expect all these things to happen on a day.

A. No.

THE CHAIRMAN: It's a process that takes place over time and it was drifting into November, as we now see.

A. Yes.

THE CHAIRMAN: As you were going ahead.

A. Yes. So the important features of what we shall call the "new freeze-drying cycle" or "revised freeze-drying cycle", were, at that time, no changes to freezing. That came later with the observation that we made on scale-up in production. But nonetheless, one of the key features of each of the cycles that we ran in the pilot scale freeze dryer was this phenomenon called "supercooling". Probably because the dryer was smaller and cooled more efficiently than our production dryer.

In fact, when we first saw it we thought there was something wrong with the trace, and then we understood what it was. So the successful cycle had supercooling albeit that inadvertent. We didn't understand the significance of that at that time.

Then its key features were a much lower primary drying temperature, leaving the product and the conditions required in terms of pressure and condenser temperature, to allow that to happen; leaving the product to sublimate, instead of driving the product to dry. So much longer, lower temperature, more conservative primary drying phase; and then a defined time and temperature in secondary drying, instead of what could be a variable feature in drying with this pressure hold test. So these were the key features of this new design of cycle that we applied to the high purity product, and it was also seen to be successful with Z8.

MR MACKENZIE: Thank you, doctor. And for the record, when you said when you when you first got the results, you thought there was something wrong with the trace, you indicated with your finger a V or a dip.

A. Yes, when you see that supercooling is a phenomenon by which the product will cool to below zero -- will chill to below zero without freezing, an aqueous solution will

go to below zero without freezing. You see it in pharmaceutical products because they have been filtered to eliminate any particles of bacteria, so they are very pure. There is nothing to initiate the nucleation process that's needed for freezing. So it cools below zero and then suddenly freezes. So you get this discontinuity in the temperature trace.

Q. We may come back to supercooling when we come on later to 1986. I would like to move on now, if I may, to another memo, please. This is SNB0136680. This is a memo from Dr Foster to Dr Perry dated 18 December 1985 on the subject is "Factor VIII progress and options".

A. Yes.

Q. Did you get a copy of this memo at the time, doctor; do you remember?

A. I doubt it. I'm not clear. My name is not on it but it would have been unusual for Peter not to discuss things with me before he set them out --

Q. We will look through it together. He starts:

"This is a brief summary of where we are with the NYU Factor VIII project and the various options that are available to us to achieve a product heated at 80°C for 72 hours."

A. Yes.

Q. He starts with NYU project and the difficulties with

heating and sets out various options.

A. Yes.

Q. Over the page, please, at page 2. As regards standard Factor VIII products, three options are set out. Firstly, trying to heat the existing NY product at 80 degrees for three days and secondly, 2.2, trying to purify the existing Factor VIII NY a little further. Then, 2.3, copy the BPL method.

A. Yes.

Q. In short, I think, Dr Foster's preference, as expressed in this memo, was to continue to prioritise the NYU project but to have fallback options if that didn't come to fruition, in particular 2.2, purifying the existing NY intermediate purity product a little further, et cetera. Does that accord with your recollection --

A. Yes, that's fine. Can you run back up to the date of the memo, please?

Q. Yes, the first page is 18 December 1985. So just before Christmas 1985.

A. Yes, and we saw in the earlier sheets -- we saw the handwritten sheet from Peter, which I think is about him taking photographs of product. We were talking about lysine. So this is the stage where we were still trying to make the high purity product heatable, but beginning to work, or some way along working, on the fact that the

freeze-drying cycle we have developed for the high purity Factor VIII gives us improved heating properties in the improved -- in the further purified, intermediate purity. This is the overlap we talked about.

Q. Yes. In particular, doctor, we have heard evidence about a meeting at PFC on 23 December 1985 between Dr Perry, Dr Foster, yourself and Mr Cuthbertson?

A. Dr Cuthbertson.

Q. I'm sorry, Dr Cuthbertson, of course. And this memo, I think, is a precursor to that meeting?

A. Yes, it is.

Q. Do you remember that meeting?

A. Yes, I do.

Q. What was discussed?

A. What was discussed were the options on how we should proceed and which option was the one that could most rapidly be introduced into production. It was a very short meeting, as I remember.

Q. How long do you think it lasted?

A. I doubt if it lasted more than an hour.

Q. What were the opposing views and what was the outcome?

A. I don't know that there were many opposing views. My recollection is that the general agreement was that if we could produce -- that if we could produce a product that was able to be more severely heat-treated and give

us a further assurance against the safety of HIV transmission, then that really is the route that we should take. So the route that took us most quickly into production to do that is the one that we should follow because, remember, this is still December 1985. We still didn't know how HIV infectivity is going to develop, if it's going to develop. We have only had routine testing for HIV in -- what was it? -- October 1984. So we are still seeking to make as safe a product as we can.

Q. So going into the meeting, you had been responsible for seeking to develop the NYU product. You had also, we have seen, undertaken experiments with what became known as the "Z8 dry heating method"?

A. Yes.

Q. So going into the meeting, did you have a view as to which of these two options should be prioritised?

A. Yes, I had a clear view, yes.

Q. And which option and why?

A. My clear view was that we should pursue what became the Z8 product. The reasons were that, although we had made great advancements with the New York University process, we hadn't been able to freeze-dry it in a way that we could heat-treat it, terminally heat-treat it, severely, at 80 degrees or around 80 degrees. It is not that we

had a preference for this method, because the NYU process was originally taken on board to facilitate pasteurisation. It's just that if we could do this, this would give us what we would consider a secure safety step to get the process into production. Because, remember, in addition to purifying the product on ion exchange chromatography, formulating it -- because it's a very high purity product -- to prevent it adhering, if we then had to carry out a pasteurisation step, then we are adding a number of different unit operations to the existing Factor VIII process.

So we have a much longer and more complicated -- Factor VIII is already a complex molecule to process -- a much longer and more complicated process to put into practice. If we have to add to that as well pasteurisation, then that increases the complexity of the process even further.

In order to achieve this more complex processing, we required to specify, purchase, commission and introduce into routine use, a number of additional items of equipment. This would have taken some time to do. In fact, I think at that time I had specified the equipment, but the importance in specifying the equipment was we had to resolve which parts of the NYU process we were going to use before we were able to

specify the equipment required for it.

To some extent you can specify the equipment with a degree of manoeuvre, that the process will fit. So my view was that to introduce multiple additional complex steps, to purchase the equipment and to be able to commission and validate that equipment, would take a considerable period of time.

In order to modify processing that we understood with the addition of a single unit operation -- because what we were able to do in the Z8 process was combine much of the processing to make it fit inside the existing working day. One of the things to remember is that PFC had no shift working system. So all of this had to be fitted into essentially a nine-to-five day. There was no shift working system at PFC at that time.

Q. So each step in the manufacturing process had to take place in the nine-to-five day?

A. Yes, we had -- knowing this was going to come, we had started on what we called a "stop-off process" in the NYU project, such that we could stop the processing and resume it on a following day. But even if you do that, it's still occupying time. And then you also have a freeze-drying cycle that, by this time, because of the requirements we have just described, I think was maybe five or more days longer. It's a week's cycle, more

than five days. It would sometimes go on the freeze dryer on a Monday and come off on a Saturday, when it was a Z8. And the same length of time would have been required for the high purity product. Compared to the cycle for the intermediate purity product that lasted only two or three days.

We also had relatively limited freeze-drying capacity at that time. We had the SM200 and the SM600, two large-scale -- well, the SM200 was small -- production freeze dryers.

Q. Am I right in thinking that in short, at the end of 1985, your preference for Z8 was based on an opinion that it would be a quicker, easier way to achieve severe heating than NYU?

A. I hesitate to agree with "easier" but it looked more doable. And as for the 8Y process, we knew a bit about the 8Y process, but the main consideration there was that if we are going to take this process into production, and run very quickly with a scale-up and reduction to routine practice, it's better that we run procedures and processes that we know instead of transferring, for example, to the procedures needed for 8Y, which, although similar, were different in many important respects.

Q. We will come back to that later but one final question,

if I may at this stage, we know that during 1985 PFC were producing and issuing a Factor VIII concentrate heated at 68°C. Why was it that at the end of 1985 the aim was to achieve more severe heating?

A. We were still as yet unsure that 68 for 24 would be safe for HIV and also, although there was not definitive proof that severe heat-treating where Jim and his team had managed to go, to take the temperatures we hadn't imagined were possible, although there wasn't definitive proof of prevention of non-A transmission, it was clear that -- it was -- not necessarily clear but it held out the hope -- you know, if we can take severe terminal dry heat treatment to another plane almost, it held out the hope that we might be able to inactivate other viruses.

Q. Including NANBH virus or viruses?

A. Including those that may be responsible for non-A non-B Hepatitis, because we did not know what those were at that time.

Q. Sir, it may be an appropriate stage to break.

THE CHAIRMAN: We will have a break.

(11.05 am)

(Short break)

(11.28 am)

MR MACKENZIE: Thank you, sir.

Dr McIntosh, we finished before the break with the

decision taken at the end of 1985 to prioritise the Z8 project. I would like now to look at what happened in that regard in 1986.

We have with other witnesses spent some time on this so I will perhaps not take too long on it but presumably, initially in early 1986, further work would have been undertaken in the laboratory on the Z8 process?

A. Yes, to prepare large laboratory scale preparations for study in the routine quality control assays that were required for Factor VIII, and also for further studies on freeze-drying. And also to demonstrate that we could reproducibly prepare material at that volume.

Q. Could we perhaps briefly look at document PEN0171384. These are some handwritten notes. In the top right-hand corner, it is dated 31 January 1986. If we can perhaps just scroll through them, we will see they relate to various what appear to be experiments, but in January and February 2008. Perhaps we can just scroll through the following pages, so you get a feel for the documents.

A. Yes, if you stop at this first one.

Q. Sorry, the first page?

A. Yes. There is -- a key feature of adapting the zinc precipitated material for use as a finished product, was

to be able to concentrate it and to adjust the formulation. So this is the added step we put in to existing processing. "UF" means ultra-filtration.

I think you will have heard from Dr Smith about using size-exclusion chromatography to formulate or desalt. This is an alternative method. It's like -- in fact, the membranes that were used for this were originally developed for kidney dialysis. So it's like dialysis. It allows you to exchange the small soluble molecules in the mixture. So this is a key feature of adapting the zinc precipitated -- the supernatant from the zinc precipitated material to becoming a finished product --

Q. Yes?

A. -- ultra-filtration stage.

Q. I'm not going to go into the details of what work was undertaken in the laboratory in the first part of 1986 in respect of Z8, but I think these notes illustrate the work that was undertaken. One point which occurred, doctor, the notes relate to the period January and February 1986. I just wondered what, if any, work was carried out on Z8 in March, April and May 1986.

A. It would have been further work on freeze-drying and on formulation of the ultra-filtered material. In particular, if we were to fit this additional unit

operation into production, we would require to carry out the ultra-filtration stage as rapidly as possible. So I would imagine that in this experiment in early 1986, we were using a type of ultra filter. It's called a hollow fibre membrane. And in that period we looked at laboratory scale versions of what's called a plate and frame, a flat bed ultrafilter, which was ultimately the type of ultrafilter that we used in production.

So without going back and looking at laboratory notes, I couldn't be exact but I would estimate that a large part of the work in that time would have been preparation for the scale-up of the ultra-filtration stage in the preparation of the zinc heparin alhydrogel precipitate for Z8 manufacture.

Q. We know the first pilot scale run of the Z8 process took place at PFC on 23 June 1986.

A. Yes.

Q. For that to happen, was any new plant or equipment required or did any adjustment or work to existing plant or equipment have to take place?

A. For the first -- although we call them "pilot scale", these were carried out in the production part of the building. We moved there as quickly as we possibly could in order to use production equipment, in order to familiarise the staff in production on what was a new

process. The main item of equipment was the ultra-filtration equipment that I have just referred to. All of the other equipment required could be taken from the existing manufacturing process.

Q. I'm sorry, the ultra-filtration equipment, was this a new piece of equipment that had to be ordered --

A. Yes. We had experience of ultra-filtration in the development of intravenous immunoglobulin, but the type of ultrafilter used, as I explained earlier, was a type called a hollow fibre ultrafilter. In this case -- this was new for us -- we were using what is called a flat bed or plate and frame ultrafilter.

Q. Okay. We know that the second pilot scale run was carried out on 28 July 1986 and that on 4 August 1986 the fist large-scale production run was carried out.

I think there were then problems encountered. Is that correct?

A. Yes, these large-scale production runs were not to make clinical grade material. In order to achieve the development as quickly as possible, production of the previous product, NY, had been suspended or halted, to give us full access to production, and a decision was made to prepare material at as large a scale as possible but for experimental purposes. And so it was in these first scaled-up procedures that we encountered a number

of processing problems. I can't remember exactly the sequence. The first one was actually related to the speed of ultra-filtration.

Even though we had anticipated that this would be a difficult step to add in, and our proposed solution had been to increase the surface area of the ultrafilter, which was easier for us to do in a flat bed or a plate and frame ultrafilter, as it's called, that really wasn't sufficient to get us to reduce the processing time required. So we needed to increase the flow rate of the material through the ultrafilter, and to do that we needed a much more efficient pump, but one that would pump at faster speeds with low shear, without damaging the material we were using. This required us to research a particular design of pump, which we accessed and built into later pilot scale work.

Q. What about freeze-drying? Was that a problem which appeared?

A. I don't think -- do you have, in the outline of that particular pilot experiment, I think in the papers you gave me --

Q. Yes, we have the first pilot scale run sheet, the second pilot scale run sheet. Would one of these sheets help?

A. Yes.

Q. If we could perhaps then go to the document

SNB0079049. This document relates to the second pilot scale run which took place on 28 July 1986. Does that help?

A. I'm not sure if it was in these pilot scale runs that we encountered the freeze-drying problems related to freezing. Some of the early freeze-drying problems related to control of the production freeze dryers, and the distribution of coolant from the condenser to the shelf -- between the condenser and the shelves.

The dryers had to be adjusted so that they would provide greater cooling to the shelves than had previously been used in the earlier production cycle. Also the method of controlling heating and cooling, we had to introduce additional control technology to give us finer control over the heating and the cooling.

The problem you may be alluding to, which is the issue of the correct -- or the best structure on freezing, I don't think occurred until later because from these early pilot runs, we would freeze-dry some material on a production dryer and some material on our pilot dryer in order to corroborate, as it were, our earlier evidence of driving.

So because of the relatively small scale, even in these pilot runs of the material that was freeze-dried, I'm not sure that what you call the "supercooling issue"

had arisen by this time.

Q. I think that may be right. If we look, for example on this further document, SNB0076080. This is a letter from Dr Perry, I think we can see at the bottom of the page, to Dr Boulton of 29 August 1986. Dr Perry states:

"While we now have material which can be used for trial (beginning September) in Dr Ludlam's patients, I am not at this stage convince that it has a proper GMP pedigree or that it represents our definitive process. We have recently encountered an 11th hour problem with freeze-drying, which we are now addressing with some considerable urgency."

So certainly by the end of August 1986, it appears as if the problem with freeze-drying has appeared.

A. Yes, and that would be with the first of the larger scale batches.

Q. I understand. Could we also, please, go to another document which may help. It's PEN0171434. This is headed "supercooling experiment, 25 September 1986, "z8-6-005 SM200."

If we go to the bottom of the page, I think we can see you are the author of this document, doctor.

A. Yes.

Q. Does this help in identifying --

A. Yes. By this stage, as we commented earlier, the

features of what had been the successful freeze-drying cycle in the pilot plant dryer, one, were that we observed supercooling, that we had the lower primary drying temperature, the longer sublimation period and had defined conditions for secondary drying.

So if you could run to the top of this again. So when we attempted to freeze-dry the first of the larger batches in production, although we would see supercooling, it would be intermittent, in a sense, inadvertent, and we identified that the vials from these runs, that would better withstand severe dry heat-treating, were the ones which had -- I'm sure you have heard this story before -- the ones that had a very fine or had had a very fine ice crystal structure on freezing.

So we reasoned that if we wanted to get this in a predictable way, then it may well have been the supercooling that caused this to happen. So what we needed to do was, instead of hope for supercooling to occur, in this situation we needed to design a freezing cycle that would induce supercooling. So it would happen in a reproducible way and in a uniform, way across the batch. So these are the first of the experiments to determine whether or not we can do that on a production scale dryer.

Q. Was that the main change which was made to the freeze-drying step at that stage, namely to ensure that supercooling occurred on a regular basis?

A. Yes, it was a little more involved than this first experiment. We were using a chilled shelf, plus 10 shelf, because that's what had been recommended by people who had published earlier on this technique. Although this experiment was successful and did give us good freeze-drying and heating characteristics, on re-solution the products contained very small amounts of precipitate. We reasoned that this was because we had a product that contained cold, insoluble globulins, as fibrinogen and fibronectin are; holding it at a chilled temperature would cause those to form.

So we then refined the supercooling conditions to actually use an initial temperature that was below zero, such that we would still get supercooling but the product would not spend too long in the chilled temperature zone that caused the precipitation, and this was successful. It was a continuation of developing the appropriate supercooling conditions.

Q. Okay. I think the next document in the chronology, please, is SNB0067564. We can see from the top the development review group, "Notes for a meeting to be held on 15 October 1986". If we can scroll down,

please, to paragraph 2, there is reference to Factor VIII, introduction of Z8 process. It requires further developments in formulation and freeze-drying to enable heating at 80°C for 72 hours to be achieved reproducibly.

A. Yes.

Q. The reference to "further developments in freeze-drying", is that a reference in short to supercooling?

A. Yes.

Q. The reference to "further developments in formulation", in short, what's that a references to?

A. The existing NY intermediate purity product had quite low salt content and we were able to increase the salt content in Z8 without taking it outwith an acceptable physiological formulation for infusion.

So the main development in the formulation of Z8 was increased ionic strength. There may have been an adjustment in the sucrose content of the formulation. I'm not sure about that. I think it's perhaps it stayed at 2 per cent. But the main formulation development was in the increase in ionic strength.

Q. Is that anything to do the conditioning of plasma?

A. No.

Q. Is that something separate?

A. Yes, conditioning of plasma is right at the front end of the process. Would you like me to say something about conditioning or ...?

Q. I don't think so for my benefit, unless the chairman would like to explore that.

THE CHAIRMAN: I think it has got an interest because of the interplay between the Scottish and the English scientists over the relevance of conditioning, which I suspect you remember --

A. Yes.

THE CHAIRMAN: -- fairly clearly. I think that my interest at the moment would be when it was appreciated that conditioning was a factor that improved the process overall and why.

A. It had been appreciated that the conditioning of plasma -- well, first let's -- if we have time -- let's deal with what conditioning is, conditioning or tempering, if you understand it.

Plasma comes in plastic packs of 250 grammes, or if it's plasmapheresis plasma, bigger. Some plasmapheresis plasmas are prepared in plastic bottles. So although maybe 30 million litres of plasma a year are processed round the world, it's all in tiny frozen packs. So the first thing that has to be done is to remove the pack from the plasma.

Because you do not want to thaw the plasma because the control of the thawing will give you the cryoprecipitate that you need for the preparation of Factor VIII, you need to soften the plasma in such a way that the plastic becomes soft enough to remove from the frozen plasma pack without thawing the plasma contained inside.

In arriving at conditions that are optional for removing of the plastic pack, some manufacturers identified that this conditioning or tempering would also influence the yields of cryoprecipitate when the plasma was finally thawed.

PFC/SNBTS had published on this earlier. So it was already appreciated that conditioning was critical to the yield and quality of cryoprecipitate prepared at PFC. So much so that the modifications to the PFC building included a plasma conditioning unit, where the plasma could be taken from the cold freezer at minus 40 and the temperature increased in a controlled way in order to yield the appropriate quality of cryoprecipitate and allow the plastic to be removed from the pack.

So this is something that happens at the very beginning of the process and demonstrates that the temperature history of the plasma can have a big

influence on the quality of the cryoprecipitate, and then obviously the quality of the cryoprecipitate itself has a big influence on the subsequent processing stages.

THE CHAIRMAN: That was all well established really before this period began?

A. Yes.

THE CHAIRMAN: So in your case it was incorporating into the procedure something that was already standard practice?

A. Yes, there was no change -- there was no change to the plasma conditioning procedures that were used in the initial Z8 process.

THE CHAIRMAN: That's all I think I need to know at the moment.

MR MACKENZIE: Thank you, sir.

A. I should add, there were questions later about the temperature history of the plasma that influenced the process but we can talk about --

THE CHAIRMAN: We will come to that.

MR MACKENZIE: Doctor, to continue the Z8 chronology, could we next, please, look at SNB0060335? You will see this is a letter from Dr Cash to Dr Perry dated 15 October 1986, in which Dr Cash states:

"A note to confirm that in the circumstances I believe the time is appropriate for PFC to commence production of a Factor VIII concentrate (Z8) which will

be heat-treated at 75°C for 72 hours.

"It would be my hope that continued efforts are put into producing a Z8 product which is heated at 80°C for 72 hours ..."

Et cetera.

So is it the case that at this time, PFC was able to produce Z8 heated at 75 degrees but some work was still required to produce a product which could be heated at 80 degrees?

A. Yes, this was while we were working on the issue to get the appropriate crystal structure and the decision was made, or we put it -- and Professor Cash as the medical adviser has agreed -- that we could proceed with what was still much more severe heat treatment than we were able to apply in the NY process, if you remember, which was 68 for 24 hours. Here we are applying 75 for 72 hours. So it still represents a very severe heat-treated process.

Also, comparisons are not straightforward in terms of time and temperature. There are other things to be considered: residual water content of the product, how it's formulated, how the product is closed, whether it's closed under a vacuum or under an atmosphere, and the heat treatment method itself.

So our belief was that 75°C for 72 hours represented

a significant advancement on 68 for 24 hours, and rather than not prepare material, we should prepare material of that type while we further advanced to 80 degrees.

Q. Was the supercooling adjustment required to achieve the 80-degree temperature reproducibly?

A. Yes.

Q. I understand.

The next document, please, is SGH0016672. We can see this is a note of a clinical trial review meeting on 1 December 1986. You weren't, I think, present, Dr McIntosh?

A. No.

Q. But can we go to page 4 of the document, which is 6675. We can see an item 9, a reference to Z8 heat-treated at 75 degrees for 72 hours and Dr Perry reporting that this product was now available for half-life and recovery studies.

A. Yes. The first clinical grade batch, I think, went to issue in early December and it was also in December that we started the manufacture of the first 80°C batch, which would have been available early the following year, I think, maybe February.

Q. I think we can see that if we finish off with two final documents. The next one is PEN0171437. We have looked at this before in the Inquiry but we can see this

is a batch issue history document. In the top right-hand corner we can see 75 degrees and we can see this product was placed at issue on 2 December 1986.

A. Yes.

Q. We can also see, I think, from the details on this sheet, in particular the batch number and perhaps expiry date, that presumably this 75-degree product was produced in October 1986?

A. Yes, the expiry date -- it was the habit at PFC to give the expiry date as the length of time from the date of filling, two years from the date of filling. So that would have been prepared in October 1986.

Q. Then finally, please, the next batch issue sheet for the 80-degree product is PEN0171470 we can see in the top right-hand corner 80 degrees, placed at issue on 11 February 1987.

A. Yes.

Q. And I think from the batch number and expiry date, we can see this 80-degree product was manufactured at PFC in December 1986.

A. Yes.

Q. Which ties in exactly with what you have told us.

A. Fine.

Q. Thank you, doctor. Before leaving Z8, I think it may be helpful for us to look at some differences in the Z8

manufacturing process and the 8Y manufacturing process. Could we please do that with reference to document LIT0010617.

A. Yes.

Q. We have looked at this before in the Inquiry, a publication by Dr Winkelman and others in relation to the 8Y process, but in particular the next page, please. Page 618.

In the right-hand column towards the bottom, we, I think, see the main manufacturing steps in the 8Y process set out there and on to the next page. Are you able to help us, doctor, in drawing our attention to the main differences in the 8Y manufacturing steps and the Z8?

A. Yes, I can do that.

As you suggest, the easiest way is to follow the headings given under the manufacturing method.

Q. Yes.

A. First, under "Cryoprecipitate Extraction", the first thing to notice is that Mrs Winkelman gives a yield of cryoprecipitate of around 10 grammes per kilogramme of plasma. PFC at that time, we would have had a heavier cryoprecipitate, 11.5 or 12 grammes per kilogramme of plasma.

We could have -- I mean, I imagine you are asking me

to look at the differences with a view to how could it have been applied at PFC?

Q. I think that's right. It's really that one, playing devil's advocate, would say, why didn't PFC simply adopt and apply the 8Y procedures? Were there any difficulties in doing that?

A. If we had wanted to try to reproduce exactly the cryoprecipitate they had at Oxford -- we were using a continuous thin film thawing technique that had been developed by Peter Foster. It gave a very high yield Factor VIII into the cryoprecipitate and was one of the key features of the NY process. Here, Oxford are using simple batch vessel thawing. Also, centrifugation that we used at PFC was using a design of centrifuge called a multichamber centrifuge to offer us improved temperature control. Here the design of centrifuge used was a Sharples, which was a tubular bowel design, and it gives much higher separation co-efficients but is less easy to control in temperature, and perhaps less hygienic to operate. It's an older design of centrifuge.

So in taking on board, if we had decided to do the 8Y process, we could have just gone with the cryoprecipitate we had, but that would have likely have meant that we would have had to make adjustments to the

processing parameters to cope with the different cryoprecipitate that we prepared. If we had wanted to try and replicate exactly the starting cryoprecipitate that was used at Oxford, we would have required to specify, purchase and commission a different thawing vessel and specify, purchase and commission a Sharples -- it's a high speed centrifuge.

Moving on to the -- those are the key points that are numbered. Other points -- although, because in this account Mrs Winkelman doesn't give the conditioning as we were referring to earlier, or plasma thawing procedures. But that's less important. They would have been easy to adapt without further equipment.

Also, if we had to use a Sharples high speed centrifuge, we would have needed to reconfigure the coolant supply. These centrifuges produce a great deal of heat, industrial continuous flow centrifuges, and require cooling. The coolant at PFC was a water/ethanol mixture, operated at minus 29 degrees. So this would flow round the jacket of the centrifuge. In a Sharples centrifuge, this requires a continuous flow loop, that's to say it's uninterrupted. For the coolant supply in a multichamber centrifuge, the coolant is sprayed onto the bowl, so it requires an open cooling set-up with a drain. Not necessarily open in processing terms but in

terms of its engineering design. So we would have needed to, as I say, purchase a different thawing vessel, a different centrifuge and redesign the cooling supply to the centrifuge.

The next step is the heparin precipitation, and the equipment used for that is not different than much of that we would use for the zinc precipitation step but I think, as has been pointed out earlier, the use of high concentrations of heparin would not have been compatible with the Factor VIII assay type that was used at PFC and we would have had to change to the assay method.

If we then move on to the next step, which is -- so by now in the 8Y process, the Factor VIII is in the supernatant of the heparin precipitate. So to recover the Factor VIII from that, the 8Y process carries out a precipitation with high concentrations of glycine and salt, which is similar to the precipitation method actually used in ZHT. That's where the 8Y method was derived from. So again, this would require a Sharples centrifuge and that would be the same issues as previously. You would require to specify, purchase and commission the Sharples centrifuge and also to alter the nature of the coolant ring supply in the PFC manufacturing plant.

You would not be able to use the same Sharples centrifuge in this step as you used in the earlier step because we would be in two separate parts of the building. As processing moves, so the specification of the area moves on until you eventually end up in a constant(?) sterile filling, which is a very high specification sterile area.

Then, when you have precipitated the Factor VIII from the heparin supernatant, the next step -- Mrs Winkelman has the removal of saline, the removal of the high concentration of salt and glycine. Here they are using Sephadex G-25 chromatography, size-exclusion chromatography, which we didn't use at PFC. We developed ultrafiltration for that technology. So again, if we were to take exactly on board what 8Y was doing, we would have had to purchase and specify, purchase and commission chromatography columns together with the associated vessels and pumps. There would also have been buffers to prepare and have ready for manufacture.

Which would have been a similar to the issues with introducing the NYU process, where we were going to introduce chromatography steps. And in fact, in introducing the NYU process, the complexity of introducing the additional steps was one of the issues

that counted against the introduction of the NYU step.

In finishing, the key feature here is that -- and when I looked at the transcripts from earlier, I noticed a bit of interest in this. NY was stoppered under vacuum. That's to say, at the end of freeze-drying, the vials were stoppered in the vacuum that existed in the chamber at that time. This wasn't the practice at PFC.

At the end of freeze-drying, the vacuum was broken with sterile dry nitrogen and the products were stoppered under atmosphere, under sterile dry nitrogen, providing a chemical environment and also to provide conditions that we considered would be helpful in preventing any bacterial ingress.

This would have meant -- to move to stoppering under vacuum, which some manufacturers did do, would have meant the introduction of new equipment for testing that the vacuum was present in each vial, sometimes referred to as "spark testing", as a technique that's used, where you have to identify that there are no leaks and that the vacuum has held in each of the vials that you have stoppered under vacuum.

This would also have meant changes to the heat treatment procedure. Heat treatment procedure for 8Y was different than that for PFC, as well as a product -- 8Y been heated while it was under vacuum. 8Y was heated

in an oven that operated at 80°C. At PFC we measured the temperature in the product and adjusted the oven so the product ran at 80°C. So to do that when the vials were evacuated would have meant additional experimentation and commissioning and validation of the heat treatment step.

I don't imply these as a criticism of the 8Y process when I look at the notes, as if I'm running through the 8Y process and critiquing it. I'm not. This process was a great breakthrough in the temperatures and times that the freeze-dried products could stand to, but it's just that comparisons are not always simple. Heat treatment will depend upon the nature of a product, the freeze-drying cycle, the formulation, the residual water content, the way a product is finished in the vial and the method by which the final heating is carried out.

Q. Thank you.

I should perhaps pause and ask you, doctor, what was your reaction when you first heard that down south the fractionators were able to heat Factor VIII to 80 degrees?

A. I thought this was a terrific breakthrough, absolutely, yes.

Q. Were you surprised at all?

A. Yes. I mean -- yes, I have to say, I was surprised,

yes. I hadn't considered the problem of would it be possible to heat-treat freeze-dried products at higher temperatures. I hadn't been directly involved with that at that time. The problem or the project that I had been set was to develop a method to prepare high purity material that was suitable for pasteurisation. (Pause)

Will I continue?

The other points to note are in terms of processing time, which we have touched on earlier. The 8Y process contains two further additional unit operations and in Z8 we designed the process to have only one single further unit operation in order to be able to fit it into the existing manufacturing time, because we did not have a shift working system at PFC. I think the 8Y process would have been a whole additional unit operation step, difficult to fit into the available processing time, because my understanding, certainly from talking to Mrs Winkelman and others at times, was that the process ran from start to finish, it didn't have a stopping process.

The other feature of the 8Y process which might have caused us some difficulty was its yield. Yield is stated in Mrs Winkelman's paper as 190 units per kilogramme of plasma. There is other evidence, I think, in the Inquiry where the yield was lower. Certainly we

were hoping for a much higher yield in order to be able to sustain the output of Factor VIII that had taken Scotland to the very good supply situation that it had, and at Oxford they weren't trying to make England and Wales self-sufficient in blood products, it's a small unit.

Q. Looking at matters another way, doctor, back in 1985 -- so let's say the end of 1985 -- what did you consider were the main features which allowed the 8Y product to withstand heating at 80 degrees?

A. The view that Mrs Winkelman had and Dave Evans, Peter Feldman, it's this new pure product that allowed them to withstand heating; that's to say the absence of impurities that were less heat stable was what allowed it to become pure. And I think Mrs Winkelman comments on that at the end of the paper.

I would have initially had no reason to disagree with that but shortly after that, from our own work, the position I would have taken is that it is not purity per se. What the pure product or the pure product allows you to do is to freeze and freeze-dry in a manner that permits the product to be heat-treated. So it's not a proper of the purity per se. If you had filled 8Y at 500 mls in a 1 litre bottle, you couldn't have heated it. It's as simple as that. So it's not a property of

the product per se, but the properties of the product allow you to process it in a way that can be heat-treated.

Q. So purity is a necessary but not sufficient factor in achieving severe heating?

A. That's right, you need sufficient purity to allow you to process and prepare the product in a manner that can be heat-treated.

Q. What's your view today on why it was that 8Y was able to be heated severely?

A. My view hasn't changed. In talking to those who worked with Jim, we know that in order to have freeze-dry 8Y, they had to take particular measures. In order to freeze it, they had to take particular measures. 8Y wasn't frozen on the freeze dryer, the original products were frozen in a freezing cabinet. This would have given them very fast freezing conditions likely to give a fine crystalline structure. And then when I was investigating this possibility, we got from Oxford a copy of their freeze-drying cycle and although it was different from the one we were designing, all of its main features were similar. There was supercooling, there was a very long, slow primary drying period and there was a defined time and temperature in secondary drying.

So that confirmed my view that it was not the purity per se of 8Y that made it heat-treatable but that the purity allowed you to process it in a particular way that made it heat-treatable.

PROFESSOR JAMES: Could I just add, would you agree that ironically it was those features that were not included in the patent which were probably quite critical to the successful production of the 8Y?

A. Yes. But I don't think they were deliberately excluded.

PROFESSOR JAMES: Oh, no, no, very far from it. They just perhaps didn't appreciate their importance at that time.

A. Yes, indeed.

MR MACKENZIE: Another devil's advocate question, doctor: rather than suggesting PFC should try to have copied all of the steps in the 8Y process, could PFC have simply adopted some of the steps, perhaps what you would have regarded at the end of the 1985 as the key steps, with a view to producing a higher purity, severely heated Factor VIII earlier than Z8?

A. So you are suggesting that --

Q. The hypothesis is this, that at the end of 1985, could you have looked at the 8Y process in the way we have done today and said, "Well, we don't need to copy every step and everything they do, but we could choose one or a small number of steps to copy and apply here, and that

is likely to result in us developing our own higher purity, severely heated Factor VIII quicker than we could if we went down the Z8 route"?

A. No.

Q. It's a hypothetical question.

A. It's very much a hypothetical question. No, I don't think so. I don't think neither Oxford's understanding of their own process nor our understanding of what the key parameters were was sufficiently developed at that time in order to be able to make what would be a very sophisticated judgment to select key parameters from a process and emerge with a process design which would allow severe heat-treating at 80°C, when this was a brand new, hitherto unachieved development. No. I don't think so.

THE CHAIRMAN: It's quite difficult to take the engine out of a Ferrari and put it into a Ford and expect to get the same performance.

A. Yes, especially if you have never studied engineering before. Exactly. Or that particular type of engineering.

MR MACKENZIE: Thank you, doctor. I think I have taken you some distance from your statement. I should perhaps now return to the statement and complete it if I may. We are at page 1237, the top of page 4. We have covered

much of the ground already. We had asked:

"What changes in the manufacturing processes were made and when to enable Z8 to be produced?"

We have gone over that in some detail. We then asked:

"What was the original timescale for the production and introduction of Z8 and if that timetable was not met, when and why did it slip?"

You very frankly say:

"The timetable for the introduction of Z8 was to complete the development as quickly as possible."

A. Absolutely.

Q. A point of detail in the next sentence:

"In mid 1986 the production of NY for heat treatment at 68 degrees for 72 hours was stopped."

A. That is obviously an error. It should be 68 for 24 hours.

Q. For 24 hours? Thank you. We can then read what else you say there, thank you.

The next question, 4, at the bottom of the page, we asked whether:

"... PFC's work on the development of NYU resulted in any delay in the introduction of Z8."

Your answer is over the page at page 5, where you say, in short, no. We can take your written answer as

read.

A. Yes.

Q. Question 5. We asked about clinical trials. That's not a matter within your knowledge, so I won't ask you further about that.

Question 6 was the standard question asked as to whether any wider management, organisational or other issues resulted in any delay in the introduction of Z8. Your written answer, over the page at page 6, I proposal simply to take as read because we have heard quite a lot about this from other witnesses and your position is consistent with others.

Question 7, similarly, we ask about the informal contact and exchange of information between PFC and those down south, and you have given some evidence on that earlier that, in short, that was not a difficulty. I think the rest of your written answer we can take as read, please.

In a similar vein at page 1240, question 8, we asked questions about the CBLA, Central Committee on Research and Development in Blood Transfusion. Again, we have covered this ground in some detail and I'll simply take your written answer as read, in particular given you had no knowledge of this committee, et cetera.

Then on to the next page, please, 1241. This is

page 8, question 9. We are back to the question of:

"Were more formal links between PFC and the fractionators down south desirable?"

Again, I think we will simply take your written answer as read for reasons I have mentioned earlier. Then I'll perhaps finish with question 10, please, at page 9. We asked:

"Why was PFC able to make available for clinical use Factor IX concentrate that had been dry heat-treated at 80 degrees for 72 hours in October 1985 but Factor VIII concentrate that had been subjected to a similar heat treatment regime was not available for clinical use until May 1987?"

You explain this has been answered in part in the witness statement from Dr Foster. About half way down you say:

"I would add that although NY and DEFIX shared the same dose form (ie freeze-dried products for reconstitution in water for injections before use), they were very different products. The protein contents and the structure and type of the proteins contained in each of the products were very different, as were the chemical formulations in which the products were prepared. The fill volumes (10 ml for DEFIX and 35-40 ml for NY) were also significantly different as were the

vial sizes; 30 ml and 65 ml respectively. It would not necessarily be the case therefore that because one freeze-dried product could be heat-treated at 80°C that other (with very different characteristics) could also be heat-treated in the same way.

"It should also be noted that unlike Factor VIII production, there were no yield constraints on the production of Factor IX concentrate. Only a relatively small proportion of the plasma fractionated at the PFC was needed to produce enough Factor IX concentrate to meet the demands of the NHS in Scotland."

Finally, over the page you say:

"In Factor IX concentrate production, stored intermediate product can be selected for further processing. In this way, high potency material could be selected (and less potent material discarded) to ensure that the final heated product had the required level of activities."

What do you mean by that sentence? That in Factor IX concentrate production, stored intermediate product can be selected for further processing?

A. Factor IX processing method is very different from Factor VIII. A proportion of the plasma, at most 20 per cent, goes for adsorption on another ion exchanger. It's a batch adsorption process not a column

process in this case, in the PFC Factor IX process. So then the ion exchange is collected and then packed in a column and the Factor VIII is eluted, and a number of different fractions are taken from the eluate. Those fractions will contain, depending upon how the Factor VIII eluates from the column. So you get, in a perfect column, a normal distribution of activity. So as you elute the material, there will be one amount in the first fraction, more in the second, then you will reach a break and then it will drop.

So, because you have no constraint, effectively, on the material you can use for Factor IX manufacture because you only require a smaller amount to meet the needs in Scotland, you can select those high potency eluates or high quality eluates, such that you can then withstand the drop of activity on heat treatment. I think the recovery on heat treatment for Factor IX was about 60 per cent, which you couldn't have done in Factor VIII. You would never have been able to make enough Factor VIII to supply the health service, if you took that yield loss.

Q. I see. Then in the final sentence you state:

"There was no such room in manoeuvre in the development of heat-treated Factor VIII products at PFC, where achieving an acceptable process yield was critical

to meeting the demands for Factor VIII concentrate."
A. Exactly.
Q. I have no further questions, Dr McIntosh. Thank you.
THE CHAIRMAN: Can I just ask you for clarification on one matter? You have mentioned that there was no shift working at PFC, and that in the context in which you were drawing attention to the continuous nature of the 8Y production process. Why not just extend the working practices at PFC to accommodate the continuous process?
A. Well, the continuous -- you mean it had to run from start to finish?
THE CHAIRMAN: Yes.
A. Not a question -- not something within my powers.
THE CHAIRMAN: That's fine; it wasn't part of your management responsibilities?
A. No, not at all.
THE CHAIRMAN: Mr Di Rollo?
MR DI ROLLO: Sir, I have no questions for this witness, thank you.
THE CHAIRMAN: Mr Anderson?
MR ANDERSON: Nor I, sir.
THE CHAIRMAN: Mr Johnston?
MR JOHNSTON: I have no questions, thank you.
THE CHAIRMAN: I wish I could say you were unique in not exciting any adverse criticism at all, but thank you

very much for coming. I think you are giving us an insight into what actually happened, what was necessary to convert initial thought into a really practicable working regime and I'm very grateful to you for doing that.

A. Thank you very much.

MR MACKENZIE: Sir, the next witness is Mr Murray, who is, I think, here.

MR ALEXANDER MURRAY (affirmed)

Questions by MR MACKENZIE

MR MACKENZIE: Good afternoon, Mr Murray.

A. Good afternoon.

Q. I don't think you have given evidence to the Inquiry before, so we should perhaps start with looking at some biographical details. I think in short, Mr Murray, you were employed at the SHHD, the Scottish Home and Health Department, with certain responsibilities for health matters, between December 1983 and 1987.

A. Correct.

Q. I think, in particular, was your job title a principal officer?

A. No, I was a senior executive officer.

Q. A senior executive officer?

A. Unfortunately, a grade below principal.

Q. I see. We haven't yet looked at the SHHD structure and

I think what I'll undertake to do is to try and agree a note which sets this out, which may make following things a little easier.

For today's purposes, Mr Murray, let me have a go at trying to set out the SHHD structure as you remember it.

A. Yes.

Q. If I get anything wrong, let me know.

Starting at the top, one would have the Secretary of State for Scotland, one level below a Junior Scottish minister with responsibility for health?

A. Not quite. In between there would be the Minister of State who was responsible for health matters in the House of Lords.

Q. Thank you. Then underneath the political aspect, looking at the career civil servants, would one start with the permanent secretary of the Scottish Office?

A. Yes. Sir Douglas Haddow at that time.

Q. I see. And there would only be one?

A. Yes.

THE CHAIRMAN: I probably shouldn't say but my impression is that there was only every one Douglas --

A. Exactly, yes.

MR MACKENZIE: I have tripped myself up already.

Let's go back to the politicians. We have the Secretary of State for Scotland; that's an easy start,

I think. You then mentioned a Minister of State for Health matters in the House of Lords.

A. Well, he was a Minister of State for all Scottish Office matters.

Q. All Scottish office matters?

A. Yes. There had to be a spokesman in the House of Lords.

Q. In the Lords, yes. Then the level below that -- throughout the 1980s, for example, was there always a Minister of State for all Scottish matters in the Lords?

A. Oh, yes.

Q. And below that we have a Junior Scottish minister with responsibility for health?

A. Yes.

Q. We looked at the permanent secretary of the Scottish Office. One down from that there would be a secretary of the SHHD?

A. Yes, that's right. In Civil Service grade terms, they would be deputy secretaries but their title was "Secretary".

Q. Okay. And presumably there would be a secretary of SHHD and there would be secretaries of other Scottish Office departments?

A. Yes.

Q. So, sticking now with the SHHD, we have the secretary.

Underneath that is the next layer the Undersecretary of the SHHD?

A. Yes, and he -- and up to then it was always a he -- would be the senior officer responsible for health, solely responsible for health.

Q. Were there a number of undersecretaries of the SHHD or only one?

A. There would be at least one other on the administrative side, responsible for home, the home part of the SHHD.

Q. I understand.

A. And as regards the professional side of the department, there would be officers at undersecretary rank.

Q. Okay. The next level down, Assistant Secretary of the SHHD?

A. Yes.

Q. And again would there be a number of assistant secretaries in the SHHD?

A. Yes, under the undersecretary there were a number of divisions.

Q. Yes.

A. Each division was headed either by an assistant secretary or, rarely, a senior principal. I forget how many administrative divisions there were but, just as a help to visualise, let's say six or seven --

Q. Okay.

A. -- administrative divisions. That won't be the right number but it will give you an idea of roughly how it worked.
Q. Okay. Mr Murray, at the time you were at SHHD, between 1983 and 1987, the assistant secretary, as far as you were concerned, I think, initially was Mr John Davies and then Mr Duncan Macniven?
A. Yes, John Davies at that time was a senior principal. He was succeeded by Duncan Macniven, who was an assistant secretary. There was a slight hiatus between those two appointments and possibly -- I know it does appear in the documentation. It might be a bit confusing but there was a slight gap and one of the branch heads, a Mr George Cole, acted as head of division. That was early in 1986.
Q. Okay. Under the undersecretary level do we come to principal?
A. Assistant secretary level. Under assistant secretary we come to principal, or rather we come to senior principal and then principal.
Q. Okay.
A. It's a long hierarchy.
Q. It certainly is. I take it you were not a senior principal or a principal?
A. No.

Q. Were you one down again?
A. Yes.
Q. A senior executive officer?
A. I was a senior executive officer at that time.
Q. I think in the documentation we have seen reference to minutes between yourself and Mr Davies and Mr Macniven?
A. Yes.
Q. Do you remember who was the senior principal and the principal during your time at SHHD?
A. The branch did not have a principal.
Q. Right.
A. The structure of the division was that there was the assistant secretary, and the division had about four branches -- four or five branches. I was the head of branch 3 and I was directly responsible to the head of division, whether senior principal or assistant secretary.
Q. I see. So you were the head of branch C?
A. Branch 3.
Q. Sorry, branch 3, my mistake. And your title was "Senior Executive Officer"?
A. Senior Executive Officer, yes.
Q. Did you have any officers beneath you?
A. I did. The branch had four staff. There was one SEO, one HEO -- that's "Higher Executive Officer" --

one Executive Officer and one Clerical Officer.

Q. I understand.

A. I don't know the contemporary equivalent of those --

Q. That's fine. I think we will leave the structure there. Sir, what we will try and do is I think we will try and put something in writing and circulate it and agree it so the Inquiry has that going forward.

THE CHAIRMAN: I suspect it's just going to emphasise the tremendous overburden of officers between Mr Murray and the Secretary of State for Scotland. But we will see.

MR MACKENZIE: Mr Murray, you have provided two statements for us. I'm only going to look at one of these with you and that is the statement relating to the question of compensation for clinical trials.

A. Yes.

Q. So could I go to that statement, please? The number is PEN0171868. I am afraid, Mr Murray, I'm going to have to spend a little time going through the various documents referred to because there are quite a number we haven't looked at yet at the Inquiry.

What I should perhaps say is that, having done that, there are two propositions I'm going to put to you at the end for your comment. So I'll let you have them now so you can think about them as we go through the documents.

A. Thank you.

Q. The first proposition I will suggest is this, that the issue of compensation for participants in clinical trials of PFC products was an issue on which the SHHD required to lead because any compensation would involve public expenditure and would also involve liaison between government departments.

The second proposition that I'll put to you after looking through the documents is that the time taken to resolve the issue of compensation between the matter first being raised in November 1983 and compensation being agreed in February 1987 was, on the face of it, unsatisfactory.

So those are the two points I'll suggest at the end and I'll ask for your views on them, but obviously feel free to comment on any matter as we go through the documents.

A. Thank you.

Q. I think we should start, please, when the matter is first raised in November 1983 by Dr Ludlam. I should pause to say, Mr Murray: your statement, understandably, begins in March 1985 but I think we had asked that you look at these prior documents.

A. Yes.

Q. Have you had a chance to do that?

A. I have, yes.
Q. I'm grateful.
A. I have read it.
Q. I'm grateful. Could we start, please, with SNB0015188? We have, I think, looked at these before in the Inquiry, the minutes of a meeting of the haemophilia and blood transfusion directors held on 14 November 1983 in St Andrew's House. I think the chair, Dr McDonald, will have been a medical officer at SHHD.
A. Yes.
Q. It has been pointed out to me, Mr Murray, that that's an error on my part. These are the minutes of the meeting -- it's a different group; it's the Haemophilia and Blood Transfusion Working Group. I think the chairman at this stage is not in fact a medical officer at SHHD; I think it's Dr McDonald of Glasgow Royal Infirmary. I think we will come on --
A. My apologies.
Q. It's my mistake. I think we will come on later to see a different meeting. But this one is, as I say -- but we do see in attendance Dr Bell as an observer, who I think was from SHHD?
A. Yes, that's right.
Q. Yes, and we can see that under the reference to

heat-treated Factor VIII concentrate:

"Dr Ludlam and Dr Forbes reported on their clinical evaluation of a trial batch of the new heat-treated product prepared at PFC."

And there is a reference to one of Dr Ludlam's patients experiencing adverse reactions.

That, I think, is the context. The next page please. At the very bottom we see, "Any other business: Compensation for clinical trials":

"Dr Ludlam said that he would like to bring to the group's attention his concern about the lack of formal arrangements for compensation for patients who willingly participate in the clinical evaluation of products and may be disadvantaged as a result."

A comment by Dr Bell, and then:

"Dr Cash agreed to raise the matter with the CSA, who could take legal advice and liaise with SHHD."

So I think that's the first reference we have in the document, Mr Murray.

The next reference, please, is SNB0015252. We can see from the heading these are the minutes of a meeting of the directors of the SNBTS and the haemophilia directors, held in St Andrew's House on 2 February 1984. We can see Dr Bell of SHHD chairs the meeting and Dr McIntyre is present. If we can go to the last page,

please, under paragraph 10, headed "Compensation and clinical trials", it's noted:

"Dr Ludlam expressed his concern about an apparent lack of guidance and compensation arrangements for patients who take part in clinical trials and as a result might suffer damage.

"Dr Bell thanked Dr Ludlam for the articles which had been circulated but was not in a position to give directly relevant advice at present, though he mentioned the arrangements which existed for blood donors throughout the UK.

"It was agreed that Dr McClelland would prepare a paper on this subject for submission in the first instance to the BTS subcommittee of the CSA."

The next document, please, is Dr McClelland's paper. It's SNF0013013. I'm not going to go into the detail but could we, please, go to page 3, which is 3015, Dr McClelland's recommendation, 5.1:

"For volunteer studies and for immunisation of donors and staff volunteers for harvesting of immune plasma and lymphocytes, the SNBTS accepts the principle that there is a moral responsibility to compensate."

5.2:

"The SNBTS explores the means of obtaining appropriate forms of insurance."

5.3:

"The legal office be consulted with a view to preparing guidelines, based on the ABPI [the Association of British Pharmaceutical Industry] documents and modified as appropriate, which would be used in the conduct of all SNBTS trials involving both patients and volunteers ..."

A reference to the SNBTS ethics committee scrutinising any guidelines. Over the page, please, at 3016, we can see that Dr McClelland enclosed a copy of the then ABPI guidelines.

The next document in the chain, please, Mr Murray, takes us to March 1985 and this is SNF0010241. These again are the minutes of a meeting of the directors of the SNBTS and haemophilia directors at St Andrew's House on 7 March 1985. Dr Bell again the chairman. Dr McIntyre of the SHHD in attendance.

Could we, please, go to page 5, and under paragraph 8, "Compensation and clinical trials":

"It was generally agreed that the current situation was unsatisfactory and Dr Cash explained the difficulties that the SNBTS had perceived in attempting to resolve the problems through the CSA. Dr Ludlam requested that some action should be taken urgently.

"It was agreed that the SNBTS would submit a paper

to the CSA with a view to discussion at the next BTS subcommittee meeting, and Dr McIntyre undertook to raise the matter within the department."

I think the last document we need to look at at this stage, before coming to your statement, is SGH0031964. This is a letter from Dr Cash, dated 11 March 1985, to Mr Mutch, who was the secretary of the Common Services Agency. The title is "Compensation of volunteers submitted to procedures within the SNBTS in the event of adverse reactions".

I think, in short, Mr Murray, the matter isn't dealing solely with the narrow, perhaps, point raised by Dr Ludlam of seeking compensation for patients or volunteers undertaking trials of PFC product; the matter has been widened out to wider issues of compensation as well.

A. It has.

Q. Yes.

A. I think that's a significant point.

Q. Okay, we will follow that through in a later documents and we don't lose sight of that.

A. Yes.

Q. If we could, just sticking with this letter, please, the next page, at the bottom, Dr Cash states:

"I would suggest that there are several steps which

now ought to be taken:

"(a) clearance in principle from SHHD;

"(b) if (a) is acceptable to SHHD, then

"(i) establishment of a body to consider claims (already exists for anti-D and apheresis);

"(ii) legal office prepares guidelines based on ABPI documents, which would be applicable for all relevant SNBTS work."

Over the page:

"(iii) that (b)(ii) be submitted to SNBTS ethics committee for a comment;

"(iv) approval of BTS subcommittee."

If we look at the cc, we can see this letter was copied to the transfusion directors and to Dr McIntyre of the SHHD.

That's all by way of setting the scene before we come back to your statement, please. Could we now go to Mr Murray's statement again? You tell us in paragraph 1 that:

"I have little or no recollection of these matters and my statement is based on a reading of the documents made available to me ..."

Could I pause, please, Mr Murray and ask: has reading any of these documents recently rejogged your memory at all or does the position remain that you have

no recollection beyond what's in the documents?
A. That's rather a difficult one to answer. I have in fact no memory of these matters. When the issue was first raised, I was quite surprised. I had just no memory of this whatsoever. In fact, dealing with BTS matters generally, my memory is much worse there than in relation to other responsibilities I had at the time, such as the ambulance service. Asking myself why, I think the reason is that, in dealing with the BTS, the matters are extremely technical, for example, making it much more difficult perhaps for me to remember issues, whereas with the ambulance service they are hopefully more common sense and practical. So I offer that as an explanation.

I have no memory but as soon as I read the documents, they all make sense, if I can put it that way; I can follow them easily and with no difficulty, but with no actual direct recollection.

Q. Okay.
A. Is that --
Q. I understand. I should also have asked, when did you retire?
A. I retired on the last day of 1995.
Q. Yes. So former work matters may not have been at the forefront of your mind perhaps since 1995. Would that

be fair?

A. Thankfully not.

Q. No. I hope they are now.

A. I am afraid so, yes.

Q. So that's Dr Cash's letter to Mr Mutch. Then your statement. We saw paragraph 1. In paragraph 2 you tell us that your involvement:

" ... would appear to have begun in March 1985, when Dr McIntyre minuted John Davies (my senior officer), alerting him to the concerns of SNBTS and clinicians regarding the language of a compensation scheme for clinical trials and the possible consequences of this, particularly for heat-treated Factor VIII."

We can perhaps briefly go to that minute. The reference is SGH0031969, and it's headed "Clinical trials of therapeutic substances provided by SNBTS". I think I might just go to the second page, to see what's said at the end of the minute.

THE CHAIRMAN: We've crashed.

(12.48 pm)

(The short adjournment)

(1.45 pm)

THE CHAIRMAN: Yes, Mr Mackenzie?

MR MACKENZIE: Thank you, sir. Mr Murray, I think we had reached March 1985 before the break.

A. Yes.

Q. If we could return, please, to this document, SGH0031969 at page 1, please. This is the minute from Dr McIntyre to 15 March 1985. I think before lunch we made a distinction between, if I could call it, the narrow compensation point raised by Dr Ludlam initially, namely compensation for patients or participants in clinical trials of PFC product, and then I think we saw wider compensation points raised in Dr Cash's letter to Mr Mutch of 11 March 1985.

A. That is right, yes.

Q. So bearing that distinction in mind, between the narrow and wider compensation issues, I think this minute, if we look at it, deals with the narrow, I think, compensation issue. If we go about half way down, the heading, of course, is "Clinical Trials of Therapeutic Substances Produced by SNBTS". About half way down we see:

"At a recent informal meeting of the Scottish haemophilia directors and the directors of the SNBTS, the question of compensation and clinical trials was raised, as the number of products being produced at the PFC for which clinical trials are necessary, is gradually increasing; the most immediate of these is heat-treated Factor VIII. The clinicians concerned

would like the legal position to be stated quite clearly and in particular to be reassured that compensation would be paid without prolonged legal wrangles to any unfortunate volunteer or his dependents."

Over the page, please, the final paragraph states:

"At the meeting referred to above it was suggested to the clinicians that the problem should be raised in the first instance with the CSA as the management body responsible for the SNBTS and the PFC. This suggestion however was not accepted with any great enthusiasm in view of past experience. I now understand that following the meeting Dr Cash has written to the CSA in respect of SNBTS but of course the problem relates also to the clinicians involved in the clinical trials. No doubt you will be hearing more about this from CSA but the above is by way of 'early warning' and to indicate that we feel this is a matter of some importance -- which might be solved along the lines of the arrangement for compensating blood donors involved (by immunisation) in the production of anti-D immune plasma. Happy to discuss."

Then we see, I think, some handwritten notes by Mr John Davies, who I think was above you at the SHHD?

A. He was the head of division.

Q. Thank you. In particular, I think, his handwritten note

to you, Mr Murray.

A. Yes.

Q. Can you read that for us, please, bottom right-hand corner of the screen.

A. Yes, this is reminding me that John was not the most lucid of handwriters but he was a certainly a great deal better than myself:

"We can expect it to come straight into us and would you set in train some investigations. Finance 5 and (I suppose) CLO -- but for the latter I would rather wait to see what Mr Mutch does."

Q. So Mr Davies is asking you to make contact with your finance division?

A. Yes.

Q. And possibly, I suppose CLO, albeit a wait and see in that regard. I think, Mr Murray, that seems to be your first involvement in the question of compensation from the documents.

A. It is, yes.

Q. I'm grateful. If we can return, please, to your statement to continue with this chronology. Back to PEN0171868. We have dealt with paragraph 2 by looking at that minute. Paragraph 3, we see that on 22 March 1985, Dr Cash copied to Mr Davies and Dr McIntyre, his letter of 11 March to Mr Mutch. The

reference -- we don't need to go to it -- is SGH0031963.

At paragraph 4 of your statement:

"On 22 March 1985 --"

I'm sorry, before that I think we should look at this document, SNB0057320, which is a letter dated 19 March 1985 from Dr Ludlam to Dr Boulton. In the second paragraph he states:

"As you will no doubt have heard, we discussed at some length the testing of new blood products at the haemophilia BTS directors' meeting at St Andrew's House recently. As you know, one of my patients had a reaction ... and I'm, therefore, a little more apprehensive about testing further batches. Clearly these require urgent clinical evaluation. Although I raise the question of compensation for individuals who suffer materially as a result of testing new products at St Andrew's House some time ago, there has been little progress. The commitment of either the CSA or Scottish Home and Health to give reasonable compensation has not been demonstrated to my satisfaction. I'm reasonably conversant with the principal reason why this is difficult to achieve."

I think this letter is copied by Dr Cash to SHHD. Could we go back, please, to your statement,

paragraph 4. You say in paragraph 4:

"On 22 March 1985, Dr Cash wrote to Dr McIntyre conveying Dr Ludlam's specific concerns and observing that if there was no speedy resolution, then the whole of the SHS heat-treated Factor VIII programme would be very seriously affected."

We can go to that letter, please. It's SGH0031958. We can see the letter is, as you say in your statement and we can see the reference to:

"The enclosed letter has come out of the blue and is a cause for considerable concern."

I think that must be the letter from Dr Ludlam to Dr Boulton of 19 March 1985 we have just looked at. In the second paragraph, Dr Cash asks:

"I would be most grateful if you would use your good offices to do anything you can to assist us.

" ... I wonder whether a call from you might be sufficient to do the trick. In the meantime, I will also have a chat with him."

Then returning to your statement, please, in paragraph 3 about half way down, you pick up:

"On 28 March, Dr McIntyre drew these concerns to the attention of Mr Davies."

We should go to that, please. It's SGH0031957.

We can see that on 28 March 1985, Dr McIntyre has

minuted Mr Davies and copied it to Mr Calder. Who is Mr Calder?

A. He was the chief pharmacist to the Secretary of State.

Q. Thank you. In his minute, Dr McIntyre refers to the letter from Dr Cash enclosing the letter from Dr Ludlam, and we see half way down the minute:

"You will be interested to know that the problem is not confined to Scotland and Mr Smart, chairman of CBLA has written in similar terms to Dr Harris, the DCMO at DHSS".

If we look at the handwritten note at the bottom right-hand corner, please, we will see, I think, Mr Davies writing to yourself, Mr Murray, stating, I think:

"I believe you are already looking into this, though as far as I can recall, the CSA have not written in."

Et cetera. If we go back to your statement, please, to continue with the chronology, to see what happens next. We are on, I think, now to page 2 of your statement, and we do now hear from the CSA in that you say that:

"On 2 April 1985, Mr Wooller, the general administrator of the CSA, copied to me a memorandum he had sent to the CSA legal adviser on the issues raised in Dr Cash's letter of 11 March, suggesting that in the

meantime, SHHD may wish to give preliminary consideration to these issues."

If can go to this letter, please. It's SGH0031952. In this memorandum, or letter perhaps, Mr Wooller writes to you, Mr Murray, and states under heading "Compensation of Volunteers Submitted to Procedures within the SNBTS in the Event of Adverse Reactions":

"Further to our brief discussion of this matter on 1 April 1985, I enclose a copy of the letter dated 11 March ..."

That's the letter from Dr Cash to Mr Mutch --

A. Yes.

Q. -- raising the wider compensation issues:

"... with a copy of the memorandum which I have today sent to the legal adviser.

"I will write to you again when the legal adviser's advice has been obtained. In the meantime, you may wish to give preliminary consideration to the issues raised by Dr Cash."

If we can return to your statement, please, at paragraph 6, you explain that in April 1985 you wrote to the DHSS explaining the present position and suggesting a mutual exchange of deliberations. If we can go to that, please, it is SGH0031951. This is headed

"Compensation for Trials of Therapeutic Substances", and you enclose a copy of Dr Cash's letter to Mr Mutch, and you explain you are:

"... presently seeking advice, from our finance division and our CLO on the issues raised by Dr Cash, which I understand are the same as those raised with yourself by BPLA. A further point which we are exploring, and not mentioned in Dr Cash's letter, is the position of the clinicians involved in such trials."

Et cetera:

"I would be grateful if you could let me know the result of your own deliberations. There certainly seems no reason why we should not reach a common conclusion on how to deal with this issue."

Then if we could go back to your statement, please, at the end of paragraph 6 you tell us that:

"On 10 April SHHD finance advised me that treasury approval would be required for any proposals for a compensation scheme."

We don't have to go to that letter but for the record it's SGH0031950. Sticking with paragraph 7 of your statement, what next occurs is that:

"On 2 April 1985, Mr Calder, the chief pharmacist, minuted Dr McIntyre in reply to a request for comments on the issue of compensation."

We should perhaps look at that, it's SGH0031948. If I can perhaps focus on three points. Firstly, the heading is "Chemical Trials of Therapeutic Substances Produced by SNBTS." In the second paragraph he says:

"First, let me say that you will require to receive legal advice from our own lawyers and also, I suspect, from the legal department of CSA."

After his three numbered points he says:

"I'm sorry I cannot be more helpful and I'm sure that before we go any further, we should get legal advice on what can/cannot be done in these particular circumstances."

Then back to your statement, please, if we may. Half way through paragraph 7, we see:

"On 10 April 1985 Dr McIntyre copied Mr Calder's minute to Mr Davies saying 'I understand from Mr Murray that the secretary of the CSA is raising the matter with their legal advisers and perhaps we should defer further action until this legal advice is available. As the clinicians are much concerned about this matter, I trust the legal advice will not be too long in coming'."

I will provide a reference for that minute without going to it, it's SGH0031947. You also note that on that minute on 11 April, Mr Davies had replied:

"We are indeed expecting CLO to be consulted. This is part of an exercise to persuade the CSA to take themselves decisions properly theirs. While it would doubtless be possible to consult our solicitor's office in parallel, I am not persuaded it is necessary to do so. As to how long it will take, that depends on the lawyers."

You say there in your statement:

"The position of SHHD was that it was for the CSA to bring forward proposals concerning a compensation scheme."

To pause at this stage, I suppose it could be said that Dr McClelland had tried in his document back in 1984 to set out what he saw as a way forward, and then I think Dr Cash then in his letter to Mr Mutch in March 1985 had tried what he saw was the way forward. Could it be suggested really that at that stage matters were unresolved, both the narrow compensation issue first raised by Dr Ludlam and the wider compensation issues in Dr Cash's letter. Given that really these compensation issues were unresolved, that perhaps was the time for SHHD to step in and try and resolve the matter one way or the other?

A. As far as SHHD administration was concerned, the issue had only been raised with us in March and it was our

belief that that issue was now being considered in the forum in which it should be properly considered. That is the CSA.

Q. Two points arise in that regard. Firstly, I take your point that as far as the SHHD administration was concerned, that matter of compensation first came to you in March 1985. I think as the SHHD medical officers were concerned, they were certainly aware from November 1983 of Dr Ludlam's concern about compensation.

A. That is the case, yes, as in the previous documents, yes.

Q. The other point you mentioned about CSA being the appropriate forum for compensation to be dealt with.

A. Hm-mm, yes.

Q. Presumably that could only be as a first step, in that any CSA proposals in that regard would require approval from SHHD, perhaps including the Treasury.

A. Certainly treasury, yes.

Q. Yes. So the CSA as a forum could only do so much.

A. The CSA as a forum? The word "forum" popped into my head.

Q. It's a good word?

A. It's a good word but as the preliminary report makes clear, in effect the SNBTS is responsible to the BTS

subcommittee and the CSA management committee. I think the preliminary report itself makes that very clear. Those are the two immediate bodies responsible for the management of the SNBTS.

Q. Yes. So the CSA are immediately responsible but ultimately, surely, the SHHD, and beyond that, the appropriate minister is ultimately responsible.

A. Yes.

Q. Yes. So if the CSA were not able, for whatever reason, to adequately resolve an issue, might there be circumstances where the SHHD would step in to try and resolve it?

A. Yes.

Q. Yes. Does it follow from what you have said that, as far as you were concerned at this time -- so we are now in about April 1985 -- your position would have been that while in theory there may come a time when it would be appropriate for the SHHD to step in and try and resolve an issue, you didn't consider the time had come yet?

A. At that time we didn't know there was an issue to resolve.

Q. Well, certainly you were aware as at April 1985 of Dr Cash's letter --

A. Oh, yes, but I mean, at that time we did not know there

were any potential difficulties within the CSA.

Q. So at that stage your view would have been that the issue was in the appropriate forum?

A. Yes.

Q. The CSA, and let's wait and see what they bring to us?

A. Yes.

Q. Okay. In the next paragraph, please, of your statement, paragraph 8, you explain that:

"On 29 April 1985 I wrote to Mr Wooller conveying the particular points raised by Mr Calder as regards clinicians."

I'll give the reference without going to the document. It's SGH0031944. You then say:

"I followed up this request on 21 June."

That's essentially a reminder on your part to try and prompt Mr Wooller to come back to you. I'll give the reference again. It's SGH0031940. Then:

"On 12 July he replied to me with the legal adviser's comments on these points."

If we can go to that, it's SGH0031937. This is a -- what is the correct word, Mr Murray? Is it a letter, a memo, a minute?

A. What I would call a letter, Mr Wooller frequently called a memorandum. There was a difference in the language between us and the CSA at times.

Q. Okay. So this letter or memo, from Mr Wooller to yourself of 12 July 1985, headed "Compensation of Volunteers Submitted to Procedures within the Blood Transfusion Service":

"Further to my letter of 1 July 1985, I enclose herewith for your consideration a copy of the reply received from the Central Legal Office to the point raised in your letter of 29 April 1985."

Can we then go to that reply, please? It's SGH0031938. This is a memo, a minute, from Mr Griffiths of the Central Legal Office to Mr Wooller on the subject of compensation of volunteers submitted to procedures within the Blood Transfusion Service, albeit, I think, if you, Mr Murray, had been waiting for this to deal with and solve all of the issues that had been raised, I think you would have been disappointed reading this because we can see that it deals largely with a discussion of negligence. That's not to criticise the solicitor because we don't know what information or instructions or brief he was given, but it's simply to --

A. He seems to have, I think, addressed issues raised by Mr Calder.

Q. Yes.

A. But no wider.

Q. I understand, and we don't know if he was asked to consider any wider issues. We don't have that documentation with us.

A. Right.

Q. So in short, a discussion of negligence but really the whole point was can there be a no fault scheme, no fault compensation. So like isn't meeting like here.

A. That's right. It's not a meeting of minds.

Q. No. So that's not solving things, which I think you very properly are aware of, Mr Murray, because your next letter is SGH0031936. This is your minute of 6 August 1985 to Mr Calder, copied to others, and you say:

"Please see the attached reply from CSA to my letter of 29 April. This does not seem to take us very far forward.

"As regards the points raised in Dr Cash's memorandum, this is still being considered by CLO; I am advised that a further letter will be sent to us once their legal advice is available."

We can then, I think, go back to your statement, the top of page 3, paragraph 9. You explain that:

"In a minute of 16 August 1985 to Mr Davies in connection with papers for a meeting of the BTS subcommittee on 21 August, I outlined the steps taken

and the present position."

Can we go to that minute, please? It's SGH0031933. Under item 3, "Compensation of Volunteers", you set out the history, that:

"Dr Cash's letter of 11 March to Mr Mutch was copied to the department and on receipt, I asked CSA to seek CLO advice on the points raised by Dr Cash. Following this there was an exchange of minutes with Mr Calder and Dr McIntyre, following which I wrote to the CSA on an additional point based on material supplied by Dr McIntyre and Mr Calder. While the CSA have replied to that additional point, they are awaiting CLO advice on the main issues raised by Dr Cash's letter.

"CBLA have raised similar points as DHSS ..."

And you have been in touch with them:

"This whole matter is a most complex one which I suspect raises basic issues much wider than those simply relating to the BTS. The attached file may be of help in understanding the issues involved."

Back to your statement, please, to complete what happened next. In paragraph 10 we see that:

"In a minute to Mr Davies of 21 August 1985, Mr Hugh Morison ..."

I think Mr Morison was higher up in the structure again?

A. Yes, Mr Morison was the departmental undersecretary for health.

Q. Thank you. And Mr Morison explained that:

"... explained that at a meeting that day of the BTS subcommittee he had said SHHD would pursue the compensation issue with DHSS as a matter of urgency ..."

Could we look at that minute, please? It's SGH0031927. If we go to item 3, I don't think we can improve on the words of the minute which states, under "Compensation of Volunteers", and this is Mr Morison speaking:

"I said that we would pursue the question of compensation of volunteers who have adverse reactions with DHSS as a matter of urgency; it would, however, be necessary for the agency to clarify the boundaries of their proposals before we took the matter forward. I explained that the question would be required to be considered in a GB context; Dr Cash said that the English service had already approached DHSS about it."

Back to your statement, please, Mr Murray. Paragraph 11:

"In a manuscript note of 10 September 1985 to Mr George Thompson (next in line after myself in the branch) ... "

Is that up or down?

A. Down. Mr Davies was up, Mr Thompson was down.

Q. Thank you:

"... I explained that I have confirmed with Mr Wooller that the CSA were pursuing Mr Morison's point about the boundaries of their proposal with SNBTS and CLO ..."

I'll provide the refers without going to it. It's SGH0031926. Paragraph 12 of your statement tells us that:

"In November 1985 I wrote to DHSS ..."

If we can go to that, please, it's SGH0031925. This letter to the DHSS in November 1985 is headed "Immunisation of Volunteers, Compensation for Injury". Then if we can go to the third paragraph, please:

"I also discussed with you in April this year the question raised both by Dr Cash and by BPLA, of compensation for (a) volunteers (either BTS staff or donors) who suffer adverse reactions through the receipt of medication or immunisation for BTS purposes and (b) patients who agree to receive newly developed BTS products on an experimental basis."

Again, you say:

"As I mentioned in my letter in April, it would seem desirable for these questions to be considered in a GB context and I shall let you know of whatever further

clarification emerges from the agency. In the meantime ..."

You invite the DHSS to keep you updated of any progress they make. Then, returning to paragraph 12 of your statement, please, you refer to a reminder you sent the DHSS a 11 February 1986. I'll give the reference without going to it. It's SGH0031933. You then say in your paragraph:

"From the documents made available to me, it does not appear that I received a response from DHSS on the issue of compensation."

If there weren't enough individuals involved in the matter by this stage, enter somebody else. In paragraph 13 of your statement, you tell us that:

"In February 1986 Professor R H Girdwood, the chairman of the SNBTA, raised a number of issues with the minister, Mr John MacKay, including compensation for volunteers in SNBTS research projects."

If we can go, please, to that letter, it's SGH0020739, a letter of 19 February 1986 from Professor Girdwood to Mr Mackay. Starting:

"I am writing as chairman of the SNBTA (which represents the interests of donors) about a matter which has been raised with me, but about which I am anxious to avoid any publicity. This is the possibility that

insurance policies of a blood donor might be loaded under certain circumstances ..."

This really, I think, relates to donors who donate blood which is used in the production of immunoglobulin. Does that seem right?

A. It seems right. I confess --

Q. I think that's the primary concern, understandably, perhaps, of Professor Girdwood --

A. Yes, this had to do with life assurance associations. I came across some documentation. The question of whether people involved in such matters would have -- their insurance policies would be affected in some way.

Q. So that's a matter that arises in the wider consideration of compensation?

A. Yes, it's running parallel, you might say.

Q. Yes, thank you.

A. A number of threads to this.

Q. Yes, thank you. Page 2 of this letter, the top of the page:

"In addition, I do not know whether compensation would be given if something unexpected was alleged to have developed as a result of a research project ..."

That may be a reference to patients but we don't know from the terms of the letter.

Then, returning, please, to the bottom of page 3 of

your statement, half way through paragraph 13:

"A draft reply for the minister prepared by Mr George Paul (acting head of division) which drew heavily on advice offered by medical colleagues who explained, as regards compensation schemes, that there was at present no formal compensation scheme, though each case would be considered on its merits."

For the record, I'll give the number of that document as SGH0031291, and also provide a number of a draft reply by the minister to Professor Girdwood, which is SGH0031922. We are at page 4, I think, now of your statement, Mr Murray, paragraph 14. And we are now in August 1986, which I think is now at a time when Z8 is being scaled up by PFC. And 14:

"At a meeting on 20 August 1986, chaired by Hugh Morison, the BTS subcommittee noted that the national medical director had held a useful dialogue with the legal adviser ..."

We will go to this minute to see exactly what's minuted, please. It's SGH0020455. These are the minutes of this meeting of the subcommittee held on 20 August 1986. If we can go over the page, please, under subparagraph (iv), "Compensation of Volunteers":

"The subcommittee noted that the national medical director had held a useful dialogue with a legal adviser

concerning arrangements for the compensation of volunteers and agreed that the general manager should now pursue the bringing forward of firm proposals."

It's perhaps not clear from the face of the minute in isolation, Mr Murray, as to what exactly is meant by "volunteers"; does that mean donors as per Professor Girdwood's letter or does that include patients who volunteer to participate in a clinical trial of a PFC product?

A. I am afraid I can give no authoritative interpretation of that.

Q. Although --

A. It's just wide.

Q. Although, put it this way, you were certainly still aware at this time in August 1986, that both the narrow compensation issue remained live, as did the wider compensation issue.

A. Yes, correct.

Q. Then go back, please, to your statement in the final sentence of paragraph 14, where you say:

"I note, however, that the minutes do not state to whom the proposals are to be brought."

If you had read the minute at the time, to whom would you have understood the proposals were to be brought?

A. Very possibly to the BTS subcommittee.
Q. And from that subcommittee, where would they go?
A. From that subcommittee to the department.
Q. Yes. Then in paragraph 15 of your statement, you make a comparison between Mr Morison's minute of 21 August 1985 concerning the BTS subcommittee meeting, which I think we have looked at, and then minutes of the BTS subcommittee meeting on 20 August 1986:

"... the matter of a compensation scheme for clinical trials had remained with the CSA, which was to 'clarify the boundaries of their proposals'/'pursue the bringing forward of firm proposals'."

I discussed earlier with you, Mr Murray, that in theory you accepted there may come a point where, if the CSA, as initially the correct forum to deal with an issue, was not in fact dealing with an issue, the SHHD may consider it appropriate to step in and resolve the issue. We are now at August 1986. We know that both the narrow compensation issues and the wider compensation issues set out in Dr Cash's letter of March 1985 remain unresolved. Could it be said that that was an appropriate time for the SHHD to step in and resolve the matter?

A. Two points. The BTS subcommittee met more than once a year. I don't know how frequently it met but it would

appear that -- well, there was a possibility that there may have been urgent discussion at a BTS subcommittee meeting within that period, but there does not appear -- or at least I'm not aware of any documentation.

The other point is that there is a close interrelationship between the department and the CSA committees, insofar as senior officers of the department sit on both the BTS subcommittee and the CSA management committee. The drawing of firm distinctions can sometimes be rather difficult.

Q. Yes. I'm sorry, are you finished?

A. No, I have finished.

Q. To illustrate that point, if we do go back to these minutes, SGH0020455, we can see that the meeting of this subcommittee, the vice-chairman was Mr Morison from the administration side of SHHD, and we can see also present was Dr Forrester, I think, from the medical side of SHHD. Does that perhaps illustrate the point you have just made?

A. Yes.

Q. Although in response, could it equally be said that really both parts of SHHD, the medical side and the administration side, were particularly well placed to see that the question of compensation wasn't being resolved by the process or steps to date, and therefore

there was even more of a need for SHHD to step in and sort it out?

A. The only answer I can give is evidently not.

Q. To be fair to you, you certainly weren't sitting on this subcommittee. It's persons at a higher level than you. I understand that.

Could we then, please, look at another document, SNB0058711? We are back to Dr Ludlam writing to Dr Cash on 11 December 1986, saying:

"I was pleased to learn recently from Frank Boulton that 8Z is shortly to be available for clinical assessment. I have obtained ethical approval to undertake recovery and survival studies in haemophiliacs. I am now awaiting an appropriate commitment from either PFC, SHHD or DHSS concerning the question of indemnity should any of the patients materially suffer as a result of assessing the new Factor VIII product.

"As you know, I raised this a long time ago with SHHD and there has been no response."

So looking at matters from Dr Ludlam's perspective, it is now three years since he first raised the matter and one can perhaps understand his frustration that the compensation issue that he raised has not been resolved.

Then to complete the chronology, please, back to

your statement -- I should perhaps say for the record, when I suggested, Mr Murray, that one could understand Dr Ludlam's frustration, you nodded your head, at least from Dr Ludlam's perspective. Is that correct?

A. Could you repeat that.

Q. I'm sorry, it's my fault. When I looked at Dr Ludlam's letter and I suggested that at least from his perspective, one could understand him being frustrated in the matter not having been resolved since he first raised it, I think you nodded your head in agreement to that?

A. Yes, I would agree with that.

Q. From his perspective at least?

A. Yes, certainly.

Q. Back to your statement please. In paragraph 16 you explain that:

"In a manuscript minute to me of 30 December 1986, Mr George Thompson explained that Dr McIntyre and Dr Forrester had informed Mr Macniven, who by then was head of division, that Dr Ludlam was seeking some form of compensation scheme before embarking on the testing of heat-treated Factor VIII. We could no longer wait for clarification from the CSA, and Dr McIntyre had suggested a compensation scheme on the lines of a previous treasury-approved scheme."

If we go to document SGH0031920, the minute is essentially to the same effect as you set out in your statement. We can see about half way through it:

"However, there is now great urgency in that Dr Ludlam is declining to administer the 'new' Factor VIII (when existing stocks are exhausted in February) ... "

So that's where the urgency arises here?

A. Yes.

Q. "... unless he has received notification of some form of compensation cover; precisely what he requires is not evident but may emerge in the agency's clarification of the boundaries of this proposals which is presently awaited. We cannot however wait! Suggested by Dr McIntyre is, as before, compensation on the anti-D lines."

Then back to your statement, please, paragraph 17:

"On the same date Dr Cash wrote to Dr McIntyre referring to a telephone conversation that day. Dr Cash requested a formal response on the question of a compensation scheme for heat-treated Factor VIII trials similar to the one already in existence."

We can go to that but I think we have seen it before. It's SGH0031919. We have looked at this before, I think, in the Inquiry, Mr Murray. It's, as

you say in your statement, Dr Cash's letter of 30 December 1986 to Dr McIntyre, and Dr Cash essentially seeks compensation on the same basis as blood donors who undergo immunisation/boosting for the procurement of anti-Rh(D) immune plasma.

Then back to paragraph 17 of your statement, please. The second half of what you set out in paragraph 17 I think we will come to later on because that refers to a note of February 1987. So I'll stick with the chronology just now and come back to that.

A. Right.

Q. Over the page at page 5, please, paragraph 18. You say:

"It would appear that Dr Ludlam's letter of 11 December 1986 had prompted Dr Cash to contact Dr McIntyre concerning a compensation scheme for clinical trials of heat-treated Factor VIII. Prior to December 1986, compensation arrangements for clinical trials of heat-treated Factor VIII appear to have been subsumed within general consideration of a general compensation scheme in relation to clinical trials for BTS purposes."

I think the documents we have looked at bear that out, don't they?

A. Yes. It would appear that at the beginning, the issue of heat-treated Factor VIII was what prompted and was

the initial driver of the idea of a general compensation scheme.

Q. But that rather grew arms and legs perhaps?

A. Yes.

Q. And you say in your statement:

"It does not appear that anyone had previously proposed compensation arrangements specific to clinical trials of heat-treated Factor VIII."

I suppose it could be said Dr Ludlam had, at least that was his concern: the narrow compensation point.

A. I'm speaking in relation to what formally had been put to the admin side of the department.

Q. I understand. In paragraph 19:

"On 7 January 1987 Dr Forrester minuted Mr Macniven regarding an assessment of risk to volunteers and attached a copy of a statement received from Dr Cash."

We have looked at that in the Inquiry previously. So I'll simply give the reference numbers without going to them. It's SGH0031912 and Dr Cash's lengthier statement is SGH0031913. You then explain in paragraph 20 that:

"It would appear that between 7 and 12 January, I spoke to both Treasury and DHSS to explore the possibility, in a GB context, of a compensation scheme for heat-treated Factor VIII trials based on previous

treasury-approved compensation schemes."

Then paragraph 21:

"On 12 January 1987 I minuted ... SHHD finance division with a draft letter for him to send to the Treasury."

We don't have to go to that but the reference is SGH0031883. Then in paragraph 22 of your statement you explain that:

"On 12 January 1987 Mr Brunning of DHSS wrote to Treasury seeking agreement to compensation arrangements for the proposed clinical trial of Factor VIII, drawing similarities with arrangements for previous whooping cough trials."

I think we should go to it. This is SGH0031891. So this is a minute from Mr Brunning of the DHSS to Mrs Wiseman, at the Treasury, concerning Central Blood Laboratories Authority clinical trials of Factor 8Y, so in England. We see the final sentence is:

"This matter is rather urgent; a speedy reply would be appreciated."

And also a reference to seeking, I think, compensation, along the lines of the ABPI guidelines.

The initial, I think, response from the Treasury is not a positive one. If we then go, please, to SGH0031890 Miss Z Everest-Phillips of the Treasury

chambers replies on 12 January 1987 as regards the CBLA request for compensation for clinical trials of Factor 8Y in England. In short, it's not a positive response from the Treasury. I think a further approach is required before the Treasury will relent. I think matters are quite nicely set out back at your statement, please.

Go back to your statement, page 6, paragraph 23:

"Mr Kernohan from the SHHD finance division wrote to Treasury on 14 January 1987 seeking agreement to arrangements for compensation in the event of injury during clinical trials of Factor VIII".

We should go to that, please, it's SGH0031881. I won't go through this letter in detail but we can see it's headed "Clinical Trials of Factor VIII Arrangements for Compensation."

It's clear, I think, by this stage that it's the narrow compensation point initially raised by Dr Ludlam that is the one at issue.

A. Yes, this -- Norman Kernohan's letter was the one which had been drafted by myself.

Q. I understand. Thank you. Over the page, to page 2 of this letter, the paragraph at the top states:

"In none of the previous arrangements has any compensation been claimed and it is not anticipated that

any claims will be made for these Factor VIII trials. It is unlikely, therefore, that there will be any resource implications (and any which may emerge, will, of course, be contained within the current financial provision)."

If one were to pause and if one were Dr Ludlam reading this paragraph more than three years after he had first raised the point, he may be a little surprised as to why it had taken three years to deal with the narrow compensation point, given what's stated in that paragraph, that:

"In none of the previous arrangements has any compensation been claimed and it is not anticipated that any claims will be made for these Factor VIII trials. It is unlikely ... there will be any resource implications ..."

It's perhaps a little puzzling, at least if one were Dr Ludlam, why the matter could take over three years to resolve.

A. I think that hopefully in my statement I have set out the steps of the previous year. Prior to that, it was not really within the remit of the administrative side of SHHD. I think I would also add that, not so much from memory but simply from reading the newspapers, that the issue of compensation in the NHS is one which I'm

sure the Treasury would take very seriously and that the case has to be properly made.

Q. I'll come back to some of these points but just to complete just now with the chronology, so back to your statement, please, at page 6 and paragraph 23, you explain that:

"Having seen on 4 February a draft DHSS response to Treasury ..."

I'll give the reference without going to it, SGH0031879:

"... Mr Kernohan wrote again to Treasury that day ..."

This is 4 February 1987:

"... addressing the concerns raised by Miss Everest-Phillips of the Treasury in her letter of 12 January to Mr Brunning."

We should go to that; it's SGH0031873. This is a letter from Mr Kernohan of the SHHD -- or rather Scottish Office finance division -- to Miss Everest Phillips. Treasury. Did you draft this letter, Mr Murray?

A. Probably, yes. Possibly after discussion with medical colleagues as well. But I would have drafted it for Norman.

Q. Because you would have understood the issues, the

substance of the letter, in a way that Mr Kernohan probably wouldn't?

A. I suspect that I drew very heavily on what I was informed by medical colleagues.

Q. Yes. And again, the letter is on the same narrow point of compensation for clinical trials of Factor VIII products, and you make the case in the letter for that.

Returning to your statement, please, you explain that in short you were successful, in that Treasury approval to a compensation scheme for Factor VIII trials was given to both DHSS and SHHD on 5 February 1987. We will go to that, please. It's SGH0031871. This is a letter from Miss Everest-Phillips of the Treasury to Mr Brunning of the DHSS in relation to clinical trials of Factor VIII. I think perhaps she is replying to the requests made from both Scotland and England for compensation.

A. Yes, that is my understanding, yes.

Q. In the second paragraph we can see that Miss Everest-Phillips remains sceptical, which, without being unfair to the Treasury, may be their instinctive reaction to requests for money.

A. Yes.

Q. But one can then see later on, half way down, she says:

"I do accept, however, that there is a very real

problem in Scotland."

Then, finally:

"On this account and taking into consideration Dr Smithies' assurances about the unlikelihood of any claims being made, I can confirm agreement to arrangements for compensation along the lines of the ABPI procedures. Any claims arising from this should, of course, be met from existing resources."

That's perhaps the sting in the Treasury tail.

A. Yes.

Q. Just to finish this off, back to your statement, please, in paragraph 23, the last sentence:

"On 6 February 1987 I wrote to Dr Cash confirming that SHHD agrees compensation arrangements for the clinical trials of heat-treated Factor VIII."

So:

"I confirm that the SHHD agreed ... "

Yes, the compensation arrangement. I'll give the reference without going to it because we have gone to this reference before. It's SGH0031870.

Can we then, please, go to this -- we are almost finished this chronology, please -- go to this document SGH0031855.

Mr Murray, I had a little difficulty understanding when this document was written and also the document on

the next page. If we start with this document, I think it appears to be -- you may have suggested in your statement -- it may have been a note written by yourself to Mr Macniven and Mr Morison.

A. Yes.

Q. For the purposes of a forthcoming meeting on --

A. Yes, I think -- yes, this would be my myself briefing Mr Morison, via Mr Macniven, for his attendance at a BTS subcommittee meeting on Wednesday, 25 February. This should be me putting him in the picture at that time. It would have been written certainly before 23 February because, according to Scottish Office records, that was the date when I began a period of extended sick leave. So it would have been written before the meeting but for the meeting.

Q. Okay. I understand that because under paragraph b that's written as if -- a historical perspective, that the issue of clinical trials had blown up over the New Year but was now resolved, and I can understand that. But if one goes over the page, please, to the next document, I couldn't quite work out the date of the next document and where it fitted in the chronology.

A. I think this is c following on b from the previous page.

Q. Right, oh. So is this relating to the wider compensation issues?

A. Yes.
Q. I understand.
A. They are both under the same heading, yes.
Q. I understand.
A. B and c.
Q. So the two pages in this document are written at the same time?
A. Yes.
Q. And b relates to the narrow compensation issue of clinical trials for --
A. Yes, to the crisis at that --
Q. Yes, and then c is the wider compensation scheme?
A. Yes.
Q. Thank you for that.

Just returning to your statement, please, Mr Murray, to complete it, in paragraph 24 you explain:

"I was on sick leave from later in February 1987 until early May. I note that during my absence a minute of 26 February by Dr Forrester records that he understood from Dr Perry that trials had already begun."

I will give the reference for that without going to it. It's SGH0031853 and we are still trying to clarify, Mr Murray, exactly when clinical trials began but it appears to have been in Edinburgh in March, but we note that further adminicle as well?

A. Thank you.

Q. Then paragraph 25, you explain:

"As regards the CSA considerations, Mr Wooller wrote to me on 23 July 1987 enclosing, for SHHD approval, suggested procedures for dealing with claims of compensation arising from clinical trials."

I will give the reference without going to it. It's SGH0031736 with SGH0031737 and SGH0031738. Then you explain:

"I set in train SHHD assessment of these before taking up a new post at the end of that month."

Was that elsewhere in SHHD or a different department?

A. Scottish courts administration.

Q. Thank you. And no doubt at the time thought nothing more about compensation until now.

A. Yes.

Q. So.

A. There is possibly a sigh of relief at the end of that last sentence.

Q. Thank you for so fully in your statement setting out the chronology in the documentation. Having now gone over that with you, can I perhaps come back to the two propositions I started with for your views comments on them.

So to remind you, the first proposition was this, that the issue of compensation for participants in clinical trials of PFC products -- this was the narrow compensation issue -- was an issue that SHHD ought to have taken a lead on because any such compensation would involve public expenditure and liaison between government departments. What's your response to that suggestion?

A. After having been in the bureaucracy for nearly 40 years, I think it must have entered my bloodstream because I'm going on give a qualified answer, which is that as a retired layman, I would say yes, but if that question had been addressed to me in that post, I would have referred it to solicitor's office.

THE CHAIRMAN: You would have refered it to?

A. Solicitor's office, the Scottish Office solicitor's office.

THE CHAIRMAN: At great length, Mr Murray?

A. No doubt.

MR MACKENZIE: Thank you.

And the second proposition or suggestion was this, that the time taken to resolve the narrow issue of compensation between November 1983 and February 1987 was unsatisfactory.

A. I'm sure that for Dr Ludlam it was a great deal more

than unsatisfactory. Yes. It was unsatisfactory. And the reasons why will be spelt out in your report.

Q. Why do you think it took so long to resolve that?

A. I don't know what was in other people's minds. I can only say that when it became a matter of importance, critical importance to the administrative part of the department, we did act on it extremely quickly. Certainly from the end of 1986 onwards, when the issue was presented to us as a critical one, we did move very quickly.

Q. I understand that point but does it answer the question: why did it take so long?

A. It doesn't. It passed -- in reviewing the papers, not from my memory but from my reading of the documentation, there would appear to be a fragmentation of attention. And we have -- we have the meetings of the regional directors and those responsible for haemophilia, we have the BTS subcommittee, we have the CSA central administration, we have Scottish Home and Health Department medical officers and then we have the administrative side of the department. The answer to your question, I think, lies in those structures.

Q. And my final question, if I may, is, with the benefit of hindsight, can you suggest any ways in which the narrow compensation issue could have been resolved sooner?

A. Only if I had the power to go back and make the actual changes. I think I must have referred back to my previous answer. As you say, it grew legs and, you know, how it could have been made to run faster through all these different hoops, I'm not able to give you a very satisfactory answer, I am afraid.

Q. But we are back to questions of structure and organisation?

A. Yes.

Q. Thank you, Mr Murray.

Sir, that completes my questioning of Mr Murray in respect of this statement and compensation. Mr Murray has kindly provided another statement on different matters which I don't propose taking him through because they raise some wider issues about formal contact and exchange of information between Scotland and England. I think we have covered these issues in considerable detail with other witnesses and with all respect to Mr Murray and his statement, I don't think the contents of his separate statement will materially assist you, sir, in resolving the issues in C3. So I would intend simply referring to Mr Murray's second statement, which forms part of the record but not taking Mr Murray through it.

THE CHAIRMAN: This is PEN0171594] is it?

MR MACKENZIE: I'm grateful, sir, it is. And I don't propose saying anything more about that, unless you would like me to, sir.

THE CHAIRMAN: Mr Murray, really over all this documentation, did you not get even a hint of a recollection of frustration?

A. This may sound strange but until I saw the documents, I had no memory --

THE CHAIRMAN: Indeed, you said that.

A. -- of this issue whatsoever, none whatsoever. But in reading the documents, a strong flavour definitely came through.

THE CHAIRMAN: Perhaps I should ask one more question: was this typical of the rapid progressing of issues through the administrative structure at the time?

A. Not totally untypical.

THE CHAIRMAN: That is possibly a satisfactory civil servant's answer.

Mr Di Rollo?

MR DI ROLLO: No, thank you, sir.

THE CHAIRMAN: Mr Anderson?

MR ANDERSON: I wonder if I may just have one moment.

(Pause)

THE CHAIRMAN: Professor James has a question that might or might not help Mr Anderson.

PROFESSOR JAMES: I wonder, Mr Murray, in the light of what we have been hearing this afternoon and your experience, and in light of the clear administrative excellence and expertise of the SHHD, whether you can think of any good reasons why, if the CSA had not existed, there would have been any adverse effect to the administration of health in Scotland?

A. In the introductory, or at least in early chapters of your interim report, you record criticisms of the CSA. Certainly, I think that, going back to the Civil Service hierarchies and numbers of officers within the department that pump the ranks --

PROFESSOR JAMES: Precisely.

A. -- that bureaucracies tend to create hierarchies and a flattening of the hierarchies, if I can put it that way, may well have achieved better results.

PROFESSOR JAMES: It seemed to me that, as a matter of fact, there were competent individuals, and in your description of the hierarchy of the SHHD you referred to them, who were really doing pretty much precisely the same as, for example, dealing with the ambulance service, as was the remit of the CSA. And you yourself had said that most of the material committees of the CSA actually had very substantial cross-representation from relevant individuals from the department.

A. Yes.
PROFESSOR JAMES: So I just wondered, as a matter of fact, really, whether if a fairy had waved her magic wand and the CSA had disappeared, there would have been any bad effects that you could think of.
A. We would have gone back to the administration of the NHS before the CSA was created.
PROFESSOR JAMES: Thank you.
THE CHAIRMAN: I think that may be precisely what the annual report of 1974, that is quoted, might have been suggesting.
A. Yes.
THE CHAIRMAN: Mr Anderson, has that given you time?
MR ANDERSON: It has given me time. Thank you, sir. I have no questions.
THE CHAIRMAN: Mr Johnston?

Questions by MR JOHNSTON

MR JOHNSTON: Just a couple of short points, if I may.

Mr Murray, at the end of your paragraph 6 you mention that your department's finance department advised you that Treasury approval would be needed for a compensation scheme and you give a reference there, which I don't think you were actually taken to.

I wonder if we could look at that. It's SGH0031950.

You see there we have a memo dated 10 April from

Mr Kernohan, addressed to yourself.

A. Yes.

Q. And he says:

"There is little I can say on the financial aspects. If the department wishes to go ahead with the compensation scheme, then we shall obviously be required to seek Treasury approval."

Then he asks for certain further information and then the only other points that occur to him he notes at the end:

"(a) the very general nature of the cover which Dr Cash is seeking, unlike earlier specific schemes, he seems to be looking for an indemnity covering all experimentation carried out by the BTS."

He says:

"The legal advisers will no doubt have a view about this."

And then we have a second point to do with the clinicians referred to in Dr McIntyre's minute and whether they are non-BTS or not?

A. Yes.

Q. Does that seem to be the wider issues that's being considered there or the Factor VIII issue, or were you not able to express a view?

A. The -- it would be the wider issue, insofar as -- we

don't seem to have a copy of my -- unfortunately we don't seem to have a copy of my minute of 4 April, but my minute of 4 April is likely to have been relatively, relatively, short, but enclosed a copy of Dr Cash's letter to Mr Mutch.

Q. Thank you.

A. So it would have been the wider scheme.

Q. Yes. And just looking at the reference to the need for Treasury approval, can you say whether you think there would have been any prospect of getting Treasury approval for a scheme that was limited to Scotland, as opposed to a GB-wide scheme?

A. I don't think so. It has been said earlier that the Treasury take a very critical look at all new expenditure, and would certainly have been sceptical, to say the least, of something pertaining only to Scotland, that England did not appear to need. If England could do without it, why shouldn't we?

Q. If there were to be a UK-wide or GB-wide scheme, can you identify who you think would be responsible for that or for encouraging it to move along?

A. Not really. I don't think I could give any really definitive answer to that. As in most things, it would be whoever was most committed, had most to gain, would take a lead.

Q. Thank you, very much.

I have no more questions, sir.

THE CHAIRMAN: Mr Murray, thank you, very much.

A. Thank you, sir. Thank you.

MR MACKENZIE: Sir, the next witness is Mr Duncan Macniven.

THE CHAIRMAN: It is ten past three.

MR MACKENZIE: I'm sorry, yes. It may be an appropriate time for the break.

THE CHAIRMAN: Yes, I think that after that exhaustive examination of documents, we should rise.

(3.10 pm)

(Short break)

(3.26 pm)

MR DUNCAN MACNIVEN (sworn)

Questions by MR MACKENZIE

MR MACKENZIE: Thank you, sir.

Good afternoon, Mr Macniven.

A. Good afternoon.

Q. You have provided two statements. They will come up on the screen. I'll start, please, with PEN0171604.

This statement in paragraph 2, 3 and 4, sets out your biographical details and we can see --

A. Except for my date of birth, of which I'm perfectly proud actually.

Q. Well, at the risk of committing a data protection

violation, feel free to tell us, Dr Macniven?

A. 1 December 1950. You can go along to Register House and get my birth certificate very easily.

Q. I have heard it has gone downhill recently.

Anyway, in paragraph 2 we see you joined the Scottish Office in 1973. Then in paragraph 2, we come to the SHHD, where in early May 1986, you were promoted to assistant secretary, now known as deputy director. And we see that was your first post in health. You were responsible for five topics, the first was NHS land and property; the second was supplies and emergency planning; thirdly, ambulances and blood transfusion, which were both run by the NHS Common Services Agency. The fourth was health service building policy, essentially how to build a good hospital, and the fifth was services for disabled people.

We see you had about 40 members of staff working under you. We see you were head of this division until summer 1989, when you left to head a team elsewhere. And we see you then became the Registrar General for Scotland in August 2003 until your retirement in August 2011.

The rest of this statement, I propose simply taking as read so it will form part of the Inquiry record, but I think it raises wider issues which I think, having now

heard detailed evidence on top C3, I don't think will materially assist the chairman in deciding on the issues which arise in topic C3. So with the chairman's permission, I think I'll simply put this statement to one side and move on to the question of compensation.

Your compensation statement, Mr Macniven, we can now go to, is PEN0171866. In paragraph 2, we can see the matter you were asked to comment on, and in paragraph 3 you tell us that:

"I recall the subject but can no longer remember, nearly 25 years later, the detailed sequence of events. So this statement is based on consulting the papers provided to me by the Inquiry and also my division's file on the subject."

Mr Macniven, before looking at these papers, did you have any recollection of this question of compensation or is your evidence really based on a reading of the papers or what?

A. My evidence is based mainly on the reading of the papers. I remember one key meeting with the haemophilia directors in February 1987 because it was such an interesting meeting, and I think it was one of the few, if not the only time, that I met the haemophilia directors.

But otherwise, I don't remember the to-ings and

fro-ings.

Q. Yes. That meeting, was it perhaps February or March 1987?

A. February 1987. I think it was 6 February 1987.

Q. Yes, that's the meeting at which the good news was brought to the haemophilia clinicians that compensation would be available for clinical trials of the Factor VIII product?

A. Correct.

Q. Yes. We understand, of course, that you joined the SHHD in May 1986, so really a number of the compensation related documents precede your time in that division, but I think we did ask, perhaps even just in the last few days, to have a look at Mr Murray's very full statement and also the documents preceding his statement, so the minutes of meetings in 1983, 1984, 1985. Did you have a chance to have a look at those various documents?

A. Yes, briefly.

Q. I'm grateful. Have you also had a chance to sit in and hear some of Mr Murray's evidence today?

A. Correct, his evidence this afternoon.

Q. I'm grateful. I think that's a sufficient factual background or understanding for you to have, but I don't need to start back in 1983 and go over all of

the documents.

A. Good.

Q. So I'll pick up at your statement, please. We are on to paragraph 4 and you explain that:

"As I made clear orally at a meeting with Dr Ludlam and others on 9 February 1987 ..."

Is this the meeting we referred to?

A. Correct.

Q. Thank you:

"We fully recognised why Dr Ludlam was reluctant to trial new blood products without being able to give patients reassurance about compensation in the unlikely event that harm befell them in the trials."

You explain:

"SHHD did not have delegated authority to agree a 'contingent liability' by offering to compensate patients as Dr Ludlam advocated. We required the approval of the Treasury, which was concerned to ensure that the compensation was a proper use of taxpayers' money."

I think we can all understand that?

A. That's correct and if I might add a point that may help you.

Q. Yes.

A. It's clear from the papers, although I have no

recollection of it, that Chris Ludlam had been reassured orally, I think, probably by Dr Bell and perhaps Dr Forrester, that there wouldn't be a problem. But understandably he wanted, or, as time went on, decided that he wanted written reassurance; a perfectly understandable attitude for him to take.

Q. When you say Dr Ludlam had been "reassured orally", when was that reassurance given?

A. I don't know. It was -- there is reference to it in the papers that you have provided me with. In letters from Chris Ludlam, I think, which indicated -- indeed, I think you had one up on the screen earlier, which indicated that -- I think the one you had on the screen said:

"I need a formal assurance that compensation will be available."

There had therefore been previous oral, informal assurances given by my colleagues in the department.

Q. When you say there had previously been given informal oral assurances from colleagues in your department, is that an inference you draw exclusively from the documents you have looked at or is that something you have any recollection of?

A. I have no recollection of it. It's purely from the documents that I read.

Q. Okay. So that's something we can bear in mind when we go back over the documents in due course.
A. Indeed.
Q. Then, please, paragraph 5 --
THE CHAIRMAN: Before you leave it.
Mr Macniven, you have put "contingent liability" in inverted commas, is there a reason for that?
A. Yes, because I regard it as a term of art, not a phrase in common parlance. It's a matter that -- the public service entering into a contingent liability, that is a liability to pay money if a certain contingency occurs, is a matter that Treasury has traditionally taken a great interest in, and behind Treasury, Parliament, because of the possible public expenditure implications that that would have. So that's the implication of what I regard as a term of art.
THE CHAIRMAN: You would normally put in your budget for anticipated expenditure that was going on emerge in the course of the budget period.
A. Yes.
THE CHAIRMAN: You would then get an allocation within a vote and you would have to spend within that.
A. Correct.
THE CHAIRMAN: The contingent liability is something that lies outwith that framework. Is that right?

A. Not quite.
THE CHAIRMAN: Not quite.
A. As the -- as the Zoe Everest-Phillips's letters that you saw before coffee time showed, we were expected to meet this liability, if the liability crystallised, from within our budgetary allocation.
Q. I think I understand that so far as the period involved is concerned but if time went on and these claims began to emerge, what would have happened?
A. We would have done our best --
THE CHAIRMAN: To budget?
A. -- to budget for what would then have become no longer a contingent liability; it would have been an actual allocate.
THE CHAIRMAN: Sorry, Mr Mackenzie.
MR MCAKENZIE: Thank you, sir. Mr Macniven, returning to paragraph 5 of your statement, please, you tell us that your division's file suggests that your involvement with the subject began in December 1986, prompted by Dr Ludlam's letter of 5 January 1987 to Dr Cash -- we have looked at that -- of which you had had forewarning from your colleagues, Dr McIntyre and Dr Forrester, on 29 December 1986. I think that last reference -- we don't have to go to it -- it's SGH0031920. Then we see you say:

"I took steps to seek the urgent approval of Treasury to a compensation scheme (the letter of 14 January 1987 from Mr Kernohan in my finance division to Miss Everest-Phillips at Treasury)."

The reference there, without going to it, is SGH0031881. We saw that DHSS had made a parallel request because the same issue had arisen in England, and:

"After an exchange of letters with Treasury seeking clarification of the need for a scheme, Treasury approval was given on 5 February 1987."

We saw that:

"This was communicated to Dr Cash by Mr Murray's letter of 6 February and to the haemophilia directors (including Dr Ludlam) at the meeting ... on 9 February 1987. As Dr Ludlam's letter of 9 January 1987 shows, we had in the meantime kept him informed of the action we were taking and he was then aware that we expected to be able to give in the near future the reassurance he sought."

I think really, as Mr Murray made the point, there is no doubt, I think, that when the matter arose again in December 1986, things moved pretty quickly in government?

A. That's correct.

Q. Including liaison with the Treasury?
A. That's correct. It was interesting to see earlier this afternoon Treasury responding on the same day to a letter from DHSS. The stops were pulled out when the matter became urgent because we were very keen to avoid holding up the clinical trials. Chris Ludlam's letter, I think, referred to the need to dispose of the matter by the end of February and that was the target timescale that we were using for that urgent action.
Q. Yes, and in paragraph 6 of your statement, Mr Macniven, you say:

"There is an important factual point on which I am unclear from the papers I have seen: did the delay in obtaining Treasury authority delay clinical trials?"

I'm not going to go over what you say, other than noting the points you make and, without trying to pre-empt any ultimate conclusions, the picture that I think emerges so far, the working hypothesis, seems to be that clinical trials took place in Edinburgh in March 1987, that it may have been that the delay in resolving the compensation issue delayed the start of trials by two to three months and it may have been that the delay in Z8 being available earlier delayed its use for previously untreated patients by two to three months but, because of the batch dedication scheme, the

compensation issue may not have delayed the availability of Z8 for patients already prescribed Factor VIII.

So I simply give that working hypothesis as some beginning of an answer to the points you raise, but the matter still remains outstanding and PFC are still undertaking certain further investigations in that regard --

A. That's interesting. I wasn't able, from the papers, to come to a conclusion. I recollect only this, that -- the chairman asked Sandy Murray a moment ago whether this was a common sort of thing, all this to-ing and fro-ing, and I, who have no recollection of the details of this to-ing and fro-ing -- I think I would have remembered, and particularly remembered, getting a roasting at the meeting on 9 February 1987, getting a roasting at the meeting of 9 February 1987, if we had delayed the start of clinical trials. That was what we were aiming not to do and I think I would have remembered if we had failed in achieving that aim.

Q. Perhaps that depends on how angry Dr Ludlam was or how frustrated and how he exhibited any anger or frustration?

A. I think you have imputed to Dr Ludlam a considerable frustration: five years or something, or perhaps not quite that long --

Q. Just over three.
A. -- four years after he had originally raised the matter. I don't think he would have missed me as a sitting target at the meeting of 9 February if he had been minded to.
Q. Yes, the important point perhaps being if he had been minded to.

Really, Mr Macniven, only two further points. I think you may have heard the two propositions that I put to Mr Murray. I quite appreciate you only joined this department in May 1986 and perhaps were really only involved in the later stages of the compensation issue and when things did move quickly. But having now had the opportunity to look at prior documents and consider the matter more fully, can I, please, put the first proposition to you, that the issue of compensation for participants in clinical trials of PFC products was an issue the SHHD ought to have taken a lead in because any compensation would involve public expenditure and liaison between government departments.

A. I don't think that these are the right criteria for SHHD involvement. Clearly, the Secretary of State -- at least my recollection of the Health Service Act is that the Secretary of State is responsible for the health service in its entirety and therefore I, working for the

Secretary of State, had a part in that responsibility. But it doesn't follow that, because expenditure was involved, SHHD had to be taking the lead. There were a great many things in the health service that involved expenditure, which it would have been impracticable, even if it had been sensible, for SHHD to take the lead in.

Q. I understand that. How about the question of liaison between government departments, in particular seeking Treasury approval and perhaps liaison with the DHSS as well?

A. Absolutely. Seeking Treasury approval was absolutely ours. I interpreted you as asking Sandy Murray a slightly different question. Taking the lead in putting together a compensation scheme?

Q. Yes.

A. As distinct from seeking Treasury approval for that compensation scheme?

Q. I think the particular proposition put to Mr Murray was the narrow compensation point, so taking a lead in resolving Dr Ludlam's concern.

A. Yes, I think that, to move on, if I may, to your second question, the way to have resolved this much more quickly was to stick to what Dr Ludlam was asking, stick to the narrow question, which, as we demonstrated in

early 1987, was relatively simple for Treasury to answer. Yes, they came back with reservations and further questions for us to ask but they fairly speedily agreed to the narrow proposition.

The delay was engendered for a number of reasons but because people were uncertain about what breadth of compensation scheme we were talking about: Were we talking about a scheme that involved all clinical trials of all possible future SNBTS products? That's a larger blank cheque for Treasury to write out, or to approve us writing out, than the narrow scheme, which they were used to, as we saw earlier, in other contexts.

Q. I think my final question to Mr Murray was: with the benefit of hindsight, how could this matter have been resolved sooner, and I think your answer from that would be separate out the narrow and wider issues.

A. Correct.

Q. I understand that. One final, perhaps, matter for you, Mr Macniven. I can quite understand the position that there is a structure which involves the SNBTS, the CSA and the SHHD and, because of that structure, it might make sense for matters to be dealt with initially at a particular level on the structure or in a particular forum. But from looking at the documentation, knowing that Dr Ludlam first raised the narrow issue of

compensation in November 1983, knowing it then got subsumed and perhaps muddled a little by wider issues of compensation, was there a place for the SHHD in recognising that, "The narrow issue has become muddled with the wider one, so let's step in and deal with the narrow one first because that can be done relatively quickly and easily." What would be your response to that suggestion?

A. Yes, I entirely agree, and that's precisely what we did in the last few days of 1986 and the first month of 1987.

Q. So, with the benefit of hindsight, it may have been better if that had happened earlier?

A. If there were no other things on our desk, but, you know, understandably, this Inquiry is concerned with one aspect of the work of the health service, and a very, very important one, but, as paragraph 3 of the first statement that you referred to this afternoon makes clear, there were a great many other things that were happening in the health service at the time. We were not sitting idly by, waiting for an opportunity to look at this again.

I would also say -- but this is really me looking at Sandy Murray's statement, rather than my own direct involvement -- that we were keeping on eye on it; there

was evidence of some limited progress, which indeed materialised around the time that Chris Ludlam issued his ultimatum on the narrow compensation issue.

Q. Although I think Dr Ludlam had made a similar ultimatum at least a year earlier, possibly before, when heat-treated Factor VIII first became available, albeit he was persuaded to withdraw that ultimatum and to proceed with clinical trials in the absence of compensation. But that may be a matter of which you were unaware, given it was before your time.

A. Yes, I'm not aware in detail on that.

Q. Thank you, Mr Macniven.

I have no further questions, sir.

MR DI ROLLO: No, thank you, sir.

THE CHAIRMAN: Mr Anderson?

MR ANDERSON: I have no questions, sir.

THE CHAIRMAN: Mr Johnston?

Questions by MR JOHNSTON

MR JOHNSTON: I would just like to ask one in fact. It's picking up a point that Mr James put to Mr Murray. You may have heard that, Mr Macniven.

The question was, if by the stroke of a pen or, I think it was actually said, the waving of a wand, it would have been possible to remove CSA, whether that would have made any difference in practice to health

matters in Scotland. You heard his answer, I think. I wonder if you would care to provide an answer to that yourself.

A. Yes. Essentially, in dealing directly with the matter in the way that Mr Mackenzie has alluded to just now, we were cutting the CSA middleman out of the process; we were not following the normal channels. But on the more fundamental question of whether it was worth having the CSA -- I'm not an apologist for the CSA but I worked very closely with it in a number of guises, not only the SNBTS but also the Scottish Ambulance Service and the Central Legal Office and the building division indeed. The CSA was a kind of holding company for a number of specialist services offered to the health service as a whole in Scotland.

Before the CSA was set up, these would have been dealt with, I think I'm right in saying, by the department itself without the input, in terms of governance, of the Health Boards, which run -- ran -- 90 per cent or something -- a very high proportion -- of the health service in Scotland.

I think what the CSA's structure brought to governance was the involvement not only of the department in the way that we observed earlier this afternoon, but of the health boards. It was chaired by

a serving or recently past Health Board chairman. It was subject to that governance within the health service, which was, I'm sure, designed to ensure that it served its clients, the health boards, more effectively than if it had been run in-house by the department.

As I say, I hold no brief for the CSA, and indeed I was at times frustrated, a frustration that you, chairman, have detected very well -- frustrated by the CSA's inability to get a grip of some of the issues, and the bringing in of Jim Donald as general manager of the CSA about the same time as I came to the department in 1986 was intended to strengthen it.

There was an awareness that it was not functioning as well as it might have done. But that, I think, was the rationale for its existence, and the rationale has a logic to it, I think.

THE CHAIRMAN: Up to a point I think I can see some of that but of course we know that the SNBTS management committee was looked upon as having an executive, and not simply a governance, role in relation to topics that I think we would feel the specialists, who depended on them for a decision, didn't think they were up to, frankly.

A. That's a judgment that you are probably better placed than I to take. You have spent immeasurably much more

time on this topic than I ever did.
THE CHAIRMAN: Yes. Mr Johnston?
MR JOHNSTON: Thank you. I have no more questions.
THE CHAIRMAN: Mr Mackenzie? Mr Macniven, thank you very much. I hope that the Scottish courts and other activities you have had don't bring you to another Inquiry in the near future.
A. I hope not. Thank you.
MR MACKENZIE: Sir, there are no further witnesses today.
Tomorrow we have the final C3 witness, Professor van Aken, but then after that, sir, I think we may have a little time in the morning and Dr McClelland is available to answer questions on topics B2 and B5. I think the other parties did not have an opportunity, when he was here, to answer questions on those topics.
THE CHAIRMAN: Well, if he can come, that sounds very convenient, and we can have a fair amount of time for that.
MR MACKENZIE: Yes, sir. Professor van Aken's statement is roughly six pages. We have covered, I think, the facts of topic C3 in some detail, so I do envisage Professor van Aken finishing, I would hope, by the 11 o'clock break.
THE CHAIRMAN: Then it does sound as if we should try to make use of the time available, and we will see how we

get on with that.

So tomorrow morning, gentlemen and ladies.

(3.55 pm)

(The Inquiry adjourned until 9.30 am the following day)

I N D E X