Friday, 9 September 2011

(9.30 am)

THE CHAIRMAN: Good morning.

PROFESSOR CHRISTOPHER LUDLAM (continued)

Questions by MS DUNLOP (continued)

THE CHAIRMAN: Yes?

MS DUNLOP: Thank you, sir. Good morning, Professor Ludlam.

A. Good morning Ms Dunlop.

Q. You have provided for us a statement on our topic B3, which concerns the first part of the story of viral inactivation. I will ask you one or two questions on it. It is not especially lengthy.

But before I do that, I wanted to look at a couple of photographs with you, please. We looked at these photographs on Tuesday and they are photographs provided from PFC. It's the photos of cryoprecipitate. The photos themselves are [PEN0121695].

This is just a digression, Professor Ludlam, as is probably obvious. But when I was looking at the photographs of cryoprecipitate and -- thank you, we have the first of the two photographs here. Do you see that pot? That's a pot of cryoprecipitate. Can we look at the next one as well, please. I had just had some thoughts about the evidence that you and one or two others have given about treating patients with

cryoprecipitate.

The second photograph makes the substance look very gelatinous, very stretchy. I just wonder, when you see those photographs, can you explain to us, perhaps by reference to your previous evidence, about how difficult it was, how you treated patients with that?

A. Yes. There is a difference between this cryoprecipitation for manufacturing processes from cryoprecipitate that we use to treat patients. If I could perhaps go back to the blood donor session, where donors give blood. It is collected into a polythene bag. It's a small pint's worth of blood. Attached to that bag are a series of other bags --

Q. Yes.

A. -- with little tubes. So it's a closed system. And after the blood has been collected, it's cooled and centrifuged and the pint of blood in the plastic bag is then put in a device, a V-shaped device, and squeezed. The plasma is on top, the red cells at the bottom, the white cells and platelets in the middle. And my understanding of how the blood transfusion does this, they squeeze it manually, but someone is watching it, squeeze off the plasma into the first bag, clip it and then can squeeze off the platelets into another bag.

Actually, I may have got that wrong. They may start

off by preparing platelet-rich plasma, spinning it slowly, so that the top half of the bag has plasma plus platelets in it and they may squeeze that off into another bag, what's called platelet-rich plasma, and then they might spin out the platelets of that and use the plasma from that.

Either way, you end up with a poly bag with fresh plasma in it, cooled plasma. That's then clipped and sealed, heat-sealed, and you then cut that bag away from the red cell bag and platelet bag. You then freeze that very rapidly in acetone and cardice so that it becomes like a frozen lollypop in a plastic bag. You put that in a fridge at 4 degrees overnight, and very slowly this lollypop of plasma thaws and the thing that you are left with that doesn't dissolve, doesn't melt, is cryoprecipitate, cryo cold precipitate.

You then take the poly bag, centrifuge it and squeeze off the supernatant plasma. The cryoprecipitate has a lot of fibrinogen and fibronectin and Factor VIII. It's rich in Factor VIII. The supernatant plasma has other clotting factors and is known as "cryo" or "supernatant plasma". That can actually be used for making other concentrates for other clotting factors and that was talked about, I think, in the preliminary report, particularly some studies in Glasgow.

This individual pack that has had the cryoprecipitate concentrated at the bottom is from one donor.

Q. Sorry, Professor Ludlam, I certainly don't mean to interrupt. We do understand all of that. It was really a very simple thought, that if cryoprecipitate has that sort of gelatinous sort of texture, it must make it very hard to work with when you are treating an individual patient, or does the cryoprecipitate that's used to treat an individual have a different texture?

A. If I could just finish the story.

Q. Fine.

A. These packs are then put back in the deep freeze and frozen, usually individually. So if you want to treat someone, an adult required, say, 20 packs, that was the amount of Factor VIII that was necessary for therapeutic infusion, you went to the deep freeze, you picked out 20 packs and you put them in a 37 degree water bath. It's when it's warmed up to 37 that the fibrinogen and so on goes into solution and then it is not particularly viscous.

I agree, what is shown in this picture looks as if it's probably quite a cold environment or at least this is treating the cold precipitate that was in that previous photograph.

Q. I see. So the answer is really to do with the viscosity of cryoprecipitate at different temperatures?
A. I think so, yes.
Q. Right, thank you.

We had understood, I think, from the evidence in the first half of the Inquiry that treating individuals with cryoprecipitate was messy and difficult and I just wondered to what extent the actual texture of the cryoprecipitate was a contributing factor but it looks as though it wasn't anything like as difficult as we might think from the picture.

A. That is not making up an individual dose.
Q. Right, thank you.

Let's look at your statement, which is [PEN0121688]. You had the same schedule of questions as everybody else. We sent out the same schedule. We weren't really expecting everybody to have a shot at answering everything because obviously some people can answer some questions and others can answer others, and as would be expected, as a haemophilia clinician, you are not in a position to answer many of the more technical questions to do with what happened at PFC.

But in the first paragraph you remind us that you have provided a document headed "Long-term safety monitoring for transfusion-transmitted infections".

That is [PEN0120351]. I suppose the point you are really making here is that, as haemophilia clinicians, you saw yourselves as feeding into product development. Would that be correct?

A. Very much so.

Q. Right. Can we have a brief look at the appendix then, please, [PEN0120351].

Professor Ludlam, this document was gone through in considerable detail on 17 June, so I certainly don't propose to go through it again. I think I only have two questions on it.

The first arises from paragraph 4. I see a reference there, reference 6. You say that research in which you were involved:

"... demonstrated that, despite screening of donors, about 10 per cent of susceptible patients became infected each year with Hepatitis B virus."

I looked at reference 6. It's an article about the incidence of infection with Hepatitis B in 56 patients, I think Edinburgh patients, between 1971 and 1979.

A. Yes.

Q. So what struck me was that you didn't arrive until 1980?

A. Yes.

Q. So what happened? How did you become involved in the research? Was it something that was ongoing when you

arrived?

A. Yes, it was ongoing. I tried to make this clear in my statement, in this document, that from about 1974 there had been an interest in the viral safety of clotting factor concentrates initiated by my predecessor, Dr Howard Davies, in conjunction with the virologists, Dr John Peutherer, and in this case his colleague, a junior colleague, was Dr Chris Burrell, who was a virologist.

They had started some of these studies, as you say, before I arrived. When I arrived, the study you have just referred to hadn't been completed and Dr Peutherer and myself and Dr Stirling sat down on quite a number of occasions to draw the information together. It required quite a bit of going back and looking through patients' case notes and so on, and that's why it wasn't published, I think, until 1983.

Q. Yes. You see from paragraph 4 that you make the point that the then current screening tests for Hepatitis B weren't detecting all infectious blood donations. I take it, therefore, that you would understand why, in the 1970s, PFC were working on a project to try to remove Hepatitis B from Factor IX?

A. Yes.

Q. And that would seem a sensible thing to have been

researching.

A. Certainly, yes.

Q. The other point that struck me, Professor Ludlam, when I was looking at this statement through B3 eyes, arises in connection with paragraphs 17 and 18. So could we go, please, to page 4 of [PEN0120351].

We are jumping forward quite a long way in time here to the meeting that took place on 10 December 1984. It was a meeting between UKHCDO reference centre directors, blood transfusion colleagues and senior staff from Edinburgh and Elstree on 10 December. There was a major discussion about whether to introduce heat treatment of concentrates, and you say it was not an easy decision to make because of the possible adverse effects of heat treatment on the clotting factors and other proteins:

I have heard that the decision to go ahead with recommending the use of heat-treated products was reached by quite a narrow majority. Is that right?

A. There wasn't a vote taken that I recall but I remember the meeting very well because it was very stressful and trying to make a decision on really minimal evidence. I think some of us were a little disadvantaged because a lot of the developments in the commercial field of heat-treating concentrates, the sort of initial studies, were a bit kept under wraps by the commercial companies,

they weren't very much in the public domain, and particularly working up here in a very much NHS environment and not wanting to use commercial products, we were a bit out of -- if I can put it this way -- the network of commercial companies, who would come round and see directors to discuss matters with them.

So there was very little published and so it was difficult to know just how much heat-treated material had been used in patients and over what period of time. I don't think I was aware that I think the Travenol product did have an FDA licence a year or two before, I think, in 1982, if I'm not mistaken. But I don't know how much had been used.

So there are a number of us sitting round the table who knew of some of these developments but didn't know the extent to which the products had been tested.

Q. Right.

A. And there was this very big anxiety, that we could make the treatment of haemophilia a thousand times worse if heating produced these neoantigens that have been well discussed, I think, in this Inquiry.

Q. Yes.

A. You see, a quarter of haemophiliacs develop inhibitors anyway and if we had altered the molecule slightly and 100 per cent developed inhibitors, then we would have

virtually no effective treatment for haemophilia, apart from FEIBA, and at that stage it wasn't clear how big the epidemic and the consequences of HIV were going to be at that stage. Only a very small number had developed clinical AIDS or other symptoms.

So it was very, very difficult and a decision was nearly made not to heat-treat and it was only because two or three people were quite forceful in their views that the decision was made. It was clearly the right decision but it was not easy.

Q. I can imagine, professor, but what struck me about this little piece of narrative was that the 10 December was also the date of the general distribution in Scotland of heat-treated material. So for practical purposes you in Edinburgh were going to have to use heat-treated material. Is that not right?

A. Sorry, I don't remember knowing that, if you like, there was only one option before I went to that meeting.

Q. I see. I think I was just interested in the practicalities of it, that what you are describing here is a situation in which it was UKHCDO that took the decision to heat-treat, but actually here SNBTS already had heat-treated the stock. So in a practical sense that was going to be the route for you to follow anyway.

A. I think it had heat-treated a month's worth of stock,

and they had quite a stock, I think, of NY. It was only a few days before that we had given, I think, four patients test doses of the 68-degree, two-hour product, without adverse effect. But it takes, as you probably know, several weeks for patients to develop inhibitors, if they are going to. But December 1984 was a terrible month and we had so many difficult dilemmas to try and wrestle with but that was a decision that was made and that was what we went with.

Q. So I suppose, because in general the decision-making process is of some interest to us, if you had been one of those who was very forcefully of the opinion that heat-treated concentrate was the way to go, and you had been in the minority, would you have abided by the majority decision or would you have gone ahead and used the heat-treated material because you personally thought that was the right decision?

A. I went to the meeting with a fairly open mind. I could see the difficulties and the dilemmas because we had discussed this. I think there was a meeting at Scottish Home and Health Department, I think at the end of November, where we had talked about this and considered it.

The drift of international opinion was towards heat treatment. The MASAC, the National Haemophilia

Foundation and Medical Advisory Committee in the States, I think in October 1984, had made a recommendation for heat treatment. That was heat treatment of US commercial products that had been shown to cause a lot of antibody positivity, anti-HTLV positivity, up to 90 per cent in US patients. And I think part of the difficulty here in the UK was that we thought the donor population was much less likely to be silently infected, a much lower level than that in the US, particularly -- dare I refer back to the video that was shown some time ago, the World in Action 1975 programme.

Q. Yes. I wonder, if can I just press you for a yes or a no to the question?

THE CHAIRMAN: Do you remember what it was? It's the dilemma that we face quite a lot, arising out of autonomy. And the question is quite simple: given the way people asserted their own individuality of judgment, had you been in the anti- camp, how would you have reacted when you went back to Scotland? Would you have used PFC's new heat treatment or would you have said "No, forget that month's supply. I want to go on using the old stuff"?

Is that the way to put it?

MS DUNLOP: Yes.

A. I mean, I was coming round to the view that it was

probably safe because of what I heard at the meeting. If you want me to go back --

THE CHAIRMAN: No, with great respect, it is not a question of what your professional judgment of the effectiveness or otherwise was, it's really a question of organisational judgment and whether you would have stood out for your own view and done what you thought was right, irrespective of what was developing in the wider community.

A. I appreciate the question. If I'm going to stick out against the opinion of my senior colleagues, whose view I respect, then I have to have good reason for doing so.

MS DUNLOP: Yes.

A. My reason for feeling unhappy was knowing that Factor VIII is a rather fragile molecule, and subsequent studies have shown how fragile it is and how it can give rise to antibodies. But my colleagues, who are just as well informed as me and whose opinions I respect, felt that it was reasonable to take this risk. Therefore, I went along with it. If I hadn't gone along with it, then I would have to have been very clear what evidence I had for not going along, rather than just a feeling of unease.

Q. I appreciate it's a hypothetical but have you seen Twelve Angry Men?

A. A very long time ago, yes.
Q. Right. So at that UKHCDO meeting, you are Henry Fonda and you are sure that heat-treated product is the way to go and you are the only one in the room who thinks that. So you are not going to be able to persuade all the others round the table -- I'm changing the script slightly -- would you have gone back to Edinburgh and said, "Go ahead" or would you have said, "I must be wrong."?
A. It's very difficult to rerun history.
Q. Yes.
A. I think -- I'll play for time.
Q. You can say "don't know" if you want. We will take a "don't know".
A. No, I'll play for time. I arranged -- you will see why in a moment. I arranged for four patients to receive this 68, two-hour material at the very beginning of December, I think the 4 or 7 December, comes to mind, so just a few days before this meeting. I think I would have waited two or three weeks to see whether any of these patients developed an inhibitor to the clotting factor and if they had, then I would have not wanted to use it and if they hadn't, well, that's another reason for feeling secure that it was probably a reasonable thing to do.

Q. So I think we can sort of count you as Henry Fonda, can we? I think we understand the position, professor, let's move on.

Going back to your statement, [PEN0121688], we have heard from Professor Cash yesterday, and indeed you were here so you heard it too, about the period at the end of 1982 really, where he was very anxious that when the day arrived that there was NHS heat-treated product, there should be sufficient patients available on whom the product could be trialed. So he didn't want the commercial fractionators to have access to all the previously untreated patients in the UK.

You have been asked to look before at a letter which seems to chime with that philosophy. I thought we would just look at it again, if we could, please. It's [SNF0013211]. Admittedly this is slightly later in time but you are, I think, in this letter, politely refusing Miss Spooner's suggestion, or any suggestion that your patients should become involved in the trial of commercial material. Is that right?

A. That's correct, yes.

Q. Right, can we go back to the statement then, please?

You say you remember the discussions about trying to avoid using commercial, virally-reduced concentrates on a named patient basis. And to use them in clinical

trials if possible, under a clinical trial exemption arrangement, and you say this was set out by Professor Bloom in his 24 June 1983 letter.

We have looked at that before too, but let's just look at that again, please. That's [SGH00022175].

Much of this letter is concerned with recommendations about treatment but if we go a little bit down, we see at the bottom of the page one of the additional points referred to concerns proposed trials of hepatitis-reduced Factor VIII:

"There is no evidence that the processes involved in the manufacture of these inactivate any other hypothetical viruses. However, it is [go to page 2, please] still important that the effectiveness of imported hepatitis-reduced concentrates, vis a vis hepatitis, is subjected to formal clinical trials in mild haemophiliacs, notwithstanding our general recommendations above. Directors are urged not to use these concentrates randomly on a named-patient basis."

Do you remember yesterday, professor, it seemed that the dilemma, perhaps around about Christmas 1982, was between, on the one hand, clinical trials versus rather random named-patient usage -- that's one question that has to be resolved -- and then there is also another question, which is clinical trials or no clinical

trials, because clinical trials are likely to facilitate the obtaining of a UK licence. Does that encapsulate the mood of the time?

A. Yes, I think I would put a slightly different slant on it than perhaps Professor Cash. I wasn't aware of the discussions that he alluded to with the DHSS, which he interpreted as trying to promote trials. Maybe these could be done in other countries.

What we were anxious about was individual commercial companies approaching individual haemophilia centres and saying, "Look, we have got some of this new heat-treated product, would you be kind enough to try it in one or two or three or four susceptible patients on a named-patient basis?"

When you do that, there may not be a protocol for following them up, and as I'm sure you are aware, what emerged very shortly after this was the ISTH protocol for testing viral safety of products in Florida. And it's a very rigorous schedule, so rigorous that it was almost impossible to keep patients in because it was fortnightly blood samples for 16 weeks and then I think one or two at monthly intervals thereafter, and particularly for small children that's quite an ordeal.

I think there was a view that different haemophilia centres would be approached, they would be given a few

bottles of this new heat-treated concentrate, they would do, if I can put it this way, rather poor studies. They would give it to the patient and do a few blood tests thereafter. And those would almost certainly be valueless because the only way we could assess viral safety was by doing these ALT estimations of liver function every fortnight, and if you missed, I think, more than two, then that patient was rendered ineligible by the ISTH proposals.

Therefore, there was a situation where a lot of these susceptible patients would be, as it were, used up and the amount of systematic data collected would be rather small, whereas if the manufacturers had gone to the CSM with a clinical trial -- made an application for CTX, they would have to put in a protocol and then all the patients going into that trial would be subject to that protocol and so they would all be properly studied.

So there would be some hopefully useful information gained from that. That's what the debate was about and, as you know, these number of patients, as you saw, perhaps when we came to do it in Scotland for Z8. It took us several years to accumulate 13 patients.

Q. So the way you were putting it, it wasn't so much a matter of promoting clinical trials, it was a matter of electing for a much better way of assessing these new

products than this random named-patient usage?

A. Yes.

Q. Yes.

THE CHAIRMAN: Professor Ludlam, I can understand the objection to random testing from the point of view of you and your colleagues in respect that it reduced the number of people who were potentially available for proper study. What was the advantage to a pharmaceutical company of staging random tests, when they wouldn't lead to licensing, approval or any other form of official recognition of the validity of the outcome?

A. I think at this stage there wasn't the ISTH protocol and there was, if you like, some doubt as to how rigorous the testing should be, how often should the blood samples be taken. If you don't want to demonstrate hepatitis or don't want to detect it, then you would take infrequent blood samples.

THE CHAIRMAN: Yes.

A. And unless the manufacturers said, "If we give this to you on a named-patient basis, in return you must take fortnightly blood samples," then maybe a named-patient basis would be all right but that is not, I think, how the product was being offered.

THE CHAIRMAN: I see.

A. But they didn't come to me because, you know -- for reasons that are well established. So I'm a bit surmising but I sat in through some of these discussions nationally and certainly Professor Bloom was -- and Dr Rizza were very, very keen, repeatedly, to have CTX studies, not named-patient. It's right through lots of the documents of this time.

THE CHAIRMAN: It doesn't paint a very attractive picture of the pharmaceutical industry if they were prepared to resort to staging tests so as to avoid an adverse outcome.

A. I'm being a little hard and I apologise. I don't really mean to be that hard on them but there wasn't, if you like, an established protocol, I think would be a better way to put it.

MS DUNLOP: Right. Can we turn to look at your own personal participation in trying out product, and we know that that was NHS product.

Can we move to page 2 of the statement, please, which is page 2 of [PEN0121688]. There is a longer answer headed "paragraph 26" and that was the question that asked about this topic.

You say that you received a letter from Dr Cash dated 13 June 1983, inviting you to infuse three patients with heat-treated Factor VIII, batch NY761.

That letter is actually [SNB0065498].

There has obviously been a telephone conversation between the two of you about it beforehand. I think we know that the situation wasn't 100 per cent as people at PFC had intended it because they had wanted to use a matching pair, as it were, you know, half of a particular batch would have been heat-treated and the other half wouldn't have been, and that presumably would have been the best experiment to see what the effect of the heat treatment was but the unheated half had failed a pyrogenicity test.

So all they had was the heat-treated half. He says:

"We have a small amount of heat-treated material only."

They didn't want to waste it so he says:

"If you are able to show in 2 or 3 patients that its behaviour was broadly similar to previous data you, Chris and Frank have collected on cryoprecipitate and intermediate VIII, then it would considerably boost the confidence of the PFC team and, I should hasten to add, the Licensing Authority ..."

Then he goes on to say that he would turn your attention to the point you rightly raised with regard to the possibility of molecular damage during the heat treatment process. I'm going to ask you about that

next, I think, really. It would make sense to go to the correspondence about that but we will just finish looking at this letter. There is a suggested protocol and the profile of batch NY761:

"The osmolality is higher than existing products."

In a nutshell, osmolality of Factor VIII?

A. It's the degree of salt solution in the finally reconstituted vial. In plasma the sodium solution is at a concentration of 0.9 per cent. It appears that the salt solution here was probably above 0.9 per cent, not a problem if it's a little bit raised but it's likely you would be injecting a stronger solution, as it were, into the blood stream, it's very rapidly diluted as it goes in, and I think most products aim to be what's called isomolar, the same osmotic strength as the plasma.

Q. What effect does that have on a patient then if it's higher than 0.9 per cent?

A. If they received a lot of that product, I mean, a litre or two, it draws in fluid from outwith the blood vessels, so the tissues will get a bit lax but more importantly the blood volume would expand and it would probably leak out into the lungs, so you would get pulmonary oedema and breathlessness. But to get that you would have to infuse large volumes of hypertonic.

Q. Is this similar reasoning to why we should cut our salt intake to keep our blood pressure down?

THE CHAIRMAN: That's an essay in itself.

MS DUNLOP: Professor James is shaking his head.

A. I'm not an expert. I wonder if I should attempt to answer it. I think rather not.

MS DUNLOP: Let's not go there.

Can we just look at the second page of the letter then, please? "Practicalities". Frank Boulton is going to be arranging for you to get the vials of batch NY761 and then he is also suggesting that you might consider giving an infusion to a von Willebrand's syndrome patient.

Just to look at your letter about the possible molecular damage. That was [SNB0064708]. We have looked at this already. But we know that you had written in March 1983 to Mr Watt, articulating your concern about neoantigens. Is the final paragraph a separate point or is it connected to the neoantigen concern?

A. Well, it's to do with the functioning and potentially neoantigens of the von Willebrand factor. We have been talking all along about Factor VIII but Factor VIII adheres to the von Willebrand factor in the plasma, so they go round as a twosome, and the von Willebrand

factor is essential for what we call primary haemostasis. When you get damage to a blood vessel, it's the von Willebrand factor that acts as the sort of glue that sticks the platelets to help seal up the hole in the blood vessel. And if heat treatment was to damage the von Willebrand factor, then maybe it wouldn't be such good glue and therefore maybe you would have a more prolonged bleed after trauma.

Q. Right. I wasn't aware of a reference to Factor VIII ristocetin. Is that a correct pronunciation?

A. This, I think, is dated 198 --

Q. ... 3?

A. ... 3. There was a lot of debate in the early 1980s as to whether the von Willebrand factor and the Factor VIII were the same protein or were they two proteins, and my mentor in Cardiff, Professor Bloom, was really instrumental in demonstrating they were two separate proteins. So they tended to get sort of rolled together in their name. Nowadays it would be VWF ristocetin co-factor activity. It was a time of transition.

Q. Thank you.

In the second paragraph you are mooting the possibility of looking at the inhibition of Factor VIII concentrate activity by a variety of anti-Factor VIII inhibitors. Could you simplify that a little bit please

and explain what you were suggesting?

A. If you give Factor VIII to a patient with haemophilia, as you know, about a quarter of them will develop antibodies.

Q. Yes.

A. But they will produce antibodies to one or more specific parts of the Factor VIII molecule. The Factor VIII molecule is very large.

Q. 2,351 amino acids, I believe?

A. You are right.

Q. Thank you.

A. It's a very large protein and so it has quite a number of different, if you like, bits that stick out and interact with other proteins or with other cells. And some patients produce antibodies to one of these parts of the molecule, some to others.

Q. I understand.

A. So it would be theoretically possible -- and practically possible as well, if you have the right facilities -- to take, if you like, native Factor VIII and see how it reacts to a panel of patients' antibodies that may all be slightly different and your heat-treated Factor VIII and see how it reacts with the panel, and if the heat-treated Factor VIII reacts differently with the panel, then you will begin to suspect that the surface

characteristics of Factor VIII might be different.

Q. I understand. You have a library or you had a library of these different inhibitors?

A. We had patients, we had roughly half a dozen or a few more patients with these inhibitors, whom we had stored samples. So that's a possibility. We could have acquired some from colleagues elsewhere.

Q. Right. Thank you. I think I have a better understanding of what you were wanting to do.

In fact, we know that actually some work was done. I think Dr Joan Dawes was involved. Is that right?

A. Yes.

Q. And results were positive. There wasn't any particular concern demonstrated as a result of Dr Dawes' work, I think?

A. That's right.

Q. Can we move away from that letter then, please, and go to this question of the two slightly different reports of what happened to the patient. The first, in terms of time, I think, we should look at is the meeting, the minutes of the meeting. Yes, that's the meeting between the haemophilia directors and the SNBTS directors on 14 November. If you bear with me a moment, I'm not sure that I actually have the reference to that in my list.

[SNB0015188]. It has actually been the first item

of substance discussed. We can see for ourselves what your report is said to have contained. So you had actually only tried it on one patient. Is that right?

A. That's correct, yes.

Q. Is that because there was an adverse reaction, you didn't move on to try it on another one or two?

A. I think that must be the reason, yes.

Q. Yes. I appreciate it's a long time ago. So in terms of its actual activity, it seems to have worked reasonably well. Is that correct?

A. That's correct, yes.

Q. But then you said:

"The patient experienced minor adverse reactions on each occasion and had become anxious. It wasn't clear whether or not the product was the only cause of his upset. Dr Forbes had just received a supply of material from a different batch and was about to put it to trial."

So that was one account and then there is the letter of 11 January 1984, which is [SNB0015311].

Let me reassure you, professor, I don't suggest that this is a big point at all; it's just that there does appear to be a bit of a discrepancy between the report at the meeting and the report in the letter. The report in the letter seems to sound like a more significant

adverse reaction. I think it's probably the quantitative terminology used. You know, on the one hand we had "minor adverse reaction" but here it says "significant and unacceptably adverse reactions".

I know one possibility, you say, is that the minute taker might have got it wrong?

A. I think there are a number of ways in which patients can react, as I think I may have mentioned in my witness statement.

Q. Hm-mm.

A. A major reaction would be if they got anaphylaxis, they dropped their blood pressure and their pulse went up and they nearly died. That can happen, particularly with cryoprecipitate. I have had patients who have done that on cryoprecipitate and have ended up on ventilators. So some of these reactions are not trivial, they are very major. Obviously I am afraid I can't remember exactly how I described it at the meeting. The note-taker was not, if you like, a doctor and I -- there were clearly reactions.

If it's helpful, what I can add to that is I have recently looked at this patient's notes. Unfortunately he is no longer alive but I have his notes and I have been back through his notes and he is not an individual who reacts to either cryoprecipitate or Factor VIII

concentrate. Some patients react to practically everything you give them, particularly in those days when they were relatively impure, other patients who get no reactions at all and the majority of patients in the middle who react some of the time. I went back through a good bit of this patient's notes and I couldn't find any reference to any reactions, and as you know, in this letter there is attached a description of him receiving concentrates, trial concentrates on a number of other occasions.

So I think he is not someone who normally reacts to concentrates. Here he has reacted. And then, as you see, I think it was on 7 December, so that was after the meeting at the Scottish Office, I gave him an infusion of ordinary Factor VIII and he didn't react and that emphasised in my mind that these were real, organic reactions.

Q. Indeed. I think our interest in the apparent discrepancy was really twofold: firstly, whether this hiccup interfered with progress, I suppose; and then secondly, whether the writing of the letter -- and this, I freely admit was speculation, but whether the writing of the letter was connected in some way with a case that had to be made for funding or something of that sort. My understanding of the first is that it didn't derail

or delay progress towards a heat-treated product. Does that accord with your understanding of this event?

A. I think so, yes.

Q. And as far as the second is concerned, you say you don't have any recollection of whether there was any use to be made of the letter?

A. No -- I'm sure Professor Cash didn't prompt me to write the letter or to emphasise any particular aspect. I was a bit surprised by the question --

Q. Right.

A. -- that was posed. No, it was just a straightforward letter. I'm a bit embarrassed it was a month after the last infusion but I suppose Christmas had intervened. But I have set out there my view, and although in a sense it was "a minor reaction", this was a product potentially -- and this was what's called a benchtop production of 9,000, or the aim was to produce 9,000 units. That it would have been quite unacceptable to scale up this without doing further studies, if it gave even these sort of degrees of reaction, because you couldn't accept this as being a viable product for treating patients.

Q. I quite accept that, professor, and I think we understand the point that even if a reaction can be described as "minor", that doesn't make it acceptable.

So I think we can move away from that.

Can we go back to the statement, please? That's [PEN0121688] at 1690. We also referred in our questions to a circular letter from Professor Bloom, Dr Craske and Dr Rizza, listing virally inactivated concentrates. Can we just have a look at that letter, please, it's [DHF0028963]. Is this actually part of the correspondence leading up to your letter back saying that you don't think you will be participating in any commercial trials? It looks from a time point of view as though this must have been part of the build-up to that?

A. I think it might have been because my letter was dated some time in April, I think.

Q. Yes, it's 10 April, your letter saying that you are preferring not to. It does look to have been quite a systematic plan actually, if we look at what's said. So listing the products currently available, including at 3:

"Heated NHS Factor VIII. One brand is manufactured at the PFC in Edinburgh and will be shortly available. The second manufactured at Elstree should be available later this year."

Actually we see a reference also to Behring and no doubt a predictable consequence of the low yield of the

Behring product, that it might be coming in at around 40p per unit, which I take it at that time would have been jolly expensive. You probably don't carry around in your head what the price would have been prior to 1984?

A. Prior to heat treatment, my recollection is that Factor VIII was about 10p a unit in this country. I may be wrong. It was round about that.

Q. And the letter goes on to say that:

"All products, except those derived from NHS Factor VIII, are coming from plasma imported from the USA and carry a putative risk of transmission of AIDS."

Can we look on to the next page, please? It's really quite a methodical approach here to possible trials and coordinated by Oxford as well?

A. Yes, this was an attempt to prevent the companies arranging for giving it to patients on a named-patient basis if there was a national arrangement.

Q. But I think perhaps even also if there were going to be localised clinical trials, that there was to be some co-ordination of that too?

A. Yes.

Q. Yes?

A. This is why we have a national organisation.

Q. Well, indeed.

Can we go back to your statement then, please, [PEN0121688] at 1690?

This is picking up a point that I think Professor Cash made as well about the attempts in early 1983 to establish dialogue between PFC and Dr Rizza. So with a view to possibly having some English patients available for trials of Scottish product as well, contact seems to have been made, and I think the letter you are referring to on this topic is [SNB0073483]. If we could have a quick look at that, please.

So Mr Watt to Dr Rizza, 22 February 1983. I don't think he actually says in terms in the letter -- or not in this letter -- that he is wanting to test the product on patients in England but he certainly seems to be keeping Dr Rizza informed, and actually also I think seeking some advice. We can see that Mr Watt is to some extent rehearsing possible ethical issues with Dr Rizza as well. We can see that towards the foot of the page.

A. Yes.

Q. Can we look on to the next page, please? Can we go back to the statement again, please, at 1690? I'm not going to ask you any questions about Hemofil T because we have talked about Hemofil T a lot this week and I think we have the picture about the early trials of it. But can we move down and look at your answer to our question 36?

Perhaps it would do no harm just to glance again at the question. So can we go to the schedule of questions, please, which is [PEN0121531]? Question 36 starts on 1538.

We can see question 36. Can we just read to the end of it, please, by going on to the next page?

Then reverting to your answer, and I'm reading from the second sentence of the first paragraph:

"If effective heat treatment against NANBH virus (es) had been part of the routine manufacturing process and all concentrates issued after the beginning of January 1984, then it is likely that batch ..."

Which I think is referred to as "0090" for short:

"... would not have contained infectious HIV."

But you say that:

"The question suggests a misunderstanding about the initial reasons for developing heat treatment. It was to prevent hepatitis."

I don't think, Professor Ludlam, that we failed to understand that the efforts that began in the 1970s and the early 1980s were in the context of hepatitis, firstly perhaps Hepatitis B and then latterly non-A non-B hepatitis as well, but you seem to be saying that there wasn't a read-across between the work that was being carried out to develop a heat-treated product and

the threat of AIDS.

We have looked already this week at some of the material from 1983. We looked at a talk Dr Foster gave at the Royal Infirmary in March 1983 in which he does mention, in the context of heat treatment, that AIDS may be a possible problem or issue. We have also looked at his memorandum dated 3 May 1983 and I should let you have a look at that. That's [SNB0073635].

We have studied this memorandum in some depth already but the thrust of it, I think, really is that Dr Foster is referring to the then current strategy, which was pasturising up to 30 per cent of the total Factor VIII and using that for patients who had mild or moderate haemophilia, but then suggesting that it may be necessary to develop a different strategy:

"The possibility that another more serious infectious agent, AIDS, is now involved suggests that we may need to review this strategy."

Just perhaps scrolling down to the bottom of the page, in this first part of his memorandum explaining his thinking. Then a question of timing and then over on to the back, please, he does what I have been referring to as a "worked example" of what might be possible in reasonably early course.

Then just as another example of documentation from

the time, can we also look at [DHF0024489], please? This is from England. I think this is actually dated July 1983. I don't see the date on it at the moment but the date may be at the end. Central Blood Laboratories Authority, headed "AIDS: progress with heat treatment of human plasma products". We can see that actually the theme of this is that very read-across, heat treatment in the possible context of AIDS.

Can we just look down through it, please? It does say:

"Heat treatment of blood products is still primarily directed at the inactivation of transmissible viruses causing hepatitis in recipients."

Can we look on to the next page, please? "AIDS":

"The syndrome is likely to include in its aetiology transmission of an infective virus. This aetiological observation has promoted more activity in the area of blood products' pasteurisation with the empirical view that a virus is involved and, as with hepatitis virus, is likely to be partially or completely inactivated by heat."

And then goes on to discuss means of heat treatment. I think there is another page as well. It's the final page and there is the date, 26 July 1983.

So it does look, Professor Ludlam, as though at

least some of those more directly involved with developing heat treatment processes were making that read-across and thinking, "We may need to deal with AIDS as well". Would you accept that?

A. I fully accept that.

Q. Yes.

A. But to have instituted heat treatment in January 1984, I think would have jumped the gun because there was no way of knowing whether the virus that causes AIDS was heat sensitive or not. It might have been like parvovirus that's extremely resistant to heat. Hepatitis A was being discussed, I think, yesterday, that is relatively resistant.

So if, if you like, clotting factor concentrates had been heated on the offchance it might inactivate the virus -- it might well have done because we now know that it's very heat sensitive but we didn't at that time -- then people like me would have been even more anxious about neoantigens for absolutely no proven gain, just a possible gain. Even December 1984 when the heat treatment was introduced, as I am sure you are aware, there was some uncertainty as to how effective it would be.

So I don't think there is anywhere in the world that would introduce heat treatment on a large-scale

in January 1984 for concentrates. Had it been introduced then, I think the question was: would it have prevented the very unfortunate episode of the -- I wish it would have done, but my understanding is that that batch was made in November 1983 and, if you like, would have missed out on the heat treatment.

Q. I'm sorry, the question didn't make it clear. It was kind of rolled into the premise of the question that exactly the same would have happened in January 1984 as happened in November/December 1984, so that stock would have been recalled and heat-treated as it were, and there would have been a recall of product.

So if you include all these details in your premise, then as a matter of practicality, it could have been prevented, and obviously it's part of our function as an Inquiry to probe whether that's something that ought to have happened, which is simply why we asked the question.

Everybody has answered it, I think, or pretty much everybody to whom we put this schedule, and I'm just baldly summarising here, but their answers have really revolved around three points: firstly, that it was not clear at the start of 1984 that the AIDS agent had been found -- and we know about the whole Barre-Sinoussi/Gallo debate, if you like. Secondly,

that it was not clear that that AIDS agent, whatever it was, would be inactivated by heat and in this context there was some negative information about Hemofil and the continued development of hepatitis. Then thirdly, it was not clear that a heat-treated product would not cause harm to patients. So I take it that you would align yourself with all three of those points of view?

A. I think that's what I have been trying to say.

Q. Yes.

A. Yes.

Q. There is one other factor also, which I think is only mentioned by Dr Smith. Do you know Dr Smith? Did you ever meet him?

A. Oh, yes.

Q. All right.

A. Not recently.

Q. He is certainly a very well known name in this area.

A. He is a delighful man.

Q. Can we look at his statement, [PEN0121551] at 1565, please? This is Dr Smith's statement. Don't be thrown by the fact that it is shown as answer 34. It is in fact the same question but he makes several points in response, but the one I wanted to put to you is the second bullet. He says:

"I'm not sure that in early 1984 it was generally

perceived that AIDS had entered the UK donor population. No test was generally available, validated for application to large populations of donors."

That's true as well, isn't it, Professor Ludlam?

A. Absolutely.

Q. And that must be part of the answer?

A. Yes.

Q. Yes. Thank you very much.

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: In relation to cryoprecipitate and the photograph you were shown earlier by counsel to the Inquiry, am I right in thinking that that cryoprecipitate comes from plasma which is obtained from a large number of donors?

A. Yes, that's pooled plasma.

Q. Pooled plasma?

A. Yes.

Q. So it would be wrong to think that that's similar to the cryoprecipitate that would be obtainable from a small number of donors and therefore virally safer than that one would be?

A. Yes, that's correct, yes.

Q. The second point I wanted to ask you about was in relation to Factor IX and heat treatment in respect of

that. As we know, the heat treatment for Factor VIII came in sooner than it did for Factor IX. In December or towards the end of 1984, do you recall what information you were given about when Factor IX would be heat-treated successfully or what the sort of timescale was in relation to that? Were you given any information? Do you recall what it was at that time?

A. I know it was discussed. I can't remember whether a timescale was offered. There was concern about, as you probably know, thrombogenicity after heat treatment, quite apart from solubility and efficacy, and I think it was a matter of getting the animal studies done, I think was probably what was holding it up.

I'm sorry, I don't remember if we were told how long that would take.

Q. Did you give any consideration yourself to what to do in the meantime in relation to patients who were receiving untreated or unheat-treated Factor IX?

A. Yes, I did. Because I had a few patients with particularly moderate Haemophilia B. That was difficult. I think there was commercial heat-treated Factor IX of unproven safety from a donor pool that was likely to have many more HIV positive donors in it, versus NHS clotting Factor IX.

We knew at that stage in December 1984 that the

prevalence of anti HTLV-III positivity in Haemophilia B was very much lower than in Haemophilia A, and we presumed that that was because the virus to a large extent was excluded in the manufacturing process, excluded from the final Factor IX product.

So Factor IX was seen as a much safer product from the point of view of HTLV-III, even unheated.

So the national recommendation was to continue to use unheated NHS Factor IX concentrate in those who had already been exposed to it and to use fresh-frozen plasma in patients who hadn't been exposed to it, if possible. If they had severe new patients with severe haemophilia, they might anyway have to be put on to the concentrate but to use UK concentrate.

So it wasn't an entirely black and white issue. It was in a sense slightly easier to not use the heat-treated commercial because the epidemiology at that stage was that patients were much less likely to get infected with anti HTLV-III. Does that help?

Q. Thank you very much. Yes, it does.

THE CHAIRMAN: Is that all?

MR DI ROLLO: Yes, thank you.

THE CHAIRMAN: I wondered if you did want to go back to the information we have already heard about, when Factor IX did become available, you remember it's set out in

Kasper, but I don't know whether you want to go back to that.

MR DI ROLLO: No, I'm content.

THE CHAIRMAN: Mr Anderson?

MR ANDERSON: I have no questions.

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: No, thank you very much.

THE CHAIRMAN: Anything you want to follow up with?

MS DUNLOP: No, Professor Ludlam is free to go.

THE CHAIRMAN: Those are words that usually have some comfort for the witness, Professor Ludlam. I don't know whether that's a permanent comfort or merely a temporary one.

MS DUNLOP: I think Professor Ludlam will probably only have to come back once more. I hope that's good news too.

THE CHAIRMAN: For the time being, thank you very much.

A. Thank you.

MS DUNLOP: Sir, I did say it was likely to be a short day and indeed so it has proved. So I don't have any further witnesses.

THE CHAIRMAN: Thank you very much. I hope you all have a good weekend.

(10.54 am)

(The Inquiry adjourned until Tuesday 13 September 2011 at 9.30 am)