Wednesday, 14 September 2011

(9.30 am)

DR BRUCE CUTHBERTSON (continued)

Questions by MS DUNLOP

THE CHAIRMAN: Yes?

MS DUNLOP: Good morning, sir. We have Dr Bruce Cuthbertson back with us this morning.

Good morning, Dr Cuthbertson.

A. Good morning.

Q. You haven't been here, in fact, since day one and we are now at about Day 46.

THE CHAIRMAN: I hope you don't feel disadvantaged.

A. Not in any sense, no.

MS DUNLOP: You have missed quite a lot but since you haven't been here since March, I thought it would be useful actually to look again at your CV. That is WIT0030196.

I have to say what particularly leapt out at me, if we scroll down the page, was your description of yourself as a "virologist". We did have Dr Foster say to us a couple of times last week, "I'm not a virologist," so that rather leapt out at me and I thought here are some questions for you.

I also noticed the work you did for your PhD. Can we go just a little bit up, please. Your thesis was

entitled, "A Study of the Immunological Mechanisms Responsible for High-Titred Antibody Production in Healthy Donors." Just a couple of questions about high-titred antibodies, Dr Cuthbertson. Does that really mean a high antibody score, if you like?

A. It does, yes.

Q. If someone has a high antibody score, that's indicative of a strong immune response. Is that right?

A. Yes.

Q. But the opposite is not necessarily true?

A. No, antibodies are only one part of the mechanism we have for fighting virus infections.

Q. So if somebody had a low score, it wouldn't necessarily mean that they had a weak immune system?

A. No, not necessarily but some patients have very low levels of ability to produce antibodies, called hypogammaglobulinemia patients, and those patients do indeed have poor resistance to some viral infections.

Q. That description of somebody as having a low ability or a poor ability to produce antibodies, is that across the board?

A. Yes, in those particular patients it is, yes, which is partly why we produced the product intravenous immunoglobulin, to administer passively acquired antibodies to those patients to help them fight off

viral infections.

Q. Do you have other patients who perhaps can't produce a specific kind of antibody? They can produce antibodies to other pathogens but not to something in particular?

A. Well, ability to respond rapidly to any microbial attack is part of how we are resistant and clearly, if you can think of populations, for example, that hadn't seen measles before, then part of their exquisite sensitivity to measles is an inability to produce rapidly an immune response.

Q. Just some of the terminology, Dr Cuthbertson, we might benefit from probing a little bit. I say that in general but also because next month we will be moving to look more directly at Hepatitis C and topics connected to it. There are a number of virological concepts that are obviously mentioned by some of the witnesses for those hearings. I'm going to try and begin that block with a bit of an examination of Hepatitis C virus in general.

So knowing a bit about that, I think, in advance is quite helpful. Can I perhaps go to Dr Foster's glossary. There are some terms in it which we should perhaps look at. Dr Foster's main research paper, which I think you have probably seen before, is [PEN0131309].

Not so much a research paper actually but a briefing paper, giving a lot of general information, which has been helpful to us.

Can we look firstly at the description on 1310 of an antibody? We see that near the top. I take it you agree with that description, do you?

A. Yes, it's perfectly correct.

Q. One of the things I have noticed is that scientists often define concepts to lay people in terms of what the substance in question does but I think it's also quite helpful to us to know what it is. So we can see there that an antibody is a protein and it's produced as part of the body's immune response to a foreign invader. Is "antibody" synonymous with "immunoglobulin"?

A. Antibodies are immunoglobulins, yes.

Q. Right. And I think --

THE CHAIRMAN: But are all immunoglobulins antibodies?

A. Basically, yes.

THE CHAIRMAN: So there is a straight synonymous relationship, is there?

A. The word "immuno-" is the word that shows that it is in fact part of the immune response, and "globulin" is just a description of the type of protein.

THE CHAIRMAN: Yes.

MS DUNLOP: In fact the glossary at page 1312, we see

defines "immunoglobulins" as:

"Plasma proteins involved in fighting infections, (commonly known as antibodies)."

In this context, I think it may be helpful to talk also about antigens and is the defining characteristic of an antigen, this as something that causes the formation of an antibody?

A. In effect, yes.

Q. Do you want to say a little bit more about that?

A. An antigen is any substance -- and it needn't necessarily be on a microorganism, it could be on a red blood cell -- which stimulates an immune response and is seen as being, in effect, foreign by the body's immune system, and the immune system is a very complex interaction of cellular mechanisms which generate the response and some of these cells, called B lymphocytes, generate the immunoglobulins which in fact bind to that antigen and help generate an immune response to that particular agent.

Q. So this is part of the body's technique for fighting the antigen?

A. Yes.

Q. It doesn't always work, though. Is that right?

A. Well, it doesn't always eradicate the disease because some organisms have found ways of getting round it one

way or another.

Q. I think the one we would be particularly conscious of would be HIV, where the antibodies do not succeed in beating the virus?

A. No, and also -- obviously the virus has ways of evading the immune mechanism, surviving.

Q. We also see reference -- and this is in the context of Hepatitis B -- to surface antigen and core antigen. What is the difference between those two types of antigen?

A. Okay, well, in effect any virus is a fairly simple set of molecules. It's basically packaging some nucleic acid and there are two forms of viruses, those that are packaged with DNA and those that are packaged around RNA, but they are indeed packaged. And in Hepatitis B it's a DNA virus and there are proteins that coat, if you like, the DNA and they are the other core proteins. And then round that is a series of surface antigens and round that is a lipid envelope. So in effect there are four main parts to a hepatitis virus. Uniquely the Hepatitis B virus produces an excess of the so-called surface antigen and that is liberated in fairly large amounts, which enabled us in the 1970s to develop a test for Hepatitis B for detecting that particular antigen. So the surface antigen is what is on the outside and

it's what the bulk of the protein content of the actual virus is, but the core proteins are in the middle and surround the nucleic acid.

Q. You said "uniquely", so these ideas of a surface antigen and a core antigen wouldn't be found with Hepatitis C?

A. No, it's a slightly different virus. It's an RNA virus. It has a series of proteins but it doesn't have a separate surface and core antigen.

Q. To go back to immunoglobulin, we have seen reference to intramuscular immunoglobulin and intravenous immunoglobulin. I think we can work out that that's about different modes of administration, but can you give us any examples of either?

A. Well, it's not so much examples of the type of immunoglobulin, it's simply a statement about how they were manufactured. The early immunoglobulin products that were manufactured by fractionation were found not to be tolerated if they were given intravenously and could actually cause fairly severe reactions. So they were given intramuscularly. And they were given intramuscularly to people who were exposed to particular agents, be it smallpox or whatever. PFC used to produce about seven or eight of these things against different agents.

But they could only be given intramuscularly, which

was (a), painfully because you got a dose of the stuff in the buttocks, and also it restricted the volume that you could actually give. So for the particular patients we were talking about earlier, the hypogammaglobulinemia patients, who needed a larger volume, we needed to find a way of making the product tolerable for intravenous administration.

We did that by eliminating some other proteins that were contaminants of the immunoglobulin preparation but which raised a reaction when they were given intravenously. So the words "intravenous immunoglobulin" mean that it has been largely more highly purified and treated in some way to eliminate these other proteins, so allow us to give them intravenously in a fairly large volume on a regular basis, which was what these patients ultimately got.

Q. To go back to the general and the specific, in other words, the patients who have a general immunological defect and needed the whole panoply of immunoglobulins versus people getting a specific one, would it be right that tetanus would be an example of an injection of a specific immunoglobulin?

A. Indeed. For things like tetanus and Hepatitis B, for the virus varicella-zoster, which causes chicken pox, we deliberately selected donors who had high titres of

antibodies against those agents and then we selected plasma from those donors and fractionated it discretely in smaller pools to make these so-called specific immunoglobulins. And they were then issued for those particular indications.

The normal intramuscular immunoglobulin or normal intravenous immunoglobulin was collected from the same plasma pools that we used to make Factor VIII or Factor IX and any of the other products. So it therefore had the normal spectrum of antibodies that were in the donor population.

Q. You have no doubt at some point seen Dr Foster's flowcharts but I think we understand that the arrival of immunoglobulin is one of the horizontal journeys, slightly lower down the page, after the production of Factor VIII and Factor IX?

A. Yes.

Q. So that comes from, I suppose, cryo-depleted plasma?

A. That's correct. We took out the cryo first and then we would take out the Factor IX by adsorption and then we would go into the cold ethanol fractionation process and that would result in a fraction that contained immunoglobulins that we would process further and then dispense.

Q. Right. Thank you, Dr Cuthbertson. I think that is

enough for just now and if we spot other terms as we go through that we don't quite understand, we will ask you again and obviously if there are points that anybody else wants to pick up of a more general nature, then that's something that they can do.

Can we go to Dr Cuthbertson's statement, please, which is [PEN0130025]?

You tell us on the first page that you are a current employee of SNBTS and you have worked with them since 1974. In fact, between 1974 and 1980 you were at Belvidere in Glasgow. Is that right?

A. That's correct.

Q. Can you tell us a little bit about what you were doing there?

A. When I was first recruited it was indeed to set up systems to select donors to make these hypoimmunoglobulins. So I was working with a consultant virologist, Dr Bobby Somerville in Belvidere where he had already got various systems for determining human antibodies, and we kind of developed and fine-tuned those so that we could select plasma from particular donors with the high titres that I mentioned earlier, and that basically involved growing up viruses and setting up systems to detect high titres of antibodies, and at the same time, as you noted earlier, I did work

on my PhD to see if we could elucidate any ways of identifying the mechanisms that led to such donors producing high titres of the antibody, because some of them produced quite quick antibody responses which fell away quite quickly and others produced higher levels which persisted much longer, and those were obviously the ones that we were trying to capture. So we were looking for systems to try to easily determine who these donors were and what the mechanisms were.

Q. I don't want to digress too far but I suppose there must be a huge body of research into what it is that makes some people much better at producing high titres of the antibodies than others?

A. Absolutely. There is a whole wealth of literature on this topic.

Q. Yes. So you were at Belvidere Hospital in Glasgow and I think at that time there was a connection with Glasgow University too.

A. Yes, it was the Glasgow University teaching laboratory for virology and Dr Somerville was a university lecturer.

Q. Right.

A. It was also the infectious diseases hospital for West of Glasgow and there are now buildings -- It has been built over, it doesn't exist any more.

Q. Yes. And the east end, really, out London Road?
A. Yes.
Q. Yes. You returned to PFC in 1980?
A. Yes.
Q. I think at that point you were the microbiology manager. Is that right?
A. That's correct, yes.
Q. In due course you succeeded Dr Perry as quality manager, quality control manager. Is that right?
A. That's correct, yes.
Q. And that's really when he stepped up to become, first acting director and then director of PFC.
A. I was officially appointed in 1985, after he had been officially appointed as director. So I suppose I kind of acted up in the interim.
Q. Right. Just moving down the first page, please, we can see the reference to the 1970s and helpfully, Dr Cuthbertson, you have reproduced the questions from our snapshots and landmarks paper and have then given your answers. If we turn over on to the next page, it follows from what you have said that you weren't directly working on any of this research at PFC in the 1970s?
A. No. I was aware of it but wasn't involved.
Q. Right. You did quote at the top of page 2 from

a package leaflet insert, and I suppose that sentence about what has been done with the plasma before it has been used to make the Factor VIII concentrate is probably quite hard for a layperson to understand. You were basically telling those who read the leaflet insert that the plasma had been screened for the Hepatitis B surface antigen?

A. Yes.

Q. And that's that creature you were describing to us a little while ago?

A. That's correct.

Q. Yes. We can see actually the shorter notation for that at the top, the block capital "HB" and then the lower case, "s" and then the capital "A" and the lower case "g". That's the common notation?

A. Yes.

Q. And just while we are at it, the common notation for the core antigen would be the same but with a "c"?

A. That's correct.

Q. Right. In fact, as far as the antibodies are concerned, we also quite frequently see reference to the antibody to the core antigen, and that's shown usually as "anti-" and then "HB" with a lower case "c". So capital "HB" and lower case "c". Is that right?

A. That's correct.

Q. Is that an antibody to the surface antigen?
A. Yes.
Q. So it would follow a similar pattern of notation?
A. Yes.
Q. Just so that if we see these abbreviations, we know what we are looking at. This sentence in italics is telling the reader that a technique, reverse passive haemagglutination, which might mean something to a professional but wouldn't really mean anything to a patient, I suspect, has been used. Reverse passive haemagglutination or radioimmunoassay:

"... and the preparation has also been examined by more searching techniques applied in at least two laboratories external to the laboratory of manufacture."

What was meant by "the laboratories external to the laboratory of manufacture"?

A. Well, each donation was, as it says there, from 1970 onwards, was tested for the presence of HBsAg, and reverse passive haemagglutination is a fairly crude test in an agar gel system, where you actually put antibody in one well, the serum in the other and if there is the presence of antigen, then you actually got a line of precipitation in the middle, where the antibody and the antigen formed a complex.

It was a very crude test and pretty low sensitivity.

Radioimmunoassay was a much more sensitive test, whereby an antibody which had a radioisotope attached to it was used to detect the presence of the antigen. And in those days the antibody was bound to a bead.

So the bead would capture the virus and the radioimmunoassay would detect the bound antibody after you had washed off all the excess serum. And that was introduced and similar methods are in use today, except we don't use radioisotopes any longer.

That was done within the BTS. The two external laboratories, one was actually still in the BTS but was in a research laboratory run by Dr Robert Hopkins at the Edinburgh blood transfusion service, and the second one was the expert laboratory of Professor Dane at the Middlesex Hospital.

So each batch of our product at that time was sent to those two laboratories and they used the most sensitive variety of radioimmunoassay that they had available to see if they could detect the presence of the HBsAg in the final product.

Q. Right. Radioimmunoassay, usually abbreviated to RIA, is something I think we will see when we come on to look at our next topic, which is the introduction of the screening of donated blood for HIV. That's in only two weeks' time. Some of the earlier tests for HIV

antibodies involved radioimmunoassay, and I think perhaps you have just alluded to a disadvantage, which is that that meant working with radioactive material?

A. Radioisotopes, yes.

Q. And people in due course became anxious to move away from that. Is that correct?

A. That's correct.

THE CHAIRMAN: Dr Cuthbertson, it's a long time since we have heard of beads. Could you just remind us. This is a column --

A. No, they were small beads. This system was produced by an American company called Abbott. There were beads, a quarter of an inch in diameter, to which antibody to HBsAg was bound.

THE CHAIRMAN: How? What does that mean?

A. Fixed; fixed to the surface of the --

THE CHAIRMAN: You didn't take a paint brush and dab it on --

A. No, it was a chemical reaction to cause the antibody to stick. It was done in a large vat. I actually did see this in Chicago. It was done in a large vat where they bound the antibodies on to a bead. You then basically put a bead into a small tray that had wells that the beads fitted into. You then added in your sample, incubated that for a period of time to allow any antigen

to stick to the antibody that was on the bead, then washed away the antibody, then you added your radio-labelled antibody. And if any of that stuck, then you knew you had some HBsAg probably, although there was actually a confirmatory test that enabled you to determine if that was actually the case.

I don't know if that helps you.

THE CHAIRMAN: I think that's slightly different from what we heard before.

MS DUNLOP: Sorry?

THE CHAIRMAN: I think what I had in mind was an earlier description of an adsorption process in which the beads were put into a column and material was run through that.

A. Well, it's the same principle but done in a unique scale for one bead to one sample.

THE CHAIRMAN: Right, and that in effect is what was bought in from Abbott ready prepared?

A. Yes.

THE CHAIRMAN: Right.

MS DUNLOP: Yes. We will hear a bit more about Abbott in two weeks' time and about the early tests for HIV.

Just to complete looking at that paragraph, however, we see another two sentences in italics, which are a quote from the leaflet and perhaps rather easier to

follow for a layperson, that:

"None of these tests are of sufficient sensitivity to eliminate the possibility of transmitting hepatitis. Methods for examination of the product continue to be developed but the risk of transmission cannot be disregarded."

Again, it's interesting to see that at the moment but we will in due course come on to look in more detail at the sort of information that was provided to people about the risk of hepatitis.

I suppose when that was written, people were still thinking of Hepatitis B but by that point there would also be an awareness that there was other hepatitis that was neither A nor B?

A. That's correct. Obviously we would have known by the time this leaflet was written that we hadn't eliminated hepatitis by the methods that we were using to screen for Hepatitis B.

Q. Yes. I don't want to ask you anything about paragraph 2, Dr Cuthbertson. Can we move then and look at the next page? That's page 3 of [PEN0130025]. We don't really need to look at anything before paragraph 5.

I need to correct a misapprehension to which the question has given rise, I think, on the part of

a number of witnesses that we were trying to make some suggestion that work was going on everwhere in the rest of Europe. It was purely the research by Behring that we had in mind when we wrote this paragraph, and we wondered whether the research which began at PFC in 1981 was in response to the news of the Behring work and the answer that we have had from everybody seems to be that it was. So I think we understand that now.

A. Yes.

Q. You say that the Behring product was never licensed in the UK nor available to treat Scottish haemophiliacs. We have seen a reference to its having been available commercially and I think we will see another such reference this morning, but the commercial availability was pretty limited as far as the Behring product was concerned. Is that your understanding?

A. Yes.

Q. Yes. Can we then turn to the next page, please? You go on to talk about the Factor VIII study group and can we look, please, at the paragraph at the top, paragraph 6.

We did talk about the first meeting and how Dr Prowse in fact is the person who mentions pasteurisation, but our understanding of why that was is that it was simply Dr Prowse giving an overview of the various different viral inactivation techniques, or

techniques for dealing with the viral threat, as at that time. He wasn't specifically saying, "I'm researching pasteurisation"?

A. That's correct.

Q. I wanted then to look at paragraph 7 to the first meeting of the safety subgroup. You were on the safety subgroup. I think it was group D. Is that right?

A. That's correct.

Q. Yes. Can we look, please, at [SNB0058387]?

We can see that the safety group, group D, comprised three people. Dr Pepper was the secretary. So he did the writing. Is that right? He wrote the reports?

A. He did, yes.

Q. And Dr Somerville, whom you knew from Belvidere, and yourself. Can we just move down the first page, please?

We can see that Dr Pepper had a discussion with you on 9 February 1982 and then he had a separate discussion with Dr Somerville the following day. I take it that was just to do with availability?

A. I can't really recall but I assume so. I assume he had to do a report fairly quickly and that he therefore had separate meetings because that was the only times we had available.

Q. Yes. There is a very succinct summary at the bottom of the first page, which I think, if we think about it, we

can follow the points that are being made. The first sentence is saying that you really need a good test for the virus before you can decide how effective your virus inactivation technique has been?

A. Hm-mm.

Q. I suppose that's common sense really. You need to be able to measure the amount of virus at the end of whatever process you are putting in place to see if it has worked?

A. That's the ideal situation although, as it happens, many products were issued on the basis that they were heated, without any really virological evidence that the processes worked.

Q. Yes. So in a perfect world you would have an accurate means of measuring the virus --

A. Absolutely.

Q. -- at the end of whatever process you are putting in place but it doesn't always happen that way. Then the summary goes on to say that the group -- that's the main group -- should work on that and there was a subgroup dealing with that:

"Any attempts to heat or irradiate the concentrates of Factor VIII presuppose a more purified, more stable concentrate than those presently available."

So two different concepts really being alluded to

there, that there has to be further work to purify the concentrate and also it has to be stabilised against the effects of heat or whatever other agent is introduced. Is that right?

A. That's based on the fact that -- as I think Dr Foster has told you in some detail -- that Factor VIII is actually a very unstable molecule and that steps have to be taken to stabilise it against any measure of heat.

Q. Yes. Then at the bottom we see that the thinking at this point is that heat is better than irradiation which is better than adsorption in terms of likely success.

Can we look at the second page, please? There is an introduction, which reveals, I suppose, Dr Pepper's thinking but perhaps the thinking of the other two of you as well. Dr Pepper posing what looked to have been some relevant questions at that time. First of all asking what would be the effect of doing nothing, which he goes on to answer in the paragraph underneath the questions, saying that he doesn't think that doing nothing is an option.

Then in his second question, wondering what is the nature and quantity of the risks in Scotland at this time:

"Are we worrying about a problem which exists elsewhere?"

But going on to say that it wouldn't be safe to operate on that basis. He says that:

"Although Hepatitis B is decreasing to levels lower than non-A non-B hepatitis, there are significant amounts of the latter in England, and Scotland may also have a significant problem but more data is urgently required."

Then thirdly:

"Are current developments in other associated areas moving at such a pace that any realistic timescale for our projected work may well end in shelving the whole project, for example genetic engineering of Factor VIII and/or synthetic antigen vaccines or production of neoclassical vaccines."

I'm not sure what a neoclassical vaccine would be.

A. Just a new version of a traditional vaccine, ie some kind of heat-inactivated microorganism.

Q. Right.

A. But obviously genetically engineered vaccines were available shortly after this report.

Q. Yes.

A. Particularly for Hepatitis B.

Q. It's interesting to see the report focusing even then on the need to bear in mind what the context is, so there would be no point in starting on a project which is

going to be overtaken by a more attractive scientific development?

A. Yes.

Q. Yes. Can we then just scroll to the bottom of the page and on to page 3, please.

There is a mention of the targets, viral risks, Hepatitis B and a probable two or more hepatitis non-A non-B and various other agents mentioned. Then on to the next page, please. We find some predictions. He says at the end of the first paragraph on page 2:

"It seems likely that developments in non-A non-B will follow the same route as Hepatitis B but over a considerably shorter time span, for example five years versus ten years, due to technological gains, notably in genetic manipulation."

As a prediction it wasn't bad, was it, Dr Cuthbertson?

A. No, I think Hepatitis C was finally isolated in 1989. So if this was written in 1982, then --

Q. Or even 1988 perhaps, although it's a little bit difficult to discover quite what the extent of the achievement in 1988 was. And of course the discovery was to some extent connected with genetics?

A. Indeed.

Q. Yes. Can we just scroll down again, please?

It makes another cogent point:

"Obviously, to be attractive, inactivation must be cheap, reliable and capable of killing more than one virus. I would also add that in my opinion it should be developed within two years, any longer than this is too unpredictable as regards other developments."

Then on to the next page, please. Discussion of the complexities in looking at the viruses and saying:

"We do not have any data on the DNA/RNA of non-A non-B viruses."

This is in the context of talking about radiation but then going on to say in the next paragraph that:

"An alternative to gamma irradiation is heating (pasteurisation)."

And a reference to the Behring work. At that point unfortunately, only one paper had been published in German:

"Estimates by PFC indicate 8 per cent yield, which is rather low."

Going on to say that:

"The process clearly only works because large amounts of protein (fibrinogen) are removed prior to the heating step and these preliminary steps may well be responsible, both for the removal of hepatitis and the low yields."

THE CHAIRMAN: Before you leave that paragraph, could I ask you just a little about the one paper published in German?

I think from the text it's clear that it was known that that paper existed in February. When was it translated? It's by Mr Zolg and I think it must be around about October or something like that, on other information.

MS DUNLOP: I think, sir, actually it was 1981 because Dr Foster was absent due to ill-health.

THE CHAIRMAN: I'm sorry.

MS DUNLOP: During his absence --

THE CHAIRMAN: You are absolutely right. So it's not available just in German. Did you only know of it in German at this stage?

A. No, no. By this stage I knew about it because of the translation. And because we had started, as you know, in doing work in our own sort of variant of that process, and in fact by the time that this report was written, then obviously we had started working.

THE CHAIRMAN: So what is the significance of the reference to it being in German?

A. I think it just means that it's not in the routine English canon, that's all.

THE CHAIRMAN: I see.

A. It was an obscure publication, which wasn't widely available in the English literature.

MS DUNLOP: I think from our limited learning in this area, Dr Cuthbertson, we do recognise some of the points being made in this paragraph, that it's desirable to get rid of as much fibrinogen as possible before you move to pasturising, and indeed he says that that's true of both heat inactivation or gamma irradiation.

Can we move on to the next page, please? There is a return to the topic of assays. Mention of the beta propiolactone work, which also we have seen mentioned.

Can we go a little bit further down, please?:

"Assay of infectivity is the major problem to be faced in this work. At present only one assay is established: that in chimpanzees."

It's quite interesting just to note what the climate then was as far as chimps were concerned.

A. Yes, there was a colony in Liberia, I think, which was available at some expense but in very limited amounts.

Q. So in 1982, chimpanzee -- I'm not very sure whether the scoring out is meant to indicate that it wasn't $8,000, it was £8,000. Anyway, I suppose we could do the maths and work it out but there is a cost figure given for each chimpanzee and how much they cost to look after and to have the tests carried out.

A. I think that's supposed to be a dollar sign.

Q. Yes. It says:

"Each chimpanzee will cost about £10,000 per six month trial and a straightforward experiment ..."

Can we go right down, please? Maybe it's on to the next page:

"... would cost £60,000 minimum."

Then we see that there are owl monkeys in Panama and they may offer an alternative. Geographically very inconvenient. You certainly wouldn't want your assays being carried out in Panama:

"The most attractive possibility would be a tissue culture assay for hepatitis virus."

Then we see some action proposals. You look to have been given some pretty complicated homework, Dr Cuthbertson.

A. Yes.

Q. Hm-mm. And Dr Pepper is investigating radiation and doing some work with marker viruses. Then on to the next page. Dr Somerville is looking at literature and speaking to personal contacts. Then finally a section on the resources which will be required, and we see over on to the next page, staff, animals, and so on and then it's even contemplated that somebody might have to go to Panama or Liberia. I take it Dr Somerville didn't ever

actually go to Panama or Liberia in search of chimps or owl monkeys?

THE CHAIRMAN: Professor James is suggesting it's akin to being sent to Siberia.

MS DUNLOP: Right. Can we put that away then, please?

THE CHAIRMAN: Before you do, this seems, admittedly to someone who doesn't understand all these things, to be an extremely wide-ranging exercise for PFC to undertake, looking at it in the whole.

A. This was an SNBTS subgroup, so it was led by, you know, a senior researcher within our headquarters R&D team, but in fact this was just a sort of mind dump almost, you would call it nowadays, of all the things that we could and couldn't look at, and some of the more impractical things that Dr Pepper suggested in this document were gradually weeded out, I suppose.

THE CHAIRMAN: I think that one can see that, going through the later stages as the list begins to attenuate, but just trying to get a feel for what was happening at this stage, I think one has to try to form a view whether this was a practicable research project or series of projects being proposed or was simply an exploration of the possibilities out there that would have to be narrowed down in time.

A. I would describe it as the latter, that this was an

exploration of possibilities. With a relatively small organisation like SNBTS, clearly we couldn't cover everything that was suggested in this paper and it was really just ideas, I think, from Dr Pepper that then went back to the main Factor VIII working group to see which, if any, of those we could follow up, and obviously we continued to meet to "whittle away", as I think you have put it, some of the less practical stuff and we did, as we will perhaps come onto, some experiments to weed out some of the ideas anyhow.

Q. So it's an exercise that becomes more respectable the less significance one attaches to it, or is that unfair?

MS DUNLOP: Is it blue sky thinking?

A. Blue sky thinking, yes. And in that regard I think it's quite a good paper because it was trying to think out of the box.

Q. Yes. There was another meeting fairly swiftly on 30 March. Can we have a look at the document that relates to it? That's [SNF0013799]. We can see the trio mentioned, Drs Pepper, Somerville and Cuthbertson, but in fact, if we look a little bit further down it was just you and Dr Pepper, I think, because if we go down, there are apologies from Dr Somerville. Maybe it's on the next page.

Can we turn on to the next page, please? Yes,

apologies for absence were received from Bobby Somerville.

Then there is a summary of the state of play:

"Three courses of action are being undertaken simultaneously."

We can read these for ourselves. And the statement that:

"PFC ..."

That's Dr MacLeod and Dr Foster:

"... should continue their work on the heat processes developed by Behringwerke."

And a description of that.

THE CHAIRMAN: I was fascinated by the question mark. At that stage was it envisaged that the team would be increased in size or is this just a possibility that someone else might be involved or what?

A. I have really no idea. I assume that it was just an acknowledgment that at PFC there was a team other than those two lead individuals that were working on it. I don't think it was a suggestion that from this meeting that that team needed to be aggrandised in any way.

MS DUNLOP: Could we go back up the page, please?

I didn't really look at the summary but we can see that there is still reference to the possible assays which might be available.

Can we go on to page 3 then, please?

Some very complicated chemistry, I think. And further down, an interesting point, I think, under the heading "Infectivity Assays" about whether, because heating at 60 degrees for ten hours was now widely held to be effective in destroying infectivity, it might be possible to dispense with an infectivity model completely, and noting that that was what Behring were doing.

A. Yes, I think that's correct.

Q. Yes. Then Dr Somerville was contacting various people in North America with a view to arranging infectivity trials of Hepatitis B and non-A non-B in owl, no doubt monkeys. Going onto the next page, please. Various thoughts about what might be possible with different animals. It says:

"Unfortunately, on paper at least, the owl monkey is unlikely to be susceptible to human hepatitis virus B and non-A non-B. The latter are ..."

I think that's ...?

A. DNA.

Q. DNA, yes, it's a "D":

"... DNA viruses, belonging to a separate class ("slow viruses") from the Hepatitis A virus."

I think that's not all correct as we now know.

A. In the light of current knowledge, that's wildly inaccurate.
Q. You had better correct it for us, Dr Cuthbertson.
A. Well, Hepatitis C is an RNA virus and doesn't belong to a separate class of slow viruses. It's part of a fairly well understood group of flaviviruses.
Q. The slow viruses or lentiviruses would include HIV, though, is that right?
A. Yes.
Q. Yes. But I suppose it just shows us that virology has progressed a lot --
A. A huge amount.
Q. -- in the almost 30 years since this was written.
A. Yes.
Q. Right. Can we go further down, please? Still talking about assays, I think, largely. And then on to the next page, please.
There is discussion of the procurement of infective material. I suppose it stands to reason that for research purposes, you really need to have some virus or viruses?
A. This was on the presumption that we would actually be handling the actual agents of either Hepatitis B or non-A non-B hepatitis. In the end no meaningful work was ever done with those viruses. Most of the

meaningful work on virus inactivation systems was done with model systems.

Q. Yes. We see in this section a bit of discussion of the infectivity of NHS or commercial concentrates in first time haemophiliacs and Dr Pepper is recording, I think, a bit of a discrepancy in the information. He has been told by Dr Craske that infectivity in first time haemophiliacs is 100 per cent and by Dr Rizza that it's 50 per cent, but he goes on to say:

"We must assume that all batches of NHS Factor VIII concentrate and commercial concentrates of 5,000 donations or more are positive for non-A and non-B".

And I think goes on to theorise that you have probably got non-A non-B hepatitis in the building, as it were. Is that right?

A. Yes.

Q. But no practicable means of extracting it for research purposes?

A. That's right.

Q. Yes. Then, if we look on to the last page --

THE CHAIRMAN: Dr Cuthbertson, can I ask you a little about the animal tests that are proposed here? I get the point that Dr Pepper's first paper can be looked upon as blue sky thinking, covering the range of possibilities. Was this sort of level of sophistication in animal tests

and so on and the use of live viruses ever reasonably within the contemplation of SNBTS at this stage?

A. Probably not. In retrospect, at the time I think we were exploring all options, and this was definitely a live option. From the literature we know that several of the US fractionators did use a chimpanzee model to attempt to determine whether inactivation procedures were successful. With the retrospective scope in full swing, we know that the data they got from these studies didn't predict whether or not their products were free from transmission of non-A non-B hepatitis.

THE CHAIRMAN: I appreciate that and I think it's a slightly different point. I think what one must do is try to gauge the ambition, as it were, of PFC at this stage, to get a measure of where it saw itself in relation to major pharmaceutical companies, who, one might think, had far greater resources available to do an exercise of this kind.

A. That's absolutely correct but clearly at the time of this meeting in May 1982 we were still actively looking to see if we could, if you like, circumvent the expense of the chimpanzee studies by, if you like, inventing another model. Whether that was wishful thinking or not, I think is another question.

THE CHAIRMAN: There is nothing wrong with wishful thinking

in this sort of area.

A. But it was clearly still being actively considered as a possibility.

THE CHAIRMAN: Without wishful thinking, one never gets invention, I suppose.

A. That's exactly right.

THE CHAIRMAN: But you would have seen it at this stage as a possibility that was worth keeping in mind as a real possibility and not just some sort of theoretical dream?

A. Yes, I think at the stage that this paper was written that was still seen as a possibility. I think we got into the real world quite quickly not too long after that. When this was written, it was seen as being potentially realistic.

MS DUNLOP: Yes. I think the page we are looking at, page 6, is really just making that point about, perhaps slightly frustratingly, an understanding that the viral contamination means that there is virus in the plasma that you are receiving but that, because science hasn't advanced as necessary, it is not possible to recover it. Can we just look to the bottom of the page?

Can we go back to Dr Cuthbertson's statement then, please? [PEN0130025] at page 0028. We have looked at what was happening in the first part of 1982 as far as the Factor VIII study group is concerned and your safety

subgroup. We then went on to talk about Dr Foster's attendance in Budapest in July 1982, and he got another Behring paper. It's actually quite complicated to chart all the different Behring papers that were circulating at this point, abstracts and publications in journals and so on, and I'm not going to do that again because we have had a look at the chronology of the different publications.

But one that I did want to look at is the Golden Notebook, which is [SNB0045880]. This is from an internal Behring publication. Our hypothesis is that it was first produced in a relatively rough form and then the company had it produced in a more professional-looking manner, so that they could distribute it beyond the company. I take it you are not in possession of any detailed information about what happened with these pieces of work? No?

A. I am afraid not.

Q. No. It doesn't matter in the slightest.

Can we look at page 3, please? Actually, to get the sense of it, can we just look at the page immediately before? This is an interesting little piece of narrative. Reading from the right-hand side:

"As yet there have been no systematic investigations of the prevalence of non-A non-B hepatitis among

haemophiliacs but from the increasing number of case reports, it's apparent that hereto there has been a shift in the virus spectrum similar to that which has occurred in post-transfusion hepatitis type B, having been partly replaced by type non-A non-B. The latter form has proved especially dangerous among patients with haemophilia, as it may occur despite the existence of immunity to Hepatitis B and frequently runs a chronic course."

I just thought it was interesting, that reference to type B having been partly replaced by non-A, non-B. Is that just an empirical observation, that more people are getting non-A non-B than used to be the case?

A. I assume that's exactly what they meant and, obviously, because Hepatitis B-positive donors could be identified through testing, it meant that the level of infectivity with Hepatitis B had clearly dropped and that non-A non-B was now the predominant form of hepatitis seen in haemophiliacs.

Q. Yes. I just wondered if there was any implication in that about what happens if the viruses go head to head. It is, obviously, simply speculation on my part, but I was interested in some sort of notion that the non-A non-B virus was becoming dominant in some sense.

A. I don't think that's what they are implying. I think

they just simply mean that the incidence of type B hepatitis had reduced and therefore the predominant type of hepatitis was identified as non-A non-B. I guess, if you have got a haemophiliac in the past who had been co-infected with B and non-A non-B and the B was diagnosed, you wouldn't have known that the non-A non-B was there.

Q. Yes. So there has been a masking in the past?

A. Prior to the availability of a test, then the only diagnosis of non-A non-B would be clinical.

Q. Yes.

THE CHAIRMAN: I don't think I had quite read it the same way as Ms Dunlop. I thought that there were two factors that might have been behind this. One was that before 1974, talking about serum hepatitis, there really wasn't a distinction between B and non-A non-B. Then one had an HBsAg test that enabled one to identify Hepatitis B and so it was known that there was something else.

A. Yes, I think that's correct.

THE CHAIRMAN: And then out of that came screening, so that the screening would take out of circulation quite a lot of blood that had HBsAg in it, and simply this meant that, in terms of numbers of what would be seen, NANB was becoming more prominent, but not because there was more of the infection about, simply because it was

distinguished in the first place and becoming more clearly identified, in the second place?

A. I believe that's correct.

MS DUNLOP: Yes.

THE CHAIRMAN: The next sentence, of course, is quite important, isn't it, that "the latter form has proved especially dangerous among patients with haemophilia at this stage," as showing a commercial operator recognising the risks associated with NANB hepatitis.

MS DUNLOP: Yes. Can we also look at page 5 of this piece, please? Actually, to get the sense of this, I think we need to look at the page before, please. It says:

"Proof that the heating step is essential ... "

I think this is slightly cut off down the right-hand side: Presumably:

" ... essential [in or to] producing a hepatitis-free preparation was obtained by experiments in chimpanzees ... four chimpanzees, which were given a dose of non-heated Factor VIII concentrate with experimental HBV content had attacks of Hepatitis B."

And then on to the next page:

"The concentrate which had been heated in solution to 60 degrees for ten hours was no longer infectious: The four chimpanzees which were given the heated material intravenously showed no clinical signs of

Hepatitis B."

It goes on to say that:

"As the chimpanzees also remained free from non-A non-B hepatitis, and as the concentrate used for the experiments had been manufactured from pooled plasma, it seems reasonable to assume that any non-A non-B hepatitis viruses had likewise been eliminated and inactivated."

But of course, they couldn't be as sure because they didn't have a test for the non-A non-B virus?

A. That's right, yes.

Q. Then on to the next page, please. Saying that proof that the product was free from non-A non-B hepatitis must await further clinical observations. Then going on to talk about clinical trials in patients.

Can we go back to your statement, please? We were on page 0028.

One of the things that struck me when I was looking at this, given the period of the early part of the 1980s in which it's written, was that the commercial manufacturers are certainly not saying non-A non-B hepatitis isn't really very serious, and PFC is not saying non-A non-B hepatitis isn't really very serious. It seems to be being taken for granted that tackling the hepatitis threat, even if it's a non-A non-B threat

mostly, is something that should be being undertaken.

A. Absolutely. That's why SNBTS set up the Factor VIII working party.

Q. Yes. I think it's perhaps interesting to look in other pockets, which we are investigating, and see views about the severity of the disease, but they don't appear to have coloured the research approach at all.

A. No, I think we were, obviously in the early 1980s, aware that non-A non-B was an increasing problem.

Q. Yes. Right. Can we move on through the statement then, please? There is a reference to the study group meeting in October 1982 and you explain, as I think we have already understood, on page 0029 that the principal reason for prioritising heat treatment was that the other options were being discounted effectively. So it was emerging as the main candidate because of less than positive results with the other options.

A. Yes, that's correct.

Q. Then you go on to explain about the protocol, the 60 degrees for ten hours being proven in the context of albumin. And of course we understand that there is a frustrating quality to the use of particular stabilisers, that some stabilisers may well stabilise the Factor VIII and enable you to heat the product but at the same time they may stabilise the virus too. So

you are not really any further forward. You need to find a stabiliser that preferentially stablises the Factor VIII and not the virus?

A. That was always the trick.

Q. Yes.

A. Or at least you got substantial heat inactivation of the virus but with minimum reduction in potency of the product. That was our target.

Q. Yes. On to the next question. The autumn of 1982. And then you answer on page 0030 a question in relation to communication between Scotland and England. You say:

"There was always good communication between SNBTS and colleagues at BPL Elstree and PFL Oxford."

Did you have a counterpart in England with whom you liaised?

A. In the early days with Dr Smith himself because, as I said, here he was my boss initially when I joined SNBTS, but the most likely person I liaised with was Terry Snape, who was the quality manager designate in PFL and then moved to BPL.

Q. Right.

A. And later with Dr Harrison who developed some of their virus inactivation validation techniques.

Q. At what stage would Dr Harrison come on the scene? Is that later in the 1980s?

A. 1985/1986, something like that.
Q. And you talk about some correspondence in 1982 and the meeting in December 1982, which I don't think we really need to go into again. I think we understand what the different dilemmas were around about that time in relation to the advent of commercial heat-treated product.

Can we just look at the next page, please, 0031?

I hope we didn't create a fog by asking the question about whether there was a "not" missing from Dr Cash's letter but Dr Cash was initially, I think, willing to believe that there was but we have had Dr Perry's explanation of what he thinks Dr Cash was saying and you, I think, align yourself with Dr Perry?
A. Yes, I read Dr Perry's statement in his witness statement and I agree with his interpretation but ultimately it's Dr Cash that wrote the letter.
Q. Yes. Of course. It's a form of torture to ask somebody what was in their mind when they wrote a letter in 1982. So I don't know that there is anything else to be gained from pursuing that?
THE CHAIRMAN: Have we reached a consensus that there should not be a "not"?
MS DUNLOP: The weight of the evidence, sir, is that the "not" is not missing.

THE CHAIRMAN: It's also the more Machiavellian interpretation of the letter at the time and that might just fit, Dr Cuthbertson.

A. I couldn't possibly comment.

THE CHAIRMAN: No, indeed. I think I have more freedom than you have in that respect.

MS DUNLOP: We followed this chain of events a little bit further and you have commented insofar as you are able. Then into 1983. You think the synopsis in the preliminary report is substantially correct and that the key issues were as described and you reiterate that you always enjoyed good communication between SNBTS and colleagues at BPL and PFL.

Then on to the next page --

THE CHAIRMAN: Just before you leave that, I have spent some consideration time over the last week looking at all the evidence we have had so far on this and it does appear that there was very good cooperation at the scientific and technical level. One might think that there was not the same commitment to cooperation at other levels, particularly at management and perhaps even at regulatory levels. Did you ever have any sense of being constrained in your contacts with your colleagues south of the border by policy considerations coming from above?

A. No, not really. I think in those days probably at scientific and technical level we had slightly more freedom than we later had to actually indulge personal communications. I mean, it was well enough known that at senior management level there was not a meeting of minds between the directors of the two institutions but I think we all just worked round that rather than through it, if that makes sense.

THE CHAIRMAN: But it's not just in the public sector. There is evidence that Dr Prowse had very good contact with Hyland, for example, and was able to get intelligence about their process that simply wasn't in the public domain. So one gets the impression that the scientists are talking to each other.

A. That's right. We met at meetings and within the constraints of commercial sort of restrictions, there was quite free exchange of data and information.

MS DUNLOP: So whatever tensions there were, were really, just so that we are clear about this, Dr Cuthbertson, between Dr Lane and Mr Watt?

A. Absolutely.

THE CHAIRMAN: And they didn't inhibit the scientific work that was going on?

A. No.

THE CHAIRMAN: They were just circumvented.

A. They were circumvented, exactly.

THE CHAIRMAN: Yes, thank you.

MS DUNLOP: Can we move on to the next page then, please, 0032?

We asked firstly about a meeting of the haemophilia and blood transfusion working group on 22 March 1983 and obviously you weren't there, and then we asked also about Dr Foster's memorandum of 3 May and we have looked at that, I think, exhaustively, possibly exhaustingly as well, and the ensuing correspondence, which is covered in question 18. Dr Cuthbertson, you have reproduced in your response on this page Dr Foster's three-stage plan.

A. Hm-mm, yes.

Q. Which I think we understand. You go on to say that an attempt had been made to link this -- that is the expenditure on heat treatment -- with an upgrade to the PFC:

"... to assist in responding to criticisms of the facility resulting from inspections by the Medicines Inspectorate."

I think we understand that that was exactly what was going on. You say:

"This is actually a significant issue."

I just wondered if you could explain a little bit more your comment that this is a significant issue.

A. All I really meant was that -- I suppose the -- I think that linking the two events was perhaps a bit expedient and wasn't actually correct because the Medicines Inspectorate hadn't actually generated any criticism of our manufacturing processes, rather about the building and facilities, and I suppose I just wanted to highlight that the two weren't really linked.

Q. Yes. I think --

A. But obviously, when it comes to funding, you have to play a game and if the game involves you being slightly economical with the actuality, then so be it.

Q. I think we do appreciate, Dr Cuthbertson, that the mention of there being a pot of up to £650,000 would clearly be a factor that would operate in the minds of those presenting the bid for funding?

A. Correct.

Q. Yes. But you say:

"This stratagem clearly was not accepted by SHHD and a separate bid for funding was requested."

I think we now understand that sequence of events.

Sir, this would be a good moment at which to break. If that is suitable.

THE CHAIRMAN: Yes, I think so.

I don't think that Machiavelli, in giving his advice to the Prince, would ever have thought that instilling

skills in manipulation was something wrong.

(10.53 am)

(Short break)

(11.15 am)

MS DUNLOP: Thank you, sir.

Dr Cuthbertson, I would like to go back to your statement at page 0033. That's document [PEN0130025] at 0033. Another point we were trying to probe in 1983 was whether there was in people's minds a read-across from the work that they had been doing to try to inactivate non-A non-B hepatitis, and I suppose all hepatitis in concentrates, whether there was a read-across from that to AIDS. In that connection, can we have a look at [SNF0013730]?

We see that this is a set of minutes of your subcommittee from a meeting that was held on 15 June 1983. The three of you are listed.

In the first place, if we look at page 2, just to bring ourselves up-to-date with what had been happening, we can see a big section on heat inactivation, a progress report is set out there.

I think I need to ask you a little bit about model viruses, Dr Cuthbertson, but not so much that we get confused. I suppose this is Dr Pepper writing but no doubt informed by you.

A. Yes.

Q. You say that:

"As a target virus, vaccinia, as suggested by BOB ..."

Is that Behring?

A. No, that's the Bureau of Biologics.

Q. "... vaccinia is most useful."

Can you tell us a little bit about what vaccinia is, please.

A. Vaccinia is the vaccine for smallpox that was given to most of us in our youth. And it's a fairly large DNA virus and is quite resistant to heat. As such, it was seen as being a reasonable model for Hepatitis B. So what we were trying to do when we selected model viruses was to take viruses that were perhaps not the actual viruses of concern but might mimic some of their properties when we were studying them.

Vaccinia had a significant benefit that we already knew exactly how to culture it because we had been doing so since the 1970s and could get it in particularly high titres. So in the very first pasteurisation study, in the beginning of 1983, we collected that plus herpes simplex, which was another DNA virus, as the two models that we looked at when we were evaluating the efficacy of our heat treatment process.

Q. Yes.
A. And the sort of selection of model viruses actually became almost an industry and people developed different thoughts until eventually there was some regulatory guidance on this in the 1990s, but it was kind of too late.
Q. So in the early years of work with model viruses, there must have been a degree of guesswork as to what would be the most important characteristics to match, was there?
A. Absolutely. And to be honest, in the early experiments we used vaccinia for the reasons I said because we could actually grow that to very high titres, and that was quite a useful thing because obviously the more you can put into the Factor VIII solution to simulate the heat treatment process, the more inactivation you can actually detect.
Q. Yes. We can see some results here. These are log kills for vaccinia polio 2. What is the significance of the 2?
A. It's polio virus type 2. There are just various different forms of polio virus.
Q. And herpes simplex. I understand the theory, that you are trying to find viruses which are as closely analogous to the agent that you are trying to kill as possible but I suppose in their own right, these

experiments are also interesting because they give you comparative success rates for different protocols?

A. That's correct. You can use them to try and determine the efficacy of the heat treatment process, and the sort of statement down there about 60 degrees for ten hours followed by a 30-minute period at 70, that was a protocol that we evolved because the initial evaluation was that the sucrose or sorbitol stabiliser, sucrose as used by Behring or sorbitol as used by us to get round the Behring patent, did in fact stabilise viruses to heat, whereas in albumin, if you added vaccinia virus, you could inactivate seven or eight logs within an hour, at 60 degrees for -- and Factor VIII stabilised by sucrose and sorbitol, then even over a 24-hour period you got significantly less inactivation than that. So we evolved this protocol where we added in an extra 30-minute period at 70 to get the same degree of kill as we had seen in the initial studies in albumin.

Q. Right. Trial and error?

A. Kind of.

Q. Yes. Right.

THE CHAIRMAN: Was 30 minutes the maximum it could tolerate?

A. Without losing significant amounts of Factor VIII, yes. But it proved to be effective and the protocol that we

evolved was heating it to 60 degrees first and then raising the temperature to 70 for half an hour.

MS DUNLOP: I think even trial and error has been renamed in some quarters because I have heard it described as "guess and check".

A. What we effectively did was we heated at 60, we heated at 70, and obviously we found that 70 was much more effective in inactivating viruses but still retaining some Factor VIII activity.

Q. Yes.

A. So it's a bit more scientific than just guesswork.

Q. I'm sorry, I didn't mean to be insulting.

Can we scroll down through this, please? Then comfortingly, I suppose, no evidence of neoantigens. Perhaps if we can quickly move through the other reference I want to take from this, which is on page 5, but if we just have a look at the other pages on our way.

Other non-heat treatment. Then if we scroll down that, please, and then on to the next page, page 5. This is actually a section that we have quoted in the preliminary report because this whole section is entitled "AIDS".

It seems clear from this, Dr Cuthbertson, that your subgroup at this point is seeing a read-across from the

work that you are carrying out to the new and emerging threat of AIDS. Is that right?

A. I think that's right. I mean, in the time this was written, it still hadn't been proven that this was a viral agent but I think, if you were to ask most experts, then there was a strong belief that it was likely that it was so. And so we were just speculating in that meeting as to what we might have to do if it proved to be one of those viruses that was particularly resistant to heat.

Q. Yes.

A. As it happens, it turned out it was a virus that was not particularly resistant to heat, which was very fortunate.

Q. Yes. So insofar as other witnesses have suggested a kind of compartmentalisation where we do not need to think about AIDS because we are working on hepatitis, it wasn't really like that?

A. Basically, as we have said already, this was a kind of think tank-type committee and we were obviously having to think of what the worst possible outcome was.

Q. Yes.

A. And it was conceivable that processes that inactivated non-A non-B hepatitis would be insufficiently robust to inactivate AIDS and that's really what the thrust of

this bit of discussion was.

Q. Yes. Can we go back to the statement, please? That's [PEN0130025] at 0033.

We talked about the renewed contact with Professor Johnson, which I don't need to ask you about. The next page, please, where the departure of Mr Watt is covered. In paragraph 21 I just wanted to ask you one question, Dr Cuthbertson. You say:

"I do not believe that his planned resignation slowed down the development programme."

I just wondered if you had expressed it like that to draw a distinction from his sudden departure, which was at the end of 1983?

A. No, I think neither really had a huge impact. Mr Watt was a figurehead leader, I think other people have probably expressed, and he was brilliant at pushing things forward but his team were empowered to get on and do the work and I think we just continued to do that in sort of tribute to him, if you like.

Q. Yes. You then say in your answer to 22 that:

"Prior to his departure, it was well known within the PFC management team that the relationship between Mr Watt and Dr Cash was not especially harmonious."

I just wondered who was in the PFC management team at that point?

A. Well, there was himself, Dr Perry, Dr Foster. There was a chief engineer, a Mr Lines.
Q. Was it the same as the heads of department?
A. Yes.
Q. Right.
A. I can't remember who else. But those were the key players.
Q. So quite a small group?
A. Mr Grant, the head of manufacturing. There was six or seven.
Q. I see. Can we then move on to the next page, please? 0035.

You make some reference here to this amended protocol, if you like. So rather than a straight ten hours at 60 degrees, the idea of nine and a half hours at 60 degrees with 30 minutes at 70 degrees.

I just wanted to look at a letter from that time, which is [SNB0073841]. This is Dr Foster writing to Dr Smith on 23 August 1983, just bringing him up-to-date with what has been happening at PFC, in particular in relation to Factor VIII.

I think this is the same work as you were describing a minute or two ago, is it, Dr Cuthbertson?
A. Yes.
Q. We see that at the bottom of the letter. Your

time-temperature, is that? Time-temperature study?
A. Yes.
Q. "... of vaccinia Factor VIII is virtually complete. We found that Factor VIII concentrate survives fairly well for up to an hour at 70 degrees."
So it was that that made the bolt-on of a short period at a higher temperature attractive, was it?
A. That's correct.
Q. Yes. And at that point the regime is described as nine and a quarter hours at 60 degrees and three quarters of an hour at 70 degrees. So a bit of tweaking at the margins?
A. I think that's correct.
Q. Yes. On to the next page, please.
You are still looking at other viruses but you had yet to find anything as stable as vaccinia. So vaccinia not easy to work with perhaps but reasonably straightforward?
A. It was, yes. Unfortunately we did find one that was more stable and that was mumps. So we did later do more work with a different virus.
Q. You did more work with mumps?
A. Yes, which was actually interesting because it is very easily inactivated under normal conditions but the stabiliser seemed to stabilise it preferentially. But

we still managed to get a substantial degree of inactivation.

Q. Is mumps a DNA virus?

A. No, it's an RNA virus.

Q. It's an RNA virus, right. Okay.

Can we go back to the statement, please, at 0035? You make a comment, which we should note, in your answer to question 24. We had put to you a document from the Central Blood Laboratories Authority and you highlight some thinking in it which isn't quite accurate. Can we look at the document? It's [DHF0024489]. This is the Central Blood Laboratories Authority and I think this is 26 July 1983. The particular passage concerned is at page 3. That's it there in the first paragraph. Heating at 75 degrees for ten hours or heating at 60 degrees for 24 hours, and that's dry heat?

A. Yes.

Q. As I understand it, the point you are making is that the writer or writers of this paper thought that all you had to do was achieve more heat for longer than the existing albumin protocol, if you like, and it's not as simple as that?

A. It's not as simple as that. The reason that freeze-dried Factor VIII withstands heat treatment is because it is freeze-dried and there is not the same

level of water there and the same is true of viruses. You help protect the viruses from inactivation in the same way as you do the Factor VIII. So it's not simply a question of heat and time, it's a question of the stabilisers, the format that the product is in and a whole range of other complex things that lead to the degree of inactivation that you finally get.

Q. And I suppose this is writing of its time?

A. Exactly.

Q. That was the impression that people had but it was subsequently appreciated that that wasn't quite right?

A. That's correct. And it led to a whole industry of virus validation studies.

Q. Right. Can we go back to Dr Cuthbertson's statement, please, at 0035?

You go on to mention the knowledge, which we understand was quite widespread in the summer of 1983, that the Hyland product, despite being marketed as a heat-treated and virally safer product, had transmitted hepatitis to three chimpanzees.

Can we just have a quick look, please, at [LIT0010369]? This is the article from the Lancet in July 1985, at which we have already looked, Mannucci and Colombo and others, and the relevant information is on page 371. So can we go to the third page, please,

where this is described? Can we scroll a little bit down, please?

The reference concerned is on the right-hand side. We see the writers just after the footnote number 9:

"The high prevalence of NANB hepatitis and the absence of HBV transmission in our subjects ..."

That's the people:

"... are in contrast with the HBV transmission and absence of NANB hepatitis in chimpanzees given the same heated concentrate. These differences indicate that the animal model is not reliable for NANB hepatitis transmission studies."

To lay people it is interesting, Dr Cuthbertson, that the results are kind of a mirror image of each other and I do appreciate that the product that was given to the chimpanzees was loaded, as it were, with virus, but even so is it just a physiological difference?

A. I assume so. I mean, the chimpanzee model was obviously established principally as a mechanism for measuring infectivity of Hepatitis B and then non-A non-B became a bolt-on. Exactly why it was such an unreliable model for non-A non-B when it proved to be reliable for Hepatitis B, I assume is physiological variation and all sorts of things that I wouldn't even begin to speculate

on. But it's definitely the case there are a number of chimpanzee studies which showed a lack of infectivity with non-A non-B with products that subsequently were proven to transmit.

Q. Right. Would you not have expected that the people would also have got Hepatitis B or is that just to do with the loading of the doses?

A. I think that's to do with the loading of the doses. Obviously, Hepatitis B is actually a fairly hardy virus, difficult to inactivate. I think we were lucky in the fact that we were able to eliminate most Hepatitis B by screening. So any Hepatitis B that was present in the final product would have been at very low levels and perhaps the heat treatment there was enough to inactivate these very low levels.

Q. Yes.

A. It was also the case that increasingly in the 1980s, haemophiliacs were being immunised with Hepatitis B which obviously --

Q. That was exactly the next question I was going to ask you, Dr Cuthbertson, and I was wishing I had asked a haemophilia clinician: was there a practice of vaccinating patients with haemophilia against Hepatitis B? But there was.

A. As soon as there were reliable vaccines available, and

to be honest I can't remember exactly when that was, haemophiliacs were vaccinated.

Q. Because of the appreciation of this very risk?

A. Indeed.

Q. Yes. Just in passing, Dr Cuthbertson, I have seen a reference to viral interference. At a kind of general level, is it true that if there is more than one virus in a subject they can interfere with each other and perhaps produce unpredictable results?

A. I could only say that it has been known to happen but I'm not an expert on that.

Q. Right.

PROFESSOR JAMES: I think that was a sort of concept that was played with in the earlier days of virology, particularly when HIV came along, that really turned out not to be correct.

A. That sounds fair.

PROFESSOR JAMES: Yes. I think that's how that word kept coming around but nothing came of it really.

MS DUNLOP: Thank you.

Can we go back to the statement then, please, at 0035? Indeed on to 0036.

I think we have already mentioned the safety subcommittee meeting on 15 June 1983 and we have looked at that. Then 25. Dr Smith to Dr Foster

in January 1984, reporting on the English work on dry heat treatment. That leads us into what had been happening in Scotland insofar as dry heat treatment is concerned, and you deal with that in your paragraph under question 25.

It's perhaps most convenient to look at this through Dr Foster's progress report, dated 25 December 1983.

Can we go to that, please? It's [PEN0121500].

We can see that this is Dr Foster's progress report on studies to improve yield and quality of Factor VIII concentrate.

Perhaps we should just move through it quickly. The early pages are not where we need to go at the moment but just to see what the state of play was. This is various process steps or even in some cases, I think, platform technologies. I hope I'm not using that term wrongly. And then on to the second page. This is all about the addition of calcium. We remember that being described in Dr Foster's briefing paper. Then on, please, through 3 and on to 4.

Zinc fractionation and then heat treatment. What's narrated here in section 3.2, that's the wet heat treatment that is being discussed there. We can see mumps coming in. And then on to the next page. At 3.4, it is interesting to note that reference to neoantigens.

Last week we looked at some correspondence from early 1983, in which Dr Ludlam was raising concern about the formation of neoantigens and we know that Dr Joan Dawes became involved in doing some work to try to allay those concerns, and that seems to be a report of her work there. Is that right?

A. That's correct, yes.

Q. Yes. Then we see under section 4 discussion of other heating methods, and this is now a reference to dry heat experiments at PFC:

"Initial results suggest that the viral kill is less than that achieved by heating in sugar solutions at 60 degrees for ten hours."

Then if we look on to the next page, please, we can see a table of results but these are the wet heating results?

A. Yes, that's right.

Q. Which correspond to the earlier section in the progress report, I think.

A. Yes, and the thing that's called "improved conditions" is the 60 degrees for nine half hours followed by half an hour at 70.

Q. Right. Are these your experiments? Were you involved in these?

A. I was in charge of doing all these virus experiments at

that time.

Q. Right.

A. They were actually all done in Glasgow at Belvidere because we didn't have virus facilities in PFC and there was, what we called in those days, a "technician", although I'm not sure what we would call him now, who set them up and jointly we read them.

Q. Right. Your dry heat experiments were initially recorded in a handwritten note, which we will just look at to confirm perhaps that we prefer the typewritten version, but the handwritten version is [PEN0121669]. If we look at that, this is your writing?

A. It is indeed. I'm not proud of it but that's my ...

Q. And it's headed up "Dry heating of virus in Factor VIII". To make life a bit easier you have prepared for us a typewritten version of these notes. So can we go to that? That's [PEN0121673]. If we go into the document, you have narrated the steps you took.

A. Yes. As it says in the text, this was an experiment that was done jointly with Dr Pepper. It was basically done to see whether dry heating would give equivalent inactivation to what we were seeing in the liquid process. So if you like, it was a kind of a control. To freeze-dry the product to do the study, we had to use a research drier that Dr Pepper had in his laboratory.

So the first seven comments are really just the way that the experiment was carried out and the results section are a very crude summary of the results that we got.

Q. We can see number 1, which is striking as an immediate practical problem?

A. Yes.

Q. That once the material had been heated at 70 degrees, it was insoluble?

A. Indeed.

Q. Yes.

A. And obviously we chose 60 and 70 degrees because they were the temperatures that we were using for the pasteurised product.

Q. Yes.

A. So we were trying to get a comparator and ...

Q. And again you are using vaccinia and mumps to see what the viral kill is. Is that right? Then if we look down through, we can see you tabulate the results. If we go down to the bottom and on to the next page, please.

We have results for mumps and results for vaccinia, and I think we will just take your word for it that if we studied these for a while we could ourselves, I hope, understand that the viral kill was less?

A. Basically, it was a serial titration, where you did a number of dilutions at ten-fold dilution series and

then inoculated them into tissue culture and the vaccinia virus kindly produces plaques for every virus that was in there. So we are looking at a 10 to the minus 4 dilution that had an average of 57.5 plaque former units in the inoculum of 0.1 of a ml. And after 60 degrees for three days, that had reduced to about 39, which was effectively a 3 log reduction, whereas in the product that we were looking at, the liquid product, we were looking at an 8 log reduction.

Just to put that into perspective, an 8 log reduction means 100 million viruses per inoculum being inactivated, whereas this shows about 10,000 viruses per 0.1 ml being inactivated.

So the difference in them, because it is a logarithmic scale, is enormous. So it was a much less effective virus inactivation process than the liquid process that we were studying and for that reason we kept going with the liquid process at that time.

Q. Yes. Can we go back to the statement, please, at page 0036? Just to note in passing that around this time there was also the clinical trial of batch NY761, and we know that one of Dr Ludlam's patients had an adverse reaction. We have asked a number of questions about that.

Just by way of follow-up to that little episode, you

have directed our attention to a further letter, which we will just look at. It's [SNB0074147]. This is Dr Foster writing to Dr Ludlam on 10 February 1984 on this topic, and I think really just wondering where to go next as far as the clinical trials are concerned.

A. Yes, that seems to be correct.

Q. Saying, "We have got a better batch now available". And I suppose asking some questions of himself really, as to why the results differed between Glasgow and Edinburgh. Not terribly keen to keep using this particular patient as a guinea pig. And can we just look at the end of the letter, please, on the next page. Can we go back to the statement, please, at 0037?

We are now reverting to the answer to our question about the possibility of changing tack, around about the turn of the years 1983 to 1984. And you have already mentioned this, Dr Cuthbertson, that there really were very much more positive results available in Scotland for the wet heating method than anything that you could discover about dry heating.

A. That's correct.

Q. Certainly as far as viral inactivation was concerned, and Dr Foster also made the point to us that the data from PFL didn't actually include those sort of tests. The use of model viruses to work out what the kill would

be?
A. No, they didn't have access to that technology at that time.
Q. Sorry, they didn't?
A. They didn't.
Q. They didn't, yes.
A. Which is why later on we did some experiments for BPL.
Q. Yes. In relation to their severe dry-heated product, yes?
A. That's correct.
Q. Yes, we will come on to that. We should just look at [SNB0074059]. Just to get it in. This is the Factor VIII study group meeting on 12 January 1984 and this topic is discussed. If we look at page 4, please. You were there but only for the morning. If we go to page 4, is it you? Did you present these results to the group at this meeting?
A. I assume so, yes.
Q. Right. So pages 4 to 5, I think, set out the position.
A. I think that's just a summary of the results we had had at that time.
Q. Yes. And on to page 5, please. Right down, please.
So around this time the answer to the question about changing tack was that there wasn't anything that made you want to change tack, and you have explained why that

was?

A. That's correct. Of the two processes, it was clear that one gave a much better degree of virus inactivation and that was the horse that we were backing at that time.

Q. Going back to the statement at 0037, we asked some more questions about costing and timescales and I think we could perhaps just take your answers on these matters as read. Perhaps we should note, though on the next page, this is very minor Dr Cuthbertson, but I think the timeline was probably being set slightly before April 1984 because the meeting of the Blood Transfusion Service subcommittee was in February 1984.

A. Okay.

Q. You have made the point earlier in your answer that:

"Nowadays it's believed that the development of a new process, from development through clinical trialing to final licensing and routine issue, will take of the order of five years."

So quite a significant increase in time taken since those days?

A. Yes, principally the regulatory process is very lengthy, and quite rightly so. New products need extensive clinical trialing and development to demonstrate that they are safe to be administered to patients.

Q. Yes.

A. So, yes, to get a licence now from inception to completion, in some cases five years is even less time than it might take. So we were actually working at pretty fast tracking in those days.

Q. Yes. I think the next few answers we can take as read also. The question about Dr Craske's source of information and then another reference to funding. Just in that reference, however, in that response, I wasn't sure I understood the point you are making in the second sentence. You said:

"Lack of funding could have delayed scale-up once the revised product had been subjected to satisfactory clinical evaluation."

Firstly, are you talking about something which didn't actually happen?

A. All I am saying -- I was saying that -- to actually do the experiments that we did, didn't actually require any substantial funding at all. If this process proved to be clinically effective, then, without adequate funding to deal with the amount of sorbitol that we were planning to use in the process, would have required some funding. So scale-up would have required funding.

Q. Yes.

A. But the actual development of process did not. That's the point I'm trying to make.

Q. Right.
A. But I'm sure if that had been the case, the funding would have been forthcoming.
Q. Can we move on then and look at 31?

We understand that the months at the end of 1984 are central in this story and you refer in your answer, 31, to Dr Foster's report. It's interesting, I think, to look at Dr Foster's report from Groningen just to note something that we haven't specifically studied before, which is the then current rates of infection. You mention this in your answer.

Can we look then, please, at [SNB0086528]? This is page 2. We can see these little tables. We see in the first table the results of anti-LAV tests on various recipients of blood products, which were given at the meeting. And particularly strikingly, Factor VIII recipients in the United States of America and Austria. 234 people tested, of whom 74 per cent were LAV positive.

As we, I think, understand, and indeed Dr Foster had predicted in his memorandum in May 1983, the strongest correlation between the degree of haemophilia and the likelihood of being positive is with those whose haemophilia is severe.

A. Yes.

Q. We also note, interestingly in the light of what's said about Factor IX, quite a high percentage of infectees from Factor IX treatment as well, 39 per cent. Then with Factor IX, again the same correlation, that the patients whose haemophilia is severe had the highest percentage of infection.

So that's just a snapshot at that point in the autumn of 1984.

A. Yes.

Q. Can we go back to the statement, please? At 0039. We are now talking about the group of patients who have been described as the "Edinburgh cohort". Question 32.

You mention the preparation of a paper and that was looked at by the Inquiry in June. On to the next page, please.

I think we all understand that PFC did move very quickly to introduce dry heat treatment and the circumstances of that have already been rehearsed. But you point out to us in your answer 33 that really it's quite a complex picture. You say that the data in this report -- that's the studies that were done with the assistance of Cutter and they were mentioned in the MMWR -- we have looked at that -- as a sort of preliminary communication, and then there is a full publication in 1985. You say that those data were never

replicated.

A. No. Well, the Cutter study, which was then fully published by MacDougal et al in 1985, talks about almost total inactivation of four logs of HIV in two hours, and talks about basically, therefore, they extrapolated that degree of heating to show, or to infer I suppose, that 20 hours at 60 or 68 degrees would give something like 40 logs of inactivation of HIV.

That study was replicated in a number of laboratories and the degree of inactivation, after 24 hours at 60 degrees, varied from one and a half logs to about four. So it would appear that, because probably it was done in a laboratory with a freeze dryer that may not have exactly replicated the conditions used in manufacturing, that they contrived to produce a product that was particularly susceptible to inactivation of HIV.

So in some regards we were very lucky that that was the finding because that encouraged us, as an organisation, to introduce heat treatment very quickly.

Q. Yes. You instance as factors which can affect the degree of viral kill: residual moisture content of the freeze-dried Factor VIII and product formulation.

A. The only significance of this, I suppose, is that one of the products, which was manufactured by Armour, which

was heated at 60 degrees for 30 hours, subsequently did actually transmit HIV and was withdrawn. So, I suppose they were unlucky in that they had a particularly dry formulation and presumably were able to protect, in effect, the HIV to some extent.

Q. Yes.

A. So we were lucky, I guess, that we had quite an aggressive Factor VIII freeze-drying cycle, and it would seem that we did actually get reasonable inactivation of HIV in our process.

Q. Do you think part of the explanation for the Armour problem was that they had a particularly dry formulation?

A. Yes.

Q. Right. So, what, having a tiny bit of residual moisture content might actually help?

A. There is no doubt that that's the case.

Q. Yes. Moving on to 34, Dr Cuthbertson, we are interested in trying to tell the story of this period as accurately as we can and I know that you have seen other documents and you have probably had conversations with other witnesses about what people's recollections are of that little period of time at the end of October and beginning of November 1984.

A. Not recently, but we did when we put together that

particular document.

Q. Right. I'm interested in asking you, not a great deal about it but I do want to ask you about your own personal recollection and if you could try, if you would, please, to put out of your mind what others may have said or any prompts you have had, and tell us: do you have a personal memory of discovering that there had been infection of patients at Edinburgh Royal Infirmary?

A. I can remember two events very clearly. The first is that Dr McClelland phoned me and told me that there had been infection found, or evidence of infection anyhow, in three Edinburgh haemophiliacs. It was definitely Dr McClelland, and I remember that quite clearly.

I also remember clearly a meeting with him and Dr Perry approximately a week to ten days later, where we went through the analysis that he had done with Dr Ludlam, which showed, of the 16 that had been identified by that time, which batches they had received. I can actually remember that without recourse to any written documentation.

What I can't recall from memory is whether Dr McClelland phoned me before or after Dr Perry and Dr McClelland went to Groningen, which is, I think, the question you are trying to get me --

Q. Yes, you are ahead of me.

A. I cannot honestly remember that detail.
Q. Yes. Dr McClelland didn't go to Groningen. He was off sick.
A. Yes, but I mean, in the paper that we submitted it says that Dr McClelland contacted me on 1 November with the batch that was given to those three patients. It also says in that note that we then recalled the batch. What actually happened from the note that I have got is that on that date I contacted Dr Urbaniak in Aberdeen to ask him to put that batch in quarantine. So piecing it all together, there was definitely contact with Dr McClelland on 1 November. Apparently he was off sick but I guess he probably still phoned even though he was sick. I presume he wasn't incapacitated. And that we definitely did a formal recall of the batch on 7 November. So I'm assuming that the meeting that we had had with Dr McClelland to analyse the breakdown of the 16 recipients must have been on the 5th or the 6th.
Q. Right.
A. And there was at least one previous telephone conversation, and whether that was the first or second, I can't honestly remember.

So to piece it all together, to make it all fit, then Dr McClelland must have contacted me when Dr Foster was still around with the general information, phoned me

again on 1 November with the details of that particular batch and then we had, as I said, a meeting the following week, where we reviewed -- I couldn't call it a spreadsheet, it was a handwritten note that he had prepared, which showed which batches each of the 16 patients had received. And that, as far as I can recall, is my understanding of the detail of these events.

Q. What about Dr Foster? Do you remember a time when he was not with you but in a room close enough to hear your conversation?

A. Dr Foster has told me this many times over the years but I genuinely can't recall such an event, but I have no reason to believe it's not true.

Q. Right. Indeed.

A. It's certainly true that he was in an adjacent office and I'm sure when the information came from Dr McClelland, that my voice would have risen by several octaves.

THE CHAIRMAN: And decibels.

MS DUNLOP: Can we move on, please, through the statement. I'm happy to take your answer 35 as read. For the most part you are covering ground we have already covered with other witnesses.

Then question 36. You give quite a lengthy answer

and we have also already looked at the detective work that was done when you started to find donors who were positive for the virus after October 1985, and there was a look-back to see what had happen to their previous donations, and we understand that it was demonstrated that none of those donations could be linked to patients becoming infected.

A. That's correct.

Q. Yes. There was an article also published in Vox Sanguinis and we looked at that yesterday. You say on the following page, 0042, that:

"It is clearly true to say that earlier introduction of dry heat treatment could have prevented the transmission of HIV to those patients. The infection of any number of Scottish patients was clearly an individual tragedy for those concerned and I'm very sorry indeed that this occurred. However, it is worth putting this into context."

You say:

"18 out of 32 recipients of the implicated batch developed evidence of HIV infection but if SNBTS Factor VIII products had not been available, then it is certain that non-heat-treated commercial Factor VIII products would have been used and the final proportion of infected patients in this cohort would have been

significantly higher."

You go on to list a number of different reasons why the dry heat treatment process wasn't introduced sooner. Dr Cuthbertson, again, I think we can take this as read. We recognise the thrust of most of your comments. For example, that the virus hadn't been linked to AIDS at the start of 1984, that there was, of course, the unhelpful information from the Hyland product in people, and the chimpanzees receiving Hepatitis B and the patients going on to develop non-A non-B hepatitis with that product, and then there was the neoantigen concern. Then you also mention regulatory constraints.

It does seem fair to say, however, that that wasn't a problem at the end of 1984 and you actually drew our attention to a letter we should look at in connection with this. [PEN0130125]. Can we just look at the heading, please? "DHSS Medicines Division". Dr M E Duncan is writing to Dr Cash following a telephone conversation, 26 November 1984. He or she says:

"May I confirm that the licensing authority wishes to encourage all companies involved in the production of Factor VIII to use a dry heat process in the course of manufacture. We are inviting each company to consider this proposal and hopefully to make early abridged

application for a new product licence."

We know that that did happen with the commercial products early in 1985.

A. Yes.

Q. Then back to the statement, please, 004. You conclude that by pointing out:

"It is only with the benefit of hindsight that it can be concluded that earlier introduction of heat treatment was a sound option. More rapid introduction of dry heat treatment was not justified on the basis of knowledge at the time and we could easily have introduced a less safe product with reduced yield which still had the capacity to transmit HIV. History could then have judged us harshly for being excessively rash in introducing a product too quickly."

In conclusion, Dr Cuthbertson, may we just check your supplementary responses. [PEN0121692].

We can see the questions that were put to you in further correspondence. We have covered number 1, at least for the moment. You have sent a copy of the leaflet that we talked about at the outset. There is then a somewhat embarrassing question for which I accept responsibility, to do with spelling, which we don't need to dwell on at all; it's all my fault.

Then we asked about the experiments in November 1983

and that was the question which prompted you to submit your handwritten notes and very fairly type them up for us as well.

So there isn't anything in those supplementary responses that I need to cover in any further detail.

Thank you very much, Dr Cuthbertson.

A. Thank you.

Questions by MR DI ROLLO

MR DI ROLLO: Sir, there is just one point I wanted to ask about Factor IX and the timetabling for heat treatment in relation to that.

Obviously, as we know, successful heat treatment for Factor IX came in later and what I wanted to ask you is whether any indication was given from PFC as to when that was going to come in. If such an indication was given and if so, what was the timetable that was given, do you recall that?

A. Well, I can't recall exactly in what format that information was given. I'm sure that there was ongoing discussion with the haemophilia directors through the regular meetings that were held. I think they understood fully that we were developing such a heat-treated product and that, as you will know from other witnesses, that involved fairly extensive animal studies before we were convinced that it was safe to

infuse. We pushed that forward as fast as possible but I cannot recall how exactly we informed the treating clinicians of the timelines for its development, other than to reiterate what other witnesses have said, that we did for a period of time stop issuing PFC Factor IX, pending its development.

So I'm sure we communicated that very thoroughly.

Q. Would they have understood that this was something that was on its way reasonably soon --

A. I think so.

Q. Within months rather than years?

A. It was definitely a fast track process and we were, as we said, just tidying away one element, which was the potential thrombogenicity of the product.

Q. So they would have understood that it would be something reasonably soon?

A. Yes.

Q. All right, thank you.

MR ANDERSON: I have no questions, thank you, sir.

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: I have no questions.

Further Questions by MS DUNLOP

MS DUNLOP: Sir, I do want to ask one further question, which I should have asked earlier.

Dr Cuthbertson, just on the matter of recall of

product, we do have some information from Dr Perry but I should ask you too because you were acting up, as you told us earlier, during 1984, as quality manager. Is that right?

A. Yes.

Q. When the Factor VIII heated product was to be given to patients in exchange for their unheated product, as I understand it, the fact that this was the plan was intimated by PFC down the line.

A. Yes.

Q. So what contribution to that did PFC make?

A. Because the distribution chain from PFC was through our regional transfusion centres, in other words, we supplied direct to the five Scottish regional transfusion centres in Edinburgh and Glasgow, Aberdeen, Dundee and Inverness, we did not know exactly to whom the individual vials of product were issued. So we transacted all of our recalls through the regional transfusion centres. So basically, we asked them to recall product, be it whatever it happened to be. They then had the details of who they had onward issued those products to and then they asked for the recall in a chain letter-type basis, I suppose you would say.

So in the case of general recall, there was a letter went from Dr Perry in this case to the regional

transfusion directors and they then transacted the recall from individual haemophilia treatment centres, who then onward requested the return from their patients.

Q. Right.

A. So that was the way it basically worked.

Q. Yes. And with the urgent recall, that is the implicated batch, as it's known, you explained to us a moment or two ago that you actually made the connection with Dr Urbaniak by phone. He was the director in Aberdeen at the time. So that's an example of that sort of contact. You contacted him and he would presumably contact the clinicians?

A. In Aberdeen the situation was marginally different in that they actually did issue it direct to the patients, or direct to the wards for treatment of the patients. So they had very tight control of issues and could recall directly from the ward.

Q. So depending on local circumstances, what happened next would involve the patient at the end of the chain being told to hand back those boxes of Factor VIII that you have in your fridge?

A. For those that were on home therapy, that's right.

Q. For the hospitals it would presumably be more straightforward to get it back from the pharmacy or the

ward storage or wherever the hospital happened to keep it?

A. Although it sounds cumbersome it was actually remarkably effective and people realised the urgency and dealt with these things very expeditiously.

Q. In the Aberdeen connection, we do have a very detailed account -- and I can't remember if it was you personally who prepared it; I think it might have been -- of the product coming back from Aberdeen, and I think pretty much everything is accounted for, save for a difference between two patients. It's not quite clear who had what number of vials between two patients but the overall total is all accounted for.

A. For one of those patients we know that the product was recalled before they were next transfused. So I mean, it was effective in that regard, although the patient unfortunately had already received four vials.

Q. Thank you, sir. It was just that additional matter.

THE CHAIRMAN: Yes, thank you very much.

MS DUNLOP: Sir, I am afraid again I don't have a witness for the afternoon. So it's another shorter day and we have Professor van Aken coming tomorrow.

(12.23 pm)

(The Inquiry adjourned until 9.30 am the following day)

I N D E X