Wednesday, 4 May 2011

(9.30 am)

PROFESSOR CHRISTOPHER LUDLAM (continued)

Questions by MS DUNLOP (continued)

THE CHAIRMAN: Yes?

MS DUNLOP: Good morning, Professor Ludlam.

A. Good morning.

Q. I think before we go back to Koch's Postulates, a loose end I should tie up from yesterday is the article by Drs Barbara and Tedder, which we mentioned yesterday, and I did not have my hard copy at the time but I do now.

It's [LIT0013739]. This is an article from Clinics in Haematology, October 1984. Drs Barbara and Tedder are both virologists. Is that correct?

A. Correct.

Q. Yes. In the article they rehearse a number of viral infections, transmitted by blood and its products. We can look at the introduction, in which they emphasise -- and we can see this if we look at the bottom of the first page -- that:

"The characteristics of agents lending themselves to transmission by blood or blood products centre around their presence in blood or its components which has been taken from [in italics] apparently healthy donors. Thus these agents often will have a combination of a long

incubation period with a prolonged and high level of viremia."

I understand the point that they are making there to be that almost by definition these agents that are transmitted by blood and its products have some kind of silent period because the person appears healthy when they give blood?

A. That's correct, yes.

Q. If we move to the next page, there is a section headed "The nature of the viral agents", and there is a short list, at the bottom of which we see the agent of AIDS, HTLV-III. So given that this is the autumn of 1984, this is really quite a recent addition to the table.

Then moving through the article, we can see on the next page Hepatitis B, and if we go on, we will find, after sections included on Hepatitis A, non-A non-B, if we go on to HTLV, which is on 702, [LIT0013739], page 10. I think we all understand that there are obviously HTLV I and II, as well as HTLV-III, and there is a short introduction there saying, at the bottom:

"There are three closely related viruses in the HTLV group. Two that are well characterised are the human T-cell leukaemia viruses, type 1 and 2 ..."

Then on to the following page, we find the discussion of HTLV-III:

"The implications of AIDS in blood transfusion, a topic that has overshadowed NANB, has been reviewed recently and the infectious complications have been considered elsewhere in this issue."

At that point they are saying:

"Two haemophiliacs with AIDS, one of whom has died, have been reported in the UK, and 21 haemophiliacs with AIDS have been identified in the USA up to November 1983."

I'm trying to work out exactly when this article was finalised. Sometimes you can get the date when it is submitted for publication or something like that but I couldn't see it:

"In addition, 18 American patients have been identified who are thought to have acquired AIDS following transfusion of whole blood, packed cells, fresh-frozen plasma or platelets ... most of the transfusion-associated cases occurred in those areas of the USA which had the highest incidence of AIDS in the population."

It was really the next paragraph I wanted to put to you:

"The transmission of AIDS by pooled clotting factor concentrates is less controversial. Since, as a group, haemophiliacs are well studied, it is unlikely that

there should have been an illness like AIDS unrecognized before 1980. Little significance should be attached to reports of abnormal lymphocyte profiles in haemophiliacs; nevertheless there is no doubt that there have been deaths of haemophiliacs due to AIDS in the absence of other established risk factors and that, unlike those associated with transfusion, these cases were scattered throughout the USA."

We saw yesterday, professor, that a lot of different individuals reported altered immunology in patients with haemophilia but Drs Tedder and Barbara are saying that little significance should be attached to those reports. Do you agree with that?

A. They are virologists and until the virus was identified and the antibody test developed, there was no other way of studying this condition other than by immune tests. These were patients who presented, when they developed AIDS, with profound immune deficiency and they were therefore investigated for immune deficiency with laboratory investigations.

It then only seemed reasonable to look at at-risk individuals initially in the gay community, and subsequently in people with haemophilia, to see whether they may have similar abnormalities to those who had AIDS as a surrogate marker. That is the best you can do

under these circumstances. Later on in this article, Professor Tedder and Dr Barbara actually go on to suggest the use of some immune tests for deciding whether, I think it is that patients may be infectious or HIV -- I'm sorry, I forget the exact details, but they recommend, because there aren't any other markers, that the best you have are immune tests. So we have to deal with what we have at the time.

Q. Yes, but I suppose the point they seemed to me to be making was that, firstly, this is plainly being written after the work by Gallo in the earlier part of 1984, which had linked AIDS and HTLV-III, and they seem to be saying, firstly, that, as far as they are concerned, the hunt is over, and the agent which is causing AIDS in people of homosexual orientation and also people with haemophilia, the hunt is over. Is that what they are saying?

A. I think by October 1984 there was little doubt that HTLV-III was the cause of AIDS.

Q. Yes.

A. I'm very happy to accept that. However, we don't know or we didn't know until the antibody test was produced, just how many people might have been infected. We don't know whether everyone was equally susceptible. It may be those who had abnormal immune tests were more

susceptible to the virus when exposed to it. So I'm happy -- very happy to agree. I have no difficulty that by this stage, this time, HTLV-III was almost certainly the cause but there were still a huge interest and a developing interest in the immunology for monitoring individuals. For example, patients who were anti-HTLV-III negative, we didn't know at this stage whether they were truly not infected with HTLV-III or whether it was in some latent form in them, not expressed, or whether the test, the antibody test, was just not sensitive to pick up low levels of antibody. So the false negatives.

So one of the ways that we monitored these patients was to look at their immune function serially. As I'm sure you are well aware, those who were demonstrably infected with HTLV-III showed, over a period of time, declining immune function, whereas what we were able to demonstrate very clearly was the immune function did not change in those who were anti-HTLV-III negative, and that was important evidence that these individuals were not infected latently with HTLV-III.

Q. I can certainly understand, professor, the point you make, that there were many unanswered questions, and indeed even today there seem still to be unanswered questions, but your acceptance that you indicated a

moment ago that by the autumn of 1984 that this virus, HTLV-III, was the cause of AIDS, including in people with haemophilia; does your acceptance extend to that?

A. Yes.

Q. Right. The point that Drs Tedder and Barbara make in this paragraph however, about it being unlikely that there should have been an illness like AIDS in people with haemophilia caused by some other phenomena, that was a valid point even in 1983, was it not?

A. Yes.

Q. Yes.

A. Yes.

Q. Can we think about Koch's Postulates? Perhaps I should start by putting this in context, is that how do we get to Koch's Postulates in this Inquiry? Because a number of people perhaps who are here listening or reading the transcript may be wondering a bit about the background to this because it is threatening to become very complicated.

A number of doctors have mentioned Koch's Postulates to us in our preparations, in particular when we have looked, as we have done, at a government line about there being no conclusive evidence that there was a connection between AIDS and blood products. Dr Winter suggested to us that the thinking behind that line may

have been to do with Koch's Postulates, so we have sought some input on the postulates for that reason, and also indeed, we see them referred to in Dr Evatt's article, "A tragic history of AIDS in people with haemophilia". He mentions Koch's Postulates. So Dr Koch is around. But it may be, professor, that it threatens to distract us from what one might term the bigger picture.

So perhaps if we could bear that in mind, I should ask you, would you be able to explain for us, in terms that we can all follow as lay people, the essence of Koch's Postulates?

A. I did a --

THE CHAIRMAN: At what date?

MS DUNLOP: As originally formulated.

THE CHAIRMAN: I think that might be important.

A. I did a little homework last night.

MS DUNLOP: I expect we all did, professor.

A. My understanding is that Koch's Postulates have four components, and although they were originally laid out for bacteria, it is at a time when viruses -- this is 1890, and viruses were really not on the agenda, but I think it really refers to an infectious agent. But his postulates were: the bacteria must be present in every case of the disease. The bacteria must be

isolated from the host with the disease and grown in pure culture. The specific disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy, susceptible host. The bacteria must be recoverable from the experimentally-infected host.

Those are my understanding of the four conditions of Koch's Postulates.

Q. So certainly looking at that particular formula, which I imagine a number of us have been able to discover from various websites, looking at that formula, the first thing that's striking is that it would be very difficult to satisfy those postulates if the organism hadn't been isolated. That would be impossible, wouldn't it?

A. Yes.

THE CHAIRMAN: So we can't possibly say on this approach that Hepatitis C is caused by a virus?

PROFESSOR JAMES: We can't say that Hepatitis C infection satisfies Koch's Postulates.

THE CHAIRMAN: Yes. If this were the only test, we couldn't say it was caused.

PROFESSOR JAMES: Some of those postulates have now been abandoned?

A. Yes, I thought there were now culture methods for Hepatitis C.

MS DUNLOP: Well, as we understand it, professor --

Professor van Aken covered this with us, and it has not been possible to culture Hepatitis C, as we understand it.

THE CHAIRMAN: Of course there may be some lab somewhere where they are not quite ready to publish. But I only introduce it because I don't want us to get hung up on this.

In relation to maths there is an expression "spurious arithmetical accuracy", which was applied by a Cambridge professor, where data accurate to two decimal points was invariably worked out to n decimal points by people who didn't quite understand the start, and I'm beginning to wonder whether we have a case of spurious linguistic specificity in Koch's Postulates that is going to lead us down a similar avenue.

MS DUNLOP: I think with that in mind, professor, just some short propositions which I can put to you and you can tell me whether you agree or disagree. The first would be that this is really more in the territory of an infectious diseases physician or perhaps a virologist, is it?

A. Yes.

Q. So we may be able to ask Professor Lever about it as a professor of infectious diseases, and he will certainly be familiar with current thinking on

Koch's Postulates. The second is that they work better with bacteria than with viruses. They were originally devised in an era where people were talking about bacteria?

A. They were devised -- and viruses were very difficult to isolate and grow at the end of the 19th century, yes.

Q. Right. And Koch's Postulates work best where the organism has been isolated, cultured and that sort of forwards progression can be experimentally achieved. It is very much more difficult to see how they would work in the backwards direction, where you have somebody with a disease and you are trying to find out what is causing that disease. Is that a reasonable proposition as well?

A. Yes.

Q. Right. And the last one was a question: is it the case that in clinical medicine, when confronted with a disease they don't really understand, doctors would say, "Oh, well, we can't satisfy Koch's Postulates; therefore, we can't make any assumptions about what is or isn't causing the disease". That doesn't sound particularly realistic and I wondered if academically one might say that but in clinical medicine that sounds improbable?

A. In clinical medicine, one, the whole time, is working with incomplete data and information and you have to

make many assumptions that may not be backed up by scientific evidence.

Q. Do you remember yourself around this time, 1983 in particular, Koch's Postulates featuring in the discussion?

A. No.

Q. Perhaps that says it all.

Professor, I wanted to ask you next about your own studies of altered immunology in patients with haemophilia, and to do that I would like to look at [PEN0150445] at page 4. I would like to look, please, in particular at the passage we see beginning with a bold section in brackets, "Schedule230910/Paranumber1i". Where you say that you were:

"... aware in 1982 of the first MMWR report of the pneumocystis pneumonia in three haemophiliacs."

In paragraph 5:

"In the absence of any patient with an AIDS-defining illness, the only way to potentially investigate individuals to assess their possible susceptibility was to assess their immune function by laboratory testing. By 1983 it therefore seemed important, as it did to many other haemophilia physicians, to investigate the immune status of patients under my care. The historical

background to the assessment of immune dysfunction in haemophilia is set out in appendix 2."

Then paragraph 6:

"My studies of immune function were initiated in 1983."

I just wondered, professor, if you can be slightly more specific. Can you remember when in 1983 it was?

A. I think it was quite early in 1983.

Q. Towards the --

A. Towards the beginning, sort of January/February/March.

Q. Right. You say you were:

"... surprised to observe that many patients had immune abnormalities very similar to those reported from homosexual men and haemophiliacs residing in North America. The preliminary results were published in the Lancet ... in response to a letter a month earlier which inquired if any studies had been undertaken in a non-AIDS endemic area of the world ..."

Can we look first at what I think was the trigger letter, if we can call it that, for your response? That's [LIT0010911]. Do you recognise this letter, Professor Ludlam?

A. Is this the one from Dr Gordon?

Q. Yes. I'm sorry, it's one of these situations where, because of the column structure of the page, it is

difficult to see the whole thing at one time. But, yes, it begins towards the foot of the left-hand column. Just to let everyone have a look at it, I think.

(Pause)

Remembering from yesterday, Professor Ludlam, your description in one of your statements -- it's actually, I think, in [PEN0150385] -- of the four possible causes or four principal causes, and number 1 was an incident of haemophilia, number 2 was liver disease and then number 3 was antigen overload, I think we were calling it for shorthand, and then number 4 was the virus.

It looks to me from the first paragraph as though Dr Gordon is making reference to numbers 3 and 4 as competing theories. Is that correct? Right.

Then he is going on to say in the last paragraph that:

"It would be very useful to know what is happening in a country where cases of AIDS have not yet been reported ..."

That, in essence, is what he is saying?

A. Yes.

Q. Did you read this at the time?

A. Yes.

Q. And what was your reaction when you read it?

A. Well, I thought that we were studying individuals with

haemophilia who were treated with blood products collected in what appeared to be an AIDS-free population, and therefore perhaps the results that I was beginning to gather might be able to address the question that Dr Gordon is posing.

Q. Right. In other words, you thought you had what he was looking for?

A. Yes.

Q. Right. So you wrote --

A. Yes.

Q. -- to the Lancet?

A. Yes.

Q. We have that letter too. That's [LIT0010416]. Again, I think we need to give people a moment just to look at this. You and three other people in fact, who had been working with you in your research into altered immunology in people with haemophilia. Is that correct?

A. Yes.

Q. (Pause).

Professor Ludlam, the first question about this is that the timing of it is interesting because this publication is really almost exactly at the time when Dr Gallo was announcing in America that he had found a link between this virus, now known as HTLV-III, then known as HTLV-III, and AIDS. So given that you were

really -- sorry --

THE CHAIRMAN: The data --

MS DUNLOP: I'm a year out. Yes, sorry. I need to retract that.

THE CHAIRMAN: It is nearer to the time --

MS DUNLOP: Yes, it is nearer to the time when in France the LAV virus is being isolated. But at that stage you were particularly interested in possibility number 3, the possibility of the antigen overload theory, rather than the virus?

A. That was the conclusion from these studies, or that it is another ubiquitous virus that was in the population of people with haemophilia.

Q. So, rather than perhaps "a new virus", you were favouring the antigen overload or an existing virus as the cause.

I wanted to ask you: when the Gallo material came out the following year, what was your response to that? Were you surprised? Sorry, before you answer, just to flesh it out. Why I was confusing myself earlier was that you did have a further article on the same topic in the Lancet in June 1984. It was that one, actually, that came out around about the time when Gallo had published his results. So perhaps in your answer, if you could cover more your response in 1984, when you had

an article in the pipeline following theory number 3 and Gallo came out with his evidence that really the explanation was explanation number 4. What was your response?

A. I had no difficulty in accepting and it was very welcome news that a virus had been identified, absolutely. And what we learned as we went along in this area -- because I wasn't an immunologist by training -- these sort of tests had only been around for a relatively short time -- but the immune system has only a number of limited ways of responding to viral stimulation or provocation and so there are lots of possible reasons why you can get these immune changes. It's not just an AIDS virus.

Q. Can we go back, having looked at your letter in the Lancet in response to Dr Gordon, in which you explained the work you had been doing and, I suppose, what must have been at that stage preliminary results, were they? You say that, the preliminary results of the study of haemophiliacs in Southeast Scotland.

A. But if I may say, they cast doubt over the extent of infection with a putative virus in other patients with haemophilia elsewhere in the world. That was one of the inferences from this.

THE CHAIRMAN: I would like to understand that more clearly.

You were talking about absolute lymphocyte counts and within that context a disturbance of the helper/suppressor ratios. How did that cast doubt on the issue?

A. We make the assumption that in 1983 -- which we now know was true -- that the patients I had studied did not have HTLV-III, did not have AIDS, but the similar abnormalities were demonstrated and reported from North America in people with haemophilia; and the question was being raised: do all these people who have abnormal lymphocyte tests -- haemophiliacs with abnormal lymphocyte tests in North America -- are they latently or subclinically infected with an AIDS virus? And my data was suggesting they may not all be infected.

MS DUNLOP: Yes.

THE CHAIRMAN: On the assumption that there was no AIDS, as it were, around in your population?

A. Correct, yes. We now know that to be true at that time.

THE CHAIRMAN: Yes.

MS DUNLOP: We maybe need to look at that in a moment but one device which may be slightly easier for us to utilise in understanding this, Professor, is the device of a Venn diagram.

I think we understood yesterday that if you were drawing a circle to show all of those with altered

immunology -- that's the CD4/CD8 ratio, for shorthand -- then people who went on to develop AIDS, almost all of them would be in that circle. They wouldn't occupy the whole of that circle because there would be some people with altered immunology who didn't go on to develop AIDS. But people with altered immunology, apart from those who go on to develop AIDS and who don't yet have altered immunology but who perhaps already have the virus -- so there would be a big circle with a significant overlap with another circle and only a small part of the other circle.

I'm probably not explaining that very well. I think I could draw it, but do you follow the picture I'm trying to paint?

A. I think I do, yes.

Q. Is it correct?

A. If I understand it correctly, you are saying that amongst the individuals with abnormal immune tests -- there are two populations; there are those who have HTLV-III and there are those who don't.

Q. Yes, essentially, but I think you made the qualification yesterday that even some of those who have HTLV-III might not yet have the sort of altered immunology that you are studying here?

A. There is another group, if you like, that have normal

immune function.

Q. But for them it is presumably only a question of time before their immune function changes to become disordered in the way that you have been describing?

A. Yes.

Q. Right.

THE CHAIRMAN: Ms Dunlop, the reference to drawing it isn't just a cast-off that should be ignored. I'm conscious that Professor Lever's method of communication quite often requires a visual presentation too, and I rather think that there would be many people who don't know what a Venn diagram is. Perhaps we could think of that as a way of helping communicate. Flip charts are not my favourite means of communication.

I prefer an epidiascope and a printout from that, but one way or another we might be able to get there.

MS DUNLOP: Yes, it's challenging material and it is just that one is casting around for a number of different ways to present it. Some may be more helpful to some readers than others.

THE CHAIRMAN: We have a nice big white wall here, an epidiascope --

MS DUNLOP: Well, I don't know what an epidiascope is but there we are.

THE CHAIRMAN: It is a relatively primitive device for

showing pictures on walls and screens, but I think if we had it, it would be a very good means of describing these --

A. An overhead projector would be very useful.

MS DUNLOP: Yes, I think the notion of a Venn diagram is to draw a circle and in that circle are all the people you are talking about. Another group of people may be in another circle, and it is interesting to see whether the circles are apart or whether they overlap to any extent. It is also possible for the second circle to be completely within the first circle. These are really the possibilities.

A. Yes.

Q. Yes. And, if I'm understanding you correctly, the one that we would choose in this situation is one circle to include all of those with altered immunology, another circle to include those who are developing AIDS, and they would be overlapping but not totally.

A. Yes.

Q. Right. Thank you.

Can we go back to your statement, please, which is 0445, and go back to where we were at paragraph 6. You do say that at that time -- and this is reading six lines from the end of the paragraph:

"I enquired extensively throughout Scotland of those

who might see individuals with AIDS, for example, genito-urinary medicine physicians, as to whether any such people had been encountered, and I did not receive any positive reports. I therefore concluded that at least in Edinburgh, patients' immune disturbances were due to a non-AIDS-causing agent, and subsequently this was confirmed when anti-HTLV-III testing became available in late 1984 and virtually all of the patients were found to be negative in 1982 and 1983."

The first point to put to you is that there does seem to be some information -- it is not very specific -- about the arrival of at least early symptoms of AIDS in Scotland in 1983, and I think you have recently seen that. For a start, if we look at [SGH0026698]. We can just see if we look at the tiny letters on the bottom left-hand side of the page:

"Gay Scotland, July/August 1983".

Just to look at that, there is an introduction. We can perhaps go back up. Read the part in slightly larger font. (Pause)

We can all read that for ourselves but there is a specific quote from Dr Sandy Macmillan of Edinburgh Royal Infirmary. He says:

"It is only a matter of time before more AIDS cases are confirmed in Edinburgh and Glasgow."

Was Dr Macmillan one of those to whom you spoke around that time?

A. He was indeed.

Q. I think you have also seen a page from a PhD thesis, which is by Bennett and Pettigrew. A thesis, I'm not quite sure; it has been rather difficult to get information about this work, but a particular page in it, page 32, [PEN0160457].

THE CHAIRMAN: Which university was it?

MS DUNLOP: It is an English university, from memory. It belongs to Nottingham, and my recollection is that we tried to get some information recently about this but weren't very successful. If you allow me a moment, I can confirm if that's right.

THE CHAIRMAN: It is just to see whether there is an easy way of getting it.

MS DUNLOP: We have the whole publication but it doesn't tell us very much about itself, and most importantly it doesn't name some of those who are quoted, and particularly it certainly doesn't name the person responsible for the words in the middle of the page that have actually been marked with an asterisk:

"We were aware of it as physicians because of medical literature but really we started seeing our first patients with clinical evidence of HIV infection

in 1983. When I felt these glands and saw some of the skin complaints, I realised what was going on and related it to HIV."

Obviously we know it wasn't called "HIV" at that time but the thrust of this is quite clear. So certainly, if you were making your enquiries, I suppose, before you wrote to the Lancet, people were telling you that there was nothing, that they hadn't come across anybody who might even possibly be developing AIDS, it looks as though that situation changed very, very quickly after your enquiries, doesn't it?

A. It does but what is difficult, and has been difficult in this whole area, is being able to identify people with early HIV infection. We dealt with some of this yesterday. For example, this quote in the middle describes feeling glands, lymph nodes. There are a lot of causes for enlarged lymph nodes in the neck, EB virus, for example, is one, lots of other causes. So you can't make the assumption that just because you feel enlarged lymph nodes in a gay man that he has prodromal symptoms of HIV.

It says "skin complaints". I'm not a dermatologist, but this is a very vague statement. What is a skin complaint? If we are talking about Kaposi sarcoma, then the patient has AIDS, and that should have been

reported. So what are the skin complaints? I find this -- when was this written? By whom? And what sort of experience did they have over a period of time?

Q. Right. I appreciate all the points you are making, professor, that it is vague, but it is not really possible to find any more information than this, and the report in the Gay News, which is slightly more specific about two men being ill, and that's a report from July/August 1983.

A. Could we go back to the report of the AIDS news?

Q. Certainly. That's [SGH0026698].

A. Again, in the large print on the first paragraph:

"Highly suspected but not yet confirmed ..."

What were the details? There were lots of gay men who fall ill from all sorts of other infections and subject to other diseases. If these were AIDS cases, then why weren't they reported? The first reported AIDS case to Ruchill, if I'm not mistaken, was in November 1984.

Q. Just for completeness, as lawyers tend to say, we did ask Dr Macmillan and we should look at his response, which is [PEN0140102]. You can see there, professor, what he says. (Pause)

So we weren't much wiser when we received the information from Dr Macmillan because, as he points out,

it is very difficult to remember after the passage of such a huge amount of time, but he couldn't really pin down with any precision when he first saw a patient with an AIDS-defining illness.

A. I don't want to give the impression that I wasn't well aware of the possibility of people being infected. It was a judgment that had to be reviewed repeatedly and I did my best to keep my antennae out.

Q. That's actually the point I was going to make, professor, that there is perhaps a danger of conflating two different things here. The first is your response in the Lancet saying that you have a group of people from a country where, as at spring 1983, AIDS does not appear to have entered the donor population. That's one point. But the other question is: was there a sense of it coming. And what we are looking at is perhaps more relevant to that aspect. So would you say "yes" to that? In the spring of 1983 given these -- and I accept these are very vague and there are quite slight mentions -- was there a sense that AIDS was going to arrive in Scotland?

A. I think by that stage there was one case in England. Am I correct?

Q. Well, there had been the one reported in the Lancet in 1981. Certainly, yes.

A. Yes, there was a feeling that it was going to very likely come and we weren't quite sure when it was going to arrive because of the long incubation period.

Q. Yes.

A. So we were very mindful of that possibility.

Q. At a meeting on 22 March 1983, if we could just quickly look at the minutes of that, [SNB0015183]. You can see it's a meeting of the working group chaired by Dr George McDonald, and you are there. There is also Dr Bell and Dr McIntyre from the Scottish Home and Health Department. Then on to the next page, you see after a discussion of heat-treated concentrate, we do come, in paragraph 3, to a discussion of AIDS and you are quoted. The letter and questionnaire been sent out to haemophilia directors. I'm not sure whether the last sentence also emanated from you but it certainly is recorded that:

"There was concern that AIDS might appear in the UK and the Haemophilia Society was attempting to reassure its members and put fears of infection from blood products into perspective."

It seems perhaps quite a low-key concern. There was concern that AIDS might appear in the UK as at March 1983. Strictly speaking of course, there had already been a case in 1981 reported in the Lancet.

I appreciate it is very difficult to try to recreate the atmosphere in 1983 but do you think that there was enough concern?

A. Yes, I do -- and bafflement.

Q. Right. Of course, we know from Dr McClelland, and I appreciate this is a different perspective but this is almost exactly the time when he started work on drafting a leaflet because of his concern about the blood donor risk?

A. Yes.

Q. And you would know at that time that he was doing that?

A. Oh, yes. It was clear that this was a possibility or probability that it would come into England and Scotland.

Q. Can we go back to your statement, please, to [PEN0150445], and pick it up at page 5 really, professor, we have already covered quite a bit of this so I'll just let everyone have a look to see what's on this page. This is still in a list of possible causes, which we have examined in one of the other documents. You have already mentioned, further down, the UKHCDO in September 1982 and then we go into 1983, and on to the next page, please. We have already trailed the fact that Professor Lever is going to explain to us the answer to the question of what caused Kaposi's sarcoma.

I don't think we need to go into that just now.

Then paragraph 13:

"It was argued it would have been inappropriate to ban import of clotting factor concentrates from the United States because of the harm that would have been experienced by patients."

Could we look back now at this point to paragraph 4 of this same statement. So if we can go back, I think it is three pages, where you have a more general discussion of change of therapeutic policy as a topic. Just to look at that. We have already been over -- not just with you, professor, but with Dr Winter and Professor Forbes too -- the dangers of untreated, severe haemophilia.

On the following page, we can just see at the top you refer to the possibility of switching to cryoprecipitate and you say that:

"Where this was recommended in Cleveland [Cleveland, Ohio] it was not accepted by the patients."

So this is a reference, I take it, to Oscar Ratnoff?

A. Yes, out of his approximately 90 patients -- and he was a very forceful individual in making his opinions known, and he was very forceful that they should change from concentrate to cryo -- out of approximately 90 patients, as I understand it, in his subsequent publication, only

five changed.

Q. That's yet another thing I want to come back to, professor, because obviously it's relevant to our enquiries.

A. Perhaps I could add that in his paper, or the letter, he describes only five patients. He describes all the other morbidity and mortality there has been in relation to HIV in this group of 90 people, and despite a lot of them becoming ill, there was still a reluctance to change to cryo.

Q. Yes. Perhaps just to finish off this aspect of Dr Ratnoff's involvement at the moment, professor, it no doubt is another illustration of the dangers of the Internet, but it is possible to trace on the Internet a memorial lecture, the Oscar Ratnoff memorial lecture, in which the lecturer says that he changed his patients to cryoprecipitate and saved many lives. It is also possible to find academic articles recording the point that you make, that actually Cleveland was a city that had a very high incidence of HIV in patients with haemophilia, and the article that you quote is actually a publication in Annals of Internal Medicine, which we have tried and are trying to obtain, but thank you for paraphrasing it for us. You have it there?

A. I have it.

Q. I see you looking. Thank you. In essence you are telling us that although Dr Ratnoff took the view that switching to cryoprecipitate would be safer, and indeed we saw that in the contemporaneous article from Science that we looked at, in January 1983 that was his suggestion, but you are saying that very few of his patients accepted it.

A. I am.

Q. I think we will firm up the reference to that paper in due course, sir, because I think we need to get it into court book.

Right, can we go back to paragraph 14, please?

You were asked about the joint meeting in January 1983 and you thought, when you sent us this, that the letter and questionnaire which are mentioned at the meeting in January 1983, was material sent out by Professor Bloom:

"The result of the survey was published in the Lancet in June 1984."

I think perhaps just to clarify that, professor, I'm not sure that it can have been that survey, if we look at [LIT0010409], can we just check from the top that that is the Lancet, June 30th 1984. I think this is Professor Bloom's publication to which you refer. Is that right?

A. Yes.
Q. We can see that he narrates the sending of a questionnaire to directors of 201 European haemophilia centres, but if we move over to the next page, please, we can see on the left-hand column at the bottom that the questionnaire was dispatched at the beginning of December 1983. So actually that would be too late to be the survey that was being mentioned in January 1983, wouldn't it?
A. That reassures me because I thought it unlikely that Professor Bloom would have sent out a circular in January 1983 and not published the results until June 1984. It is possible he sent out two circulars.
Q. Right.
A. I think is probably the situation.
Q. Well --
A. But I agree that this one refers to -- as you describe.
Q. Yes. Well, certainly, professor, it's possible. It's not really possible for us to rule out that he sent some circular around other European centres in the spring of 1983, but we haven't found any trace of it. I wondered perhaps if the questioning that's described at the joint meeting in January 1983 was actually Dr Craske. I think Dr Craske was always asking if anyone had any

information, and certainly this seems to have been a form prepared by him, circulating at that time. Is that also possible?

A. Could we go back and look at the minutes of the meeting?

Q. Yes, certainly.

A. Please.

Q. It's a very short passage. It is actually quoted in the preliminary report but I'm happy to look at the original document.

A. We had it up on the screen a moment ago.

Q. We didn't have 21 January 1983. If you will allow me a minute, I'll just get the reference for that. (Pause)

I wasn't intending, in fact, to go to this one, professor, but we can. Unfortunately the reference should be in the report and it's not. It's [SNB0015160]. It's just a very short discussion towards the end of this meeting, 21 January 1983. Perhaps if we go to the last page and work back, we can see it. There it is. Paragraph 6. It doesn't sound like a pan-European survey?

A. No, no, this is different.

Q. Yes.

A. And the date of this meeting is ...?

Q. 21 January 1983.

A. 1983. I'm sorry, I can't remember what it ...

THE CHAIRMAN: It may not, at the end of the day, be terribly important. I suppose Dr Craske and Professor Bloom might not have been operating in completely hermetically sealed circles here and one could be influencing the other as a collection of information. Really if nothing turns on it ...?

MS DUNLOP: It's relevant to the whole question of Professor Bloom's letter as well.

THE CHAIRMAN: Indeed it is.

MS DUNLOP: I think Professor Ludlam was thinking of the March 1983 meeting, and actually the reference is in the same terms. It refers to a survey in the UK. So simply that the matter having been raised of whether there was a survey going on across Europe in spring of 1983; at least provisionally it doesn't looks as though we can find any evidence of that.

A. But this shows that there was concern in the UK.

Q. Indeed?

A. In the haemophilia community.

Q. Yes. Can we go back then to your statement, [PEN0150445], and just move through it, I think, quite quickly because much of this narrative we have covered in the context of other statements.

15 we have discussed, the New England Journal, Dr Desforges. 16 we have discussed, the meeting at

Heathrow Airport. 17, a very short paragraph. New Scientist, you say didn't add anything. 18, Margaret Ragni was mentioned as well. And 19 we know about because we have also discussed it with Dr McClelland in the context of topic B1. 20, the Lancet editorial of 2 April 1983. 21, Dr Galbraith's letter.

We haven't looked at that with you, Professor Ludlam, but in short you tell us that at the time you weren't aware of it?

A. That's correct.

Q. Yes. Then 22, you say that:

"Dr Galbraith's letter was not, so far as I recall and the minutes do not record, discussed or brought to the attention of the meeting."

That is the UKHCDO reference centres directors' meeting on 13 May. In fact, Dr Galbraith's letter is marked as confidential and our understanding is that the proceedings of the Committee On the Safety of Medicines, which would include its biological subcommittee, were really treated as confidential and the workings of the body were not discussed or disseminated?

A. Those meetings, as I understand it, are very confidential.

Q. Yes. Do you know what the rationale for that is?

A. Yes. My understanding is that they mostly are concerned with licensing medicines and so there may be information that's of commercial value being discussed in relation to new drugs.
Q. So it's really commercial sensitivity?
A. That's my understanding.
Q. Yes.
THE CHAIRMAN: Are the membership details widely publicised?
A. At that time I think not.
THE CHAIRMAN: I think another factor in some of these consultative committees is that the government is anxious that there should be no lobbying of any kind, no direct contact with people forming policy views.
A. I think that's absolutely true and one or two committees that were almost said not to exist.
THE CHAIRMAN: I have been a member of one.
MS DUNLOP: We have discovered, Professor Ludlam, that Mr Watt was on this committee. We didn't realise that at first. Did you know that at that time?
A. I didn't until a couple of days ago.
Q. Well, the secrecy was obviously successful.
Then can we move down through these paragraphs. I don't want to pick up anything specific but just to let people see what you are saying. You refer to a letter of 24 June being in fact a sort of circular letter,

which I think we didn't understand at first but we do now.

And then at the bottom, paragraph 26, a reference to desmopressin, or DDAVP. Again, we have mentioned that before but its ability to raise Factor VIII levels in mild haemophilia. Is there anything analogous for Factor IX? Is there any drug you can give that for a short time will raise the level of Factor IX?

A. No.

Q. Nothing like that?

A. No.

Q. Then on to the next page. You gave a talk on desmopressin at the meeting in Glasgow in September 1980, and we have the book on that as well, Professor Ludlam. "Unresolved problems in haemophilia", containing a paper by you on DDAVP. If anyone wants to read up on that, they can.

You say -- and I think we are familiar with this from the articles to which Professor Forbes referred us -- that there were drawbacks to DDAVP. You say:

"It had potential side effects, especially of water retention and toxicity, resulting in convulsions in children and fluid overload in adults."

Does that mean it was a drug you had to use with great care?

A. With a degree of circumspection, yes. Great care in small children, and particularly if you want to give repeated doses, because of the water retention. And also in patients who have atherosclerosis. There has been at least one heart attack in an individual who received desmopressin.

So, although it's a very useful drug, it is not without its contra-indications.

Q. Right. And what's the incidence of atherosclerosis in people with haemophilia? Is it the same as the general population?

A. That's a very interesting question.

Q. I sense a possible sidetracking coming in, professor. So in short do people with --

A. In short, it seems that patients with haemophilia have atherosclerosis, similarly to people without haemophilia. But their incidence of heart attacks is much lower.

Q. And that's because you need a clot to have a heart attack?

A. Yes.

Q. Right. If we look at paragraph 32. You were asked about the Haemophilia Society view about the use of commercial Factor VIII, and you referred in your answer to vigorous campaigning from people with haemophilia for

access to concentrate, and we have already discussed that.

You say:

"Because of the limited availability of SNBTS concentrate, I had preferred to delay home treatment rather than give commercial concentrate, especially to young individuals."

What was your thinking? I'm wondering what particular point you are making by referring to young individuals especially.

A. As you know, my philosophy was based on trying to avoid commercial concentrates for all patients, and particularly trying to avoid giving small children viral infections because they have got longer to live, hopefully. My clinical decision was to delay home treatment, rather than use commercial concentrates because of the different virological spectrum of the donors.

Q. We do have a spreadsheet from you, Professor Ludlam, and we looked at that when you came to the Inquiry in March. My reading of that is that, of the 23 people who are referred to in the spreadsheet, only two of them were in fact under 16 at the time of the first positive test for HIV. Is that correct?

A. That's correct, yes.

Q. I think actually, since we have mentioned the spreadsheet, just to confirm one other point -- I don't want to go back to Venn diagrams and attempts to paint them in the air, but the patients you were looking at in 1983, you did say in the passage in your statement that virtually all of them were free of the virus. It is possible, I think, from the spreadsheet, that one or two of the patients who had altered immunology in 1983 were in fact going to go on to develop AIDS. Is that correct?

A. Yes. I'm sorry, one.

Q. One?

A. The other one died of bleeding.

Q. Can we move on to the next page, please? Again we have discussed all of this, professor. I do not want to take up time but just to let people see this particular text.

(Pause)

Although you say at the top of the page that there were no AIDS cases reported in the Scottish population, you do go on to refer in the next section to the case of AIDS of African association, and again, without going to it because we have done that before, it does look from the report in 1984 as though that person died in December 1982. So there was somebody who had returned from Africa and become ill with AIDS and died

in Glasgow.

A. But they would never have been accepted as a blood donor.

Q. Quite, but I suppose it makes a wider point about global travel?

A. Oh, indeed.

Q. Yes. We have already discussed the Bennett/Pettigrew thesis. And then in paragraph 36 you say:

"In Edinburgh commercial Factor VIII concentrate use was discontinued in May 1983."

So such limited use as you were making of commercial concentrate you reduced further. Is that right?

A. Yes.

Q. Yes. And why was that?

A. Because there was an increasing supply of SNBTS Factor VIII concentrate and because of my concern about American concentrates --

Q. Right.

A. -- from the point of view of AIDS.

Q. At this point -- that is the middle of 1983 -- there certainly seemed to have been some heat-treated commercial concentrates starting to come through. Can we look first at paragraph 8.40 in the preliminary report, please, which is page 199 in the hard copy, a chapter begins at [LIT0012479]. So perhaps 2492.

Just that paragraph 8.40, Dr Craske preparing a note on:

"... factors to be considered in the selection of hepatitis reduced products for clinical trial."

I think we need to look briefly at the reference, which is [SNF0010948]. Just to look at what was happening on the commercial scene at this point. This is Dr Craske's hepatitis working party. If we scroll on, I'm particularly wanting to look at page 3 onwards.

If we look at page 2, please, we see that this report is written on 28 September 1983, no doubt for the meeting in October 1983, but appended to it -- and this is where we need to go to page 3 -- is a document from July. We see that he is referring to the advent of heat-treated commercial products, describing what type of products there will be; category 1 includes Hemofil T. Then Factorate, which is coming. Then type 2 is chemically treated product and type 3 is pasteurised product, Behringwerke.

Then on to the following page, please. I think the form of words which correctly describes the licensing background is that at the top of the page, is it, an exception for a clinical trial certificate? So the licensing authority, as I understand it, grants a certificate for the purposes of a clinical trial. So

that enables the product to be used for these limited purposes in Britain. Am I correct about that or is this not really your field?

A. It's not quite my field but it's always better to conduct a study under what's called a CTX, clinical trial exemption certificate, because that is registered with the CSM. There is a protocol, the manufacturer takes responsibility for the product, compared with a named-patient basis, in which the physician is much more liable for the product and any adverse effects.

You would need to ask someone from the CSM who knows more about licensing, but I think to get a CTX you have to put in your protocol and probably fill out a form, and if you don't get an adverse comment within something like six weeks, then you can proceed with the study. But I may be wrong about that. But CTX is really the way to conduct these studies in an organised way.

Q. Can we scroll down, please, to where we see the mention of AIDS? We can note that Dr Craske is saying:

"Infective theory for the causation of this disease is still the one that fits all the known facts."

He says:

"In light of this, consideration must therefore be given to the possibility that Factor VIII concentrate prepared from plasma donations obtained in the USA might

be contaminated with a putative infectious agent associated with the cause of AIDS."

I think he is going on to say that it can't be assumed that heat-treated products will render the virus inactive. The last sentence on that page:

"There is as yet no product which is not made from sources likely to carry a risk of a putative virus associated with AIDS being present in the plasma pool from which the Factor VIII is fractionated and which is heat-treated."

Then on to the following page:

"This will cause a problem when the criteria for clinical trials of these products in the UK have to be considered. Since the only way of ensuring the susceptibility to non-A non-B viruses is by using patients who have not previously received Factor VIII or IX concentrate, a choice will have to be made between using heat-treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate, which appears to carry a 100 per cent chance of transmitting non-A non-B hepatitis ... there is a ... considerable ethical problem."

As I understand it, Professor Ludlam -- and you do say this elsewhere, I think we will notice it later in

your statement -- you were not interested in participating in any of the trials of these products at that time. Is that right?

A. Of the commercial --

Q. The commercial ones?

A. -- derived from US plasma? No, I wasn't.

Q. Yes. And what was your thinking?

A. My thinking was that these concentrates might contain the putative virus, putative at that stage. This is September 1983. That the risk of my patients getting HIV from these might be greater than treating my patients with NHS Factor VIII manufactured from an AIDS -- if I can call it an AIDS free country, an AIDS reduced country, Scotland.

Also SNBTS was developing heat-treated concentrates and I thought those would carry a lower risk of a putative virus.

Q. Right.

THE CHAIRMAN: Is that the end of --

MS DUNLOP: Given that it's 11 o'clock, that's probably a natural break.

THE CHAIRMAN: Professor Ludlam, Ms Dunlop passed over very quickly the general characteristics of haemophilia and we have heard quite a bit about it. But one general point I think is becoming of interest. When we visited

Newcastle, the clinician there clearly had a continuing involvement in Africa, and it's referred to in the preliminary report where he showed us photographs and gave us some description, and when Dr Winter came, he spoke of having an interest in Islamabad in particular, where there is a population largely untreated. Do you have any foreign interests of this kind that instruct one as to what's happening worldwide?

A. Not as specific as those. I have gained a lot of insight into Eastern Europe, and the difficulties there of using very small amounts of Factor VIII, in my capacity as president of the European Haemophilia Association.

THE CHAIRMAN: So you do have some broader base, as it were?

A. I go to World Federation Haemophilia meetings and meet people there who come from countries where there is very little Factor VIII, and I see some of the consequences, just from the people who come to these meetings, badly crippled.

THE CHAIRMAN: I think that if anyone wishes to follow it, to get the broader picture, that's a sort of introduction into it, if you care to follow that. We will have a break now.

(11.04 am)

(Short break)

(11.31 am)

THE CHAIRMAN: Yes?

MS DUNLOP: Thank you, sir.

Can we just go through 1984, Professor Ludlam. To do that, I think we can return to what I call the timeline. It's [PEN0150468], at page 4. Much of this has been mentioned already too, professor. Just so that we understand what you say in February 1984, particularly in the second paragraph, because it's slightly confusing, in this study it was thought that patients had antibodies to HTLV 1. In fact, they were anti-bodies to HTLV-III but they cross-reacted with HTLV 1 virus.

A. That's my understanding.

Q. Right. I'm hoping that when we read that later, it will make sense. Then Dr Ratnoff is mentioned in May 1984, and we do have that publication. Actually I think that's a different reference there but we have the letter from the Annals of Internal Medicine, which you refer to elsewhere, the reference for which is volume 102, the Annals of Internal Medicine, page 412, which I think makes the same point as you make in brackets and we will arrange for that to go into court book. The interesting paragraph in it for our purposes is that at the end. I'll just read this for now

because, I'm sorry, we don't have it in court book.

I think there are copies around, sir. It's just a single page.

THE CHAIRMAN: Is that what arrived this morning?

MS DUNLOP: It is on the right-hand side and it is headed "Haemophilia and the Acquired Immunodeficiency Syndrome."

THE CHAIRMAN: Yes.

MS DUNLOP: I suppose again, professor, there are two different points here, which we shouldn't conflate. One is that those people who did make a policy change, or who did effect some shift in their treatment, in some instances unfortunately patients were already infected, so a change anywhere in the world could have been too late, at least for some patients. But the other point is whether patients were receptive to the suggestion that a change should be made. I think perhaps it's really the second aspect that these authors are commenting on in this letter, particularly in the final paragraph. I'll just read it out for the benefit of anybody who doesn't have it in front of them:

"Curiously, this formidable morbidity and mortality has done little to shift behaviour. Among the 84 survivors ..."

That is of 91 patients who were in home therapy

programmes in northeast Ohio:

"... among the 84 survivors, only five have turned to the use of cryoprecipitated anti-haemophiliac factor, although no cases of the syndrome have been reported in patients treated with this agent."

It looks a little more reliable than searches on the internet trying to find out what happened in Cleveland, and it looks that really very little was possible by way of change of treatment product.

A. I'm sorry, I haven't got my copy because I have distributed it --

Q. I'm sorry. I'm sure you will get it back, professor.

A. I just wanted to make the point that -- if I could just have a moment to ... (Pause)

Yes, it's not clear about the severity of the patients with haemophilia and it may be the five who opted for cryoprecipitate may have had a moderate or mild haemophilia and were prepared to switch because they didn't need very much treatment anyway. They might have only had three or four infusions a year and were happy to come up to hospital, compared with a patient with severe haemophilia who might bleed once or twice a week.

Q. I take your point, professor, and it would be interesting to know that, but again, I suppose we don't

want to get distracted into investigating HIV in Cleveland, Ohio instead of investigating it here.

THE CHAIRMAN: They are all on home treatment but I don't suppose one can infer anything from that without knowing what the regime was.

MS DUNLOP: I think, Professor Ludlam, we have talked, in the evidence we heard on this topic so far, particularly with the other two witnesses, about practice in Belgium, about Finland, these being countries where cryoprecipitate continued to be used quite widely. As I understand it, in Belgium and in Finland American concentrates never really gained a foothold. The patients really, I think, had to wait until the Finns had developed their own domestic concentrates. Are you aware of anywhere in the world where concentrates were already widely used in the treatment of haemophilia and there was a large scale shift back to cryoprecipitate because of AIDS? Do you understand the distinction between --

A. Yes.

Q. Countries where they were on cryoprecipitate because that was the status quo?

A. Yes.

Q. But other countries where the possibility of reverting to cryoprecipitate may have been mooted and actually was

successfully pursued as a policy.

A. I can't recall anywhere.

Q. Right, just to carry on and look over the page. We see you mention the Gallo report and the French research. At the top of page 5 is the reference to Professor Bloom's piece in the Lancet, which we have already looked at. I think at that point it was a total of 11 because there had been three cases previously reported from Spain and then his research uncovered a further eight cases of AIDS, 179 with immune abnormalities. Then this is the other article, which I referred to earlier, from your team in Edinburgh.

A. Yes.

Q. The following paragraph which begins with "AIDS" in block capitals. Just incidentally, I think there is a typing error in the sentence beginning:

"In 1982 ..."

My suggestion for that sentence would be that it should read:

"In 1982 haemorrhage was the major cause of death amongst haemophiliacs."

A. I suspect you are correct. This was a document that is headed as a draft.

Q. Yes, I appreciate that. I did look up the article, professor, and it seems to give an incidence of AIDS

cases amongst patients attending haemophilia treatment centres of 0.6 per thousand in 1982 and 1983 but 5.4 per thousand in the first quarter of 1984. So a large rise, and that, I suppose is not surprising, is it?

In July, the Melbye article, which again we have referred to. Strictly speaking, I think this was a preliminary letter about the position in Denmark, then in the second half of 1984 the whole study was published comparing the position in Denmark and the position in Glasgow. Is that correct?

A. Yes.

Q. Just for reference, that's mentioned in the preliminary report, paragraph 8.90. Then August. September, that piece from the Lancet, also discussed in paragraph 7.92 of the preliminary report -- if people are looking for a reference to it.

Then over the page we see your report starting to come through about commercial heat-treated products. MASAC recommendations in October. November 1984 and then December. And this is the publication I mentioned a moment ago about the Scotland/Denmark work. Professor Ludlam, in our preparation we have identified two groups of patients in Scotland who acquired HIV from treatment with blood products. One group is the group in Edinburgh, sometimes called the "Edinburgh cohort",

and the other group is the group at Yorkhill. But having looked at the spreadsheets provided, particularly the Glasgow Royal Infirmary spreadsheet, there do seem to be other people -- or there must be other people infected by NHS product, Scottish NHS product. I think you say that yourself, but of your own patients, and also other people infected by commercial product.

Can you explain to us why these seem to be single instances, rather than a third cluster of some sort?

A. Well, can I say that -- I don't want to get caught up in semantics, but the patients that I looked after and look after in Edinburgh are made up, in a sense, of -- who are HIV positive -- two groups. There are what are called the cohort patients, who are those who received what we think was the implicated batch.

Q. I should add that there is a member of that group who is one of the Aberdeen patients, which I think we hadn't appreciated until recently, at least insofar as one of the Aberdeen patients with HIV received the same batch.

A. Yes.

Q. You knew that?

A. I was aware of that, yes.

Q. Yes, right.

A. But then I have another small group of patients, five, I think, who we don't think were infected by the

implicated batch. So the Edinburgh group of patients is more than just those --

Q. I'm sorry if I didn't make that clear.

A. But they are a cohort of patients, if you like. But I think, so that we are don't get confused, those that got the implicated batch are the ones I refer to as the cohort, and then there are the other small number, about five, whom we don't think were infected by the implicated batch.

Q. If one, in a sense, saw these people as being more like the Glasgow Royal Infirmary report and said: why then are those people, who arguably are about 17 in number, why is there no common thread? Or may there be one and it has just not been discovered?

A. It's a very interesting question and we have wondered about it and I have wondered about it in preparing for this Inquiry and revisiting some of the data.

One or two of the Edinburgh patients who became infected with HIV, my recollection is, did receive some cryoprecipitate. So it's possible that individual donations of cryoprecipitate could have been infected and could have infected just that individual who received it.

Q. Right.

A. There are then, I think, just a small number of patients

who seem only to have had concentrate and it is very difficult actually to know how they came about their infection, assuming that they got it from the concentrate. It's possible -- and I could go back and look at the figures again -- they might have received a very large dose, as it were, of one batch, they might have had a bad bleed and got a lot of one batch. There is, we believe, quite a bit of individual susceptibility to infection with HIV, and it's possible that these individuals were particularly susceptible and therefore just a small amount of virus that wasn't enough, if you like, to infect other people, resulted in their infection.

So it's a little bit of a puzzle. It was a lot of work going over all the transfusion records of just the patients in Edinburgh that I did with Dr McClelland as soon as this episode came to light, particularly when you have to do it with pen and pencil because the transfusion records weren't in those days computerised.

I was aware that a small amount of the implicated batch had gone to Glasgow and that one person had seroconverted.

Q. In Glasgow?

A. Aberdeen.

Q. Aberdeen, thank you.

A. Aberdeen, I'm sorry. 50 bottles of the implicated batch went to Aberdeen and one individual received, I think it was, four bottles and was later found to be positive, anti-HTLV-III positive.

Q. I can't ask you about Glasgow Royal Infirmary because that's not your hospital, but have you looked at the spreadsheet from Glasgow Royal Infirmary?

A. The one --

Q. The 12 cases that they list?

A. I have, yes.

Q. Yes. Could you see any kind of pattern or common thread?

A. I'm sorry, I don't have it before me.

Q. No, it's all right. I'm not wanting to go into this in detail, I just wondered if anything had struck you as an expert that might not strike us?

A. I saw there were two or three patients who, it seemed, had been predominantly treated with NHS concentrate, but in my mind there was a hesitation as to whether they might have received commercial at some stage. I can't remember whether they had been treated in England or not.

Q. I think we accept that there are all sorts of things that may confound us, that people may have had a treatment that has not been documented and it is not

obvious when somebody became infected; all these factors. But I just wanted to confirm that there is not something that you think we are missing about the figures from Glasgow.

A. No.

Q. No.

THE CHAIRMAN: Could I ask a little about the documentation? If one has general groups and then specific, apparently discrepant, examples, I suppose one thought what must occur is that the individual in this very mobile society might have been treated elsewhere. Are the records comprehensive enough to cover, let's say, casual holiday treatment abroad or in England or whatever?

A. Well, that's one of the advantages of having our UK national register, in that we try and pick up these extra treatments given when people are travelling. And on the whole and particularly now, I think it works pretty well.

The difficulty is that patients, if they are a visitor on holiday away from their usual centre, may well turn up out-of-hours, Saturday afternoon, they are seen by a relatively junior member of staff, who gives them some Factor VIII and sends them away. And that might not be recorded in the usual way because the usual

staff are not available.

We try and keep impeccable records but there is no other area of medicine where we try and keep such impeccable records. We can't guarantee that they are complete. Certainly if someone goes abroad, there isn't an automatic way in which their treatment will be relayed to the home haemophilia centre, although sometimes our patients attend haemophilia centres in this country and abroad and we get a letter to say that they have attended and they were treated with this product and here is the batch number and here is the amount they had.

Q. Yes. We do understand, professor, that for the purposes of the Inquiry, considerable efforts have been made to reconstruct events of the early 1980s but in many cases the clinicians will not be the same and unfortunately, of course, a lot of the patients are dead as well. That's certainly true of the Glasgow information and it's perhaps unsurprising that it's very difficult to get an accurate sense of what the explanation might be for infection in particularly that group of people.

Can we just look quickly at the next page, which is the end of 1984? Before going into 1985 I just wanted to look at a section headed "Treatment policy, 1982 to 1984", which is in [PEN0150385]. Again, professor, i

think we have covered most of this.

It's page 23. Thank you.

Professor Ludlam, this is your document that was drafted 20 years ago. I wondered if you would still say, having reflected on it further and having prepared other documents, what you say in the last sentence, that:

"There was much evidence to demonstrate that such changes were not related to a putative AIDS virus."

A. No, I think I stick -- I think that a lot of the immune changes that were demonstrated, the early ones may well not have been due to HIV.

Q. Really I just wondered, given that the paragraph begins by --

A. I can't see the top.

Q. I'm sorry, it begins in mid 1983.

A. Right.

Q. It's always difficult to know, when people are speaking, quite what timeframe they have in mind, but if we were to assume that this is meant to be the middle of 1983, do you still say that there was much evidence to demonstrate that such changes -- this is changes in people with haemophilia -- were not related to a putative AIDS virus?

A. In which population?

Q. Well, I'm just looking at a view you expressed. I suppose we can look a little higher up in the paragraph. The question you have posed is a rhetorical question:

"Was it then appropriate to change therapy throughout the UK because a few haemophiliacs had developed AIDS in the USA?"

You say:

"There was much evidence to demonstrate that such changes were not related to a putative AIDS virus."

We have spent quite a long time looking at it, professor, and it is very difficult to prove a negative. So I just wondered if that's perhaps in retrospect pitched a bit high.

A. Well, we didn't know at that time -- and in a sense didn't know for quite a long time after that -- what proportion of haemophiliacs in North America were infected. It could have been a very small number, a high percentage, as it were, who went on to get AIDS, or it could be a large number who very slowly, over a number of years, as has happened, went on to get AIDS. But at that stage it wasn't at all clear whether there was a small number in the States who were infected or a large number of people with haemophilia.

Q. So you don't want to change the wording of that?

THE CHAIRMAN: We are almost getting down to language here a bit. We do know that on your own studies, there were quite a lot of changes in the CD4/CD8 ratios in patients who did not develop AIDS. But of course, what we have is a much more general proposition, in the last two lines:

"There was much evidence to demonstrate that such changes were not ..."

That almost looks like a universal proposition, whereas we do know that some of your patients ...

A. Okay.

THE CHAIRMAN: So I just wondered whether a minor change in language would satisfy both you --

A. I think --

THE CHAIRMAN: Would you like to try that?

A. Yes.

PROFESSOR JAMES: Could you insert "necessarily" before "related"?

A. Yes.

THE CHAIRMAN: You are quite happy with Professor James' evidence in this matter?

A. I think that's a reasonable choice of word, thank you.

MS DUNLOP: We do have a lot of material from you, Professor Ludlam, which will inform our perspective on what was in your mind as a treater in 1983, and

obviously the whole of that evidence is available. So I don't want to create the impression that anything will turn particularly on this one sentence; it just rather caught my eye, that was all.

On the next page there is a quite a complex discussion of the possible viral aetiology and then you pose another rhetorical question, if we go slightly further down. We are back to the same material really. Perhaps it would be worth bearing in mind here, would it, that the preliminary results from Denmark were reported in July 1984 and that was that 14 out of 22 patients appeared to be infected. It looks to have been possibly the first of a succession of reports coming through, certainly for Europe. They were, of course, infected with LAV and we understand that at that point there was a debate about was LAV the same as HTLV-III. This is discussed in our paragraph 8.90, and 14 of the 22 had LAV.

A. Yes.

Q. On to the next page you have set out the options, and again we have discussed these possibilities -- well, we haven't discussed stop treatment because I don't imagine that was ever a realistic possibility.

Reverting to cryoprecipitate. On to the next page. Perhaps the only point to make on this page, page 26,

where you say that:

"The extent to which it ..."

That is cryoprecipitate:

"... does so [that is protecting the population of haemophiliacs from viral infection] depends upon the prevalence of the virus in the donor population. In some European countries, for example Sweden and Belgium, cryoprecipitate had been used extensively for many years prior to 1982 and in these countries prevalence of HIV infection in haemophiliacs is low."

I think we have noted that from a Council of Europe table, which has Belgium with an infection rate of 7 per cent, but the overall prevalence of HIV in the Belgian population was actually quite high, was it not?

A. It was.

Q. So this is, in that sense, a remarkable outcome?

A. Yes.

Q. On to the next page. You go on to discuss option C:

"Stop importation of commercially manufactured Factor VIII, rely on NHS product."

Which would have involved using cryoprecipitate as well, I think, as you say. Then on to the following page. I understand, professor, that this is a draft document but I think at the top of that page, the part we can see on the screen, it might be that the years

need to be corrected. Is that right? For example, "the HIV outbreak in the summer of 19 ..." that should be "84", should it? It is just the parenthesis:

"The HIV outbreak in the summer of 1983 in Edinburgh was completely silent clinically and was only discovered ..."

Or is this in drug abusers?

A. This is in drug abusers. I'm sorry, I didn't make that clear. Yes, that only came to light in --

Q. In 1985?

A. -- early 1985.

Q. I understand, thank you.

You mention Australia also and we have also looked at an article which charts the eventual position as far as HIV infection in people with haemophilia in Australia is concerned, and Dr Winter spoke a bit about that. Just for the record, in case anyone wants to look back at that, the later Rickard article we have as [PEN0120255]. Then:

"(d) develop virus-reduced Factor VIII and IX."

This is going to be examined in the Inquiry more in the context of topic B3, which is devoted to that whole area. Then option (e) about being more attentive to individuals in high risk groups as possible blood donors. I take it it is only because this is written

for a litigation in England that you don't mention the efforts made in Scotland. We do know that there were efforts made in Scotland as well. You say that:

"Efforts were made by the regional transfusion centres in England and Wales to persuade donors in higher risk groups to refrain from donating."

Dr McClelland told us about what happened in Scotland too.

A. I think Scotland was well abreast of other countries.

Q. Thank you. Then over the page.

Sir, there is quite a lengthy section in this particular statement, which I don't think really needs any examination. Perhaps we could just note for the records that going on to and including page 36 is narrative which is either, I think, uncontroversial or material we have already discussed. Perhaps the only qualification to that is that on page 31, professor, you do refer to the Lancet editorial but you put it as March 1983, but I think we have established it was actually April 1983. So just so that we don't get confused when we come to look at this in retrospect. You see that reference to the editorial in the Lancet?

A. Near the bottom?

Q. Yes. Where the writer had wondered whether the abnormalities in haemophiliacs were the submerged part

of a large viral iceberg. I think we know that that's a 2 April 1983 editorial. I don't think there was another one.

A. It doesn't say -- does it say March here?

Q. Yes, it says:

"Also in March ..."

A. I apologise, yes.

Q. Yes, it is not a major issue.

The next section. If we can move then to 35. 35 on to 36 is, as I say, I think, sir, not controversial or already covered. 37, again, stemming from the fact that this is a draft document, it might be necessary to insert some words into the third line. Well, the whole sentence really. Although the initial article identifying a possible AIDS virus appeared in May 1983, it might be make more sense:

"It was not until the confirmatory report of May 1984 that the ..."

Perhaps that should be:

"... the extent of the infection in haemophiliacs became apparent."

Would that make sense?

A. Yes, it would.

Q. Yes. Then in the following paragraph you refer to the trials. We looked at Dr Craske's letter from July 1983,

or at least his paper from July 1983, written at about the time when the trials are about to start. You say:

"Both these products resulted in a high transmission rate of hepatitis."

Actually, I think, according to a letter from Dr Walford that we looked at last week, the Hemofil certainly was shown to transmit hepatitis in chimpanzees. Just because it's your letter, professor, I think we should look quickly at [SNF0013211]. I think that "contain" should be "continued" by the way, should it? "manufacturers continued research," rather than "manufacturers contained research..." in the third last line.

A. Yes.

Q. If we just look at [SNF0013211]. Again, it is a letter we have seen before. This is on the topic of trials. I suppose this encapsulates your reasoning at that time, which you have explained to us earlier this morning. Is that correct?

A. Yes.

Q. Really two aspects to it. Firstly that your patients are not being treated with commercial product at all so far and you don't want to start, and also that there is a new higher purity heat-treated SNBTS Factor VIII coming and you are hoping that your patients will be

treated with that.

A. Yes.

Q. When you say:

"... reserve any patients we may have for the testing ..."

Would it be any particular group of patients that you would be wanting to test this new heat-treated product on?

A. Well, if we were wanting to test it for its safety for the transmission of non-A non-B hepatitis, then really the only way you can do this is to use patients who have not received blood products previously.

Q. Yes.

A. Such patients are rare.

Q. Yes.

A. At any one time.

Q. Can we go back, please, to where we were in [PEN0150385]? On to page 38:

"By December 1984 it was clear that at least two batches of NHS Factor VIII, one in England and one in Scotland, perhaps, had been contaminated by HIV and had resulted in infection of patients."

I think perhaps there is a chunk missing from the next but one sentence, I would propose:

"... the presence of antibodies raised the question

of whether the virus had been cleaned from the body ..."

Is that --

A. It should be "cleared".

Q. "Cleared", right?

A. Yes.

Q. But should it say something before "cleared", "the presence of antibodies":

"... the presence of antibodies raised the question of whether the virus had been [cleared] from the body, as is the case for most viral infections, or whether patients might harbour the virus."

That, I think, makes more sense.

The following paragraph, where you are discussing the meeting, the UK reference centre directors' meeting in December 1984, you say, this is the second sentence:

"The ideal product would have been a NHS heat-treated concentrate."

What was the second choice?

A. Heat-treated commercial concentrate -- well, or heat-treated concentrate. That was the second choice.

Q. So your view at that time would be that for those people, those patients, who couldn't have access to a NHS heat-treated concentrate -- and I suppose we would be talking about patients in England and also Factor IX patients at this point -- the second choice would be

a heat-treated commercial concentrate, rather than unheated NHS.

A. That was an extraordinarily difficult decision to make, to choose between those two at that time. There was huge discussion in this meeting even about whether or not we should recommend heat treatment of NHS Factor VIII. I remember a very protracted discussion, a very painful discussion, because we had only knowledge of some of the facts. I think what some of us hadn't appreciated is that the FDA had licensed some concentrates heat-treated in the States. There was a great deal of anxiety about heat treatment and whether this would modify the molecule of Factor VIII, such that many patients might produce antibodies. If they did, then it might well not be possible to stop bleeding in the event of haemorrhage. So this was particularly difficult if one was going to go over and recommend it as general treatment for everybody, not just two or three patients, to try and see what happened.

So it was a very difficult meeting, very painful meeting, and there wasn't unanimous agreement, is my recollection. But there was consensus that we should move towards heat treatment.

Q. Yes. And of course, for an American heat-treated product to be used in the UK for general use, it would

need to be licensed for the UK as well.

A. Ideally. Otherwise we are back to the named patient basis.

Q. Yes.

A. And that's why, I think, the CSM suddenly realised it had a problem in February 1985. But this was a very difficult decision to make, and as I have said in this report, I'm sure, some eminent immunologists wrote immediately to the Lancet saying that they were not sure that we were doing the correct thing.

Q. We can proceed to really the same period, where it's discussed in your most recent statement, [PEN0150445]. You see the same meeting referred to on page 11, paragraph 37.

A. I make reference at the end of this to two unfortunate events in 1991, when the Factor VIII molecule did become modified during its manufacture and led to an outbreak of inhibitors in two groups of patients. So it wasn't idle speculation.

Q. Yes, indeed. And you say, if we go a little bit further down, please:

"As our subsequent monitoring studies demonstrated, there were no further transmissions of HIV, despite the retrospective discovery that some batches of SNBTS plasma had been contaminated with HIV."

I think that reference must be an article in Vox Sanguinis, which we also refer to in the preliminary report. Yes. Can we go back then to 385. That's [PEN0150385] at page 39. You refer to an advisory document which was drawn up. I think we should look at that. That's [SGF0012388]. We can see that it wasn't just the reference centre directors who had discussed these recommendations, that Dr Lane, who was from BPL, Dr Cash, Dr Gunson, the blood transfusion -- Dr Mortimer, I think was a public health doctor; is that right?

A. The minutes of that meeting are available.

Q. Yes. We have that too. I was just going straight to the recommendations. Dr Craske there, perhaps inevitably.

The background; can we just go through it? Look at it until we come to the recommendations. General precautions. Donors. On to the next page, please. And the recital of current position as far as concentrates that were available is concerned. Edinburgh:

"From now on all Scottish Factor VIII will be dry heated to supply Scotland and Northern Ireland."

Then:

"Options in probable decreasing order of safety."

This is options for Haemophilia A.

But a note that actually the distinctions between 3 and 4 are debatable, and I suppose the second choice we see is single donor cryo. So maybe I should have asked you about the third choice, but between 3 and 4 caused a lot of debate, I take it?

A. Yes.

Q. Then on to the next page, if we could, please. Haemophilia B. It says that:

"Individual directors may wish to make up their own minds."

And I think, although this paragraph appears under Haemophilia B, it is meant to apply to both Haemophilia A and Haemophilia B, I take it. I think it must be because it reverts to talking about Factor VIII. It says:

"This is particularly true of unheated NHS material."

Can we finish looking at that. Go to little bit further and on to the next page, please:

"It is recommended that patients be HTLV-III antibody tested."

Then certain recommendations about information which again is another topic for further on in our Inquiry. Can we go back, please, to [PEN0150385], and again noting, I think, that from page 40 onwards you are

telling the story from this point, and again, sir, in the interests of time, just to note that the narrative continues, 41, 42. I'm not going to ask any specific questions or highlight any points. On 43 you do say:

"In February 1985, it was reported that a UK patient with Haemophilia B, treated exclusively with NHS Factor IX concentrate, had become anti-HIV positive. As a result, some haemophilia directors opted to treat patients with commercial heat-treated Factor IX concentrate instead of unheated NHS material."

I just wondered what you did in Edinburgh with your Haemophilia B patients after discovering what had happened to a number of your patients with Haemophilia A. What did you do from November/December 1984 onwards?

A. I think we went on with NHS unheat-treated Factor IX. The chance of getting infection of HIV or HTLV-III in Haemophilia B was very much less. We knew that at that stage. Probably a number of different reasons; one is the way in which the Factor IX is manufactured and may well have tended to exclude the virus. The other is that the immune systems of people with Haemophilia B appeared to be less abnormal than those with haemophilia B in the absence of HIV in both groups, and it's not quite clear even now why that should be because both

groups had Hepatitis C.

Q. Yes, I think, professor, you said:

"The immune systems of people with Haemophilia B appeared to be less abnormal than those with Haemophilia B ..."

I think that should be "Haemophilia A", should it?

A. Yes.

Q. Then lastly for this document, on the following page you say:

"HIV transmission has been reported from dry 60 degrees centigrade heated concentrate."

I think that was actually an Armour product, at least as far as we have been able to discover. Does that accord with your recollection?

A. I think that's my recollection.

Q. That, I think, is the end of our need to look at this document. If we go back to 0468, [PEN0150468]. You have noted for us exactly the point you made about the reservations of the wholesale switch to heated product. Again, perhaps we can note this narrative without particularly going through it.

(Pause)

Then on to the following page. Just for the record, Professor Ludlam -- sorry to be pedantic but it's in case people are thrown by this -- the reference at the

very, very end of that page is the Annals of Internal Medicine. If we look at the letter, you can see it is volume 102, not volume 103. So if some people were going away and looking at the hard copy --

A. You are correct.

Q. It is March 1985. The following page as well, please. Right in the middle where there is a reference to AIDS cases in haemophilia. It should be "reaching 1 per cent", not "reading 1 per cent" is that right?

A. Yes.

Q. Then September 1985, you referred to what happened in Newcastle. The 99 Haemophilia A patients. Is that all Haemophilia A patients in Newcastle then, not just severe patients? It doesn't matter if you don't know, I'm not going to take time by trying to find out. I just wondered if you knew.

A. I suspect it's all patients, because in the third line it says:

"Two patients with basal factor 8 level of 5/10 per cent were positive."

Q. Yes:

"A patient with mild Haemophilia A given concentrate for a major bleed."

As well?

A. Yes.

Q. It's just that rates at that sort of level, around about 75/76 per cent, you see in other centres, but they tend to be the rates of patients with severe haemophilia.
A. Yes, that's correct --
Q. Then --
A. -- but it illustrates the need to give concentrate to mild haemophiliacs on occasions with bad bleeds.
Q. Yes.
A. As we were discussing yesterday.
Q. I see that. Also three people who were heterosexual contacts were anti-HTLV positive too. Then on to the last page. In October 1985 that reference to:

"Evidence that heating freeze-dried Factor VIII at 60 degrees for 30 hours (Armour) does not transmit HTLV-III."

Bearing in mind that of course you think that you wrote this in about 1988, but eventually there was evidence that that was not a successful protocol.
A. Yes.
Q. So that concludes that document.

Then just to go back to your most recent statement, [PEN0150445], at the foot of page 11. This is paragraph 38 that has appeared in front of us:

"Towards self-sufficiency in Scotland, Factor VIII concentrate data collection."

The following page. Insofar as Edinburgh is concerned, you tell us in 39 that:

"Information on each and every infusion of concentrate was recorded manually in a logbook. The details that [you] included were date, product, batch number, dose and reason for infusion."

So that was a manual system in operation when you took over?

A. Yes.

Q. Yes. Then you say that in 2010, in contradistinction to the part-time clerical officer in the early 1980s, you now have two full-time staff keeping records of these matters.

A. And fairly sophisticated computers.

Q. Yes. So the computer system cuts still further the time required. It is a slight paradox. You might have hoped that computerisation would make it simpler but for whatever reason you need two full-time staff.

A. It makes it easier to analyse the use of concentrate and do the sort of studies about who received which batch that we were doing back in 1984 with the implicated batch.

Q. Yes. You are networked between the East of Scotland haemophilia centres. So you, Dundee, Aberdeen and Inverness?

A. Yes.
Q. Right. Something else that's of interest to us is covered in paragraph 42:

"Commercial concentrates for use in Edinburgh were purchased through and stored in the SNBTS blood bank at the Royal Infirmary and data on use would therefore have been readily available to SNBTS."

Then you discuss recording of the use of PFC product, and on to the next page, 43, you say:

"The important Factor VIII statistic was the amount of concentrate available in the SNBTS blood bank in the Royal Infirmary in Edinburgh. The 'monthly' deliveries from PFC ..."

Why is "monthly" in inverted commas?
A. I think they were described as "monthly". It didn't mean to say they always arrived on the first of the month.
Q. Right.
A. We expect the delivery van at some time in the month.
Q. Well, sometimes, I suppose it maybe came more frequently than once a month?
A. Yes, that's also why it's in commas.
Q. 44, cryoprecipitate. 45, UKHCDO statistics; different frame of reference for different time periods. In 46 you say:

"In Edinburgh it was agreed that the commercial Factor VIII concentrate would be bought on behalf of Lothian Health Board and stored in the SNBTS blood bank. This arrangement was agreed with Lothian Health board at a meeting in 1981. Subsequently, in 1983, it was agreed to change the arrangements and for commercial concentrates to be stored in and issued from the Royal Infirmary pharmacy."

I think you have actually provided letters dealing with both these episodes. We will perhaps just look. I think it is the 1983 one. [PEN0150480]. We can see what's happening here. This is you taking over the purchase of commercial products; perhaps more correctly, the ordering of the commercial product.

A. And that they should be stored in the pharmacy.

Q. Dr McClelland had his reservations but he was prepared to allow it to proceed.

We have seen that this whole topic of who ordered commercial product and so on seems to have featured regularly, particularly from some of the English directors, where there were various attempts made by the Department of Health to change the system, and I think it's fair to say a degree of reluctance or even opposition on the part of the directors in England to some of the suggestions from the Department of Health.

Is that right?

A. That is correct, and that goes back to the 1970s as well.

Q. Right. So quite an old story.

A. Yes.

Q. Yes. Then if we move forward to paragraph 57, please you talk about general arrangements for interactions between you and SNBTS. I don't think we need to go into this in any detail, professor. Thank you.

On a day-to-day basis -- this is paragraph 59 -- you interacted with Dr Frank Boulton and Dr Brian McClelland. In our database, Professor Ludlam, we have a whole sheaf of correspondence involving you and primarily, but not exclusively, Dr Boulton, really about the amount of NHS product you were using; how that related to other use in Scotland. You perhaps feeling you weren't getting enough or the arrangements were insecure and there being a certain amount of strain on the other side perhaps in meeting your requirements. Is that a reasonable summary of the position?

A. I think it is. It was difficult because I wanted more Factor VIII concentrate. They had a limited supply. Wherever there is limited supply, increased demand, there is stress and strain.

Q. Yes.

A. Looking back on it and the correspondence I have looked over, it was not always clear from the correspondence exactly in a sense what was on offer. You have the correspondence, we could go through it if you would like, but there is, in some parts of the correspondence, reference to numbers of bottles. Sometimes to numbers of units, and it wasn't always possible to equate numbers of units with numbers of bottles because the unitage of Factor VIII in different batches of Factor VIII concentrate varied quite substantially.

I think there was the suggestion that I had not understood the situation about the supply, what was available, in correspondence with Dr Boulton and perhaps with Dr McClelland. There is a letter from Professor Cash in October of that year saying that he thought Dr Ludlam had got his maths about right, they having sent 6,000 litres of plasma to PFC for fractionation.

I have reviewed the correspondence because it was passed to me a few days ago, and I'm interested to read in Dr Peter Foster's evidence as presented to the Inquiry, his very full evidence. He has looked at the stock levels and in this time when I was having difficulty being able to supply the patients with as much Factor VIII as I felt I had been allocated earlier

in the year, I note that the SNBTS stock of Factor VIII actually was rising very rapidly. You will see that it's 3.8 million units for 1982/1983, at a time when I felt I was being lent on very heavily to rein in my use.

So I think there may have been a difficulty in us, us being haemophilia directors and SNBTS, perhaps not being fully aware of what the stocks were around Scotland, because I think Dr Mitchell, Ruthven Mitchell, in March 1983 in a letter to John Watt refers to him having quite large stocks of concentrate and he didn't want any more; or words to that effect.

We were trying to work as a team, and I think we worked very well as a team actually. But I was being expected, not only to look after the patients but to keep a beady eye on what the deliveries of fresh frozen plasma were to PFC, and that was area that was, if you like, right outside my area of responsibility and day-to-day concern and day-to-day knowledge.

So it was a difficult time. I think we did our best between us, but it was not easy.

Q. I suppose in all this, PFC are the supplier, you are the customer, and Dr Boulton and Dr McClelland are really sort of middlemen, are they?

A. They hold the stock in the cupboard for me.

Q. Yes, but also they are monitoring what is being collected and sent to PFC for --

A. Yes.

Q. -- production in the first place?

A. Yes.

Q. Yes. Perhaps --

A. I think also there was an element of regionalisation, about how much concentrate came back to each region. It may have been dependent on the amount of fresh frozen plasma supplied from that region. That was the English system, and it was a sub-optimal system for reasons we can go into if you want.

In Scotland we felt we had a nationally funded Blood Transfusion Service and national single Protein Fractionation Centre, and the thing should have worked as a whole rather than being divided up in a pro rata basis over the divisions of the country.

Q. Perhaps you put the matter in a nutshell in your penultimate paragraph in this section. It is actually within numbered paragraph 60, but on to the next page:

"30 years on it is difficult with the information currently available to reconstruct accurately and in detail the expectations, discussions and negotiations over the supply of clotting factor concentrate."

Then the last sentence:

"There will always be tension where demand outstrips supply."

THE CHAIRMAN: Did the cooperation that you referred to extend to cooperation with other haemophilia directors and among the blood transfusion regions? Or was it just a matter between you, your BTS people, and PFC?

A. I negotiated with Dr Boulton and Dr McClelland and if they want more product, they would -- as I understand -- contact the Protein Fractionation Centre or potentially, as you see in the correspondence, other blood transfusion centres within Scotland who may have held the stock. But I didn't negotiate, either with the haemophilia centres or with other blood transfusion centres, because that was not really my lines of authority.

MS DUNLOP: Yes.

THE CHAIRMAN: Perhaps one could never hope to get a fully integrated system unless people were prepared to be open with each other right across the board? Maybe we will have to look at it in some detail.

MS DUNLOP: I think, sir, because I don't want to take up any more time on this just now, but I was imagining that we would look at the correspondence with Dr Boulton, and if you wanted -- I suspect, Professor Ludlam, if there was some particular issue that you felt hadn't been

covered or that we really needed to look at, we could perhaps make arrangements to clarify that after Dr Boulton has taken us through the correspondence. Does that seem acceptable?

A. Yes, fine.

Q. Then you have paragraph 61:

"Commercial Factor VIII concentrate use."

You have actually provided an appendix dealing with this. I think we need to keep the text, if we could, please and juxtapose the appendix, which is [PEN0150225]. Thank you.

Just so we understand the table, professor Ludlam -- I'm sorry if this is a stupid question, but every time we see "A" is that the same person?

A. Yes.

Q. Yes, that's what I thought but ...

It goes up to "K" but there isn't an "H". It is possible just you missed out "H" when you were lettering?

A. Probably.

Q. I suspect --

A. Erm.

Q. Really, I do not want to go into that at all but if we look at the text --

A. Just a moment -- let's leave it.

Q. Yes. Thank you.

If we look at the text, you really do explain this to us. A and B did not become infected with HIV from commercial concentrate but they did become HIV positive from the implicated batch in 1984.

C received commercial concentrate, you say:

"... because of apparent non-therapeutic response to SNBTS Factor VIII."

So the SNBTS Factor VIII did not work in this patient?

A. It appeared not to work.

Q. It appeared not to work, right.

Is that likely to have been something to do with purity? No?

A. No.

Q. No. Would it be easy for us to grasp a reason why it didn't work?

A. I am able to give you my recollection of the reason. My hesitation is that this patient is not party to this Inquiry -- his family are not -- they were very unusual circumstances.

Q. Perhaps we should just leave it as you have stated it, Professor, and not take it any further. We note that there were --

A. I seek your guidance.

Q. Simply, I think all we need to note is that there were clinical reasons why this patient was given commercial concentrate and that this patient did become infected with HIV from commercial product.

Then if we go on to the next page, I have already --

THE CHAIRMAN: Can you enlarge it, please?

MS DUNLOP: Here it is, yes.

We have already obviously looked at A, B and C. Patient D started on home therapy with commercial VIII. Because he lived a long way from the Royal Infirmary.

What was the logic of that?

A. He has had severe Haemophilia A. He had quite frequent bleeds. His brother, patient A, had been treated with commercial concentrate and I was lent upon quite heavily: could he not have commercial Factor VIII as well so he could have it at home? That's what he wanted, rather than coming to the Royal Infirmary for cryoprecipitate.

Q. I see. And then E. He was a visitor from abroad?

A. Yes.

Q. F had a single injection of a pure commercial Factor VIII to which he reacted but he became infected from the implicated batch. G, somebody who remained HIV negative. I, if we go down to the bottom of the page:

"Previously received commercial VIII. Retrospective

testing revealed he was HIV positive before his arrival in Edinburgh."

Then on to the following page:

"K, commercial Factor VIII. Because of a unique and complex clinical situation became infected with HIV by the implicated batch."

Then you present a summary. Just reading at the very bottom of that page, page 21:

"Thus, out of nine patients susceptible to HIV, one became infected, probably by commercial human Factor VIII concentrate, in 1981 as a result of treatment in Edinburgh and four patients seroconverted to the SNBTS implicated batch in 1984."

That is the end of your statement, professor, apart from your list of references.

I wonder, sir, I still have a very few general questions for Professor Ludlam. It is one o'clock. It might be better just to stop rather than just cram it in.

THE CHAIRMAN: I don't think you will cram it in.

MS DUNLOP: Yes.

THE CHAIRMAN: Yes, after lunch.

(1.01 pm)

(The short adjournment)

(2.00 pm)

THE CHAIRMAN: Yes, Ms Dunlop?
MS DUNLOP: Thank you, sir. Good afternoon, Professor Ludlam.
A. Good afternoon.
Q. Just to cover one topic extremely briefly, which is the topic of funding by pharmaceutical companies. You were asked, in common with the other haemophilia directors, about whether you were aware of funding in your centre by pharmaceutical companies. We can have your reply on screen; it is [PEN0150350].

You looked into this at the request of the Inquiry, didn't you?
A. Yes.
Q. You say firstly that you are:

"... not aware of any funding from pharmaceutical manufacturers of clotting Factor VIII concentrates in the 1970s. I think it's highly unlikely that there was any."

And presumably you draw that inference from Dr Davies' policy of which you have spoken.
A. Yes.
Q. Then you say you have been in touch with the Lothian Endowments Office:

"Who hold our haemostasis account. They have records of the following donations ..."

Really, only donations from 1986 onwards, probably, you suspect, largely to help staff get to scientific meetings, conferences; travelling expenses for going abroad, probably?

A. Yes.

Q. Thank you.

Professor Ludlam, there is also the matter of the article by Oscar Ratnoff and others, of which some mention was made yesterday. We don't yet have it in court book, though we will, but there are some hard copies of it. You have a hard copy, I hope?

A. Yes.

Q. The particular one, because I think you know, Professor Ludlam, that this arose last Thursday when Professor Forbes was giving evidence, and he referred to having had a telephone call from Oscar Ratnoff.

A. Yes.

Q. Professor Forbes described a case that Oscar Ratnoff had written up, and we then began looking for the relevant article, and from the descriptions given by Professor Forbes, it looked to us as though this was the article he meant. It's from the New England Journal of Medicine, February 24th, 1983. It's called "Coincident classic haemophilia and 'idiopathic' thrombocytopenic purpura in patients under treatment with concentrates of

antihaemophilic factor (Factor VIII)."

You wondered, I think, Professor Ludlam, whether the first patient, the 21-year old man, who is described in this article and who was admitted to hospital in Cleveland in December 1981, might be one of the three patients described in the MMWR report in July 1982. Because I think people may remember that the three patients described in the July 1982 report in the MMWR, namely three patients with haemophilia who appeared to have AIDS, one of them is a 27-year old man, and you wondered, I think, if the ages had become muddled. But in short, it doesn't look like that, professor, because really, in a nutshell, this patient in the Ratnoff article had splenectomy in February 1982, and the patient in the other article is described as having splenomegaly in April 1982. That, I thought, was perhaps a clue that they were different individuals. But you have had the opportunity to look at this article. What should we take from it? What is being described here, looking back now at it?

A. Can I just go back to the MMWR?

Q. Yes, by all means.

A. Because I think the patient there from Ohio -- my recollection definitely -- had AIDS-defining conditions, which is quite different from patient 1 here.

Q. Yes; right. So in fact we are in agreement, are we?
A. We are in agreement that they are completely different patients.
Q. Do we need to go back to the MMWR?
A. No.
Q. Right.
A. You ask about interpretation of these patients and their thrombocytopenia.
Q. Yes.
A. I think there are potentially two causes for thrombocytopenia in these patients. The first is HIV infection. Idiopathic thrombocytopenic purpura is a condition in which you get a low platelet count.
Q. That's the meaning of thrombocytopenia?
A. That is correct.
Q. Just so we are clear, right?
A. You get a low platelet count and it appears that the bone marrow is making lots of platelets, because when you look at the bone marrow, you see the cells that are making platelets, called megakaryocytes, are there in reasonable numbers, and the supposition is that at least at this time it was thought that a lot of these patients had increased consumption of the platelets in the circulation because there was an antibody against the platelets in the circulation as well.

The problem about ITP is it's a little bit of a diagnosis of exclusion. There is no blood test or no investigation you could do that identifies someone definitely as having ITP. So you have to exclude other causes, and amongst the causes of thrombocytopenia, we now know, is HIV infection, and a reduced platelet count occurs not infrequently in early HIV infection. So I think one possible explanation is that these are some of Professor Ratnoff's patients who had HIV.

Q. Right.

A. The other explanation -- and these two are not mutually exclusive -- is that in liver disease you, as I'm sure you know, in a proportion of patients have cirrhosis, and there is an increase in the pressure of the blood vessels in the stomach that causes the spleen to enlarge. And when the spleen enlarges, it traps more platelets within it. In an individual with a normal-sized spleen, which is about the size of a clenched fist, there are about a third of the circulating platelets, or the body's platelets are in the spleen. If the spleen enlarges then it traps more of the platelets and the platelet count decreases.

Therefore, patients with liver disease, particularly when it gets to the stage of cirrhosis, will have lower platelet counts, often in the region of about 80 times

10 to the ninth of a litre, but can vary hugely from about 20 or 30 up to a normal platelet count.

So I think in summary, these patients have at least two reasons for being thrombocytopenic. I think it would be reasonable to assume many of them had HIV and this was an early manifestation, but the manifestation may have been exacerbated by their liver disease.

Q. I see. Actually this condition is one of those listed in Dr Craske's list. If you remember we looked at that yesterday and he was asking haemophilia centre directors to let him know if they had any cases of ... and this is one of the conditions he names.

So these patients, as you say, may have been going on to develop AIDS, and as far as Professor Forbes' recollection goes, he thought it was about 1980. It looks as though it certainly might have been in 1981 that Professor Ratnoff made contact with him and asked him whether he had any unusual illnesses in his patients with haemophilia.

A. I think that's fair.

Q. Yes. You don't remember having any conversations with Professor Forbes about that, about that time?

A. Not at all, no.

Q. No. I wanted just to take you back to the transcript, because that was the other point that we looked at and

didn't complete yesterday at the end of the afternoon. We did ask you to look at an answer that Dr Winter gave on 27 April, and if we could call that piece of the transcript back again, please. It was 27 April, an answer really that one runs from page 7, Koch's Postulates -- I am afraid but without going back to them -- 7, 8, 9, 10. So can we go to the transcript for 27 April, please.

Thank you. Could we go to page 7? You see where Dr Winter says he wants to make some comments around this whole situation, "if I may at this time". That's line 15 on page 7. There is then quite a long answer that goes on to page 9, a couple of comments in particular. He says at line 16 on page 8:

"Any clinician looking at this data would have to believe that AIDS was a transmissible disorder in that it could be transmitted by blood and blood products."

On to the next page. Page 9 at line 14:

"So that became the major dynamic for British haemophilia treaters from that moment in time: an acceptance that it was a transmissible disorder, presumably a virus, and it was in commercial concentrate. Would it prove to be in British concentrate?"

I just wanted to offer you the opportunity of

articulating any disagreement you may have with that passage.

A. No, I don't think I have difficulty with it. We were discussing it vis a vis Koch's Postulates yesterday.

Q. Yes.

A. If we can leave Koch's Postulates on one side.

Q. Gladly.

A. I think the case of the baby that got the platelet transfusion, I reviewed the paper last night and the authors are a little tentative about it, about whether it's a definite case. It certainly doesn't fulfil Koch's Postulates but I think it is very good evidence that the agent responsible for AIDS was transmissible by blood, at least by fresh blood, and put that together with what had occurred in people with haemophilia, it was a potent part of the jigsaw.

Q. Yes.

A. What wasn't at all clear at that time from this evidence is the extent of infection amongst the haemophiliacs in the United States. Was this just ten patients who had developed AIDS? Were there in fact only 20 perhaps incubating it? We had no idea at that stage. We have been over the immune data and the value or not of that. Nor was it clear if someone got infected with the agent, what their chances were of getting AIDS.

So there are a lot of unknowns but was it possible that individuals with haemophilia could acquire AIDS from a blood transmissible -- Factor VIII concentrate transmissible organism. Was that possible? Then I think this strengthens it considerably.

THE CHAIRMAN: Professor, you say that the expression is rather tentative. I might have the impression that unless a scientist in a published paper could express something to the level of a mathematical certainty, the expression would always be sensitive (sic). If you can't exclude all possibilities, you do so. Is that a wrong impression?

A. Medicine is a statistical business and usually the best people are most cautious, and I think the wording of the title of this paper describing this very unfortunate child, shows -- as does their discussion actually in the paper -- that they don't say this proves it.

THE CHAIRMAN: But a person who knows the circumstances, possibly knows the authors, would value it on the basis of a wider knowledge and experience than a lay reader?

A. The little bit of research I did last night, it is clear that these are eminent individuals in their field and I think are well respected, and therefore one would attach more weight to this.

THE CHAIRMAN: The difficulty for someone like myself in

trying to commentate on this is if I were simply to take the language and see a tentative expression of a view, I think that I could easily be misled as to the weight that the paper ought to have. So really, what one would hope to get from a person like yourself is objective assessment, having regard to all the circumstances. We have Dr Winter, who clearly thought this was an extremely important stage in the development of knowledge. Do you subscribe to that?

A. I do, yes.

MS DUNLOP: The paper you were looking at last night is the writing-up of this child's situation in the Lancet, was it?

A. It wasn't actually. It was a paper they published a year or two later, describing 40 children with paediatric AIDS and how it differed from adult AIDS.

Q. Right. Just noticing that in the writing-up in the Lancet of 30 April 1983, which is [LIT0010405] -- but I don't want to go to it, please. Thanks -- they do say at the end:

"Although AIDS as a consequence of a transmissible infectious agent cannot be definitely proven in this patient, the evidence strongly suggests such a possibility."

A. I'm sorry, I did see that paper.

Q. Yes.
A. Yes.
Q. So just to note that those were the terms certainly in which they were expressing their views at the end of the paper.
A. Yes.
Q. The last comment I wanted to put to you, at the end of your evidence-in-chief, if we can call it that, as we reflect on the sort of themes that have emerged, could we, staying with 27 April, move on to page 67, please? The context of what's on page 67 is a discussion about Dr Galbraith's paper, and the discussion of it at the CSM biologicals meeting on 13 July 1983, and Dr Winter was asked at line 15 on page 67:

"Question: Of course, some of these points about supply might have been different in Scotland, Dr Winter, and I suspect, as a general proposition, you couldn't dispute that. We would need to ask the Scottish clinicians and suppliers about that but --

"Answer: I would have expected it to be different in Scotland with its much higher, relatively speaking, supply of locally donated blood for concentrate manufacture."

Then he was asked:

"Question: I suspect, from what you have already

said, that looking at these minutes now [that's the minutes of the CSM meeting] and trying to put yourself in the position of the time, you do not find these conclusions that surprising.

"Answer: Not."

And went on to say:

"They really were between a rock and a hard place."

Does that encapsulate the dilemma that was around for people in the treatment of haemophilia at that time in 1983?

A. It does.

Q. Yes. Lastly, professor, I don't know if you have looked at the series of articles by Dr Evatt and Dr Aledort from 2007.

A. I recall Dr Evatt's. Dr Aledort's I haven't looked at recently.

Q. Right. Perhaps if we just look very briefly at those. The first one, the Evatt one, is [PEN0150265], "The tragic history of AIDS in the haemophilia population, 1982 to 1984". Do you consider that this assists in the understanding of a body such as ours of what happened in this article?

A. Can I just confirm this is the reprint of the one that was in the Journal of Thrombosis and Haemostasis?

Q. Yes, it is that one.

A. It has a degree of authenticity about it. I obviously wasn't party to really any of the discussions but I know Bruce Evatt and I have no reason to believe this isn't a reasonable description from his perspective.

Q. It seemed, certainly when we read it, to be a full account of the chronology of events but it provoked quite a response from Dr Aledort. That's [PEN0120179]. This is obviously a dispute which, at least looked at from our perspective, looks rather personal, but can we take it that you didn't share Dr Aledort's view that Dr Evatt's article was self-serving and inaccurate?

A. I have no evidence for that.

Q. Finally, when Dr Evatt responded to Dr Aledort -- and this is turning on to PEN0120180 -- an observation on the right-hand side at the very bottom of the column:

"Finally the AIDS epidemic will not be the last human plague. Group dynamics observed during this epidemic replicate how experts faced with little or incomplete scientific data, often adhere to existing paradigms rather than embrace new unproven ideas to make critical decisions."

Do you agree that that occurred in this narrative? Do you think that people, particularly haemophilia clinicians, adhered to existing paradigms?

A. I think undoubtedly. The question is whether those were

reasonable. I think we learnt a great deal out of the awful events of the early and mid 1980s and that has produced a lasting, indelible effect upon haemophilia treaters and the way we look at risk. I'm thinking in terms of how we responded to the risk of VCJD.

Q. Yes.

A. We took a very pre-emptive view. That produced another series of difficulties. We provided patients with a huge amount of written information. That caused a lot of difficulties with some people.

The topic has not gone away, as I hinted yesterday, in relation to the potential for plasma-derived concentrates to become contaminated with a virus that is resistant to the viral inactivation stages that are in the manufacturing process.

Q. Yes. You must be very thankful for recombinant products?

A. That is why we were so adamant -- I was chairman of the committee that drew up the 1996 UK recommendations on therapy and our recommendation at that time was to move over and towards a recombinant Factor VIII and IX; not a view that was well received in some quarters.

Q. But now accepted orthodoxy?

A. Yes. And I am proud to say that in Scotland, as I think I mentioned yesterday, we, in conjunction with the blood

transfusion, the support of the blood transfusion, very generous support of the blood transfusion, were able to roll out a programme over several years to introduce recombinant Factor VIII, starting off with those that we felt were most vulnerable and able to gain the most from it.

Q. Thank you very much, Professor Ludlam.

A. It's a pleasure.

THE CHAIRMAN: Ms Dunlop, Professor James has been able to identify the patient 1, but in another article of the same period. So perhaps we might just get that clarified, so that one can trace it through.

PROFESSOR JAMES: I don't think it is very difficult. We have had this discussion before and we have it, I think, in the court documents already. But it's referred to as reference 10 in this paper that we have in front of us. It's the Lederman/Ratnoff et cetera, "Impaired cell-mediated immunity in patients with classic haemophilia," 1983, New England Journal of Medicine. It's next to the Menitove paper, and you will remember Professor Forbes thought that the report had been by Menitove but I think actually one of the patients described in this Lederman paper is in fact patient 1 that you identified as being the first patient in the MMW report from Ohio in the very first three cases in

1982.

THE CHAIRMAN: I don't think it is necessary to follow it.

MS DUNLOP: I'm obliged.

THE CHAIRMAN: But it does make the identity and takes perhaps the mystery out of it.

PROFESSOR JAMES: It is just that Dr Ratnoff's group were so prolific around this time in the New England Journal that it is quite hard to keep up with them.

THE CHAIRMAN: Professor, where do we go from here in the way of treatment, therapeutic products for haemophilia patients? What's happening now and how does it reflect the experience of the past, in other words?

A. In the UK, treatment of Haemophilia A and B is almost exclusively with recombinant products. The biggest challenge, I think, in these patients now is directed at the 25 per cent or so of severe haemophilia children who get antibodies to Factor VIII. This renders the injection of ordinary doses of Factor VIII, really, infective, and in a sense takes the child back to not having any good therapy.

It's unclear why all patients with severe haemophilia actually don't develop antibodies because they all lack, or virtually all lack, Factor VIII, their own Factor VIII, and therefore, when exposed to a foreign protein, why they don't actually all produce

antibodies. But they don't. It's about a quarter and some of the risk factors are known.

There is a huge amount of work going on at the moment to try and do two things. One is to understand the mechanism by which these inhibitors arise, and the other is the best way to get rid of them. There are products, as I mentioned yesterday, the FEIBA and the Recombinant 7A, which are really quite effective at stopping bleeding. Recombinant 7A has been seen to be particularly effective and a number of designer molecules, recombinant molecules, are under test at the moment that have increased activity and a longer half-life in the circulation, because Recombinant 7A has a half-life of just two or three hours, so when you inject it, after a few hours a lot of it has left the circulation.

So for people with Haemophilia A, it really is the question of inhibitors, and if you talk to mothers, parents, and ask them what their biggest anxiety is, it is the development of an inhibitor.

THE CHAIRMAN: I have seen a publication called "Inhibitor Magazine" that would make that point.

A. Right.

THE CHAIRMAN: I was just wondering where the profession stands. One of the things I'm asked to do is look at

lessons for the future, knowing really where the profession is is quite an important element in that. You have identified, have you, the real focus for the present time, without being able to exclude other problems that might emerge?

A. That's for people with Haemophilia A and B. We have quite a coterie of other patients who have deficiencies of other clotting factors, and most of them bleed less frequently than severe Haemophilia A. There are some with what we call rare disorders or rarer disorders, who do bleed quite frequently, but most of them bleed less frequently, but they are dependent on plasma-derived products.

For example, people who have a deficiency of fibrinogen. There is a concentrate of fibrinogen, plasma-derived fibrinogen. There is a deficiency of Factor XI and that's -- there is a concentrate, a plasma-derived concentrate, which is good and the only problem is it's associated with venous thromboembolism and arterial thromboembolism. So if you have an elderly person with Factor XI deficiency who requires surgery, then one has to use this material, this concentrate, rather carefully to make sure you don't give them a thrombotic episode.

These, I think, are the -- I suppose the other major

preoccupation in haemophilia is the cost.

THE CHAIRMAN: Indeed.

A. And the increasing cost. Because I'm sure you are aware, Factor VIII usage in the UK are so well collected by UKHCDO, shows it going up and up and no sign of it levelling off. And, sir, as you well know, it is not a cheap medicine. At times of health service constraint, because of financial constraint, we are very concerned that our patients may not continue to get what we think is optimal therapy.

THE CHAIRMAN: Of course, the 2009 UKHCDO report focused on this and suggested a need for haemophilia clinicians to look carefully at the quantities they were prescribing among other things. So it may be that there are some economies that ought to be looked at in terms of usage. Where would you put your usage at the moment? Are you in the upper quartile?

A. I think I'm above average. I think our usage in Edinburgh is very comparable to other large major haemophilia centres, like the Royal Free or St Thomas' in London.

I think there are ways of addressing the rising usage, for example, as I'm sure you are aware, one of the really remarkable things, I think, in haemophilia -- because haemophilia, as you have heard a thousand times,

was a ghastly condition without treatment. With prophylactic treatment in small children now, they can grow up sometimes without a bleed, or with only two or three bleeds, and they don't recognise a bleed when they get one. It has really transformed this awful condition into one where the kids are normal. Go to normal schools.

When I came here, I had to go round one or two schools for special children, extracting children, and persuading the school authorities to take them out of special schools, full of very disabled children, from all sorts of conditions, that one or two children were in these environments, not because they were disabled but just because they had haemophilia.

So the children now have the ability to go to school, sit exams, get qualifications like the rest of our children, and can earn their living and take part in social life, like the rest of us. It's a huge transformation.

THE CHAIRMAN: Could I ask you just a little bit about the Scottish capacity to meet demand? At the moment I take it there is no production of recombinant products in Scotland.

A. That's correct.

THE CHAIRMAN: Is it likely that Scotland ever could get

into the market again for that class of product?

A. It is said that you only need ten sheep producing Factor IX in their milk to supply -- I can't remember whether it is the whole of the UK's supply or North America, but you can potentially make a lot of Factor IX in milk from a few sheep or goats, I forget which.

The whole field of biotechnology is moving so fast, I would be very foolish to say that it would never come to Scotland to be a manufacturer of recombinant clotting factors.

THE CHAIRMAN: I think I read something about Glasgow having managed to make artificial blood, I think, is the way it was put, recently. Is that a factor?

A. I wonder if this is Professor Turner's work producing red cells -- trying to produce red cells from stem cells?

THE CHAIRMAN: Yes.

A. Yes, it is a very interesting, very exciting project. And you know, I don't see why there isn't the possibility -- the technology is changing -- to produce recombinant clotting factors in Scotland. We are an enterprising nation.

THE CHAIRMAN: If we leave that slightly, what's your view of the future for gene replacement therapy? Is there

a foreseeable chance of that taking over in any way?

A. That's had a rather chequered history. Haemophilia being a single gene disorder, where you could identify the mutation and you can also measure the level easily in the blood, made it an ideal condition to try gene therapy in. The genes identified, as you know, identified nearly 20 years ago, extracted, can be put into vectors. A lot of the animal work looked very promising.

When that was transferred to humans, there were difficulties. The three that come to mind were firstly that the initial experiments in humans didn't produce much of the clotting factor, and that may just have been a dose effect. Secondly -- and this wasn't in the field of haemophilia, this was in another area -- a gene that was gene therapy for an immune disorder, the missing gene was spliced into the wrong part, if I can put it that way, of the DNA, the patient's DNA, resulting in the development of leukaemia.

I think it happened in two patients. That brought gene therapy to a halt for a spell.

The third difficulty that arose, which was quite an interesting one, was, as I'm sure you know, when you are undertaking gene therapy, you put the gene you want to know [about]into what's called a viral vector, sort of

put a viral coat on it. This particular study I have in mind, which was for Haemophilia B, Christmas disease, and that was chosen because Factor IX is a much smaller molecule. It has a smaller gene and therefore can go into the vector much more easily. The study done in the States looked as if, in humans, it was going to be successful. The patient was treated, the Factor VIII levels started to come up.

The patient then developed hepatitis. By that I don't mean non-A non-B, Hepatitis C. They had inflammation of their liver and this was due to the development of an antibody against the coat of the virus that had been put round the Factor IX gene.

So the patient's own immune system produced an antibody against the viral coat, which attacked the liver and destroyed the coat and also the vector.

The latest news I have is that there is a study being undertaken at the Royal Free Hospital by Professor Tuddenham and his colleagues, in which they have put together, rather cleverly, a special sort of vector with Factor IX in it, and they have put a slightly different coat, viral coat, on the vector, and I think they have now treated three patients. When I spoke to Professor Tuddenham a short while ago, it appeared that they were getting some therapeutic levels

of Factor IX. So it was looking optimistic.

It's a long way to go, and one of the difficulties with gene therapy in haemophilia now, and one of the controversies, is that treatment with recombinant Factor VIII is now so good, why risk potential disaster with gene therapy? And so the patients volunteering for gene therapy are very carefully counselled before they finally go forward for this.

THE CHAIRMAN: Thank you very much.

Now, is there anything you want to ask?

MS DUNLOP: No, thank you, sir.

THE CHAIRMAN: Mr Di Rollo, I trust you won't take Ms Dunlop's provocative reference to examination-in-chief as an invitation for you to cross-examine.

MS DUNLOP: I wasn't sure what to call it.

THE CHAIRMAN: Do you have any questions?

MR DI ROLLO: I do have a few questions, Mr Chairman.

Obviously I will be guided by you. If you feel there is anything which you feel is inappropriate or unnecessary, no doubt you will let me know.

THE CHAIRMAN: I would normally have to know in advance before I intervened, Mr Di Rollo. Perhaps you will tell me if you are going down an avenue that ought not to be pursued.

MR DI ROLLO: I hope I won't be doing that.

THE CHAIRMAN: Very well.

Questions by MR DI ROLLO

MR DI ROLLO: Professor Ludlam, what I would like to ask you first of all is one point of clarification. You talked yesterday about the batch dedication system which you devised in 1984. I think the reference in the paperwork to that is page 6 of [PEN0150375]. I think you said you devised it in 1984. I wanted you to confirm when it was actually introduced. Was it actually introduced in 1984, the batch dedication system?

A. I can't be absolutely certain. I suspect it was towards the end of 1984 or might have been early 1985, but I'm sorry, I can't give you more information from my memory. There may be other documents that could give you further clarification.

Q. The next matter I want to ask you about is some general questions about the definition of haemophilia and how people with bleeding disorders of various different degrees, haemophilia of different degrees, might be treated.

We have heard some evidence about mild, moderate and severe haemophilia, and there has been some suggestion that not everyone agreed about the classification as to exactly where they would be. But I'm interested to know

at what point do you define someone as a haemophiliac? What is the sort of range, the maximum amount of Factor VIII that they would have to be defined as a haemophiliac?

A. It's a very interesting question and a difficult one to answer. We normally quote the normal range of Factor VIII as being from 50 to 150 per cent. If we found someone had a level repeatedly of 48 per cent, we would look, as we always do, very carefully at the history. How had they come to us? Had they had what we might call abnormal bleeding?

The other thing, as I'm sure you are aware, the Factor VIII level is dependent on the blood group and people with blood group O have lower Factor VIII levels than people with blood group A, for example. So there is -- and I suppose the next factor is I, particularly, am always reluctant to put a label on a patient as having a bleeding disorder unless I'm reasonably well convinced that they do, because it has all sort of knock-on consequences. There are other ways, of course, of diagnosing people with haemophilia. You can look at their gene, you can look at their Factor VIII gene and sequences, looking for mutations.

Q. Since when have you been able to do that?

A. At least ten years, I'm sorry, I can't --

Q. But obviously we have been interested, or talking principally about the mid 1970s to the mid 1980s.

A. That couldn't be done then, no.

I just want to make sure I don't lose the thread. You are wanting to know how you make a diagnosis of haemophilia in someone who has a Factor VIII level close to 50 per cent?

Q. Yes, and I'm principally interested in the period mid 1970s to the mid 1980s. That's really the timeline, as to how that would be done then.

A. The other thing that's important to do is to measure the Factor VIII level on several different occasions. It used to be said, you should measure it three times and take the lowest level because, as you have heard, I think, from other experts, the Factor VIII level can go up and down. It's what we call an acute phase reactant, and if you have a bit of infection, a bit of flu, it will raise the level.

There are the assay of Factor VIII, a laboratory assessment has a range around the value that you measure of several per cent.

But principally, if you are looking at someone with a level of round about 48/49/50 per cent, one would be reluctant to make a diagnosis of haemophilia without a significant history, either in that person or in

a relative.

I suppose the other thing I should mention is that it depends how you measure the Factor VIII. There are different ways of measuring Factor VIII, and if you measure it in certain ways, it is thought to give perhaps a better correlation with the clinical situation. Again, this is a rather controversial area.

In the UK there are two principal clotting assays for measuring Factor VIII, what's called the one-stage and a two-stage assay, and some haemophilia centres have used two-stage assays and some have used one stage assays. In some patients, as I say, you get different results, depending on which assay you use.

Q. Can I just ask you then what are the consequences of making a diagnosis of haemophilia for a patient at that sort of level? If someone is diagnosed as having haemophilia, what consequences would flow from that, as opposed to not making a diagnosis of haemophilia?

A. If a diagnosis is made of haemophilia, then the situation is explained to the patient that they appear to have a mild bleeding disorder but, though we call it mild, if they come by some injury or need surgery, then they should tell whoever they see, their dentist or their doctor, that they have haemophilia, and we issue, and issued, patients with cards saying they had

haemophilia and we would have entered them on the national database.

Q. Supposing no formal diagnosis then is made, I take it that if they had a bleed of some kind, if they were bleeding and the bleeding wasn't stopping but you weren't able to make a diagnosis of haemophilia, would that have consequences as to what treatment they would be given? For example, would they be given a concentrate in that situation or not?

A. Well, we wouldn't give a concentrate unless we had a diagnosis. I mean, I think, to backtrack a little bit, I would be reluctant to make a diagnosis of mild haemophilia in someone who had a Factor VIII level of 48 per cent. I might do if they had a good family or personal history of it. But just a clotting level -- if that had arisen, if that had been measured for some curious reason.

Q. How would you treat them if they were bleeding in that situation?

A. It depends what kind of bleeding they had.

Q. Supposing they were bleeding into their thigh and it was swelling up and it wasn't stopping, it was carrying on. What would you do?

A. And they had Haemophilia A?

Q. The hypothesis is that you are not making a diagnosis of

haemophilia; they don't have Haemophilia A as such. They have a Factor VIII level of 48 but you are not prepared to make a diagnosis at that stage. You don't have sufficient information to make a diagnosis. How would that affect the way in which you would treat that individual? Would you give them a concentrate is what I'm driving at?

A. I think again it depends upon the nature of the injury and the degree of swelling, the degree of discomfort, how much it was compromising the leg, the degree of pain, but I think if there was some doubt about the diagnosis, then what we would do nowadays is measure the other clotting factors because maybe they have a deficiency of some other clotting factor.

Q. I'm asking the question and in relation to this I'm really directed to the period, the use of concentrates between 1975 and 1985.

A. Between 1975 and 1985.

Q. Yes, what would you have done then?

A. If I thought they had mild haemophilia and they had a major bleed, they would probably be treated with cryoprecipitate or -- probably cryoprecipitate.

Q. You say if you thought they had mild haemophilia, but again I'm suggesting to you that you are not actually prepared to make the diagnosis of haemophilia, or at

least that's my understanding of your position, because you don't have sufficient information. The hypothesis is that somebody is just bleeding. You don't actually have the material. What you have is a Factor VIII level of 48 and a swelling, which is not stopping, and I'm asking how that would translate into the treatment you would give, notwithstanding the fact that you haven't actually made a formal diagnosis of haemophilia, mild.

THE CHAIRMAN: Before you answer. Is this still a purely hypothetical question, Mr Di Rollo? We now have a timeframe, we have a precise level of percentage of Factor VIII and rather particular circumstances. Is it hypothetical or is it an actual example that you have been asked to present?

MR DI ROLLO: It is a hypothetical from the witness' point of view but it is not a hypothetical --

THE CHAIRMAN: I think fairness might require that we know. Directly or indirectly. You can give me the information privately but I think we really have to know, if we are getting down to the particulars. It is not fair to the witness unless he knows where he is going, or it may not be.

We will have a short adjournment so that you can tell me. I won't require you to do anything in public.

(3.03 pm)

(Short break)

(3.15 pm)

THE CHAIRMAN: Professor Ludlam, having been a judge for over 20 years, I know it is always worrying when the lawyers get together for a private discussion. We usually do it by putting the witness out but on this occasion we went out.

But the position, I think, Mr Di Rollo, does become clear, that there is a general interest issue in what you have raised but perhaps we need a better context for carrying it forward.

So I think, if I can ask Ms Dunlop to indicate where the general issue might take us, although it is perhaps not terribly well defined yet, we can lay down a section, as it were, when we come back to this particular matter.

MS DUNLOP: Yes, sir, we have been thinking, particularly over the past week, that there is, in a sense, a gap in a section of topics that relate more directly to Hepatitis C, so the topics labelled "C" topics, that we don't have, as it were, the next part of the story of the use of blood product concentrates.

So what we were hoping to do is to add in an additional topic, probably immediately after C3, to look at the implications of the fact that there wasn't

a "hepatitis-safe" NHS concentrate in Scotland between 1985 and 1987, and what the implications of that were for the treatment of people with haemophilia.

So it may be that with that as a general topic, we can plug what has come to seem like a bit of a gap.

THE CHAIRMAN: Against that background, Mr Di Rollo, I would like you to postpone this particular topic. I'm not ruling that you must not pursue it in any way, but I think there are interesting issues here that I want to hear about but I would rather they were within a properly defined context.

MR DI ROLLO: Very well.

THE CHAIRMAN: Professor Ludlam, as far as you are concerned, it does mean of course that Mr Di Rollo might want an answer to a question at a later stage, but we can possibly do that in writing once the background has been developed, so as to avoid the need to ask you to come back. We will see. I don't promise not to ask you to come back but we will see how it goes.

Mr Di Rollo?

MR DI ROLLO: Thank you, Mr Chairman.

I just want to move on to ask some general questions about the history of haemophilia, and we have heard quite a lot of evidence. It has obviously been impressed upon us that haemophilia, severe haemophilia,

was a life-threatening condition and that factor concentrates brought a number of benefits.

One of the things that I wanted to ask you is: are there any figures for the mortality rate from cerebral haemorrhage before factor concentrates actually came in? In other words, are the figures to know how many haemophiliacs died of cerebral haemorrhage before we had factor concentrates, or is the information -- the evidence that we have heard about this, something just an impression from clinicians over the years? Are there any concrete figures that we have?

A. I'm sure there are data. Could I give a slightly more general answer, which I think you will find helpful?

The life expectancy in Haemophilia A, for individuals without inhibitors, rose with the use of plasma and cryoprecipitate predominantly, is my recollection. There was a small increase in life expectancy thereafter.

Perhaps I could put it round another way: deaths from haemorrhage, I think, is perhaps your question, I'm sorry. Deaths from haemorrhage diminished with use of fresh-frozen plasma and particularly cryoprecipitate, before the use of clotting factor concentrates.

Clotting factor concentrates came in, as you know, in the 1960s in some places. They weren't widely used.

They weren't widely available outside Oxford, for example, in the UK.

What has become apparent with the greater use of concentrates is that the degree of morbidity is very substantially reduced.

Q. I think one of the things that you do say is that during the second half of the 1970s until the mid 1980s, the commonest cause of death amongst UK haemophiliacs was bleeding, and especially into the brain. That's obviously at a time when factor concentrates were by that stage available; is that right?

A. Available in places, as you have heard and seen in the preliminary report. For example, in Edinburgh we were very dependent on cryoprecipitate rather than concentrates.

Q. Is cerebral haemorrhage something that can happen as a result of being infected with Hepatitis C? Or hepatitis generally? Can you end up with cerebral haemorrhage in that type of situation?

A. Hepatitis doesn't pre-dispose to intracranial bleeding except at end-stage liver disease, when a patient has cirrhosis and almost hepatic coma. They fail to make a number of other clotting factors and there is a risk of haemorrhage then. But that's not, I think, what we are thinking about here.

Q. When you arrived in Edinburgh, I think your predecessor, Dr Davies, had a policy of not using factor concentrates at all. Is that right? Either commercial or NHS. Is that right?

A. No, I think he was keen to use products derived from Scottish donors.

Q. Right. And I think the reasons for that have been kind of well expressed; that the thinking was that Scottish donors products would be safer. Is that the reason why he thought that?

A. Partly that and partly not to expose patients to viruses from elsewhere; novel viruses, if I can put it that way. Novel to the community.

The other thing I remember him saying is that there might be a degree of immunity in the population to the local viruses. Let me give you an example. Hepatitis A. Years ago many of us were infected as children or young adults with Hepatitis A and without symptoms, and were then immune to it. So if exposed Hepatitis A later in life, then you wouldn't get the clinical illness; the antibody would destroy the virus. And as I hinted yesterday, this is possibly one of the reasons why Hepatitis A was transmitted in the early 1990s by clotting factor concentrates because the recipients, the patients, had grown up in such a clean

environment that they weren't immune to Hepatitis A.
Q. Do you think in retrospect that Dr Davies' policy was very wise, that his thinking was very sensible?
A. I think for its time it was very sensible, yes. Otherwise, I wouldn't have continued with it. The downside of it, the immediate downside in 1980, was that I wasn't able to offer home treatment, home therapy to as many patients as I would have liked to have done.
Q. If you move over to home treatment, that changes things from the hospital's perspective. It means that patients no longer have to be treated in hospital, or don't have to be treated in hospital as often. Is that correct?
A. That's correct.
Q. So that would relieve beds, presumably, at the hospital; pressure on beds?
A. Certainly pressure on the ambulance service.
Q. And pressure on the nursing staff as well?
A. A bit on the nursing staff, but mostly on the ambulance service and on the doctors like myself, who had to see them each morning when they came along. Because they were mostly outpatient, not all but --
Q. But Edinburgh had managed cryoprecipitate, essentially up until 1980. Is that right?
A. There was some concentrate used.
Q. Mainly cryoprecipitate, is that right?

A. More of the treatment was cryoprecipitate than concentrate.

Q. Before you start someone with concentrate, can you just explain, what is it you have to do to the patient? Do you have to examine them or carry out any tests before you actually change from cryoprecipitate to a concentrate. In terms of treatment, what do you have to do? Do you have to do anything? Is there any test or any procedure that has to be carried out?

A. We would normally assess the patient for an inhibitor to Factor VIII before starting them on concentrate and then measure their response.

Q. How is that done exactly? You say test them for inhibitor and measure the response. What do you actually do?

A. You take the sample of the blood, centrifuge it, separate out the plasma, you then mix the plasma with normal plasma that has Factor VIII in it and leave it to incubate for a couple of hours, and if the plasma has an inhibitor in it, it destroys the activity of the Factor VIII in the normal plasma you have added to it. You measure the Factor VIII level after a couple of hours and if it's reduced, then you suspect the patient has an inhibitor and there are ways of quantitating that by doing serial dilutions.

Q. How does that affect the treatment they are given therefore, whether they have an inhibitor or not?
A. We would assess them for an inhibitor before we started and then we would assess them probably a few weeks later. If they had developed an inhibitor, then how we managed them thereafter would depend upon the level of the inhibitor and how it responded to provocation with Factor VIII.
Q. So would that affect the type of Factor VIII that they were given; whether it was commercial or NHS or anything of that kind?
A. It might do, yes. If I was going to treat a patient with an inhibitor with Factor VIII, then I would need to give large doses of Factor VIII to try and neutralise the inhibitor. And so I would want to use the purest Factor VIII that I had available because I wouldn't want to increase the concentration of, if you like, the contaminant proteins that are in the concentrate in the patient. And in the early 1980s the commercial concentrates that were available were of higher purity than the SNBTS concentrate and so I would have been tempted to use those, particularly if I was going to give repeated injections.
Q. So would it be appropriate in that type of situation to move from NHS to commercial and back to NHS again, or

would you just stick with one or the other in that kind of clinical situation?

A. Once having started to treat someone with a high purity or, if you like, in this context a commercial Factor VIII, one would tend to go on with it. In general we prefer not to switch between concentrates, just because it does expose the patient to a different population of donors.

Q. So you stick with one. You don't switch from one on to the other because of that?

A. It depends on the situation: clinical situation, the supply situation, the financial situation; a whole lot of ingredients.

Q. You have indicated, I think, that you were keen that your patients should not receive commercial concentrates. Is that right? That was your preference. Is that right?

A. That's my preference, yes.

Q. Did you ever give your patients a letter addressed to any hospital that they might come into contact, that they were not to receive commercial concentrates; that they had been prescribed NHS concentrates and they should continue to be prescribed NHS concentrates?

A. Yes, there were little slips of paper. I described this yesterday. Little slips of paper that said that this

patient had been treated exclusively with cryoprecipitate or NHS concentrate and please, if they attend your haemophilia centre, could you give them cryoprecipitate or NHS concentrate. In England it would have come from BPL almost certainly.

Q. When did you start to do that?

A. Probably about 1981/1982. Probably -- perhaps 1981.

Q. And when did you stop doing that?

A. I'm sorry, I can't answer that question. We gave everyone one of these pieces of paper and put it in there.

Q. All of your patients received that?

A. All of my patients were given these as a single issue.

Q. Why did you do that?

A. Because I was keen not to switch concentrates really, not expose the patients, if possible, without good reason, to another set of donors. In other words, going back to whether North American hepatitis was different from UK or Scottish hepatitis.

Q. Did any other clinician, to your knowledge, do that?

A. I think it was a general philosophy in the other east coast centres in Dundee, Aberdeen, Inverness, to use NHS concentrates.

Q. But did they give their patients a similar type of piece of paper?

A. I don't think so, I didn't ask them to.
Q. Right.
A. I don't know. You would need to ask them.
Q. Did you think that it would be useful to have a group of patients that had not been exposed to commercial concentrates for the purposes of being able to tell you something in due course about the respective way in which the commercial, as opposed to NHS concentrates, operated? Did you think this would be useful?
A. Yes, I did think it would be useful. Yes.
Q. I think you used the word "monitoring" yesterday in your evidence, and if a group of people hadn't received commercial concentrates, then you could monitor the effect of that, but if they had at one point or another received commercial concentrates, then it would be more difficult to monitor the effect of that. Is that fair?
A. No, I'm sorry, I cannot have made myself clear.

No, all patients would get the same monitoring. It would be possible to monitor patients who received commercial concentrates in a very similar way to those who received NHS concentrates. Perhaps I should say, in case it's not clear, I think the majority of haemophilia physicians in the UK, if you ask them, at this time, would have preferred to use NHS concentrates than commercial ones, and in a sense I was in a privileged

position to be able to take that philosophy forward.
Q. Clearly the question really is why anyone really in Scotland would use commercial concentrates.
A. Well, if I can put it round the other way, the price my patients paid was their ambulance journeys to the hospital each day, the fact that their bleeds were taking longer to be treated, that it was very much more disruptive to their lives than if I had provided them with treatment to have at home.
Q. Sorry, I think you misunderstood my last question.
A. I'm sorry.
Q. I was meaning why would anyone use commercial concentrates as opposed to NHS concentrates in Scotland?
A. I was coming to that, I'm sorry. Because they felt very strongly that they wanted the patients to be on home treatment and it appeared there was not enough NHS concentrate available to do that.
Q. Well, that's what I don't really understand: how there was enough for you.
A. There wasn't enough for me because I had an allocation and when I had used up that allocation, then in a sense I used cryoprecipitate.
Q. You didn't use commercial concentrate?
A. No, my patients didn't get home treatment.
Q. At any point?

A. Well, you have seen the figures. Ms Dunlop showed them, I think, in my report. The numbers of patients on home treatment was about six in 1979 and I put it up to about a dozen or so in 1980, and the number climbed thereafter as the blood transfusion was able to let me have more Factor VIII concentrate.

Q. And you had a good reason for that, which you have explained, for approaching matters in that way. What I'm trying to understand, and I'm not really getting -- it may be my fault, I'm sure it is my fault -- is why anybody else would do anything different in Scotland from the way you did it? Why would any other clinician use commercial concentrate? Why not use NHS concentrate, and as the availability of the NHS concentrate increased, so roll out the home treatment, as you did?

A. Because they want to get on and give their patients treatment at home so they had a better lifestyle and they grew up with better joints.

Q. But to take a risk that you weren't prepared to take?

A. Well -- I was the exception. The majority of haemophilia physicians --

Q. I'm talking about in Scotland of course. When I'm putting these questions to you, I'm talking about in Scotland, I'm not talking about the UK situation.

A. With respect, we work in a UK environment and one of the benefits of UKHCDO is that we try and work as a group, and I think very much to the benefit of the service for doing so.

As you see within any group, there is a spectrum of ways in which one practises, and resources that one has available.

But if I might be allowed to say that in England, because of the shortage of NHS Factor VIII and because of the huge benefits that patients were seeing from having treatment at home, there was huge pressure towards home therapy, and that could only be done with commercial Factor VIII. In a sense I was the stick in the mud.

Q. I understand the position in England is different from the position in Scotland from the point of view of the availability of NHS concentrate. Scotland, as I understand it, achieved something approaching self-sufficiency, whereas England never did.

I'm not asking you about England because in England they are faced with a different issue. For them it is different. They have a different decision to make. The decision in Scotland appears to have been a conscious decision to use commercial concentrate in the face of much greater availability, if I can put it like that, of

NHS concentrate.

What I'm trying to understand is, given that you have explained, as I understand it, and fairly cogently, a good reason why you would stick with NHS concentrate or cryoprecipitate and avoid commercial concentrate, why anybody else in Scotland would take a different approach?

A. Scotland wasn't self-sufficient in Factor VIII concentrate until the beginning of -- let's get the year right. I think it's 1984. If we go back to 1980, a very considerable quantity of Factor VIII was given as cryoprecipitate, whereas in England that would have been commercial Factor VIII concentrate.

Q. Professor Ludlam, I think what I would like to do is put to you a document which we have seen already. I'm not sure it was necessarily put to you specifically but it is [DHF0022149]. It is the Council of Europe Committee of Ministers' recommendation, R(83)8. We heard some evidence about this from other witnesses, and what this document indicates is that:

"Considering the growing importance of a new and severe health hazard, Acquired Immunodeficiency Syndrome, that may be caused by an infectious agent transmissible by blood and blood products;

"Recalling the basic principles to minimise the

hazard of transmissible infectious diseases by blood or blood products, drawn up in the context of the work of the committee of experts on blood transfusion and immuno-haematology;

"To expose the recipient to a minimum number of donations of blood when the transfusion is of cellular and coagulation factor products;

"To achieve national self-sufficiency in the production of coagulation factor products from voluntary, non-remunerated donors."

Then:

"To avoid the importation of blood plasma and coagulation factor products from countries with risk populations and from paid donors."

The document goes on to the following page, if we can have that up:

"Recommends the governments of member states take all necessary steps with respect to Acquired Immune Deficiency Syndrome, and in particular to avoid wherever possible the use of coagulation factor products prepared from large plasma pools. This is especially important for those countries where self-sufficiency in the production of such products has not yet been achieved;

"To inform attending physicians and selected recipients, such as haemophiliacs, of the potential

health hazards of haemotherapy and the possibilities of minimising these risks;

"To provide all blood donors with information on the Acquired Immune Deficiency Syndrome so that those in risk groups will refrain from donating ..."

Et cetera.

Were you aware of these particular recommendations in June 1983?

A. Can I say before I answer that, if I may: previous recommendations from the Council of Europe that we heard quoted from yesterday and approved by the Scottish Home and Health Department recommended the use of concentrates in preference to cryoprecipitate. That was in 1980. So this is a very different recommendation that is made.

No, I never saw this at the time. This was not discussed at all in my recollection, in any of the meetings or private discussions. I only was shown this relatively recently.

Q. Do you agree that the recommendation is sound in terms as indicated there, given the information that was available at that time?

A. "To avoid wherever possible the use of coagulation factor products prepared from large-pool plasma pools."

The difficulty is where you go from there; how you

implement that and whether it's feasible or acceptable.

Q. Perhaps another document which might also highlight a particular issue in relation to commercial concentrates would be [DHF0014394], which I think you were shown yesterday. If we go to page 5, I think you were shown this in the context that this document demonstrated that there was an awareness of AIDS in the German haemophilia population at the end of April. There was awareness somewhere, it may not have filtered down, but certainly someone was aware of it in the UK perhaps not in the medical community. But the reason I want to put this document to you, though, however, is that at page 5 it deals with a section on the Netherlands. We see that the Netherlands' position there is that:

"Four cases of AIDS have so far been diagnosed. Patients were all male homosexuals. It is not known whether these patients had received blood transfusions."

The next paragraph is to do with the selection of donors. Then it goes on:

"... a difficult and delicate problem, in the Netherlands it is felt ..."

That's again with the selection of donors. It's the final paragraph I'm interested in specifically here:

"Apart from the above questions, there is of course

the one connecting use of plasma products from areas in which the disease has manifested itself, for example, the USA. 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."

Were you aware that they had made that decision in the Netherlands at the end of April of 1983?

A. I wasn't aware of that, nor do I know actually how much they were importing before that.

Q. Again --

A. They have a history, I think, of being fairly self-sufficient. They manufacture, as I'm sure you know, Factor VIII concentrates.

Q. Again, it's coming back to the point I was trying to make earlier, which is the question of in Scotland we too had an history of being fairly self-sufficient perhaps. I don't want to get bogged down in argument as to the extent of the self-sufficiency. It does appear that in Scotland certain clinicians exercised a conscious decision to use commercial material where in fact they could have used NHS material. That's right, isn't it?

A. I'm not sure that is right. I'm not sure that the NHS

material was available to them.

Q. Well, if it was available to them, can you think of any good reason why they would have used commercial concentrate after this time I'm talking about?

A. After 1983?

Q. Yes, April 1983.

A. After April 1983. No, after April 1983 one would be much less keen to use commercial concentrates from Northern American donors.

Q. All right.

You were asked some questions by counsel to the Inquiry concerning paid consultancy and I think this arose from a document, a minutes of a meeting in 1977, where Dr Jones withdrew from a discussion about self-sufficiency because he was a paid consultant from Hyland and he declared that interest at that meeting. What I want to ask you, professor, is I assume, of course, that there was no one in Scotland who was a paid consultant of any of the US drug companies or any other drug company?

A. At that time?

Q. Yes.

A. I can only speak for myself and say I wasn't.

Q. Do you know what a paid consultant would do? Do you have any idea as to what Dr Jones would be paid to do?

A. I don't. I am afraid you would need to put that question to him, I think. I mean, a whole range of things that he could have been asked to do.
Q. Can you give me a for instance. I'm not making it specific. But in a general sense what was the whole range of things that he could be asked?
A. He might be asked about therapeutic practice in the UK, he might be asked about what sort of product developments would be looked upon favourably; those sort of areas.
Q. Have you ever heard of any other haemophilia doctor in the UK acting as a paid consultant?
A. I have been a paid consultant more recently.
Q. Right. When you say "more recently", can you tell us when that was?
A. Oh, over the last ten years, I suppose, approximately.
Q. And in the period between 75/85, which again is the reference period, really, for this particular topic, have you ever heard of any other haemophilia doctor being or holding a position as a paid consultant for any of the suppliers or the manufacturers of commercial products?
A. I don't think so but I can't say that some weren't. I lived in very much a NHS environment at that time.
Q. And in Scotland in particular, Scotland was very much

a NHS environment. Was that fair?

A. That's fair, and I mean, as I laid out in my evidence, because of that, I was perhaps a little bit more in the dark about the commercial heat-treated products that were being developed by the commercial companies because they knew that if they came to see me, I probably wouldn't view their product very favourably.

Q. Did you have much dealings with Northern Ireland at all or meet up with your counterpart in Northern Ireland, or did you have more than one in Northern Ireland?

A. Yes, indeed, yes.

Q. Was there a situation, during the reference period, that cryoprecipitate, at least there was a switch back from about 1983 onwards, to using cryoprecipitate? Is that possible that that happened in Northern Ireland?

A. I have not heard so.

Q. Right. You don't know anything about that?

A. No.

Q. All right.

Professor Forbes, when he was giving evidence last week, perhaps gave the impression -- or certainly gave me the impression that when administering or giving Factor VIII, he pretty much used what was available, ie if it was commercial, it was commercial, if it was NHS, it was NHS. Was that your experience or were you able

to dictate as to whether it was NHS or commercial material that was available?

A. I was able to prescribe in a sense what I wanted.

Q. Right. It is material that does require a prescription. You must have a prescription for Factor VIII. Is that right? It has to be a doctor that prescribes it?

A. Yes. My hesitation is that often -- in fact, our usual way of ordering it was to ring up the blood bank and say, "Could you send up some Factor VIII for Mr Bloggs". I am not sure there was always a written prescription. There is also nowadays the ability for suitably trained nurses to prescribe and administer Factor VIII without reference to a doctor.

Q. Chairman, that concludes my questions.

THE CHAIRMAN: Thank you very much.

Mr Anderson?

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

THE CHAIRMAN: Mr Sheldon?

MR SHELDON: I have no questions. Thank you, sir.

THE CHAIRMAN: Anything of any --

MS DUNLOP: There is one thing I just wanted to ask.

Professor Ludlam, what is your definition of self-sufficiency? I mean, it's a term that has been bandied about a bit and we have all been using it. We have discussed this, we can see a number of different

ways one could portray that. So when you use the term, what do you understand by "self-sufficiency" -- "that a country ..." what?

A. Manufactures from its own blood donors all the therapeutic products that are needed to treat people with congenital bleeding disorders.

Q. Right.

THE CHAIRMAN: Could I just finesse that a little?

MS DUNLOP: Yes.

THE CHAIRMAN: If certain clinicians were not using home-produced product, would it be sufficient to produce what was in demand or would one produce a surplus? Pursuing the definition of self-sufficiency.

A. Can I ask, why would you produce a surplus?

THE CHAIRMAN: Because if you are producing everything that is needed but some of the need was being met by commercial products.

A. Well, one would want to find out why the commercial products were being used and if there was good reason, then to produce, at least to seek the production of a UK lookalike.

THE CHAIRMAN: I see that it actually refers back to some of the questions that Mr Di Rollo was asking you.

One can see that in the case of a product like FEIBA, where there was no domestic equivalent available,

that part of the ultimate demand would of necessity be met by an imported product since there was no equivalent. But if one looks at it from the point of view of the producer, PFC, at certain times, if PFC were not informed of the full extent of the purchase and use of commercial products, they might perceive that they were satisfying the home market because they were meeting the whole practical demand. And I think, you know, Ms Dunlop's question has quite a lot behind it.

A. That's why I paused before answering, because there are many people who have suggested what the definition of self-sufficiency is, and I gave you, in a sense, the broadest. But the sort of workaday one is in relation to Factor VIII and Factor IX, producing enough of suitable concentrates to treat those two conditions.

MS DUNLOP: Yes. I think in reality we can imagine that there is a dynamic here, and if the producer in year 1 produces the amount that the producer thinks is necessary to cover the likely total usage but then discovers that certain users will not use his product, then the following year he may not produce the same amount; he may feel well, I will only produce the amount necessary to satisfy the people I know are going to take the product from me. It wouldn't make sense to keep on producing, as the chairman says, a surplus year after

year. So a concept, which at first sight appears reasonably straightforward, is actually not as simple as it might seem is perhaps a proposition with which we can all agree. But you have given us your working understanding of what you mean.

A. I think that emphasises the importance of actually what we were trying to do progressively through the 1980s, which was to bring the consumers and the producers together, and that was, I think, the success of the Coagulation Factor Working Party, that it brought to the producers the consumers and the government.

Q. And people have to be frank about what they are using and why, why they are using one thing and not using another thing, and there have to be as complete records as possible of the overall usage.

A. Yes.

Q. Right, thank you.

THE CHAIRMAN: To reduce it to a very practical level, we know that Professor Cash, over a number of years, tried to persuade his colleagues to go above the output of 2.75 million units, constantly to be met with the answer, "Oh, that's enough". But of course "enough" in itself raises a whole range of questions of definition. It's quite a difficult area for us, professor.

Anyway, thank you very much for your attendance on

this occasion. It may be that we will have your evidence again but we will see.

Ms Dunlop.

MS DUNLOP: There are no further witnesses for us today.

THE CHAIRMAN: Thank you very much.

(4.12 pm)

(The Inquiry adjourned until 9.30 am the following day)