Thursday, 15 September 2011

(9.30 am)

PROFESSOR WILLEM VAN AKEN (continued)

Questions by MS DUNLOP (continued)

THE CHAIRMAN: Good morning. Yes, Ms Dunlop?

MS DUNLOP: Yes. Good morning, sir. Today Professor van Aken joins us again from Amsterdam having not been here since the beginning of March.

THE CHAIRMAN: I hope you have not been missing us.

MS DUNLOP: Professor, we are going to look at two reports you have provided for the Inquiry but before we do that, I thought it would be helpful to remind ourselves of the description you gave of the set-up in the Netherlands, when you appeared in March. So I would like, if I could, please, to go to the transcript for 9 March and look at page 16.

In fact I think we should go slightly before that, on to page 15, so that we can get the context.

We have just established at this point that you are nominally retired and you have many current activities. You go on to tell us that before you retired you were the director, member of the board of the central laboratory of the Netherlands Red Cross Blood Transfusion Service, which, after you left, changed. It's now called "Sanguin". Sanguine Blood Supplier of

the Netherlands. At the time you were in charge, it was CLB. Is that right?

A. That's correct.

Q. And you generally refer to it in your report as "CLB"?

A. Yes.

Q. That's what we should understand by that and you explained at about line 15 the history of the transfusion organisation in the Netherlands, which we can perhaps read for ourselves. I think the next bit on page 16 is really the situation as it was over the period in which we are interested. (Pause)

So the central laboratory undertook fractionation of plasma and certain other activities as well, and you went on to tell us what happens as at today.

You were the director -- and we can see this from your CV -- of CLB between 1980 and 2001. Is that correct?

A. Yes.

Q. At that time you were also a member of staff in the department of internal medicine at the Academic Medical Centre in Amsterdam?

A. Yes.

Q. Can you remind us, please, what duties that position involved?

A. Since I'm an internist -- at least I was an internist --

I was treating patients with autoimmune diseases, like rheumatoid arthritis and SLE, in the outpatient department.

Q. Thank you.

Having reminded ourselves of your personal professional background, I wanted to go on to ask you what is a very basic question, but it's something that I think is useful to clarify because we are talking about heat treatment and we spent a lot of time on the topic of pasteurisation.

It may be that people who read our transcripts or who hear about our Inquiry are puzzled by why it wouldn't be a simple matter, say, to pasteurise blood and I have seen references in comments by those who are interested in these topics to the fact that other countries heated the blood or heat-treated blood and we didn't. So I wanted to ask you: why can blood itself not be pasteurised?

A. Well, this is not an unusual reaction from the lay people to ask, "Why not simple heating blood to inactivate viruses and to make it safer?" But it doesn't take into account the complexity of blood, which is not like milk or beer or whatever substance you can pasteurise, which is just composed of one element, of one protein for instance in milk, but it is a mixture of

cells, proteins, sugars, fats and a number of other smaller components like hormones and things like that. So it would be a simplification to expect that all these various ingredients of blood would stand heating to the same degree as, for instance, proteins would do.

Let's take a blood cell. A red blood cell is composed of a membrane which in fact holds the whole content of the red cell and if you heat it above, let's say, 40 degrees, depending on how the temperature is in fact, it starts to disrupt. The membrane falls apart and the contents of the cell becomes available and starts to clot, because that is again -- haemoglobin is a protein which, when you heat it, starts to clot. So you get one big clump of material, which you cannot further process.

The same holds for the other blood cells, like platelets and white cells. Every time you see the heating, the membrane is very susceptible to temperature increases.

Now, that is just the cell component. The fluid component, the plasma proteins and the other ingredients like fats and sugars, can be heated, perhaps they are not so sensitive to heat as blood cells are but still, if you heat all these proteins, you get the denaturisation, they fall apart in smaller parts in

fact, and these smaller parts react with each other. So you get again a big clump which is not further to process and therefore heating as -- it looks very simple, when you talk about it from the kitchen, for instance, from boiling an egg, but it is not as simple when you apply it to blood, which is a very complicated substance and therefore you have to take into account which substance of blood you want to inactivate and you have to take into account the characteristics of each of these components, how they will react to increase in temperature.

You can modify that. You can influence it, by adding certain substances like, for instance, amino acids or certain carbohydrates or even citrate to make the effects of heating on the protein structure less, but it always remains a risk that you introduce changes in the protein, which affect the function of it when you infuse it in patients.

Q. Right. So any idea of taking the donation of blood in the transfusion centre and subjecting it to pasteurisation is a non-starter?

A. Yes, absolutely impossible. You can do it like, for instance in the previous time I was here we discussed albumin. Albumin is a perfect example for pasteurisation process because it is a simple,

relatively simple protein, and already from the 1940s, we have experienced that if you heat-treat that, you can keep it intact and still make it more safe than without heating.

Q. Right. Thank you.

With that in mind, can we go, please, to the first of your two reports, which is [PEN0121932]. We can see that this is headed up "Penrose Inquiry: Heat Treatment to 1985".

It is perhaps relevant to make the point that we have divided the whole topic of heat treatment into a first part, which goes more or less up to the end of 1984 and beginning of 1985, and then a second part, which will look at the achievement of a concentrate or concentrates in Scotland which were safe against non-A non-B hepatitis. We are going to come to that later in the autumn.

Some witnesses -- and you haven't been one of them -- have questioned whether that's a logical division because the whole project of heat treatment in connection with factor concentrates was conceived in the context of hepatitis and it makes it look as though everything before 1985 is in some way connected with AIDS, and that's not the point we are making. It's just that there seems a sort of natural stopping point, which

one can use to divide up what would otherwise be a very long topic and I think you understand that that has been our approach?

A. Yes, I understand it. For me 1985 is a very useful date to make a split into the report because in 1985 we could simply say that the AIDS problem was largely solved. We knew the virus, we knew that heating was inactivating the virus, and there were techniques available to test, to screen donations for AIDS. So all the measures, like in the past, to make plasma products more safe, for AIDS at least, were available, but for non-A non-B that took much longer and that continued afterwards. But the experience which was collected due to the AIDS problem was also relevant for non-A non-B.

Q. Thank you.

We can see from the beginning of your report that you have been sent a briefing paper, which was prepared, I think, mainly or possibly entirely by Dr Foster, and that's the document [PEN0131309]. We have looked at that already in these hearings. You say:

"It's a comprehensive and precise description and analysis of the developments in several European countries, in particular Scotland, and in North America, concerning this topic during the period of 1981 until 2006."

You give us a little bit of history, and I think we understand that there were many unsuccessful attempts to deal with blood-borne viruses in the period particularly since the Second World War.

You go on to say in the second paragraph that:

"Of the methods using heat, pasteurisation and dry heat treatment were considered to be very promising."

You refer to the pasteurisation of albumin. We know that there was research work by Behring, which started to be publicised in 1980, and I just wondered if, around that time, there was knowledge in Europe of people working on dry heat treatment?

A. As far as I know, the sequence was that first of all people were trying pasteurisation, notably because of the reference to albumin in the past, yes? And when that was not successful in the hands of many people, there was investigations to try to see if you could change the procedure by using dry heat -- that was perhaps successful. And that was in fact because pasteurisation is a process which uses the proteins in a fluid state, which, as albumin has shown, can be very appropriate. So when it was shown that if you apply that to Factor VIII, you get immediately denaturisation of that more complex protein, therefore you get hardly any active Factor VIII at the end of the process. You

start to think, well, would it perhaps for the protein be better if we didn't do it in the moisture state, in the fluid state, but instead, in the dry state? That was, I think, quite a brave move to try that because some people were thinking, well, how can heat be transmitted in the dry state so efficiently to all these molecules in the product?

But still people have been trying it and initially it was thought that it was successful. However, that was based on very preliminary evidence and it was later on criticised and not supported by additional, both clinical and experimental evidence.

Q. Yes, and there you are referring to Hemofil?

A. There I refer to Hemofil but later on other people also have tried to dry heat.

Q. Yes. Can we have a look at one of the tables in Dr Foster's paper, please? That's the paper [PEN0131309]. This is a table that you mention in your paper. I think it's at page 1340, if we could have a look at that, please?

This is table 3, to which you refer. This table summarises the key dates concerning the development of heat-treated coagulation factor concentrates by SNBTS. We can see there ZHT. That work starting on 2 September 1981. Obviously that's the pasteurisation

project.

On to the next page, please.

Then we see the NY products, NY heat-treated, version 1, which was the product dry heat-treated for two hours at 68 degrees, and we have heard about that. We have also heard that very shortly after number NY HT1 was distributed, there was a second product, NY HT2, in which the period of heat treatment was extended from two hours to 24 hours, and we can see that and the key dates are set out in relation to both, then finally we have Z8 and we are going to learn a lot more about Z8 in due course but not today.

Professor, around about 1980/1981, at the time when you became the director of CLB, what was happening in the Netherlands as far as heat treatment was concerned?

A. Well, if I remember it correctly -- we have to take into account that it was 28 years ago, so some of my memory may not have been as good as it was at the time. But we were not as active in doing experiments concerning heat treatment as here in Scotland, to be honest.

We felt first of all that -- sorry, we did some experiments on a small scale and were very unsuccessful. We lost almost all the Factor VIII when we tried to heat in the wet state or in the dry state. So we gave up, so to say. We stopped those experiments, we relied more on

information we got from outside, to see if that could be introduced but it was quite clear that it would be very complicated and would have include changes in the whole manufacturing process.

So we waited and we followed the developments in other countries.

Q. Right. Can we go back to Professor van Aken's report, please, [PEN0121932]?

At the bottom of that page you come on to describe the work by Behring and I thought we had picked up all the papers but I think this may be a sixth documentary reference that you have given us, here referring to a paper that was published in Blut. That's a German periodical on the subject of blood?

A. That's the haematological journal of the Germans so to say. You had Germans from Switzerland, Austria and Germany.

Q. So this work, of which we have already heard a great deal, was also publicised in that journal, no doubt to similar effect, and you go on to talk about the various challenges which had to be addressed and I think we recognise these: increasing the stability of Factor VIII and thereby its yield, getting access to marker viruses and experimental animals, establishing the degree of virus inactivation and avoiding that structural

abnormalities of Factor VIII might occur which could cause inhibitors formation.

We have seen reference to concern about neoantigens and our understanding, professor, is that the worry was that the heating would cause something to form on the Factor VIII molecule which would then cause a patient's immune system to manufacture an antibody. Is that right?

A. That's right.

Q. And then that antibody would stop the Factor VIII from working?

A. Yes, and it would stop the working of Factor VIII and would also require, if you have to treat a patient with such an inhibitor, which is an antibody, then the infused Factor VIII is immediately neutralised because it is just taken up by the antibody, captured and taken away. So instead of getting a certain level of Factor VIII, you will end up with zero Factor VIII and that makes it even more complicated. So you need huge quantities of the product to get a certain level, and even that is only for a very short time. So the treatment is very, very complicated.

Q. And that very unhelpful physiological response is what we should understand when we see descriptions of inhibitor formation?

A. You see, not to be too technical or to make it too complicated, if you look at the structure of Factor VIII, you can see that there are certain parts of the molecule which stick outside, which can't come into contact with cells and with other proteins, and those parts are called "antigens" which, when they are infused or when they are not recognised by the body itself, create the formation of an antibody.

That's the sort of protection of the human body to remove substances like viruses and substances which are not known to the body. Yes? So it is purely a defence mechanism but in this case, if you talk about heated Factor VIII, you get a changed molecule, which is not completely the same as the natural substance, the natural Factor VIII, so the logical reaction of the human body is to consider that it is a foreign substance and therefore create antibodies to it. That is why we are so concerned about neoantigens.

Q. Yes. Against the background of those various different concerns, we know that PFC began their research in 1981, in response to the news from Behring. You discuss that on the second page. So can we look at that, please? That's 1933.

You narrate that in 1983 there were some clinical trials of a pasteurised Factor VIII concentrate and we

know that it was in fact one of Dr Ludlam's patients who had a negative reaction to, I think it was NY761.

So as you say, that batch couldn't be further distributed or tried because of that negative reaction, although I think we know from Dr Foster's paper that they did continue to make other trial batches and go on to try them and you are nodding at that?

A. It was not entirely clear to me what that reaction in that one patient was.

Q. Yes.

A. Whether it was beyond doubt an antibody or whether it was some other reaction, allergic reaction or whatever. But of course, that may be known by the investigators themselves but it was not clear to me from the report what sort of reaction it was.

Q. Yes. I don't think it was ever actually definitively established what the nature of the reaction was?

A. Okay.

Q. It's a mixture of different things, I think, fever in the sense of chest tightness and diarrhoea and different responses?

PROFESSOR JAMES: If I could perhaps very briefly. It seems it wasn't a Factor VIII antibody. The patient received three separate infusions on separate occasions. On one occasion, I think the first, they had an episode of

diarrhoea and the second and third they had a feeling of pressure and tightness on their chest and didn't feel very well in a rather non-specific way. Then Dr Ludlam infused them with normal product but didn't tell the patient that it wasn't the "experimental product", and actually the patient then had no symptoms. So these were non-specific reactions to the product that were more in the nature of an "allergic reaction" but no evidence of Factor VIII antibodies.

A. Thank you very much.

MS DUNLOP: On any view something that had to be taken seriously and we do understand that that was a set back at that time.

A. But I want to clarify, I'm not criticising that they made a wrong decision because I think I would have made the same decision.

Q. Yes. Then you go on through the period from 1981 to 1983 and you say that at that time:

"The commercial industry started the marketing of heated (Baxter, Behring) or chemically (Biotest) virus inactivated Factor VIII-concentrate."

You go on to talk about the meeting in Stockholm, where there was plainly discussion of these developments. Were you at the meeting in Stockholm?

A. Yes, I was.

Q. We have heard a bit about it actually in different contexts. I take it it was an important gathering?
A. It was at a time that everybody was interested to know if there was any breakthrough in the development of how the transmitting of the virus could be prevented, because the virus itself was of course still not known at that time.
Q. Yes. You are talking about AIDS?
A. I'm talking about AIDS, yes.
Q. Yes. Then you go to the next part of the story, which occurred in the autumn of 1984, and you go on to say that:

"At that time it was known that AIDS is caused by a virus, called HIV."

I think you say this later, but not then called "HIV" but subsequently called "HIV", I think in 1986. Is that right?
A. That I'm not quite sure.
Q. We certainly understand there was a lot of debate about what it should be called and there were the rival names, "LAV" from France, and "HTLV-III" from the United States.
A. Indeed.
THE CHAIRMAN: Ms Dunlop, I wonder if I could go back just a little to 1983.

MS DUNLOP: Yes.

THE CHAIRMAN: Professor, we are obviously looking for natural breaks, as it were, events or circumstances that changed the direction of research, and I was wondering whether 1983 might be a point in time at which awareness of AIDS and the need to deal with it may have caused some change in emphasis or change in direction within the research community, away from NANB hepatitis.

A. Yes, indeed. Certainly in my institute but also in various other centres in Europe there was from the very beginning on, certainly in Amsterdam, we started at the end of 1982 already to change to see how we could in fact deal with it.

The first steps were mainly because we didn't know what the substance was, what the agent was, to direct it towards how we could safeguard the blood supply by excluding certain risk donors. So, for instance, male homosexuals with frequent different contacts and those type of risk population.

That was the first step. That was what we concentrated on, and at the same time there was discussion ongoing how to deal with the treatment of haemophilia because we recognised very early already that they were specifically a risk population for developing AIDS after receiving Factor VIII

concentrates.

And that was in fact to discuss with the haemophilia patient population and with the physicians treating haemophiliacs what would be the best policy. And if we discuss later on maybe, we were fortunate enough that there was consensus at a very early stage about how to do this and we got some recommendations, or guidelines, which were made public to everybody, that we in fact wanted to use cryoprecipitate as much as possible, instead of concentrate, for the treatment of haemophilia and that we discouraged more or less -- but that was not CLB but the physicians treating haemophilia themselves -- discouraged the use of commercial concentrates.

That was the first investigations, or at least steps which were taken. In the meantime there was a lot of research ongoing into certain surrogate tests, like, for instance, you have certain lymphocytes in blood which react to this virus and grow, whereas others go down in number, so you could use the ratio between what we call the T3 and T4 lymphocytes to see if there was a patient infected with the virus.

That was in fact one of the items which we concentrated on in 1983.

THE CHAIRMAN: Ms Dunlop, I really had in mind Dr Foster's

memo of May 1983 and the change of emphasis.

MS DUNLOP: The second report deals with that, sir.

THE CHAIRMAN: It deals with it, so you are coming back to that?

MS DUNLOP: Yes, sir.

THE CHAIRMAN: Really I just want to get a feel for whether the arrival of AIDS, if I can put it that way, caused a change in emphasis, and it did for you, as it did for others.

A. Absolutely.

MS DUNLOP: I think it's unavoidable that at some points in the professor's evidence we go back to other topics that we have already looked at, and one of those is plainly the whole use of concentrates and the treatment of haemophilia. For my part I think it's useful just to establish some details of what was happening in the Netherlands over this period in general. So I'm happy to try to do that.

A. Maybe can I just add a bit? This was not what everybody agreed upon, what we did. I remember vividly, because I was in the States quite frequently, that there were two camps more or less. There was one camp which said, well, AIDS will go over, it will be just a transient period. It's just a virus which is around and blah, blah, blah. And there was another group which said, no,

if we are not taking steps now, we face a major disaster, if we don't do anything.

That was not just in the US but also some people in my country followed that line and said, well, what you are doing is just self-interest and we will see what happens later on. So it was not a unanimous opinion there. That should be taken into account, that there was a certain period of uncertainty.

THE CHAIRMAN: That, of course, is very important but we are trying to get a picture of what the international scientific community was about, and differences of opinion are very important to know and understand.

A. Yes.

THE CHAIRMAN: So, Ms Dunlop, I really do not want to interrupt your programme, as it were, more than necessary, so I'll leave it to you to decide what should be followed up.

MS DUNLOP: Thank you, sir, but I'm certainly conscious that as we go through, there are lots of tempting diversions.

Just to stay with the narrative that you have given in this report, professor, of PFC arriving at the issue of dry heat-treated product for Scotland in December 1984, we see that paragraph in your report, and you say that:

"The first dry-heated Factor VIII concentrate

prepared by PFC was issued for clinical evaluation one week later. Distribution started for routine use in haemophilia treatment. All non-heat-treated Factor VIII concentrate was recalled."

You then refer to table 1 in Dr Foster's paper, which gives an international perspective, and you have added in some countries yourself. Can we have that table then, please? We are going back to Dr Foster's main briefing paper, [PEN0131309].

Table 1 is on page 1327. We looked at this last week already, professor, and we can see the different countries tabulated there, with comments about their position as far as heat treatment is concerned.

I'll keep your report but I think we will keep the table.

The first country that you suggest adding in is Ireland. Ireland changed in 1985 to imported heat-treated Factor VIII and you refer to the report of the tribunal of inquiry in Ireland, which is usually known as the Lindsay Tribunal. So if we could perhaps just have a look at your reference there. This is not something we have in court book because it's on the Internet and there it is.

Particularly, please, if we could, pages 66 and 67. We see the heading "Heat Treatment" at the bottom of

page 66. We see the reference to Professor Temperley, who I think was a haemophilia clinician in Ireland and we can see what happened there. The BTSB is of course the Irish Blood Transfusion Service.

The tribunal commenting on a lack of initiative by the Blood Transfusion Service in Ireland in respect of heat-treated commercial products. Then if we just read on a little bit further down. (Pause)

I think this provides for us a contrast with what happened in Scotland.

A. Yes.

Q. It does tell us, just at the very top of the screen now, that:

"Unheated commercial products were replaced with heated products with commendable speed."

So once action commenced, the replacement was swift:

"In the case of Factor VIII by January 1985 and in the case of Factor IX by February 1985."

That reference to Factor IX is interesting because that again provides a contrast with Scotland because the PFC didn't issue heat-treated Factor IX until the autumn of 1985 and we understand that here a decision was taken to conduct thrombogenicity studies on the heat-treated Factor IX. Do you think that that was a reasonable step to take?

A. Going back in history, I was thinking 1981 or 1980, I was here in Edinburgh to discuss with Dr Cash studies which he was doing on the thrombogenicity of Factor IX products, both thrombin and Factor IX concentrates. So I know that already at that time that was an issue. It was not just an issue here in Scotland, it was an international issue because thrombogenicity was a side effect of some Factor IX concentrates, which was worrying because you were treating a patient who was bleeding and instead you got a thrombus. And at that time it was very unclear what the cause of that thrombogenicity was, whether it was something in the product which had to do with Factor IX and whether it was related to some impurity. It was not clear and so it was, I think, from that point of view, very good that somebody here was doing studies and had an animal model to study this effect, which we were also interested in.

And I know that the real cause of the thrombogenicity was only later on found out, when it was clear that it was related to mostly commercial concentrates, which in fact were composed, which were derived from plasma which was of a lower quality than the quality of plasma which was used by most fractionation centres. That was due to the fact that they just pooled various stocks of plasma which were

collected and not used immediately, and therefore you could imagine that there was some denaturation going on in those stocks and it was demonstrated that activation of clotting factors had occurred in some of these batches, and that activated clotting factors were also infused caused the formation of thrombus.

But that took some time before it was found out because it was not clear because the source material that was used for it was so different. So I think that the decision here to not go immediately for heat-inactivated Factor IX but instead take into account that the possibility of thrombogenicity was a correct one.

Q. I think you have told me that there is a wealth of literature on the thrombogenicity of Factor IX, particularly from commercial sources. Is that correct?

A. Yes, there is quite some interesting literature on it and on how that whole discovery of what it was was proceeded over the time.

Q. Thank you.

The next country which I thought we should mention would be the Netherlands and you actually tell us in your report what happened there, that the national fractionation centre -- and that's CLB:

"Signed a technology agreement and patent licence

agreement with Baxter Travenol of the United States in October 1984, and in June 1985 CLB introduced dry heat-treated Factor VIII concentrate when the regulatory authorities had licensed the product."

So we should understand from that, should we, that in the Netherlands your laboratory, CLB, paid to use Baxter's technology. Is that right?

A. Yes, we had a very long discussion with Baxter about -- this started in the beginning of 1984. They wanted initially that we would completely shift to their product, which we refused and then negotiations were difficult. In the end we agreed that we would pay for the licence and that we would send somebody over to learn how to do the heating, which they employed and that was introduced later in 1984. And not just for Factor VIII concentrate but also for cryo because the licence agreement also stipulated that we had to take into account that if we could not supply sufficient Factor VIII, that they would support but he said they would be able to import -- or to sell their own product.

So we were quite sensitive, a bit nervous about how this whole deal would go on, but it was for us the only way to have a rather quick introduction of this technique without going through the whole development state and all the disasters and all the negative

effects.

Q. Right. So looking at that table, we should add the Netherlands in for June 1985, should we?

A. Yes, correct.

Q. Right. Would that be true for Factor IX as well?

A. I think Factor IX was September/October.

Q. Of 1985?

A. It was two months later.

Q. Right. Just remaining, professor, with the position in your country, I wanted to go back to Douglas Starr's book, which has a description of what happened. The reference for that is [LIT0012936].

Perhaps keep the table open but go to Douglas Starr. This is chapter 15 of Douglas Starr's book. You are presumably familiar with Douglas Starr's book.

A. I have read it.

Q. You have read it? Yes. Within chapter 15 I would like to go, please, to page 16. That's our page 16 of this document.

Here we are back in Stockholm in June 1983. I think, professor, there are a number of meetings which have cropped up in our hearings at which we all feel we were personally present by now. This may be one of them.

So the meeting in Stockholm in June 1983. We can

see what happened there between Dr Evatt and Dr Aledort. Then there was an attempt to pass a resolution about future treatment of haemophilia. And a Dr Shelby Dietrich, who was an enthusiastic Factor VIII proponent.

Can we look on to the next page, please?

We can see Dr Dietrich's suggested wording at the end of the first paragraph and we see from the next section that according to Douglas Starr, the wording of this draft outraged the Dutch representatives.

I suspect that the names quoted in that paragraph are known to you, are they?

A. Yes, all people are known to me.

Q. Yes. When you were in Stockholm, do you remember knowing of this controversy between Dr Dietrich and Dr Aledort and Dr Evatt?

A. Yes, I know -- I remember the discussions which took place in various committees about what is written here. So that was a heated discussion and it just illustrates what I said earlier, that there was not a common opinion about it, whether or not the treatment should change, whether preference should be given to product from whatever source or whether it should be only safe products which would be distributed.

So I remember that Dr Evatt from CDC, who was clearly a very careful and very cautious epidemiologist,

working in CDC, was very afraid that the virus would spread and that more and more people would be contaminated and infected with it. Whereas Dr Aledort had a different opinion and was feeling that it would be a disaster if patients would have to go back to former treatment, with all the injuries and handicaps which would then surface again.

So that was in fact where the dispute came down to.

Q. Yes. Douglas Starr says that:

"In early 1983 Dr Smit --"

A. Yes.

Q. "-- had convinced Dutch medical authorities to curtail severely the use of imported Factor VIII. Now he and his countrymen tried to persuade the World Federation to take a more cautious approach to use of the factor."

So is this an accurate description of what happened in the Netherlands?

A. Yes, indeed. He was very influential. He was a haemophilia patient himself. So he represented the Haemophilia Society in Holland. He is a very intelligent and a brave fellow. He is still alive and he has never hidden his opinion under the table, so to say, he is always outspoken about what he feels, and in fact he is recognised as one of the few haemophilia patients who in fact has represented the community and

has come forward with some opinions which not everybody liked. But you see, the Haemophilia Federation is heavily influenced by the commercial sector. The commercial sector pays mostly for what is happening in the World Haemophilia Federation. So if there is somebody who is saying, "Wait a second, we don't agree with you," and feel that there is commercial pressure behind it, he is not very much liked by the others, but still he comes forward and that is what I was saying, that he is a very brave guy.

Q. I called him doctor, he is not a doctor?

A. No, he is not a doctor, he is a sociologist.

Q. Right. There was far greater use of cryoprecipitate in the Netherlands?

A. Yes.

Q. Yes?

THE CHAIRMAN: What age is --

A. Sorry.

THE CHAIRMAN: What age is Mr Smit now? You say he is still alive.

A. He is now, I think, 64. Well, he is in fact also suffering. He is a carrier of the virus. So he is not just handicapped because of the haemophilia disease but he knows that he carries the virus and he is going through all sorts of treatment courses, all of the

various AIDS treatments he has had.

THE CHAIRMAN: Having taken his own advice, no doubt, as to the product he ought to use.

A. Absolutely, because he is very well informed.

MS DUNLOP: I think we will come back and look in the context of your other report. Look again at the position in the Netherlands, but for the moment we have established where the Netherlands would go in the table.

Could we go back to the table now, please? You talked also in your report about Belgium and we do understand from our hearings before the summer that there was much greater use of cryoprecipitate in Belgium as well. The Belgians never really moved over wholesale to commercial concentrates. You say that:

"In Belgium dry-heated freeze-dried cryo was introduced in 1986 and only several years later did dry-heated Factor VIII concentrate prepared from Belgian plasma become available."

In fact you would put Belgium at the bottom of the table but subject to the explanation that they were using much greater quantities of cryoprecipitate?

A. You see, if you want to understand the situation in Belgium, it is different from the Netherlands and from France because Belgium was completely self-sufficient in plasma. They had a large plasmapheresis programme.

They collected plasma in small cities where they had a station, where volunteers came to have plasmapheresis. So they had ample volumes of plasma to supply sufficient Factor VIII for the haemophilia treatment. And they were very firm in using cryoprecipitate. And in addition you have to take into account that the danger of AIDS in Belgium was maybe also a bit different from the Netherlands because, you see, we had a large community of male homosexuals, notably in Amsterdam, but the Belgians claim their population of homosexuals to be significantly less.

However, that was I think, in retrospect counterbalanced by the fact that they have more people coming from Africa. I'm not certain that that was a good argument, that they had less risky populations there. Anyway, they were sticking to the cryoprecipitate and since they have the Red Cross there that was responsible, has good connection with the government, notably since the chairman of the Belgian Red Cross is the princess of the Royal Family and she went to the government herself to say that they didn't want importation of commercial Factor VIII. They were self-sufficient and they could do it with cryo.

Q. Yes.

A. But then of course, at a certain point they had to go to

do some heat inactivation, and they choose to inactivate cryoprecipitate.

Q. We saw in the Douglas Starr book a reference to a Dutch journalist, is it Piet Hagen?

A. Yes.

Q. And you have worked with Piet Hagen and produced a book for the Council of Europe and needless to say, we have it and there is an interesting comparative table in there about rates of AIDS in patients with haemophilia around Europe.

A. Yes.

Q. Is that right?

A. Yes.

Q. I'm not sure if that table is in our database. We certainly intended to put it in. So we will check again that that table is in court book.

I should also, because we have it, refer to information about Finland, which doesn't feature in Dr Foster's table, no doubt because the situation in Finland is different again, but we do have a statement which was provided by Professor Leikola. It's [PEN0131396]. Can we look at paragraph 9, please?

Essentially, the position in Finland is that the American companies never established a hold on the Finnish market. Is that correct?

A. Yes, that's correct, yes.

Q. So we can see his narrative from paragraph 9 onwards. Finland continued to use cryoprecipitate, 1980 to 1984, simply because there was no domestic concentrate available. But the Finnish Blood Transfusion Service developed its own intermediate purity concentrate, AHF20, in 1982 and 1983 and it was registered in April or May 1984.

It seems here to have been all about timing because in paragraph 10, Professor Leikola goes on to tell us that because of the known, since 1983, risk of AIDS from American commercial Factor VIII concentrates, Finnish haemophiliacs were persuaded not to use imported products should they be introduced to the Finnish market, and commercial preparations didn't come to the Finnish market in the 1980s.

Then on to the next page, please.

Actually we can see really quite a limited use of AHF20 for home treatment narrated in paragraph 12 onwards.

Bearing in mind that very limited use of AHF20, we then note from paragraph 13 that the Blood Transfusion Service did go on to heat-treat AHF20. So that would affect the very small number of patients who were then using it. So in fact there was no recall but we seem to

be only talking about 17 Haemophilia A patients.

So that's a brief examination of the position in some other European countries and some extra information with which to supplement Dr Foster's table, professor.

THE CHAIRMAN: Ms Dunlop, do you have more information on the background to paragraph 14, that's going to come later; Luc Montagnier actually speaking in November 1983 at the WHO meeting?

MS DUNLOP: I don't, certainly not testimony. I can look into that particular meeting --

THE CHAIRMAN: I think it's rather novel information, as far as I'm concerned at least. I haven't seen that before.

MS DUNLOP: I think it's a meeting that was attended by Dr McClelland. I think Dr McClelland went to the meeting in November 1983 and we do have information on it. It was mentioned in the context of B2.

THE CHAIRMAN: It's just I don't remember a presentation by Luc Montagnier being mentioned at all so far.

MS DUNLOP: We have the full report of it so we can look back to that --

THE CHAIRMAN: It would be particularly interesting to discover whether he was rather more positive in anything he said at that time than some of his written material would suggest. I think we know he was really not particularly inclined to make great claims for his own

research when he reported in "Science", and of course his retrospective analysis plays down his own role quite a bit. So it might be very interesting to know what he was actually saying in November 1983.

Were you there?

A. Well, I attended a number of meetings at the WHO but I don't know whether this specific meeting I was attending. I'm not sure.

MS DUNLOP: Well, we are well off track now, sir. Of course it doesn't matter, but according to John Crewdson's book, which I know Professor van Aken is familiar with also.

A. Yes.

Q. Yes:

"Montagnier, at a meeting in Brussels [the date of which isn't terribly obvious], appealed to his audience for help in convincing the scientific world that LAV was the cause of AIDS."

So it's a little bit difficult to establish what happened in that important year between May 1983 and May 1984 so far as Montagnier was concerned. I accept that it certainly appears from a lot of retrospective writing as if no one really put the pieces together until Robert Gallo did. I know it's a little bit more complicated than that, professor.

A. We come to a completely different issue, I am afraid.
THE CHAIRMAN: I don't know that we really want to take on the burden of trying to resolve the differences between Gallo and Montagnier over this. We have seen some correspondence, which was intemperate, let's say, in tone and Ms Dunlop keeps threatening me with the book that she has just had in her hand but so far I have resisted the temptation to try to read it myself.

So there are difficulties in this area and if I don't have to go down that road, professor, I think perhaps I would prefer not to. No doubt some of the gentlemen here will be very anxiously waiting to take me down that road.

The transcript wouldn't otherwise record it but there are shaking heads out there.

So I really don't want to go any further but it would be interesting to know if there were more positive assertions made by Luc Montagnier at a meeting of this kind than are perhaps reflected elsewhere, but it's not you. Professor Leikola will tell us about it.
MS DUNLOP: I think, sir, some of this will necessarily crop up when we look at our next topic, which is the introduction of screening tests, but we did say in our preliminary report that it wasn't necessary for this Inquiry to enter into the debate about who should really

be credited with the discovery of the virus and I think one of the things we did allude to was the ultimate award of the Nobel Prize, which for many people is an interesting clue as to how the matter is seen.

A. As Europeans I think we would support more Montagnier than Gallo, but we are biased I think.

THE CHAIRMAN: I suspect everyone is biased in this particular area.

MS DUNLOP: Can we go back, please, to Professor van Aken's report, which is [PEN0121932] and we are now at 1934.

We have covered the information you have given us about the connections between the CLB and Baxter Travenol and then you go on to say that you accept the statement in the PFC paper, Dr Foster's paper, that Scotland was the first country in the world to provide all patients with Factor VIII concentrate safe from transmission of HIV. Although you go on to say that in some countries commercial dry heat-treated Factor VIII concentrate was imported and used for the treatment of some severe patients before mid 1984 although the evidence that some of those concentrates were safe from the transmission of HIV became available only later.

Then in the next paragraph you allude to another episode with which we are now reasonably familiar, which

is the introduction of heated Hemofil T in 1983 and the discovery that some chimpanzees, which had been used to try out the heated Hyland product, went on to develop Hepatitis B and then indeed that the product itself, when it was tried in patients, caused NANB hepatitis.

That was so despite the experimental finding that it didn't appear to cause NANB hepatitis in the chimpanzees. Do you want to comment on what you think was going on there?

A. With your permission, I would like to go back to the previous paragraph, just to see what I would have said there about Scotland being the first country which was providing Factor VIII for all patients.

I think that needs to be highlighted to a certain extent because when I started to read for this report, I didn't know actually that this was in fact here the situation. I had my own bias, of course, and when I started to read the reports of Dr Foster and things like that, I came to the conclusion indeed that this is remarkable, that Scotland was in fact the first country which was completely self-sufficient in heated and therefore safe Factor VIII at least when it comes to the prevention of AIDS.

And that is not, I think, very well known in other parts of the world, so it was all the critique which, of

course, is connected to an investigation like this. It should also be recognised that this was a real big success in fact, despite all the problems that existed. So I would like, with your permission, just to say that because I think it's fair to say it.

Q. Right.

A. As an outsider, yes? Not being from this country. I think it's fair to compliment them on that success.

Q. Thank you.

A. Now, coming to what you said about the next paragraph, your question was in fact -- can you repeat?

Q. Yes. We have looked at particularly Professor Mannucci's involvement in the trial of this heated Hemofil product and we know that the sequence of events seems to begin in Stockholm again because he was approached in Stockholm and asked if he would become involved in trying the product, and he and several others then began to try the product out. At that point the research evidence seemed to indicated that chimpanzees given the heated product didn't develop non-A non-B hepatitis. Information then became known that the chimpanzees had developed Hepatitis B and then at some point in the autumn, I think September 1983, Professor Mannucci already realised that the product was causing non-A non-B hepatitis in the patients.

To lay people these results seem slightly confusing and I just wondered what your interpretation was.

A. Well, if you talk about chimpanzees, the chimpanzee experiments, you have to take into account that what is done is in fact you use a certain lot in which you know that there is non-A non-B present. It is coming from an infected patient, which has demonstrated beyond doubt that there is indeed this elevation of liver enzymes, which is characteristic for non-A non-B.

So that plasma, which is not further characterised but just on that parameter, is injected in a chimpanzee. So you don't know the actual quantity of HBV, of Hepatitis B and non-A non-B, which is present in that sample but that was in fact also not the purpose of the experiment. The purpose of the experiment was to see if when that lot was inactivated whether there was non-A non-B or Hepatitis B coming from it.

That is one problem with such an experiment. The second problem is how long do you monitor the animal? How long do you continue to follow the animal to see if infectious disease is occurring? These experiments are usually done in Africa, where the chimpanzees live or where they have a colony. So the circumstances under which this is going to happen are not like we are perhaps accustomed here.

So you have to take into account that there are certain limitations in those experiments, and of course the industry was quite happy to know that their inactivation method worked, at least for the chimpanzee, but a lot of people involved in the area knew that this was only part of the whole evidence which we needed.

What we needed in fact was to know the clinical experience, and there again you require certain criteria which you have to apply when you select the patients which you are going to test. This ideally should be so-called virgin patients; that is patients who have not been exposed to blood products before, which of course, when you talk about haemophiliacs is a sort of, well, a rare animal, so to say, to find. Yes?

So it's not so easy to do that and still you need to have convincing evidence. You need to get that population.

That is what Colombo and Dr Mannucci managed to do. They had, in their Lancet studies, selected virgin patients, whereas before, if you look critically at what happened before the study, it was a mixture of all sorts of patients because the main purpose was we want to have results, so long as there is no non-A non-B, it's not detected, fine.

But this was a really scientific experiment. So I'm

not so sure that there is any biological explanation needed to find out what happened here, why is this discrepancy between animal experiments and human experiments? What is the explanation for it? I think it is a matter of dosage, which was not known, what the dosage injected in the animals was, and the dosage which was used in clinical practice. That for me is most likely the reason there was an apparent discrepancy.

Q. Yes. I don't think very many chimpanzees were used, so statistically --

A. It is very, very expensive. There were hardly animals available. There were animal activists which didn't like it. So there were only a few facilities in which you could do this.

Q. Yes.

A. So it's no surprise to me that there were no more animal experiments done.

Q. Right.

THE CHAIRMAN: Ms Dunlop, I think that Professor James has --

PROFESSOR JAMES: I suggested to the chairman yesterday that another reason for this discrepancy is also probably species specificity of the virus. So it's very likely actually that chimpanzees, or that particular strain of chimpanzee even, is just not so susceptible to the non-A

non-B virus that was contained in that blood.

A. Yes.

PROFESSOR JAMES: So that's probably another explanation in addition to the one that you had offered. I don't know whether you would accept that.

A. I would certainly accept that because there are examples where we know that there are these type of differences between different sources which are part of the experiment, yes, indeed.

MS DUNLOP: Thank you.

THE CHAIRMAN: So really it's just another factor that tends to undermine the reliability of what had happened before Mannucci started testing the human clinical reactions.

A. Yes.

MS DUNLOP: Just to conclude that section, you do go on to point out that the protocol, which PFC were using at the end of 1984, 68 degrees for two hours, would be inadequate to activate the agent responsible for non-A non-B hepatitis.

A. Yes, indeed.

Q. Yes. Then you go on to quite a lengthy section about whether PFC should or could have moved more quickly, for example in early 1984, to introduce dry heat treatment of Factor VIII.

I wonder, sir, if rather than starting that we could

have our break now. It's slightly early but it seems like a good point.

THE CHAIRMAN: We seem to have an abundance of available time today.

MS DUNLOP: I hope so.

(10.50 am)

(Short break)

(11.09 am)

THE CHAIRMAN: Yes?

MS DUNLOP: Thank you, sir.

Professor van Aken, we were just looking at that section of your report which has the bold heading. You have answered it by referring us to World Health Organisation guidelines on viral inactivation and you quote from them in telling us that:

"The ability of a process to inactivate or remove viruses should take into account the reduction of virus titre achieved for inactivation processes, the rate of inactivation, the robustness of the inactivation step in response to changes in process conditions, the selectivity of the process for viruses of different classes and validation studies, which need to be well documented."

So this is guidance; we are familiar with the concept of guidance.

Then you go on to give us your answer in this particular context and some of what you say is familiar because it has been said by other witnesses.

A. Hm-mm.

Q. You make the point about the virus at letter A. And we are back to the controversy that we are not getting into. But certainly we know that article in the Lancet in May 1984, and you say:

"Thus, in May 1984 it was likely but not yet definitive that AIDS is caused by a retrovirus, the characteristics of such a virus (such as heat sensitivity) were still unknown. Consequently, if heat treatment for inactivation of HIV would have been introduced in early or mid 1984 or earlier, it would not have been based on evidence but rather on speculations about the origin of the virus."

Is there any sort of a point to be made about the fact that the commercial companies were pushing ahead with heat treatment in 1983, when the science for them was missing and they didn't have full information about the viruses and so forth?

A. You see, I think it is fair to say that they took a pragmatic approach. You could say that they may have argued, "Well, let's heat, why not, yes, and we can later on find out if it can work".

Q. Yes, their approach then must have been different because they moved ahead when for them there were still a lot of unknowns as well.

A. Yes. Well, of course that's the sort of policy you can follow. Of course, you see, you have to take into account that a commercial company is in many respects different from SNBTS or CLB because first of all you have to supply the world, so to say, your markets are all over the place, whereas SNBTS and CLB had just a country to take care of, and that is important because companies can easily, when a certain product is not accepted or not so happy in a certain country, they can move to another country, whereas SNBTS/CLB is just confined to this place and (inaudible). They have to take into account what the attitude is in the country. So what the clinicians, what the patients feel, more, I think, sometimes than companies have to do.

Therefore, I think that if we would have gone to that approach, the pragmatic approach, I would have expected that the haemophilia treaters and the patients would immediately have asked us, "What is the evidence? What is the evidence that you start heating and how do you judge the risks which are attributed to it?"

So we would have had a very difficult discussion when we were doing that pragmatic approach, and of

course everybody knows that if you start with a new method, the initial results may be promising but later on, when the number of patients grows, you see that you get a more reliable figure in terms of what it represents for the whole population, and it is not as optimistic as it looks initially.

So that is what I think this whole topic here is a clear example of. In addition, the conditions of heating were secret, mostly secrets or patented. So you couldn't just say, "Let's do it also like that". No, then you had to take into account that there was a patent.

Very important is also, I think, to mention that there were logistical consequences. Heating meant that there was Factor VIII going to be lost, and of course it depends on which technique was used whether it was very much, like, for instance, pasteurisation or whether it was slightly less but still it had logistical consequences. So if the policy in the country is to be self-sufficient, you have to take the logical steps then to increase the collection or to stick to another policy, like we have done, for instance, with cryo.

So we took, in fact, the position that we went for cryo instead of concentrates, more use of cryo than concentrate, because it was safer. That was clearly

what we could demonstrate, that if you limit the pool from which you make your product to two or four donations instead of thousands of donations, you do not need to be a statistician to be convinced that the risks of the pool are much larger than for a small pool.

So that for us was an important argument that we had both sufficient quantity and that we had a relatively safe product, which was known for a number of years and which we knew it would work.

Then of course we took into account that, like I said in the rest of my report, the inhibitor formation, which we felt was a serious risk and which we didn't know how to handle then. So the pragmatic approach which the companies took can indeed, from the outside, be seen as a, "Well, why not?" but if you go deeper into it, you see a number of things which make it less attractive to follow that pragmatic approach.

Q. Yes. What we were trying to do as an Inquiry was to make the comparison between the end of 1984 and the beginning of 1984, and say that in fact the dry heating treatment which was initiated in Scotland at the end of 1984 used equipment which would have been available, was available, at the beginning of 1984. And I don't think that is being disputed but one factor which is very different between the beginning and the end of that year

is that by the end of that year in Scotland, there was clear information that AIDS was in the donor pool and that was not true at the start of 1984.

So I suppose when one looks retrospectively, that has to have been a relevant factor as well for a country which was supplying concentrates for its own population.

A. That I cannot completely follow.

Q. Sorry, it was too long.

I'm just saying that one of the factors which must have been relevant to decision-making is that at the beginning of 1984 in Scotland, they did not realise that the virus was in the donor population. That must have been relevant to decision-making in 1984. The risk was not a theoretical one but it was an actual one because there were donors in Scotland who were affected by the virus.

A. Yes.

Q. So once you know that that is true, which was the case in Scotland at the end of 1984, that may change your assessment of the action you are required to take.

A. Indeed, yes. That's logical, yes, indeed. You include that factor in your considerations and you think, okay, now we know that there are certain donors which are infected. So our pool is in fact contaminated.

Q. Yes.

A. Yes, that's clear.

THE CHAIRMAN: I think, just if you are doing a standard risk/benefit analysis, if at stage 1 you have a potential risk which you rate relatively low because of confidence in the donor population, and at the end of the period you actually have an emergent real problem, then the risk/benefit analysis has to change.

A. Yes.

THE CHAIRMAN: I think that's the way to put it.

A. I agree.

THE CHAIRMAN: But your long answer suggested really there are some fairly fundamental differences between the approach to be anticipated of a commercial producer and the approach to be anticipated of a public sector producer, operating in a defined geographical area.

I'm not sure we have necessarily got to the root of all that. I suppose the commercial producer would tell you that he was merely responding to a way of countering some of the difficulties inherent in his existing product; he was taking blood from a wide range of sources, some of which were known to be highly dangerous. Here was something that might improve his position. He might say it's just a natural step forward and there is nothing more to it than that, whereas if you are using relatively pure sources, you have

a different approach at a very fundamental level.
A. Yes.
THE CHAIRMAN: It may be very difficult to work this out, Professor van Aken, in retrospect.
A. No, the reason that I -- you see, the pragmatic approach, yes, which you were discussing, from the outside seems quite evident, yes? And I was trying to just formulate some arguments which would perhaps give you a more complete view of what we were thinking about, yes? And indeed, one of the considerations was -- and I didn't include that at this point in my arguments -- that the quality of the source material, which the commercial companies were using, was disputed. It was certainly lower, although they didn't agree with that, than what we had here, both in Scotland and in the Netherlands.
THE CHAIRMAN: Yes.
A. So that would mean that they had to do something to make it acceptable.
THE CHAIRMAN: Yes. They could hardly admit in public that they were using extremely dangerous source material which was exposing all the patients to risk, but pragmatically, I suppose that they would know, as anyone else would, that there were risks and if there was something that was going to reduce that level of risk,

then they would do it.

A. Yes.

THE CHAIRMAN: Without apparently worrying about the production of neoantigens, without worrying about all the other adverse consequences that might arise at that stage or just not giving them the weight that you might have.

A. I think they don't just give them the weight. I think they must have known that these risks existed. I cannot imagine that they would not be informed about that.

THE CHAIRMAN: Well, Ms Dunlop, without access to their research notebooks, I doubt if we will ever get an answer to this question.

MS DUNLOP: Well, indeed.

Professor, we are skipping over HCV for the moment and looking at the next page, where you discuss how scientists at that time were able to validate their processes. I think it's Dr Cuthbertson who said to us that in a perfect world any virus inactivation process would be assessed against quantities of the actual virus. So a researcher would be able to work with the virus and see if the heating protocol that he or she had devised killed the virus but, of course, that wasn't possible until towards the end of 1984, although I think there is some interesting material about people getting

samples of virus and some people getting samples from America and other people getting samples from Paris and so on.

Is that reasonable, that in a perfect world you would want the actual virus you were trying to kill and you would want to research with it whether your methodology was successful?

A. Yes, of course. If you have the actual virus, in this case HIV, eventually the strain which was present in humans, that would have, of course, the preference. But we know that that is not always possible. So the whole concept of the model viruses coming into action, and that depends on which model viruses are the best or fit or match best with the actual virus. That's a matter of what the virologists have to inform us about, to say, "Well, what are the differences and to what extent is it the same?"

Q. Yes, and you explained to us in March that, with the pasteurisation of albumin, it has been possible to work with bovine diarrhoea virus and toga virus, and I think the chairman called them "proxy viruses". These are good proxies for Hepatitis C because, even yet scientists aren't able to work directly with quantities of Hepatitis C and discover if their processes are successful.

A. Hm-mm.
Q. These viruses, as I understand it -- and please correct me if I am wrong -- are good model viruses for Hepatitis C because there are some genetic similarities. Is that correct?
A. That's correct.
Q. But in these days, in the early 1980s, when research was being carried out on hepatitis inactivation and HIV, certainly before HIV had been discovered, any work with model viruses was largely guesswork. So it was about selecting viruses which might appear to have some of the same characteristics.
A. We talked about non-A non-B hepatitis.
Q. Yes.
A. We didn't know whether it was one agent, two agents, three agents, four agents. We didn't know anything about that. There were only guesses about what it was.
Q. Yes.
A. So it was just only after the people found Hepatitis C that it was much clearer and it could be said which model viruses would fit with this actual virus, but before it was mostly speculation.
Q. Yes. We know that in the research at PFC, some of the viruses that were used included vaccinia and mumps?
A. Yes.

Q. For example. Do you have any comment to make about using those viruses as surrogates at that time?
A. No, I wouldn't feel myself qualified to do that. I think that is more for a virologist than for me to do that.
Q. Right. Can we move on again. There is a section about Hepatitis C which we will leave for the moment and move on to the last page of this, please. This is in (iii). You say that:

"Manufacturing, consistency and integrity of the final product with regard to protein function and structure must be demonstrated."

I take it you are talking about, firstly, the fact that the product is still effective. I think that's really what you are saying in the first paragraph that we can see.

A. Yes.
Q. So once you have heated the product, you need to be sure that it's still effective and also that something hasn't been done to it that might cause harm. Is that right?
A. That's right, yes.
Q. You say:

"There are actually documented instances in the literature where heat-treated products had unexpected immuno-genicity and had to be withdrawn from the

market."

A. There are more and more, but at that stage there were a couple of instances in which it was known that inhibitor formation occurred.

Q. Then in your conclusion you are answering the question posed in the negative and you give four bullet points really which underpin your answer. We can perhaps just read those for ourselves. (Pause)

Perhaps we should read the third one where you say:

"Cell lines producing sufficient quantities of HIV and HCV were not available until mid 1984."

It was actually only HIV that was available in --

A. Sorry, that's my mistake. That should be removed. Yes, indeed.

Q. Yes. Professor, can we look at your second report, please, which is [PEN0121928]?

Another event in this piece of the chronology which caused us to reflect is the memorandum that Dr Foster wrote in May 1983, suggesting that the then pasteurisation programme might need to be accelerated, and I think you have seen that memorandum. Is that right?

A. I have, yes.

Q. Yes. You go on to discuss that in this report. Really returning to similar lines of thought, you say that:

"In 1983 it wasn't known how the agent would be present in blood. Heat sensitivity was also unknown."

And so on. You conclude at the end of that paragraph that:

"It was by no means certain that pasteurisation would be a method to improve the safety of plasma products like Factor VIII concentrate."

That is so, professor, but of course at that point Scotland has embraced pasteurisation as the way to go and is researching pasteurisation. So the question really is whether the suggestion that the programme may need to be speeded up and implemented more quickly should have been acted upon.

It certainly does seem to be the case that some who were commenting in 1983 on heat treatment programmes were seeing the possibility that that work was going to have to encompass AIDS. We have looked at some written evidence. Obviously Dr Foster is saying that in his memorandum but we have also looked at an English publication which refers to the possible need to embrace AIDS in the heat inactivation research, and we have looked at a minute of a Factor VIII safety group here which also refers to the possibility that that's going to be required. So it does seem that in 1983 people were thinking heat treatment is not just about

hepatitis, it may have to be about AIDS as well. Is that reasonable?

A. That's certainly reasonable. Lots of people were thinking along that line. What I was thinking about when I got this question is that I remember that there was a number of presumptions at that time about what could be done and what could be the origin of AIDS, and for instance there was stories about antibodies which could be added to the product and things like that. So it is not just pasteurisation. There were a number of speculations, yes?

Q. Yes.

A. And I regard Dr Foster as a very important scientist and I regard him very highly. So I'm not suggesting that this was nonsense, what he was thinking, just the opposite, but it is just that from his background, I think it was logical. He was so long involved already in pasteurisation that I can imagine that you don't want to lose that and just give it up because there is not an immediate result.

So my response to this remark here is just that I didn't see very much evidence that at that time this pasteurisation would work, therefore, I didn't feel myself in a position that I would, in retrospect, feel very supportive of that.

Q. So you didn't think that they were really in a position to move straight to pasteurisation of everything around about this time?
A. Well, they had all the experience of albumin, of course, and maybe of other proteins, of pasteurisation. So I don't dispute that the group didn't have the experience to take pasteurisation further; it was just that I wasn't convinced that this was the way to go for, but that was my bias.
Q. Right. Are you really referring in your answer to the whole initiation of the pasteurisation project, then, from 1981 onwards or are you talking about this moment in May 1983?
A. I found it quite difficult to give a clear or a very explicit answer to this because it is a situation where -- we talk about the speculation, yes?
Q. Yes.
A. And how to judge that speculation in the context of other evidence which was there, and I think for the literature, it appeared that there were some people using pasteurisation, adding n-heptane to it to stabilise the protein. So from that perspective, I could see that Dr Foster's approach could perhaps have been successful if he had continued it. That is not what I dispute. It is just that I -- yes, I feel a bit

uncomfortable to find sufficient arguments for that. I don't see where I would put it in, in fact, so to say. I found this one of the most difficult questions to answer in fact.

Q. Right.

A. Because it would mean that I had arguments to say, "Your speculation is wrong," and the whole pasteurisation issue, as it stands -- as it still stands -- is still, yes, an option, which provided that you have the appropriate stabilising agents to protect the protein and to avoid that it is going to be denatured, that you can still use it. But I don't know sufficient of that development to say, "Well, this was a good approach". So I felt not really comfortable with this.

Q. Right. What, I suppose, we can say is that when you heard the news of the Behring research in 1980 or 1981, you didn't initiate a similar programme in the Netherlands?

A. No. But we were maybe wrong. We should take into account that those conditions would denature the protein, would denature a complex protein like Factor VIII, that it wouldn't work. Again, that may be a bias but that was how we argued about it.

Q. Right.

A. But I think that as at BTS, PFC did far more research in

pasteurisation than we ever did.

Q. Yes, and of course you told us that in the early 1980s, you weren't researching heat treatment at all. So they were in a bigger sense, I suppose, a more general sense, they were working on a project that you weren't working on.

A. Yes.

Q. Namely heat treatment. What you are telling us is that the particular form of heat treatment, pasteurisation, was something that at the time you had a number of reservations about. You thought that there were some significant problems to overcome if pasteurisation was ever to work.

A. Yes.

Q. Is that fair?

A. Yes, but you see, in addition what I said in the last paragraph of the first page is that:

"It should be kept in mind that patient organisations were most afraid about the lack of sufficient products."

Yes?

Q. Yes.

A. Which is connected when you take this approach of pasteurisation, you lose Factor VIII. So you come, sooner or later, to the stage of how I'm going to solve

this logistically, and in Holland the situation was that patients, when we asked them, "Well, where do you put your preferences? Is it first of all absolute safety or is it yield and supply," yes? The answer was sufficient product.

Q. Yes.

A. It surprised us even, I would say that it was so explicit. They said, "Don't do anything to limit the supply", and that affected us going to cryoprecipitate.

Q. It sounds like a truly dreadful dilemma that you would be saying to a patient group, "You can have safe Factor VIII concentrate or you can have sufficient Factor VIII concentrate but you can't have both"?

A. Yes. That was in fact the sort of dilemma -- in an extreme form of course. But certainly in view of all the uncertainties which existed about what would work and what would not work, it was for us clear that we perhaps, if we used cryo, were just in the middle of the two. We didn't have perhaps the best product but at least we could supply sufficient.

Q. Yes. You mention some of the same considerations as being relevant in the summer of 1983. Obviously we know about neoantigens and you refer to that at the bottom of the page. So I suppose one couldn't have taken forward an existing pasteurisation project in 1983 without

robust evidence from clinical trials?

A. Yes, indeed.

Q. You would have seen that as essential.

A. Yes.

Q. Yes. You go on to mention inhibitors on the next page. Then we are back, in the next paragraph, to reviewing the various different considerations operating in the minds of those responsible in other countries, and you say what you have just said about the resort to cryoprecipitate in the Netherlands and you conclude that section by making the same point about yield.

A. Yes.

Q. That acceleration of a pasteurisation programme would most likely have led to a low Factor VIII yield and consequently fewer products.

So really what you are saying in response to the question about the memorandum and whether that should immediately have been implemented or actioned, is that you find that very difficult to comment on?

A. Yes, first of all, because I know that since I was on the board at that time, we had a number of speculations and suggestions by people -- by the scientists, yes? So you constantly had to make a decision about what will likely succeed and what will not succeed, and I can imagine that some people here would have said, "Well, we

are not going to follow that option".

Q. So it wasn't clearcut?

A. No.

Q. Yes. You then go on, professor, to discuss a question which we advanced about clinical trials of commercial products:

"Should PFC have been encouraging clinicians not to let their patients try the commercial heat-treated products?"

I think that is a reference to a view that Dr Cash took at the time. You say you are not very sure what the arguments are. You say:

"In fact, the arguments are not known to me."

But the understanding we have gained from hearing from Professor Cash and reading the material is that at the end of 1982, when commercial heat-treated products seemed to be coming, Professor Cash was anxious that the commercial companies didn't use up all the virgin patients, to use your expression, with the result that there would be no patients left in the UK, in Scotland and in England, on whom the NHS heat-treated products could be tried. Is that a logical concern? That's something that could have happened, I suppose, is it?

A. Yes, indeed.

Q. Yes. But --

A. But that doesn't mean -- as I say, that could occur that I would agree with that position.

Q. What is your response?

A. You see, maybe -- we are talking about two small countries with this relatively small number of patients, and that makes it, of course, for the clinical trials, very complicated.

So I can see his point, that he was afraid to offer -- that they would have insufficient material to do a trial but, as a producer, and as SNBTS and CLB are both producers of products, I always have felt that we have to be very cautious when you were going to direct or try to give directions for what other products, what other commercial products should or should not be used, because you are in a competitive market and in my experience it doesn't work when you are trying, as a manufacturer, to influence. That you have to leave to the government or to physicians treating haemophiliacs, but as a producer that is not your personal responsibility.

I interpreted that Dr Cash was director here of the SNBTS. So he was in fact the director of a producing institution. And therefore I would be more restrictive. I would try other ways to do this instead of so openly giving a recommendation how it should be done.

Q. Right. To go back to the situation in the Netherlands, which you refer to again at the bottom of this page, we can see that there was this cooperation between the association of physicians treating haemophilia patients and yourselves as the producer, and that the consequence of that was a much greater continued reliance on cryoprecipitate. To what extent was the government involved in that?

A. Good question. The government was -- it depends on what level you are talking about. You see, in Holland we have a structure that you have a committee which looks after the safety and availability of blood products -- at that time. It doesn't exist any more but at that time there was a specific committee.

That committee consisted of the director of the National Institute of Health, a pharmacist and somebody else, and they looked at which products were imported, whether they fulfilled certain criteria and things like that. So we also had to give them information about what products we were distributing.

Then they were advising the government. At the government level there was a section which was dealing with this. That section in the government was not interested, and that was later on criticised when the haemophilia population informed the ombudsman about the

negligence at the government level. So the ombudsman started an investigation and in fact, the outcome of that was that the government was criticised for not having paid more attention and more interest into this problem.

So the committee which was advising the government was alert but the next step was not sufficiently covered. And that was in fact what was the situation in Holland. So we had good collaboration between physicians, patients and manufacturers, where there was a sort of information exchange all the time, regularly; every two months there was an update. That information was also largely given to this committee but then at government level there was not very much activity.

Q. That committee is a committee which existed to advise the government?

A. Yes.

Q. Yes. So it was independent of the government?

A. Yes.

Q. Right.

THE CHAIRMAN: Can tell me something about the third member? Was that member also a specialist or a layperson or what?

A. That person in that committee?

THE CHAIRMAN: Yes.

A. No, I think he was -- let me think again who it was. There was a pharmacist -- there was an epidemiologist but he was somebody from the National Institute of Health.

THE CHAIRMAN: So basically three qualified people?

A. Yes.

MS DUNLOP: Who had the licensing function? Was that the government or was that committee involved in the licensing?

A. The committee was involved in the licensing but the government had to license in the end, but at the recommendation for following the advice of the committee.

Q. I see. And actually the advice which you record as having been given by the association of physicians treating haemophilia patients, you have supplied to us but I think at the moment it's only in Dutch so we don't have it in court book, but I think you provided that?

A. Yes, I provided that and the main message of that publication is in fact what I have written here as 1, 2 and 3. And in a sense it comes back to that the recommendation was: if possible use cryoprecipitate. And that holds particularly for newly diagnosed patients and children.

Secondly, if indeed there is an indication for

Factor VIII concentrate like, for instance, a major bleeding or surgery, then you can prescribe Factor VIII concentrate prepared from Dutch origin, but commercial concentrates only when there is a history of side effects following the administration of the Dutch concentrate. And therefore Haemophilia B patients use only Factor IX concentrate from Dutch donors.

Q. Yes. You say there was one blood bank in the Netherlands which used a different policy?

A. Yes.

Q. Yes.

A. Yes.

Q. Excuse me a moment. (Pause)

THE CHAIRMAN: Does that imply a degree of autonomy in the management of the blood bank?

A. You see, at that stage the situation was different. We had 29 blood banks and one CLB, and these 29 blood banks supplied plasma to us for fractionation but this one blood bank took a different position and that blood bank director imported Factor VIII directly to his blood centre and distributed it from there on, which was quite unusual but it was permitted at that time.

Later it was heavily criticised and court cases came on and things like that. So it didn't end up successfully. In fact, patients were not happy with it

and things like that.

MS DUNLOP: This advice, which you have summarised for us in the three paragraphs, that is what was referred to in the Douglas Starr extract we looked at, is it, when it says in that that Cees Smit had been involved, earlier in 1983, in the formulation of specific advice for the Netherlands?

A. Yes.

Q. Is that really what you are setting out here?

A. Yes.

Q. We see that there were two magazines where the advice was published, the Dutch Medical Journal and the magazine "Factor", and that's a magazine for haemophilia patients in the Netherlands?

A. The magazine "Factor" was only for haemophilia patients who were part of the Haemophilia Society.

Q. Right.

A. But that was 98 per cent of the -- almost every patient in Holland was a member of that society. So everybody got that periodical.

Q. And the trigger for those discussions at the beginning of 1983 in the Netherlands was the perceived threat of AIDS?

A. Yes.

Q. Yes. Then we asked a further question about commercial

products and you have given us information about licensing of Hemofil in the Netherlands, but perhaps this could be seen as academic because in the United Kingdom the commercial heat-treated products weren't licensed until February 1985. So our understanding is that there was really very limited availability before that and it would have had to have been perhaps clinical trials or named-patient use, which are the limited ways in which these products could have been used in the UK.

A. Well, I have to tell you that there was a dispute before, because, you see, this was in the 1980s, so before AIDS started we had a situation where commercial companies wanted to introduce their Factor VIII and CLB had tried to prevent that.

Q. Right.

A. And so we felt that the market was going to be endangered by that. So there was an official case for the court and the end result of that was that we were obliged to allow commercial concentrates to be imported into Holland. So whereas initially we would do that ourselves, due to that process we were not any more involved and the market was open.

Q. That position, which we are describing, where CLB had tried to prevent the importation of commercial products,

that seems to contradict what you said a moment ago about as a producer you don't get involved?

A. At that time I was not a director.

Q. Right. Your conclusion about the use of commercial heat-treated products is given at the foot of this page. You say:

"The adoption of commercial heat-treated products in the UK in advance of locally produced products would have been justified once there was sufficient and reliable data from clinical studies demonstrating the safety and efficacy of such commercial products. Hemofil T did not meet such criteria."

In fact we know that it was February 1985 that Mannucci and some of his fellow researchers did publish some evidence that in their trial of Hemofil T there had been no seroconversions to AIDS. So there was some evidence in February 1985 but plainly that's after the domestic product was being heat-treated and it's also around about the time when the licensing authority in the United Kingdom changed its position and began to give licences for those products anyway.

Q. Excuse me. (Pause)

Right. Thank you very much, Professor van Aken.

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: In your evidence you mentioned the links between pharmaceutical companies and the Haemophilia Federation, I think you referred to. Can you just tell me what organisation you were referring to when you mentioned the Haemophilia Federation.

A. Well, the name is the (Dutch spoken) but that is the Dutch, but it stands for Dutch Haemophilia Society, if I make a translation of it, and that is an organisation which is only for haemophilia patients and their parents. It exists since 1968 or something like that. As I said earlier, about 98 per cent of the haemophilia population is a member of that. They have regular meetings. They have a magazine. They lobby towards the government.

Q. This is the Dutch Haemophilia Society?

A. Yes, and they are part of the World Haemophilia Federation.

Q. So the links that you are referring to are between commercial organisations and the Dutch Federation?

A. There are no links to the commercial companies. If that was your question.

Q. Links to pharmaceutical companies?

A. No, no, there are no links. The companies tried to establish links but they want to stay independent. They talk only with us, with the CLB, when the other

companies are also invited. So there is no preferential position.

Q. It's just that you did mention that there may have been influence by commercial organisations over them?

A. Yes, of course, the commercial companies try through various means to influence the opinion.

Q. Right. Can I take you back to your first statement? That's [PEN0121932]. In the first paragraph of that, and this is in the context of heat treatment, you say that:

"Thereafter, mainly due to the growing concern about the transmission of the agent responsible for NANB and later HIV, more intense research efforts about chemical and physical inactivation of viruses were reported."

I want to ask you about the growing concern and what you were aware of at the time about non-A non-B hepatitis and the effects of that. What was the growing concern that you were aware of in relation to that in the early 1980s?

A. The growing concern was mainly related to AIDS and with regard to non-A non-B hepatitis that was at that time more or less, I would say, accepted as a side effect of transfusion and of the administration of plasma components. That had not the same urgency as it gradually got later on because in the beginning, when

I came on board in CLB on the board, that was not the main concern we had. The first real concern about transmission of the diseases, of viral diseases, was AIDS.

Q. The position, I think, you have indicated to us in relation to Holland is that when the concern about AIDS became apparent in 1983, the approach was that imported commercial Factor VIII would not be used. That was the Dutch approach. Is that right?

A. That was what the physicians treating haemophiliacs advised. But there was not a ban on the product so to say. Importation was not forbidden. Some people thought that that would perhaps be necessary but the government didn't want to forbid the importation of commercial concentrates.

Q. We have a document which is a report from the committee of experts from the Council of Europe, a report of a meeting at Lisbon between 16 and 19 May 1983. It's at [DHF0014394]. At page 4398 we will see that there is basically a report of a number of different European countries and under the Netherlands actually there are four paragraphs there. The first three paragraphs deal with, I think, information matters but the final paragraph, says:

"Apart from the above questions, there is, of

course, the one concerning the use of plasma products from areas in which the disease has manifested itself, for example, the United States. Although no official measures have been taken in the Netherlands, the clinicians, for example, those responsible for the treatment of haemophiliacs, have requested that no Factor VIII concentrate from the United States should be used in future."

Does that reflect the position in Holland at that time?

A. I must say that that wording is more stronger than what I said earlier in the official publication in the Dutch Medical Journal.

Q. Right.

A. That was in fact an advice here. It looked as if there was a sort of ban of the product. That was not what was -- as I said, there were indications for Factor VIII concentrate from commercial origin, notably whether there was an allergic reaction to the Dutch concentrate, which was considered to be an indication for commercial concentrate. So this has no exceptions to the rule. And that is what I wouldn't agree to. So I don't know who has supplied this information. It was certainly not me because at that time I was not a member of that committee.

Q. Right. Well, it's perhaps not definitive or necessarily correct but would we be right to understand that in Holland there was certainly a feeling that commercial Factor VIII was to be avoided if possible --

A. Well, yes.

Q. -- at this time?

A. Yes, that's correct.

Q. And there does seem also to have been very much an emphasis on the use of cryoprecipitate at this time?

A. Yes.

Q. And that would be cryoprecipitate that was obtained from a small pool of donors?

A. Yes.

Q. That's right.

In terms of the decision-making process there, the decision to go down the cryoprecipitate route, were patients involved in that decision-making process?

A. Yes, indeed. That was after a meeting between physicians treating haemophiliacs and the representatives of the Dutch Haemophilia Society.

Q. And did there come a point when cryoprecipitate was heat-treated in --

A. Yes.

Q. When?

A. As I said earlier, we started heat treatment of

cryoprecipitate at the end of 1984 and in March of 1985 we supplied heat-treated cryoprecipitate. Before that we had even introduced still another step, that we reduced the size of the cryoprecipitate. We went from four to two donors, to limit the risk even more.

Q. But in the absence of heat treatment, cryoprecipitate was favoured as opposed to Factor VIII products because it was regarded as being a safer option?

A. Yes.

Q. I think there was some mention in your evidence -- you weren't actually taken to this document of Dr Foster's heat treatment Factor VIII strategy. We have seen this before in this section. It's [SNB0073635]. Just looking at that document, I take it you have seen this document?

A. I have seen it, indeed.

Q. Yes. He is referring there to a situation that -- obviously a decision in Scotland had been made to look into heat treatment, to develop that, and then the strategy might be altered because of the new problem from AIDS. What he is saying there is that:

"The possibility that a more serious infection is now involved suggests that we may have to review the strategy."

And the reason he gives is that:

"Haemophiliacs most at risk are the severes rather than the mild and moderates."

He also says:

"There is already evidence of a panic recourse to cryoprecipitate."

In Holland would you describe it as a panic recourse to cryoprecipitate or an informed decision to go down that road?

A. Well, you see the word "panic" would seem to me a bit strong but no doubt there was a discussion once we started to talk with them and give the various options. The option to go for more cryoprecipitate was not what you call really welcomed because once you come as a haemophilia patient from the treatment of cryoprecipitate, you are familiar that you have to go to a hospital to get this product administered, put it into solution, to get it inserted in the needle and things like that.

So once the concentrates became available, that story was suddenly changed to: this you can do at home. You have a syringe, you have a needle. So if you have to go back again to the previous situation, that's what nobody would like to do. Yes? So it took some time and some effort to convince them that this was the option which was probably the best at the time.

But I wouldn't say that there was panic. That would be far too strong. There was a discussion and it was not welcomed but it was accepted.

Q. A different approach seems to have been taken in Scotland and it does appear, at least from certain points of view, that there wasn't a huge amount of discussion with patients as to whether this decision should or shouldn't be made, but it does appear that in Holland there was a discussion with patients about this.

A. Yes.

Q. In some detail.

A. Yes.

Q. What I would also like to ask you about is the position in relation to Factor IX.

You have been asked certain questions about that. We know that in Scotland heat treatment for Factor VIII arrived first but there was a delay in introducing heat treatment for Factor IX. I think you were asked to comment on the fact that there was a delay, and you have indicated that you think that it was reasonable that there should have been such a delay in view of the fact that they had to do certain tests over a period of time.

What I would like to ask you, though, is to give a comment on whether you think it was reasonable just to carry on treating patients with Factor IX without any

modification, given it was known that there was HIV in the donor population in Scotland. It was also known that Factor VIII could be successfully heat-treated but that Factor IX was not yet available, but that Factor IX would in due course become capable of being heat-treated.

So what I'm really asking you: in that relatively short interim period before that, what would you consider to be the appropriate course of action with someone in relation to Factor IX, whether it would be sensible to carry on giving them Factor IX or whether an alternative course, such as cryoprecipitate, should have been at least discussed?

A. Sorry, but for Factor IX --

Q. Factor IX?

A. -- cryoprecipitate is not a product --

Q. Sorry, not cryoprecipitate but some other course of action should have been taken with patients --

A. Basically, if I understand you correctly: was it a good policy that Haemophilia B patients were exposed to Factor IX concentrates without any further safety measure?

Q. That's right?

A. Is that what you ...?

Q. Yes, it is.

A. Well, there is one remark which should be included there and that is by that time -- and I'm now talking about the beginning of 1985 -- the plasma which was collected was tested, at least in my country. We started early 1985 to test for HIV. So it was not that there were no measures taken to reduce the risk of HIV. There was one major step taken and that was the plasma was tested. And therefore there was not such an urgency to include heating or whatever to safeguard Factor IX concentrates because there was already this testing procedure included.

Q. Supposing there was no testing at that point?

A. Then it would perhaps be different. Then you could argue, well, if that -- was it then permitted to let that (inaudible) go on without having a safety measure? Yes, that's a point which you can make. I must say that I can see that for those patients it would perhaps have been better if there was a heated product.

Q. Well, what other safety measure would have been possible?

A. Well, just -- well, only -- because you see, the Factor IX concentrate is made from a large pool and you can't reduce the pool without having to change the whole manufacturing. So you can't do very much. You can just try to limit the usage by saying, "We are not going for

prevention any more," yes?
Q. I follow, yes.
A. Or, "We are looking far stricter at the indications," but from the product point of view, there is not very much that you can do.
Q. Right. Yes, professor, thank you. That's all I have to ask.
A. Okay.
THE CHAIRMAN: Mr Anderson?
Questions by MR ANDERSON
MR ANDERSON: I'm obliged.
Can I just take up that last question from my learned friend in relation to Factor IX? What alternative was there in that short interim period, Professor van Aken?
A. Sorry, I thought I said the only alternative would have been to introduce heating at an earlier stage.
Q. Or alternatively perhaps introduce commercially heat-treated --
A. Sorry, yes, you are right.
Q. But other than that option, would I be right in thinking that there really was no alternative? Is that not right?
A. I don't see any other. Sorry, I should have mentioned that that was an option.

Q. Thank you very much.

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: Thank you, sir, I don't have any questions.

Further Questions by MS DUNLOP

MS DUNLOP: Sir, there is one matter which I think perhaps should be further clarified a little and it's in relation to the commercial companies and their connections.

Could we just go back to the transcript, please? I think it's page 28. I think it's this answer that you gave earlier, professor, that we need to probe slightly. You see, it's about line 19. You said:

"The Haemophilia Federation is heavily influenced by the commercial sector."

A. That's the World Federation.

Q. Exactly, yes. I just wanted to be very clear about that for the transcript. You are talking about the World Federation of Haemophilia?

A. Yes.

Q. How does it relate to the national haemophilia groups in individual countries?

A. Well, it relates, of course, to it because they are members of the World Haemophilia Federation but within the World Federation there is not what you would call a common opinion about certain things, notably when it

comes to these issues which we were discussing. So you have, for instance, the position in the US, the Haemophilia Federation in the US is sometimes quite different from the ones in European countries.

Q. Right. Where are their headquarters?

A. In Ottawa -- in Montreal. Anyway in Canada.

Q. Right. That was all, thank you, sir.

PROFESSOR JAMES: Could I add one question, perhaps?

The point about the World Federation would have been then that whereas advanced countries with well organised haemophilia services, such as Holland, Scotland, or the UK, would have really not paid necessarily an enormous amount of attention to the recommendations of the World Federation for the kind of reasons that you have outlined. Nonetheless, there were many countries where services were perhaps not so well developed, who would have paid attention to what the World Federation said very closely and perhaps that might have given opportunities for the influence of commercial companies to have an effect. Would that have been a fair summary?

A. Well, you are right. I think the World Federation of Haemophilia is clearly aware that their primary focus should be on developing countries because there the care for haemophilia patients is either non-existent or very low quality. So it's clear that they have to focus

there.

But at the same time, of course you are familiar with how such a society can work. There are all sorts of political issues which are introduced there because they are also used as a lobby organisation when certain measures need to be introduced or changed. The position of the World Federation of Haemophilia, it's looked upon by governments as a representative organisation. We have to take care of what they are saying. It is not that it is just the developing countries but some of the positions come also back to the local organisations.

PROFESSOR JAMES: Thank you.

A. Is that clear enough?

PROFESSOR JAMES: Thank you. Thank you, chair.

MS DUNLOP: Thank you, sir.

THE CHAIRMAN: Thank you very much, professor.

A. Thank you.

MS DUNLOP: We are hoping Professor van Aken is not going to leave the building but he can certainly leave the room.

THE CHAIRMAN: This is a novelty.

MS DUNLOP: We have one or two points to discuss about the next trip Professor van Aken is going on make to the Inquiry but since there is a little bit of time, sir, I thought it would be useful to mention some of the other statements we have from witnesses who haven't

attended.

We can't conclude our proceedings on this topic because we haven't heard from Dr Smith.

THE CHAIRMAN: Yes.

MS DUNLOP: And he is going to come and speak about the whole topic of viral inactivation in a oner, as it were. But apart from Dr Smith we have heard from all the other witnesses we are proposing to call in person.

The additional statements, however, come firstly from Dr McClelland, and I should draw attention to that. That's [PEN0110062]. He made the point that it's not really his area and he is only in a position to respond to one or two specific points.

He makes what I would call for shorthand, the "compartmentalisation point". He says:

"All of the work on heat treatment up to late 1984 was directed to hepatitis risk reduction."

I would suggest that that comment has to be read in the light of the evidence that we have heard and seen about people seeing in 1983 that there was a read-across from the then current research to the possibility of needing to deal with AIDS.

THE CHAIRMAN: There really isn't a very precisely defined line.

MS DUNLOP: No.

THE CHAIRMAN: Looking at it. It looks as if certainly there was continuing experimental work going on that had been directly related to NANBH but then AIDS, as it were, comes in as a superimposed layer and in the course of a relatively short time seems to take over as the primary driving factor as one gets into 1984/1985.

MS DUNLOP: Yes.

THE CHAIRMAN: But it still leaves you with a very good break point around about 1985.

MS DUNLOP: The only point I think I would seek to make is that it wouldn't really be accurate to say that until the end of 1984 no one had thought that heat treatment might be relevant to AIDS because there is plainly evidence --

THE CHAIRMAN: Dr Foster's memo is a very good indication that in SNBTS things were changing.

MS DUNLOP: Yes. He confirms, in relation to that specific question, that he was the person who attended the first meeting of the MRC working party on post-transfusion hepatitis, then he jumps from paragraph 3 to paragraph 32 and gives information, which we already have actually, about the group of patients known as the Edinburgh cohort.

THE CHAIRMAN: He merely repeats it, doesn't he? He doesn't tell us anything new.

MS DUNLOP: Yes, and he also deals with the question about Dr Perry and that's the extent of Dr McClelland's statement.

We also have a statement from Dr Pepper, which is [PEN0131391]. Dr Pepper, another chemist, at least by initial training. He has a little resume of his CV at the top. We see that Dr Pepper joined Southeast Scotland Blood Transfusion Service at a time when Dr Cash was the director. He was a senior research biochemist between 1969 and 1974 and then a principal scientific officer in Southeast Scotland Regional Blood Transfusion Service in fact. So he is arriving before Dr Cash but then Dr Cash is the director of that regional service, and Dr Pepper is working there too.

He explains the requests made of him when he joined. There is quite lot of information in Dr Pepper's statement and if we look to the next page, we can see that in 1980 Dr Cash invited him to head up and run a new unit called the Headquarters Unit Laboratory, intended to provide expert scientific advice to the national director. He was head of that unit for approximately ten years:

"The initial brief was wide, covering any subject that Dr Cash needed scientific advice on."

THE CHAIRMAN: I haven't read this before but does this give

some clarity to the relationship between the headquarters laboratory and PFC?

MS DUNLOP: It does a little, sir, yes. In the next paragraph he says he has had no formal role or responsibilities within PFC but he did sit on the committees set up jointly with them by Dr Cash. We know, obviously, that he featured in the Factor VIII study group and indeed seems to have coordinated the safety subgroup. He says he believes that:

" ... between 1985 and 1990 the SNBTS had a high reputation internationally as a result of its innovative research, development and service delivery. This was achieved by good working relations amongst staff, high morale and outstanding leadership, all the more remarkable given the modest size of the organisation, capitalisation and compared to multinational commercial competitors with multimillion budgets."

THE CHAIRMAN: If it's of any interest to anyone at all, I have got a copy of Valerie Hornsey's PhD thesis, (inaudible) I'm sure.

MS DUNLOP: Right. He goes on to deal more specifically with some of the paragraphs in our questions document. He records the same scepticism that we have heard from others about the prospects for successful heat treatment of coagulation factors, these being, as he says:

" ... exquisitely sensitive to damage and inactivation by environmental factors."

That:

"The development of a successful heating process was a very tall order. It seemed highly improbable, if not impossible, that heating would work."

Again an allusion to an issue that has recurred, the need to demonstrate successful inactivation by using animal models or using previously untreated patients.

A mention of the fact that animal models had ethical, regulatory, cost and technical problems.

In paragraph 7 he is referring to the Factor VIII study group, in particular the report of the safety subgroup, and we saw that yesterday, that there were sequential meetings between Dr Pepper and Dr Somerville and then the next day Dr Pepper met Dr Cuthbertson and then wrote a report in February 1982.

He says:

"The actual experiments on wet heating were carried out at PFC by Dr Alec MacLeod."

THE CHAIRMAN: I think I'm much happier about the status of his original report now that we have heard that it was intended to be a wide-ranging review of everything that was there, rather than a prescription of the work to be carried out by what, on any view, is a very small

research team.

MS DUNLOP: If we go on to the final page, he makes a point in connection with intellectual property and then says he has nothing to add on any of the other paragraphs.

We also sought input from Dr McMillan. You will remember, sir, Dr McMillan's background in working in genitourinary medicine. When we were doing our preparations for this topic, we did want to try to establish what the state of knowledge amongst other Edinburgh clinicians had been about AIDS in 1983 and 1984.

The letter on this topic is [PEN0160452]. We wrote to Dr McMillan in November last year and asked him several questions and he provided a relatively brief statement in response, which I think we have tendered already actually but which I will draw attention to -- it's [PEN0140102] -- Dr McMillan's contribution being, of course, relevant in the context of the leaflets topic, about when it was necessary to start publicising the risks amongst blood donors in Edinburgh and then also relevant in the context of heat treatment, so an awareness and judgment of the extent of the risk at various points in 1983 and 1984, and he is not sure if he made the statement that we quoted from a thesis about the presence of patients with AIDS in Edinburgh in 1983.

THE CHAIRMAN: It's a bit disappointing, this statement.
MS DUNLOP: It is, slightly, yes, but I think the point he is making in the first two bullets is that he thinks he saw a patient with, I suppose, early symptoms, so a pre-AIDS condition, in early- to mid-1983 and then he thinks it was some time in 1984 that he diagnosed a patient with an actual AIDS-related illness.

Then, not statements, but some further items of correspondence which are relevant in this topic. [PEN0121724]. This is a letter that the Inquiry sent to the Scottish Government. The letter asked in particular about line management of Mr Watt. We have already referred in evidence to a response from the Central Legal Office, giving the position of the Common Services Agency. Just note that this letter was sent -- it also deals with SHHD support for heat treatment of Factor VIII, which we should note from the far side. I think the letter is less important on that because we have actually, in evidence, had quite a lot of examination of documents and memoranda showing support, particularly financial, for the heat treatment project.

As far as the line management question is concerned, the response is contained in [PEN0121731]. This is just a little bit of further information about Mr Watt's

appointment and management.

THE CHAIRMAN: Yes.

MS DUNLOP: So the belief is that he:

" ... would have been formally appointed by Neil Milne, then secretary of the SNBTA, but he was recruited by and originally accountable to the late Dr R Cumming, then Regional Director of the Edinburgh Regional Transfusion Centre, of which PFC was initially a part."

Then the rest of the letter is concerned actually with financial support and funding for the introduction of the heat treatment programme, not that there is anything in it that I think is incorrect, but just that I think it should be regarded as subject to the evidence we have had; it is largely superseded by our examination of the various documents over the summer of 1983 and spreading into February 1984.

THE CHAIRMAN: Yes. The document you didn't have, the memorandum or whatever it was, by Dr Cash that eventually elicited a response along the lines of, "Get on with it and put in a proper application," was missing and you haven't found that?

MS DUNLOP: We haven't traced it but I didn't feel, sir, that it was crucial. I think Professor Cash thought he would like to have had a look at it to see if he did

advance it as a bid against the Medicines Inspectorate pot but I think the other evidence quite strongly suggests that he did.

THE CHAIRMAN: I think so but I was looking at this yesterday to see how it all came together and one possible view is that the rather thrawn argument over whether this could be brought within the Medicines Inspectorate recommendations, as it were, took some considerable time and knowing whether he did present a further argument at that stage might have been of some help. But I don't think we are bothered about it. My general view at the moment, unless anybody differs, is that Professor Cash did hang out for quite some considerable time, asserting that with a bit of imagination perhaps the work on heat treatment could be brought within the scope of the Medicines Inspectorate.

But I think you are right, it can all be worked out on the documents.

MS DUNLOP: Yes. Maybe we can have another look for it. I presume it's a costing document of some kind with the figures in it. It may not say in terms, "This represents a bid against the Medicines Inspectorate funding," but we can certainly have another look for it and see if we have it buried in one of the files.

So, sir, I have no other documents to tender as

bearing on this topic and, apart from hearing from Dr Smith, would regard the evidence as concluded. It's certainly concluded for this period of the Inquiry.

We would plan to resume again a week on Tuesday and look at the question of screening of donated blood for HIV.

THE CHAIRMAN: Gentlemen, is there anyone who would prefer to have the witnesses who have just been mentioned brought for examination or would wish to ask questions or whatever that arise out of these documents?

Mr Di Rollo, are you content to deal with them just as they are on their terms?

MR DI ROLLO: I haven't thought that there was anything further to be gained by bringing anybody along, I have to say, looking at the material that's been provided so far.

THE CHAIRMAN: There is a natural temptation on the part of the litigator to haul Sandy McMillan along and squeeze him a little to see if he can be persuaded to remember things but there is really no basis for this at the moment.

MR DI ROLLO: It is unlikely to be very productive.

THE CHAIRMAN: Yes. Mr Anderson, are you content?

MR ANDERSON: I'm of the same view, sir.

THE CHAIRMAN: Yes. Mr Johnston?

MR JOHNSTON: So am I, sir.

THE CHAIRMAN: So we will just treat them then, Ms Dunlop, as evidence that you have introduced unchallenged.

MS DUNLOP: Yes. Thank you, sir.

I have no further material.

THE CHAIRMAN: And we meet again?

MS DUNLOP: A week on Tuesday -- yes, the 27th.

(12.39 pm)

(The Inquiry adjourned until 9.30 am on Tuesday, 27 September 2011)

I N D E X