Tuesday, 3 May 2011

(9.30 am)

THE CHAIRMAN: Professor, we are treating your affirmation of the last time as simply continuing. So we won't repeat that. Forgive me just a second, Ms Dunlop.

Right.

PROFESSOR CHRISTOPHER LUDLAM (continued)

Questions by MS DUNLOP (continued)

MS DUNLOP: This morning Professor Christopher Ludlam has rejoined us to give his evidence on topic B2 and, professor, we need to start by looking at your CV and your publications because, as I said last time, you were just here to talk about some statistics and we would defer looking at your professional background until May. So that's why we need to do that today.

Firstly, your CV, which is PEN0020650. From that, Professor Ludlam, if we go to the first page in, we can see you have been professor of haematology and coagulation medicine at Edinburgh University from 1999 and other appointments in haematology, including that you have been the director of the haemophilia centre in Edinburgh since 1980 and you are also an honorary consultant to the Blood Transfusion Service, and that's since 1987.

You are a graduate of Edinburgh University, having

done your medical degree there between 1965 and 1971. We see you won a number of awards as a student.

Then if we move to the next page, you also did a BSc in biochemistry. Is that one of those arrangements where you can do a BSc as you move through your medical degree by taking a year out?

A. You take a year out and join the honours class in pure biochemistry. So it was a year's worth of pure biochemistry, which was extremely interesting.

Q. And indeed, an interest which has obviously continued until this day?

A. I nearly became a biochemist rather than a haematologist.

Q. We see that you did your house jobs with Professor Girdwood, whose name is one that we have already come across, and also Professor Woodruff. I take it that was a surgical appointment, was it?

A. Yes.

Q. You were a senior registrar in haematology in Cardiff between 1975 and 1978, and I take it you worked at that point with Professor Bloom?

A. That's correct.

Q. If we move to the next page, please, your clinical responsibilities include a general haematology outpatient clinic each week, predominantly for patients

with myeloproliferative disorders. Can you give us some instances, please?

A. These are a group of related conditions that are akin to a low grade leukaemia and they present with high platelet counts often, splenomegaly. The reason that I have an interest in them is that the principal side effect and complication of the conditions is thrombosis and bleeding. So a lot of these patients actually present with thrombotic problems.

Q. Looking at the following page, under a heading "Haemophilia and thrombosis service", we see that you see referrals from other Scottish centres with which you work closely, and there is a, I think, elsewhere, in relation to networking of systems, mention of the East of Scotland. Are you in Edinburgh connected to centres in Dundee and Aberdeen. Is that right?

A. Yes, we are the comprehensive care centre for the East of Scotland and so we have some responsibility for helping with the provision of the service and the quality of the service in the other haemophilia centres up the east coast to Dundee, Aberdeen and Inverness.

Q. And Inverness?

A. Yes.

Q. So Glasgow doesn't have a tertiary function in relation to any of the other centres in Scotland, I suppose,

apart from Yorkhill?

A. There are two centres in Glasgow, the Glasgow Royal Infirmary and at Yorkhill, and those are the only centres for the West of Scotland. So they cover a large geographical area. There is a little bit of overlap between our areas and we are both -- Edinburgh and Glasgow are perfectly comfortable with that. It depends a little bit about where the planes fly to from the outer isles, for example, whether they come to Edinburgh or go to Glasgow, as to where patients are seen or where patients have relatives in the central belt.

We are very flexible and patients can choose where they come to, but in general, for administrative reasons, I have responsibility for trying to provide the service in the East of Scotland.

THE CHAIRMAN: I wonder if everyone is hearing. Is everyone hearing at the back?

MS DUNLOP: Is that a longstanding arrangement that you have additional, as it were, tertiary responsibilities for the centres further north?

A. Yes, that's a longstanding arrangement.

Q. I noticed too on this page you mention the Scottish Liver Transplant Centre. We did actually notice that you had been involved in looking after the Reverend Black, when we were examining his medical

records, and I don't think it's difficult to imagine that liver transplant, particularly in someone with haemophilia, must be quite challenging. The input, I take it, that you are having is particularly in connection with the surgery?

A. It is challenging because the patient starts off with having usually severe or moderate/mild haemophilia but once their liver has ingrafted and got a good blood supply, then it is making Factor VIII for the patient. So they no longer in one sense have haemophilia.

Q. Right. Does that take a little while after the surgery to begin to work?

A. Two or three days.

Q. Yes. Can we move on to the following page, please? I notice that you have a subheading "UK haemophilia centre directors' organisation."

One of the things that had puzzled us in our preparation for the hearings is whether the "D" stood for directors or doctors. I think actually Dr Hay explained that in association with obtaining charitable status, the "D" was changed from directors to doctors. Is that something you are aware of?

A. Yes, I am aware, and I see perhaps it is incorrect on my CV here. Actually the change was made about 15 years ago to encourage other physicians and surgeons who

helped look after people with haemophilia, part of the broader team, to come and join our association.

Q. Right. So it was about inclusivity?

A. Yes.

Q. You say you have been a member of the executive committee from 1980 to date. In other words, was the executive committee, from 1980, the group of reference centre directors? Is that ...?

A. Yes, it went under a number of different names over the last 30 years, depending upon the exact organisation of the organisation within the UK, because it changed, as you may have seen, on a number of occasions.

Q. Yes. So today would the executive committee be the directors of the comprehensive care centres?

A. It's actually called the advisory committee. There was a small executive committee, which is the office bearers, but the advisory committee is, as you say, the directors of the comprehensive care centres, who meet three or four times a year, usually in London, to discuss matters of mutual interest.

Q. Thank you.

On the next page, if we could look at that, please, what caught my eye was a reference to your being co-chairman of the haemophilia directors' committee for Scotland and Northern Ireland, 1987 to date. One of the

questions in our minds, as we have prepared for the hearings, has been whether the Scottish directors ever met as a body. Did that happen before 1987?

A. The Scottish directors met as a group, I think, from about 1985, and this group in 1987 was set up to bring together the producers of the Factor VIII and the users, and in a sense the funders, the Scottish Government.

It was, I think, a very successful enterprise, as is explained in the preliminary report. Dr Stewart was appointed to collect up statistics on Factor VIII usage and production, and it led, over the next three or four years, to the production of a high purity Factor VIII concentrate.

A couple of years into the committee's deliberations, it was decided to change the title of the working party because it started out as the Factor VIII, but we then broadened into other clotting factors, so it became the Coagulation Factor Working Party for Scotland and Northern Ireland, and it really formed quite a useful focus for haemophilia-related activities within Scotland, and we used to have a meeting, a fairly major meeting, once a year, to oversee the work of the working party, to give it direction as to where it should be going for the following year and to get some outside help and insight into its activities. So we went to

some pains to get eminent individuals, like the chief executive for the NHS in Scotland, to come along and chair the meeting, help us with his insights and perhaps he saw a little bit about what we were doing and trying to achieve.

Q. Right. Another grouping, of course, that we have noticed in the 1980s is the grouping immediately above that, the meetings which looked to have been roughly annual meetings, involving the SHHD and the directors of the SNBTS and the haemophilia directors. So did that annual meeting continue alongside the body you have just been describing to us?

A. No, I think what happened was in the 1970s there were occasional meetings of haemophilia directors, blood transfusion and Scottish Office, hosted by the Scottish Office Health Department.

There was one of those in -- I think the last one in the 1970s was in 1977, and then they were reconvened, I think, in 1981, and then another one was in 1983 and possibly one in 1985, and then it became clear that there were a lot of activities that needed to be looked at and there needed to be more discussions, more meetings, and it was at this point that haemophilia directors started to meet themselves and the Coagulation Factor Working Party was formed, really to take forward

more expeditiously the issues under consideration.

Q. Right. Can we go to the following page, please?

You give us quite a lot of information about the European interdisciplinary working group on haemophilia and it certainly, from your narrative, looks as though you view this as a very positive development?

A. Certainly, yes, it was indeed.

Q. Not least because you have been able to help some countries where the principles of care might not have been as far advanced as they are, for example, in the United Kingdom. Is that right?

A. That's correct, yes.

Q. And we see that Professor Colvin has been involved in that as well.

A. Yes. He was the lead author and sort of chairman of the group that drew up principles of care.

Q. Then on to the following page. You have had involvement in the British Society for Haemostasis and Thrombosis. You have been president in the 1990s, and you then tell us about other national and international organisations. Unsurprisingly they all relate to haematology. Then on the following page, if we look at your research interests, your major research interests, if we go to the next page, please? Thank you. My eye caught what you say under the heading "Hepatitis B virus", where you

say that your studies found that HBV replication caused the suppression of Hepatitis C virus in co-infected patients, making it difficult to diagnose infection with the latter virus, that's Hepatitis C, which I suppose in general terms could be described as something of an elusive customer. At first blush, to a layperson, the idea of suppressing the Hepatitis C viruses might sound like good news for the patient. Is that wrong?

A. I think it is wrong because this is only observed, as far as I know, in individuals who are replicating Hepatitis B virus.

About 5 per cent of people who get infected with Hepatitis B virus continue to produce the virus from within their liver. The other 95 per cent produce an antibody and that eliminates the infection. In about 5 per cent of people, they continue to produce Hepatitis B virus and what are called long-term carriers. So the liver is busy making Hepatitis B virus, if you like, instead of Hepatitis C. It's as if it can't do both.

Q. I see. But if, through some treatment, the Hepatitis B were to be dealt with, the Hepatitis C essentially has been biding its time and would come back and take over, I suppose, as the dominant form of hepatitis, would it?

A. I'm not an expert on hepatitis treatment at the moment

but the treatment that there used to be for Hepatitis B, chronic carriers, was very similar, if not identical to what was used for Hepatitis C, in other words, interferon treatment.

Q. Yes. Then on to the next page, please. Could we scroll down a little bit under that heading "Hepatitis C virus," you see at the end of the first paragraph:

"Our studies have revealed that using second generation RIBAs, all haemophiliacs treated with non-virus inactivated concentrates have been infected with HCV."

That's something I think that doesn't come as news to us because we have already been through a lot of evidence about statistics, and it seems to be a reasonable supposition that if someone was treated with concentrates, whether commercial or NHS, before heat treatment that was effective against Hepatitis C came in, that they will have acquired Hepatitis C. That is so, is it?

A. That is correct.

Q. You also say in the next paragraph that you:

"... demonstrated that the predominant circulating genotype could change over time, particularly in HIV-positive individuals."

And I suppose, is that because of the immune

suppression?

A. In HIV-positive individuals, it probably occurs more frequently because they aren't producing as much antibody to suppress the Hepatitis C.

Q. Right.

A. That's speculation.

THE CHAIRMAN: I'm not sure I quite understand that. That's a sort of quantitative answer, "not as much as", but how does that affect the change of genotype?

A. I'm getting a little bit out of my depth because I'm not a virologist, but it is possible -- or sometimes possible -- to demonstrate that the antibodies in the circulation are against a particular genotype, and so if there is that genotype present, the antibody against it will be present and may reduce the quantity of virus and that might allow another genotype being latent in the liver to come up.

THE CHAIRMAN: So it is not just quantity, the person must be exposed to more than one type, but other factors might affect the extent to which it becomes dominant in the system?

A. Yes. And the one that's dominant can change because virtually all patients who have Hepatitis C have been exposed to at least genotypes 1, 2 and 3, because they are widespread in the population, and for reasons we

only partially understand, one type tends to pre-dominate for a period of time and then it may change; it may not.

THE CHAIRMAN: Yes.

MS DUNLOP: So for those patients who have been successfully treated for their Hepatitis C, does it tend to be the case that the treatment works against all the genotypes that have been circulating in them? It is not that they feel they have had successful treatment and then some other genotype comes back?

A. My understanding is that the different genotypes have different susceptibility to interferon and ribavirin treatment, as you may have heard, but once an individual has been treated and tested after six months of being off treatment and they don't have the virus in the circulation detectable, then they are thought to be probably cured, and therefore it is likely that the interferon has not only been suppressive in killing the genotype that's in the blood at that moment but any other genotypes that are hidden in residual places like the liver.

Q. Thank you.

On the next page there is a short reference to Hepatitis A and you say you:

"... helped to organise a study to assess the

possibility of transmission of Hepatitis A from SNBTS concentrates."

I don't know that we need to go into this but are we oversimplifying if we understand that Hepatitis A is not transmitted in concentrates? Is there some evidence that it is?

A. It is classical teaching until 1990 that Hepatitis A was never transmitted by blood transfusion. In 1980 -- I think it was in Italy -- a number of patients became jaundiced and when they were vetted, it was found that it was recently acquired Hepatitis A infection, and there was a small outbreak of it in Italy and there was one also I came across in South Africa, and possibly one or two other places, and so it was clear that Hepatitis A could be transmitted by clotting factor concentrates.

Virally inactivated concentrates probably don't transmit, almost certainly don't transmit Hepatitis A. It's a slightly more resistant virus to inactivation than, say, Hepatitis C or HIV. Of course, a lot of individuals have immunity from an early age to Hepatitis A, they are exposed to it in the community. Or rather they used to be, and what has happened as our environment has got cleaner and cleaner is that fewer and fewer young people get exposed to Hepatitis A and

therefore have immunity. It is not quite clear whether one of the possible explanations for this outbreak was that these individuals had not been exposed as children to Hepatitis A and got some immunity.

So it was an area of surprise in this field but it seems to have gone away with the viral inactivation arrangements now.

Q. Right. Can we skip on, please, to, what is in the hard copy, page 16, and this is under a heading "Regulation of haemostasis", which begins at the bottom of page 15.

We shouldn't get sidetracked into going into this in any detail but you have been involved in studies that have revealed that Factor VIII is synthesised in many organs; so it is not just a question of the liver, it is made in other places in the body as well, and you say:

"Which is contrary to the popular perception."

Where else is it made?

A. It is made in endothelial cells, the cells that line blood vessels, and that was a particular interest to me because I have had a long-term clinical and research interest in desmopressin, DDAVP, from when I was in Cardiff, and there is much interest and controversy about its mechanism of action, and this was an observation that has now been confirmed by other more extensive studies and explains, a little bit, I think,

why the Factor VIII level rises after giving desmopressin, because the von Willebrand factor and the Factor VIII probably both come out of the endothelial cells.

Q. I see. You then list research funding you have had and your teaching commitments. I noticed that, of the haemophilia centre directors elsewhere in Scotland at present, you supervised two of them for their MDs, Dr Watson in Aberdeen and Dr Kerr, I think he is in Dundee. Is that right?

A. That is correct, yes.

Q. And other activities, scientific journals, organisation of national and international meetings and then professional societies and associations, and then your duties as an external examiner. Then in a separate document, which is PEN0150074, we note your publications, a number of books, four books, and then chapters, reviews and editorials. Again, looking to me as a layperson, pretty much across the whole spectrum of haematology. I notice you contribute to Davidson's Principles and Practice of Medicine?

A. Yes.

Q. That was, I think, quite a well-known textbook. Is that correct?

A. It is, yes.

Q. Your work listed by year. If we can just go through it perhaps, without highlighting anything in particular, but have a look on to the next page, 82. Then into the 1990s, and then on through the 1990s, the Dr Stirling we see mentioned there, he is the Dr Stirling of "Liver Function in Edinburgh Haemophiliacs"?

A. Yes, he is a clinical scientist who works with me and is now responsible for running the molecular genetic service that we provide for Scotland for haemophilia.

Q. On to 1995, 1996, so on through the 1990s and indeed right up to 2010. And then after that a list of original articles beginning in 1975, looking, for example, also at areas of orthopaedics; see too from time to time obstetric aspects of haematology. I notice too, 1989, if we can go on to that, please. Yes, Dr Moq (sic), Dr Brettle, other well-known names in HIV studies in Edinburgh. You had worked in vertical transmission of HIV. That is essentially from mother to child, is it?

A. Yes.

Q. Yes. I noticed also, 1992, one that caught my eye was called "AIDS: The alternative view". What was the alternative view?

A. I would need to see -- I'm sorry. I can't remember.

Q. Don't worry, professor, it was just a title that caught

my eye. That was all.

A. I could speculate but I don't think that's helpful.

Q. No, let's not bother.

Then on to 1997, I saw reflected in an article in 1997 a notion which is certainly prevalent in the NHS in Britain, the article is called "Treatment for haemophilia by postcode". I suppose this being 1997, I should ask, at that time did you feel that there was a considerable variation in treatment around Britain?

A. Indeed. I think this -- to some extent -- related to the introduction of recombinant Factor VIII, synthetic Factor VIII, which was licensed in about 1993 or 1994 but was expensive, and I'm pleased to say that in Scotland we were able to start arranging for it to be made available to patients in 1996 and we had, as I think I have alluded to perhaps earlier in my CV, a committee chaired by the general manager of Lothian Health to oversee the introduction of recombinant Factor VIII, given the strong support by the Blood Transfusion Service, although it was not a blood transfusion product, but I mention this because we had a rolling programme in Scotland that was very much ahead of what was happening in England.

In England individual health authorities were deciding whether or not they would spend money on

purchasing recombinant Factor VIII. So there was a patchy introduction of a recombinant Factor VIII initially in England.

Q. I understand. I noticed too that in 1998 -- and this is actually two pages on -- you had written an article entitled "Funding arrangements for haemophilia within the UK". Perhaps we could just note that for a moment, but I'm going to come back and ask you a little bit about that later in your evidence.

Then another tranche of articles, Professor Ludlam, going on from 1999, 2000, 2001, right through the noughties, and indeed the list ends in 2011. And perhaps since this was written, there have been one or two more, I don't know.

A. I don't think so.

Q. Thank you.

Can we put these to one side, please, and approach the substance of your evidence. You have, Professor Ludlam, sent a number of documents to the Inquiry, and indeed there are what I would call four core documents, which deal with many of the same issues. There is quite a lot of overlap between them and I did wonder, sir, what the best way to approach that fact was, and I have decided that it would be of most assistance to the Inquiry, I suspect, if we approach

Professor Ludlam's evidence in a topic-based way. So rather than reading systematically through each of the four, we are going to look at what is said on various topics in the different statements. There is no one statement that can be left out because all four of them contain material that I suspect will be of interest to the Inquiry.

So just to identify at the outset what the four statements are, they are [PEN0150445], which is your actual draft witness statement to the Inquiry, and then various appendices. We have [PEN0150468], which is a historical summary of AIDS in haemophilia, 1981 to 1985. I should say, that was, you say, drafted in about 1988. You have also submitted a draft report, which was prepared for an impending litigation in England and Wales in 1990. This was [PEN0150385], and then finally, prepared for this Inquiry, the Edinburgh haemophilia treatment policy, which is [PEN0150375].

The other device, which I hope to employ to save time, is sometimes to mention documents that we have already looked at without necessarily going to them, and that's, I would suggest, appropriate in one or two instances, where the material is reasonably familiar.

THE CHAIRMAN: I hope you will give us a bit of a key because although it may be reasonably familiar now, some

time down the line we may need a reminder.

MS DUNLOP: I quite appreciate that, sir, and I would never refer to a document just baldly. I will say what it is, but that's a general schematic introduction, as it were, and with that in mind the first of the four I would like to look at is [PEN0150385]. This is to look at the background on haemophilia. What should come up, if we look at page 4, is a section entitled "Background to Haemophilia A and B and von Willebrand's disease". There we are, thank you.

You tell us Haemophilia A and B, congenital bleeding disorders, and about the prevalence.

THE CHAIRMAN: Could I ask just one question about the prevalence point to get it out of the way? The statement is made very generally. Is there any geographical variation or is this standard throughout the world?

A. It is standard throughout the world, although individuals with haemophilia tend to -- or used to tend to come to live close to haemophilia centres, so in a particular country there may not be an equal distribution.

THE CHAIRMAN: The reason for the question was that Dr Winter explained that his contacts with Pakistan, for example, have related to a population in Islamabad,

which he thought could be taken as a general indication of what would have happened apart from treatment. So you and he agree that there is a common prevalence?

A. Yes.

THE CHAIRMAN: Thank you very much.

MS DUNLOP: Thank you.

The first thing I wanted to ask you about, Professor Ludlam, is a point that we did also put to Dr Winter. It is just this question of spontaneous bleeding, and I wonder, do you refer here to those people who have severe haemophilia, who experience frequent, often apparently spontaneous haemorrhagic episodes?

I think I understood from Dr Winter's explanation some of the things that may cause bleeding in a joint, but if we could focus perhaps more on bleeding into the brain, the background to the question is really that if one has an understanding of haemophilia as a condition in which blood doesn't clot properly, in the sequence of events, the commencement of bleeding seems to be a prior event, and I wonder, with particular reference to bleeds in the brain, why does it start?

A. It's likely that there is -- we all have a small amount of bleeding in our brains from time to time. We all have good -- or most of us have good clotting systems

and it stops very quickly and heals up. The problem in haemophilia is that once bleeding starts, it takes a long time to stop. You do not necessarily get a greater flow of blood but it just goes on and on and on and on, and if that happens in the brain, then it often has catastrophic consequences.

Q. Yes. Thank you.

Also covered in this paragraph is a topic we have mentioned before, which is that of gradations of haemophilia. We understand that people are described as having severe, moderate or mild haemophilia, and I notice that the borderlines that you have set out for the divisions between mild and moderate and moderate and severe are 10 per cent and 2 per cent, which is slightly different from what we have in our report, which is that severe would be under 1 per cent and then moderate would be 1 to 5 and mild would be over 5. Yours, I noticed, was the same as what UKHCDO are using in 1983 and that -- sir, this is an example of just an allusion to a document, but we can see that from [SNB0017540], which we don't need to go to. Dr Winter told us that he had taken his -- he was 1 per cent, 5 per cent and then he wanted to go from 5 really up to 50 to cover all those who, even though they are in the 30s and 40s, might still have bleeding problems. I just wondered if you

could give us your perspective on where the dividing lines might be?

A. The levels of less than 2, 2 to 10 and then above 10, were thresholds that were used in the UK for a long time by UKHCDO. The reason they were chosen, I think, are very good reasons. Less than 2 per cent: If you have less than 2 per cent, you bleed much more frequently than if you have 3 or 4 per cent. People that have less than 1 per cent probably bleed more than people who have between 1 and 2 per cent but if you like, the people who have the most frequent bleeds are those with less than 2 per cent. If you have less than 1, you bleed even more.

The range from 2 to 10 is what used to be called moderate haemophilia and that includes virtually all the patients who will bleed in relation to minor trauma, twist the ankle walking downstairs, some of them get spontaneous bleeds. Often these people require treatment three or four times a year. There is also a group within this whose Factor VIII level may depend on the particular technique you use to measure it.

Those above 10 per cent very rarely bleed, except after major trauma or surgery. That was the system that was in operation until about ten years ago and I think it was a very good system because there were lots of

patients with levels up to 10 per cent who need treatment each year. Anyone over 10 per cent had mild haemophilia and needed very occasional treatment.

The International Society of Haemostasis and Thrombosis, for reasons that I have never quite understood -- and unfortunately I wasn't at the meeting at which it was discussed -- decided that less than 1 per cent would be the definition of severe haemophilia. 1 to 5 moderate and over 5, mild.

The reason I don't like that system is there are a lot of patients between 5 and 10 per cent who bleed from time to time in a year. It might be several times a year. And they are categorised with mild -- people over 10 per cent who hardly ever bleed at all. So under the new classification, the mild group is a much more heterogeneous group of patients and so that's why I prefer the previous categorisation but I have to move on with the times.

Q. Well, thank you for explaining that to us. I did look at the ISTH website and there certainly does seem to be a bit of controversy about it, with people asking, is this achievable. I don't know quite what that means but also the World Federation of Haemophilia seem to have adopted the 1 to 5 and 5 and up classification, and also I think we found the NHS referring to it as well. So it

may be that you are in a minority nowadays, would you accept that?

A. I do accept that, yes.

Q. Yes. The other point I suppose that I think we all understand is that categorisation isn't always the whole story because, if a patient is bleeding in the way you have described, then something has to be done about it. A patient with haemophilia who is bleeding -- and it doesn't really matter whether their level is 3 per cent or 25 per cent -- something could have caused them to bleed and they will need treatment. Is that a reasonable understanding?

A. Absolutely, yes. Could I make it clear that even though I think the previous classification system was better, I fully use the current one. This document was written 20 years ago.

Q. Yes.

A. That's why it is set out in this way.

Q. Yes, I appreciate that, thank you.

THE CHAIRMAN: Professor, is it entirely a matter of classification, as you have mentioned, or are there financial implications that go with the classification?

A. Not in Scotland.

THE CHAIRMAN: Not.

In Scotland.

MS DUNLOP: That is my next question, sir, that noting the article that the professor had written about funding, we had a description from Dr Winter of the sort of capitation arrangement, where a centre that had a higher number of people with severe haemophilia would receive more funding, but that isn't how it works.

A. Not in Scotland.

Q. Not at all? How is a Scottish haemophilia centre funded? I daresay we could take days on that, but in broad outline, is it to do with the number of patients at all?

A. No. Very briefly, it is financed by the local health authority. So Lothian funds the staff and facilities for the centre in Edinburgh, which is at the Royal Infirmary. The clotting factor concentrates, which are the expensive part of the service, are funded through a national arrangement, led by the National Services for Scotland and NSD, in which the health authorities are, I think -- the technical term is "bottom-sliced", a capitation fee, depending on the size of their health authority, and that money is pooled and used to purchase Factor VIII and Factor IX, the other clotting factors, for Scotland on a risk-share basis. It's a good system. I think it should be upheld.

Q. Right. This is no doubt stating the obvious but I take

it it wasn't much different in the 1980s? Certainly not in the sense of the capitation fee. That wasn't something that Scotland had in the 1980s and has moved away from?

A. No, in the 1980s the staff and facilities were provided by the local health board, Lothian Health Board for Edinburgh. Most of the Factor VIII was supplied "free of charge" to the health authority and to our haemophilia centre, and if commercial concentrates were required, they were purchased with -- well in Lothian's case, money from Lothian Health board via the Blood Transfusion Service who actually made the purchase.

Q. We want to come back to that and that's on my agenda but quite a long way further down.

So moving on to the next page, if we could, please, just a short question, professor. You mention osteoarthrosis; is there a difference between osteoarthrosis and osteoarthritis?

A. I'm not an orthopaedic surgeon but I think most of the chronic changes in bones are osteoarthrosis. Arthritis refers more to an inflammatory component. Now, there is an inflammatory component in the changes following bleeding into haemophilic joints but there is also an osteoarthrotic process in the bones. So there is both.

Q. Is the arthrotic process where the joint begins, as it

were to, seize up. Is that right?

A. Yes. It eventually turns into a process that is very like bad osteoarthritis that non-haemophiliacs get.

Q. You tell us a bit there, professor, about the natural history of severe haemophilia without treatment, and as the chairman has said, we have had some insight into that from Dr Winter, describing the situation as it currently exists in Pakistan.

He also referred to the recent diagnosis of a patient in Cambodia, who I think he said was the first patient diagnosed with haemophilia in Cambodia.

Then on to cryoprecipitate. You talk about the revolution in haemophilia care in the 1960s that resulted from the discovery of a technique for preparing cryoprecipitate from plasma. Then on to the following page, please:

"When cryoprecipitate from 10 to 15 individual plasma donations was combined and given to the patient, it was possible to raise the Factor VIII levels sufficiently to stop haemorrhage."

You say:

"During the late 1960s, this treatment became progressively available to haemophiliacs at hospitals on an outpatient basis."

At this point I would like to look at another of the

four documents, which is your treatment policy, and that is [PEN0150375]. This also talks about cryoprecipitate and we can pick it up under that heading. You talk about:

"The development of cryoprecipitate in the mid 1960s being a very major therapeutic advance for the treatment of Haemophilia A."

We do just need to clarify, Professor Ludlam, why does it not work for Haemophilia B?

A. Because it doesn't contain very much Factor IX.

Q. Yes. In the process -- I think it is the centrifuge -- when the centrifuge is used and the cryoprecipitate is precipitated out of the solution, in very crude lay terms, the Factor VIII is in the powder and the Factor IX is in the solution, in the liquid. Is that right?

A. Absolutely correct, yes.

Q. I hope that's good enough for us.

On to the following page you talk about treatment of an average bleed in an adult patient. I did just notice -- I hope this isn't too pedantic -- you do refer elsewhere, Professor Ludlam, to treatment of an average bleed requiring 10 to 15 packs, and you have here 15 to 20 packs. I wondered if we could just go forward with a sort of understanding that around 15 packs would be

needed to treat an average bleed. Is that reasonable?
A. It depends a bit on the size of the patient.
Q. Yes.
A. And the amount of Factor VIII you think might be in the individual packs of cryoprecipitate.
Q. It was just that in the passage we looked at from the previous statement, you did say cryoprecipitate from 10 to 15 individual donations had to be combined and given to the patient, but here it is 15 to 20. So just to assist our understanding, if we think of it as being around about 15, sometimes a bit less, sometimes a bit more?
A. Yes.
THE CHAIRMAN: Would that do? It does seem to me that from our point of view, what may be important is that when one thinks of cryoprecipitate coming from a single donation, there is only the beginning of the story, and unless there is a measure of the scale of usage, a misleading impression could be given. And I think Ms Dunlop's question is the right one: can we take it as a working hypothesis that 15 would be typical or not?
A. I think it depends when and upon the availability of cryoprecipitate. I think latterly we were tending to use 20 packs. It's about 1500 units of Factor VIII, which is a reasonable dose for treating a bleeding

episode.

THE CHAIRMAN: Yes. So how do we deal with it, Ms Dunlop?

A. I'm happy to settle at 15. I don't think there is going to --

THE CHAIRMAN: No, I just don't have the feeling that the actual number is as critical as the impression that it takes multiple packs to deal with a bleed.

A. Yes.

MS DUNLOP: Another point that we need to cover in relation to cryoprecipitate is its potential for home treatment, and you describe for us what happens when a patient is treated with cryo. So the packs are thawed in a water bath -- this is reading from your statement:

"... and pooled together before being infused into the patient. This was a messy, wet and time-consuming procedure. The other major disadvantage is that allergic reactions to it were relatively common. Occasionally these reactions could be serious and life-threatening. For this reason cryoprecipitate was not suitable for use by patients at home."

Professor Forbes did say that it's possible -- and maybe we should look at a couple of documents at this point. Can we look first at [DHF0023406]. Thank you.

I think if we go through this, we can see this is a document we have looked at before and it appears to

date from the middle of 1974, to have been a paper prepared probably for the Expert Group On the Treatment of Haemophilia. If we go through it, the same sort of reference, paragraph 4:

"Cryoprecipitate is tedious and time-consuming to make up."

Just at the bottom of that page it says:

"Although it has been possible to use cryoprecipitate for home treatment, both storage requirements and the inconvenience of administration make this an unsuitable material."

Then the other document was [DHF0023161]. And again we need to go through this. We see it's redacted. It is the minutes of the meeting of the Expert Group On the Treatment of Haemophilia in October 1974. Can we go through, please, on to the next page. Further down and then on to following page, please. Then:

"Optimum use of Factor VIII preparations."

Over to the next page, please. We can see that there was a paper 5. There is a name missing:

"... [may have been Dr Biggs] spoke briefly to her paper on home treatment with cryoprecipitate."

I appreciate that both these documents date from a long time ago but given that and Professor Forbes saying that it is possible but unsuitable, I wondered if

we could ask you just a little bit about what might have been involved or would have been involved for a patient home treating with cryo. I think the first thing we understand is the patient would have to have a deep freeze. Is that right?

A. Yes.

Q. Right. And then all of this thawing in a water bath, the patient would have to know how to do that?

A. He had to have a water bath at 37 degrees to melt the frozen individual units.

Q. Right. And I appreciate this is going right back to the beginning of your training but, I mean, are you familiar with the sorts of things that patients using cryo at home had to do?

A. Very familiar.

Q. So could they do it in their own bath, the thawing.

A. It is very important, when you are making up blood products, that it is done in a clean, and if possible sterile environment, and I think I wouldn't be keen to suggest that patients used their baths for warming up packs of frozen plasma, if the water was too hot, the proteins will congeal, a bit like egg white. In the hospitals we have water baths, this sort of size (indicates), a couple of feet across, carefully controlled in temperature and are cleaned regularly and

are as sterile as we can make them.

Q. So could you just walk us through what the person would have had to do at home. They would, you think, have had to have a piece of equipment, a water bath, and presumably a jolly good thermometer?

A. They would have to have a deep freeze, they would take out the deep freeze 15 packs of cryoprecipitate, put them in the water bath. They take about a quarter of an hour to melt. And then each of those packs has to have a tube put into it and the melted cryoprecipitate rolled out. Because they are polythene bags, you can roll them up and squeeze the cryoprecipitate out. You do that repeatedly 15 times, squeezed out into a bigger bag. You would then have to hang that up, connect it to a drip set, like giving a conventional blood transfusion, the patient would then have to put the needle into their vein and connect up the transfusion set to the tubing on the needle. And it would take about half an hour/40 minutes to run in.

Q. Yes. And the hypothesis behind home treatment is that this is something carried out by a patient who has an instinct that he is already bleeding or that a bleed is coming?

A. Yes.

Q. Right. And it could be done, I suppose, by a parent?

A. Yes.
Q. Dr Winter described to us one indication a parent might look for in a child would be that the child has a very hot knee or something like that, and that could be an indication that a bleed is starting or is about to start?
A. Yes.
Q. So psychologically, presumably there will have been a pressure of time, but this is a process that takes time, it can't be hurried, but things have to happen as quickly as possible?
A. Yes.
Q. Right.
THE CHAIRMAN: Professor, I'm beginning to form a picture that really is quite concerning in some ways. We must envisage a patient in a relatively remote part of Scotland.
A. Potentially.
THE CHAIRMAN: With a deep freeze big enough to store really potentially quite a large number of packs of cryoprecipitate. One doesn't know exactly when the bleed is going to come, but they might come repeatedly over a short period.
A. Yes.
THE CHAIRMAN: So there is quite a large storage problem.

A. Yes.
THE CHAIRMAN: The next thing is that the Factor VIII content of the individual packs is, within limits, quite unpredictable.
A. Yes, and unmeasurable.
THE CHAIRMAN: And unmeasurable. And certainly unmeasurable by the patient.
A. Yes.
THE CHAIRMAN: And did that have an influence on the number of packs the patient would be told to use?
A. Yes.
THE CHAIRMAN: In order to ensure that one covered the bleed, one would tend towards a larger number rather than a smaller number.
A. Yes.
THE CHAIRMAN: How on earth did stock control work in these contexts? How did one deal with it?
A. The stock control, I think, was fairly straightforward in the hospital.
THE CHAIRMAN: Yes.
A. But in a home setting, well -- I wasn't prepared to let patients have treatment at home with cryoprecipitate for all these reasons. But perhaps the most important reason, which we haven't dealt with, is the reactions. A lot of patients getting cryoprecipitate, had

reactions. Often these were mild and they would take an antihistamine beforehand, but I was looking at some information a day or two ago, suggesting that actually cryoprecipitate should only be given where adrenaline is available, and adrenaline is when you get an acute life-threatening allergic reaction, what's called an anaphylactic reaction. So for these reasons I wasn't keen and I did not have a home therapy programme based on cryoprecipitate. I concede other places did and it seemed to work for them, but it was logistically difficult.

MS DUNLOP: Yes, I think we can see that, professor. We need to go back to [PEN0150375], and you do make exactly that point, that allergic reactions are relatively common. We can see that towards the top of the screen:

"Occasionally these reactions could be serious and life-threatening."

So you say cryoprecipitate was not suitable for use by patients at home. This is obviously a topic that we will come back to about the potential for using cryo in the situation as it developed. Everything can appear to have a nuance. So whether one says it was possible but unsuitable or it was unsuitable but it was possible gets slightly different shades of meaning, but I think we understand that there were significant practical

difficulties in using it for home treatment?

A. Yes.

Q. Then you talk about your clinical experience of treatment with cryo. You say your:

"... clinical experience was that a patient who had received very little previous blood product and was treated with cryoprecipitate over a number of days for a bleed or to cover surgery became jaundiced."

Are you saying always?

A. No, but I was struck when I came here in 1980 that if I gave patients round about 100 or 200 donations of cryoprecipitate over a course of treatment, not infrequently they became jaundiced.

Q. And in what situation would they need to have about 100 or 200? Each time the patient is receiving about 15 bags worth; is that right?

A. Yes.

Q. So when would they end up having maybe 10 lots of that or ten treatments of that?

A. It might be three or four separate bleeds, they might have two or three treatments for each bleed.

Q. Then you say:

"It appeared to me that the frequency of hepatitis carriage by blood donors was approximately 0.5 per cent. Most of this was due to a putative non-A non-B virus or

viruses."

Obviously we are going to come back to that. Can I go on then, please, to the next page? This is still the treatment policy document, and just moving to the following page, to a heading "Factor VIII concentrates", you say that:

"Concentrates derived from pools of plasma to which many individual blood donations had contributed, started to be manufactured in the 1970s. Initial pool sizes were small, for example, 500 donations, but the pool size rose so that in the 1980s some manufacturers had pool sizes of many tens of thousands ..."

I think the highest number that the Inquiry team has noticed is 30,000, but you think it was beyond that at some points with some manufacturers, or is that round about the highest number you have ever heard?

A. I have heard higher numbers, I think.

Q. What's your maximum?

A. Perhaps 40 or 50. I'm sorry, I don't -- I would rather not say because it's a long time since --

Q. It doesn't matter, professor, I'm just interested in getting an idea of the largest pool sizes that may have been used.

THE CHAIRMAN: Professor, can I again ask a question at this stage? This is a very general statement about the

1970s. I have to say that when the preliminary report was written, I had just discovered but had not really absorbed the papers at a joint symposium held in Edinburgh in 1972 by The Royal Society of Edinburgh and The Royal College of physicians in Edinburgh, which gave rather a clearer insight into what had been happening in Scotland over the previous period and at that time. Are you aware of the history in Scotland in this detail?

A. Some of it.

THE CHAIRMAN: Have you read the papers of the joint symposium?

A. I am afraid I haven't, I'm sorry, no.

THE CHAIRMAN: That's the position I was in at the preliminary report, but perhaps we will all catch up in time.

A. Yes.

MS DUNLOP: These sort of bumper pools of 30,000, 40,000, 50,000, these are commercial manufacturers you are thinking of, is it, professor?

A. Yes.

Q. Yes. One of the questions which has struck us is, on discovering that the first commercial concentrate was licensed in America in 1966, we have wondered why it took until 1973 before the commercial concentrates arrived in Britain. Do you know the answer to that or

is that just one of these mysteries?

A. I don't, but I would wonder whether it might be that they could only make a limited amount and that was sold and used in the United States.

Q. Thank you. Then, just reading down through that, if we go to the foot of that page, you then refer to contamination. You describe viral contamination as an amplification system in concentrates and you say that has been responsible for the early and ready transmission of hepatitis and HIV viruses to patients, with such devastating effect.

On to the following page, a comment that the initial clotting factor concentrates were relatively impure and contained large amounts of other plasma proteins. Are we talking about only NHS product here or about commercial product too?

A. Commercial product as well.

Q. Right. Was that your experience then when you were working in Wales?

A. Yes.

Q. And was it also your experience when you came to Scotland? I'm just really trying to put a timeframe on this comment about relative impurity?

A. Oh, yes, it applied to all clotting factor concentrates around that time.

Q. Right. Would you say these early concentrates were very difficult to solubilise. I had to look that up, professor, because initially I wondered whether it just meant dissolved. But my understanding is that's really the stage before one dissolves it: tries to make it soluble and then to dissolve it. Is that what we should understand by the use of the word "solubilise"?

A. Perhaps it would be better to say "dissolve".

Q. That would cover it?

A. Yes.

Q. You say:

"The volume of reconstitution was relatively large. The early concentrates were only slightly more purified than freeze-dried cryo. The volume of a single infusion might be 200 mls to 300 mls of concentrate, as compared to 1 ml to 5 mls of recombinant factors today."

And:

"One of the difficulties encountered with the low purity concentrates produced by SNBTS in the early 1980s was that its use to cover major orthopaedic surgery could result in an acquired bleeding state due to its content of non-Factor VIII proteins."

I want to come back later in your evidence to notions of purity and potency but for just now I think we need to note that these early products were hard to

dissolve and if it was necessary to use the same sorts of volumes of water, then early home treatment must have required the patient also putting himself on a drip. Is that right?

A. Or using a large number of 50-ml syringes. For home treatment a patient would make it up with a syringe -- into a syringe. He would draw the dissolved clotting factor in the bottle, draw it up into a syringe and then inject it. But, because of the low unitage in the bottles and the large volume of water that had to be added, you could end up with several 50-ml syringes to inject. They were very fine cannulae. So it takes quite a long time.

Q. And you keep the needle in and you just change over a full syringe for the empty one. Is that right?

A. Yes.

Q. Yes. Then can we read down:

"1980. A majority of patients in Edinburgh were being treated with cryoprecipitate being prepared by SNBTS from Scottish blood donors. As described earlier, a small number of patients were receiving home therapy with NHS Factor VIII concentrate. The remaining concentrate was used in hospital, either for surgery or for patients who were allergic to all infusions of cryoprecipitate."

Then can we go back to [PEN0150385] at page 7? You have a section here, too, professor, on Factor VIII concentrate, covering most of the same ground, but you say:

"During the early 1970s Factor VIII concentrates manufactured by the NHS became available in very limited quantities."

We have had some discussion in evidence, relating to the Reverend Black, of a treatment he was seen to undergo in 1965. He had four flasks of AHG. We had some discussion then about what that might be, but our understanding is that this is likely to have been a very early NHS concentrate. Does that sound right to you?

A. It sounds reasonable.

Q. Yes.

THE CHAIRMAN: I am, of course, interested in this and slightly concerned about the language. As I understand it from the documents I was referring to, Cohn Fraction 1 was produced in Scotland at the time that Mr Black may have been treated. Is that properly described as a concentrate?

A. It's a very low purity concentrate but it is a concentrate, yes; it is a pooled product.

THE CHAIRMAN: It's one of these bits of terminology that gets us all wrong-footed, I think, professor.

A. No, it's produced from a pool of plasma. The Cohn Fraction 1 was the original purification method for Factor VIII.

THE CHAIRMAN: Thank you. Sorry, Ms Dunlop, I'm just trying to get my mind round all the terms and since the chronological sequence has to be taken into account, it becomes quite difficult.

MS DUNLOP: I'm also hoping, sir, that Dr Foster will turn out to be a historian of the production of materials in Scotland, so we can ask him too.

THE CHAIRMAN: I appreciate that's a possibility but I want to top up as I go, rather than get it all at once.

MS DUNLOP: Yes. One of the clinchers for Dr Colvin was the reference to flasks. That, he said, made it much more likely that this was an early form of concentrate rather than, say, cryo.

A. Yes.

Q. Yes. Just reading down -- we can all read that for ourselves, about the reference to home treatment and the improvement in life expectancy.

Then we move to Factor IX concentrates.

You say that:

"Initially treatment was by fresh frozen plasma."

Move on to the next page, please. You refer to the longer survival time in the recipient of Factor IX as

compared with Factor VIII. So Factor IX has a longer half life?

A. Yes.

Q. "In the 1970s treatment with concentrates of Factor IX became available like Factor VIII. These were prepared from large plasma pools prepared from many donors, but chemically they were quite different."

I think we can understand that and from what we said earlier, our crude simplification about which way the Factor VIII goes and where the Factor IX is, we can see that from one donation, it is possible to get both the Factor VIII and the Factor IX?

A. Yes, and other proteins as well.

Q. Well, indeed, yes. Is that partitioning?

A. Fractionation.

Q. All right. Can we, I think, still talking about Factor IX, go to the document that's 375. That's [PEN0150375]. Go to page 7 of that. We can see a heading "Factor IX" again. I'm not going to read it out. It looks as though initial concentrates were known to have other factors in them, II, VII and X, as well as Factor IX.

A. Yes.

Q. Was that a problem? Is it that that led to the possible thrombosis problem?

A. Yes, I think it is. The original Factor IX preparation, manufactured in Scotland, was a four factor concentrate, II, VII, IX and X, and that was superseded by a three factor concentrate, DEFIX, which has II, IX and X in it, not Factor VII.

Nowadays we treat patients with a concentrate containing just Factor IX, IX alone. If we have it. And there is a recombinant one available. The reason for this is that these other clotting factors could become a little bit activated during the manufacture, during the separation from the plasma, so that when they are injected into patients, they were a bit thrombogenic, and every now and again that patient actually developed a thrombosis, and particularly if there was some other pre-disposing factor to a thrombosis, then one was more likely to develop.

Q. By "activated", do you mean that the factor, rather than going into the patient's body and waiting until it's needed, goes in and immediately begins some kind of clotting process?

A. That's correct.

Q. Right. And I think we can understand -- and this is simple arithmetic luckily -- that, because the prevalence of Haemophilia B is very much less and because the yield of Factor IX is higher, there has been

a more plentiful supply. So in other words, self-sufficiency in Factor IX appears to have been achieved quite early in the story. Is that right?

A. That's correct, yes.

Q. We then go back to [PEN0150385] and go to page 9. We are on to von Willebrand's factor. Again you explain a bit about that. You say it is due to a congenital deficiency of the von Willebrand factor, and we do understand that both sexes are affected?

A. That's correct.

Q. So although it is congenital, it is not X-linked?

A. That's absolutely correct.

Q. Right. You tell us a bit about the symptoms of having von Willebrand's disease, and again if we can just read on to the following page, cryoprecipitate was used in preference to Factor VIII concentrate, partly because it contained a higher concentration of von Willebrand factor and because it reduced the rick of hepatitis transmission as patients with VWD only required an occasional transfusion. So they don't bleed spontaneously. Is that right? Or is that an oversimplification?

A. It is a slight oversimplification. Von Willebrand disease is probably the commonest congenital bleeding disorder but it is mild in most patients, and lots of

patients live to a ripe old age and are never diagnosed. But we see a steady stream of people with what we call symptoms suggestive of a mild bleeding disorder. They have a tooth extracted and they bleed for three or four days afterwards, or they have very heavy menstrual periods and the gynaecologist can't find any good reason for them, or a mother brings a child because he is always bruising and all her other children don't bruise.

So that's the presentation for most patients with von Willebrand's disease. There are a few patients who have what's called severe von Willebrand's disease who have virtually no von Willebrand factor in their plasma and as a result their Factor VIII level is very low because von Willebrand factor is the carrier protein for Factor VIII. So if you lack von Willebrand factor, then, because Factor VIII is unstable in the circulation, its level falls very rapidly after it has been released. So people with severe von Willebrand disease, sometimes known as type 3, actually bleed like a patient with severe haemophilia. They tend to bleed into their joints and their muscles.

Q. I see. You have then included a paragraph on DDAVP. This is something that again will crop up later in your evidence. But you give us a useful explanation of what it is. And you say:

"Its use in patients with haemophilia and VWD was first reported in 1977 and in the same year it was licensed for use in such patients. When given intravenously, it raises temporarily Factor VIII and von Willebrand factor levels by approximately three to fourfold."

And I think we already understand, Professor Ludlam, that DDAVP is not a suitable treatment for an acute bleed?

A. It can be if it's a minor bleed, yes.

Q. All right. I think we wondered, because of the time that it presumably takes for it to work, if it was adequate for an acute bleed, but you are saying there are circumstances in which it could be used?

A. Yes. If a patient has a nose bleed, for example, and comes up to the unit, we might, if their clotting levels are appropriate, give them an injection of desmopressin. We now give it what's called subcutaneously, just under the skin. You can give about 1 ml's worth of injection under the skin. It takes at least an hour to reach the maximum level. It starts working more quickly but it takes a quarter of an hour/20 minutes, to make up a bottle of clotting factor and one wouldn't want to expose them to clotting factor if it's a matter of merely waiting for half an hour for the desmopressin to

work.

Q. I see. So would you make your judgment as to whether to use DDAVP in a patient with, say, a nose bleed, depending on what their resting level of Factor VIII normally was?

A. I would make the judgment on the resting level probably on their von Willebrand factor, not their Factor VIII level, and not all patients respond to DDAVP and so we make it a practice when we see a new patient or diagnose a new patient -- we give them a test dose of DDAVP, to see whether they respond or not and how well they respond and how long the response lasts, because some individuals produce a good response but the von Willebrand factor disappears very quickly from the circulation.

Normally it lasts four or five hours and that's long enough to secure a minor bleed, perhaps a nose bleed. But it's only used for minor bleeds in patients who we know will respond or prophylactically. If someone is going to have a tooth out, for example, we might well give them DDAVP first and send them to the dentist round the corner from our unit to have the tooth extracted.

Q. Right. We do see in fact you refer to minor haemorrhage. Would it ever be used for a joint bleed?

A. Probably not because, if a patient had mild haemophilia

such that one might use DDAVP, their basal level of Factor VIII would have to be over about 10 or 15 per cent in order to get a rise up to 50 per cent with desmopressin.

In mild haemophilia, you do not get a joint bleed until you have had substantial injury to the joint and it's therefore likely -- in fact we know, in mild haemophilia you need actually to give more treatment to joint bleeds because there is a much greater degree of tissue trauma involved. An individual who has severe haemophilia just has to have a minor tweak to the joint and they start bleeding and they continue to bleed. An individual with mild haemophilia who gets a joint bleed has had to get usually a proper sprain -- if I can put it that way -- to the joint and because there is a lot of trauma they require more treatment.

One of the difficulties of this situation is that people with mild haemophilia don't bleed very often and they don't appreciate the importance, if they do get a bleed, of coming in for treatment early. So a number of people with mild haemophilia now come in days or even a week or ten days after a bleed has started and they have a very large haematoma and they find themselves in hospital for a protracted period of time, requiring concentrate treatment.

Q. I see.
THE CHAIRMAN: I think, Ms Dunlop --
MS DUNLOP: I'm just at the end of a section. I have been hoping to get to the end of a section before we have a break. Can I ask one more question and then we can move to something --
THE CHAIRMAN: It depends whether Professor Ludlam can give you a very short answer.
MS DUNLOP: It was just, in assembling a complete picture of treatment, there is also tranexamic acid.
A. Tranexamic acid is an interesting, simple molecule made synthetically, it can be given as a tablet and it inhibits the ability of the blood to dissolve clots.
Q. Right.
A. We believe that in the circulation all the time there is a little bit of clotting going on, a little bit of clots being formed, and that clot is being dissolved and when you get an injury, you get a bit of clotting to stop the bleeding, but after a little while you don't want that clot any more and it is dissolved. Otherwise, you would be covered in scars the whole time. And this medicine, tranexamic acid, inhibits the breakdown of the clots, what's called fibrinolysis. So the clots stay a bit longer. If the clots are a little bit friable because you have a bleeding disorder, then it helps strengthen

them because they are not being dissolved.

Q. Thank you.

That, sir, is a completely natural break.

(11.10 am)

(Short break)

(11.31 am)

MS DUNLOP: Professor Ludlam, could we look next at [PEN0150375] at page 4. There is a subheading "Hepatitis". Again, I don't think I need to read this out. I think we all understand that Hepatitis A and B could be excluded by the later part of the 1970s, so the other kind of hepatitis was called non-A non-B. And you say -- this is reading from the bottom of page 4:

"There was a view that hepatitis, following the use of commercial concentrates, was more severe than that following the use of NHS concentrates."

That turned out to be inaccurate.

A. At the level of Hepatitis C testing, yes. What we now know is that the majority of non-A non-B hepatitis is due to Hepatitis C. In a historical context the Bournemouth outbreak led to a lot of symptomatic hepatitis of jaundice and people being unwell, and that was following the early use of imported concentrate from North America, and that was clinically, I think, much worse hepatitis than we were used to seeing with NHS

concentrates, and I suspect that's due to the fact that the commercial concentrates contained more Hepatitis C virus in the bottles than NHS concentrates. Therefore you got a worse acute episode and you became jaundiced and sick and unwell. Whether that led to worse chronic liver disease I think is not at all certain. I don't think there is evidence that liver disease following use of commercial concentrates is worse than liver disease following hepatitis exposure from NHS concentrates.

Q. Right. The next sentence reads:

"It was also considered that the chances of an NHS concentrate transmitting hepatitis was rather less than a commercial one."

If we confine ourselves to the 1970s, I suppose particularly the very early days of commercial concentrates, when there are references to NHS concentrates being made from 100 or 200 donations pooled together, that may have been true in those early days, may it?

A. I think so, yes.

Q. Then you say:

"There was also some evidence that commercial concentrates might contain at least two viruses responsible for non-A non-B hepatitis."

Was that true?

A. There was evidence for there being more than one type of non-A non-B virus, and actually some of the evidence was from studies done in the early 1980s on NHS concentrates, but I think looking back, yes, it was all Hepatitis C.

Q. So it was a bad question. The statement, I would hope it's true, but in effect once the virus, Hepatitis C, had been found, it turned out to be the culprit.

A. For the majority of cases of non-A non-B hepatitis, yes.

Q. Yes. Then:

"Furthermore, it was not clear whether the hepatitis caused by NHS concentrates was the same or different from the causative agent in commercial concentrates."

What about that?

A. Well, I think that was perhaps based on the experience of the Bournemouth outbreak, if I can call it that, where commercial use was followed by a lot of malaise, more so than NHS. So was this a different virus or was it a different quantity of virus? And I think probably -- I have not asked a virologist -- I suspect it's because the quantity of the virus in the commercial concentrates.

Q. That's just the empirical finding you referred to a moment ago, that people seemed to be more sick, as it were, immediately after the commercial concentrate had

been administered?

A. That is one of the take-home messages from the descriptions that have been written up of the Bournemouth and associated hospitals outbreak.

Q. Yes. Our understanding, Professor Ludlam, is that ultimately -- and by "ultimately" I mean the early 1980s -- it appeared that whether a patient had received commercial or NHS concentrate, they generally acquired non-A non-B hepatitis?

A. Yes.

Q. Much of the work in this area appears to have been carried out or at least co-ordinated by Dr Craske. I presume you worked with Dr Craske?

A. Yes.

Q. And knew him quite well?

A. Yes.

Q. We have had him described as "tireless". I take it you would agree with that?

A. He was a great enthusiast for what he was doing, yes.

Q. Indeed. I don't need to take you to this but Dr Boulton's note of the UKHCDO meeting on 17 October 1983 -- and for the record, that is [SNB0017535] at page 4 -- contains a note by Dr Boulton to the effect that you had said confidentially to him -- that may have been confidential then but it isn't now --

that the report of the hepatitis working party was largely a solo effort by the chairman. Do you want to see that?

A. No, I saw it in some of the papers. No, he led the work of the hepatitis working party. He did a lot of, if I can put it, the background work, the designing of the forms, writing out the protocols and really keeping the projects rolling.

Q. You say:

"My predecessor, Dr S H Davies ..."

That's Dr Howard Davies; is that right?

A. Yes.

Q. "... had a policy of not using commercial concentrates because of the uncertainty about hepatitis viruses in the concentrates derived from plasma collected in the United States and elsewhere."

So that's your predecessor as director of the haemophilia centre at Edinburgh Royal, is it?

A. Yes.

Q. In fact, if we look at [SNB0072254] -- we have seen this letter before -- maybe you haven't but we have. This is a letter from Howard Davies to Dr Cash in December 1975 and we can see that he was wanting to get home treatment up and running, and I suppose what's interesting to the Inquiry about the letter is that he is wanting to get

home treatment up and running with NHS concentrates.
A. Yes.
Q. One of the thoughts I had about Dr Davies' policy was that it might date from the television programme but of course, this is a full year before the television programme was shown, so his reservations about the commercial products pre-dated World in Action?
A. Yes.
Q. Do you remember the World in Action programme from 1975? I think you would be a senior registrar in Cardiff at that point. Do you remember it being on?
A. I just moved to Cardiff about a month before, a month or two before the programme was shown, and I was still settling in there. And I was still getting familiar with my colleagues and the patients. I don't know whether it was shown in Wales but I don't recall there being discussion about it. There was lots of discussion about the Bournemouth outbreak but I don't recall discussions about the programme. Whether it was shown in Wales or not, I don't know. I may not have had a television at that time.
Q. Certainly one would speculate that a programme like that, featuring some of the big names of the day, would have been a major talking point. So you are telling us you don't even remember that? Even if you didn't see,

it, you don't remember people saying there was an amazing documentary on on Monday or anything like that?

A. No.

Q. No. Right. You have seen it now, I think, haven't you?

A. Yes.

Q. What's your reaction to it?

A. I think it confirmed a lot of my pre-conceptions, except that I think the plasma collection facilities were rather worse than I thought they were. They did not have a good reputation but I was appalled by the conditions.

Q. We need to go back to [PEN0150375]. Having referred to Dr Davies' policy you say:

"I did my utmost."

I'm guessing that most of these statements were not typed by you, Professor Ludlam. Is that correct?

A. I'm not a good proof reader. No, this is professional typing.

Q. Right. Yes, there are a number of others, but anyway, you did your utmost to continue this policy when you became responsible for the service in 1980. Just on that point, your becoming responsible for the service. I would like to look firstly, please, at a document [LOT0032997]. And this is the minutes of the ninth meeting of the reference centre directors, held at

Oxford on 15 October 1979. We can see that you are there, Dr Forbes is there as well, and interestingly we can see from page 2 that you seem to have been on the agenda. This is the whole question about process, and I think really in a nutshell who should be approving your appointment as Dr Davies' successor at Edinburgh Royal:

"Dr Davies thought the appointment of his successor should be approved by both the SHHD and the haemophilia reference centre directors. Dr Davies had contacted SHHD about this matter but had received no reply. Officially there were no reference centres in Scotland although unofficially the Glasgow and Edinburgh centres acted as haemophilia reference centres."

This point, professor, if it is big enough even to be considered a point, but the fact that there wasn't an official designation does crop up in quite a lot of minutes over the years. Do you remember that being a topic at various meetings?

A. I do. And I think a great deal was made out of it for very little. We were keen that Edinburgh and Glasgow were seen as reference centres. We were part of a UK arrangement for overseeing haemophilia treatment. Our colleagues in the other centres in Scotland were very happy for Edinburgh and Glasgow to be recognised as

reference centres. They didn't feel they wished to bid for that status. The Scottish Home and Health Department was a little hesitant and when I enquired a little further, it seemed they were a bit afraid there might be some financial implications of so designating us. But as you will have seen from some of the documents, bit by bit approval was given, and certainly from when I took up my appointment -- in fact, this meeting is before I took up my appointment -- I have always been part of the reference centre directors' committee.

Q. Yes. You will appreciate, Professor Ludlam, that coming to the issue cold, the Inquiry team was concerned to discover if the lack of the formal designation had ever meant that the directors in Glasgow and Edinburgh and therefore in Scotland were out of the loop in some kind of way?

A. No, we were in the loop.

Q. Yes. Perhaps the only other thing to notice about this particular set of minutes is that, if we look at page 11 -- that's [LOT0032997], page 11 -- there was a report from Dr Craske's hepatitis working party and some question about how data was to be collected.

For completeness, sir, I should say that the report -- although I'm not completely certain -- from

the hepatitis working party appears to be [SNB0017207]. If we could just quickly look at that, and in particular if we can look at page 3, which is SNB0017209, there is one of really quite a large number of pieces of information about the NHS commercial comparison. We see that just under the table 2 it says:

"Patients treated with NHS and commercial Factor VIII concentrate showed no significant difference in their liver function tests."

Do you see that?

A. Yes.

THE CHAIRMAN: Could we scroll down a little bit please? We don't have that.

MS DUNLOP: Sorry. There it is.

It really looks as though Dr Craske studied this subject more or less without ceasing from about 1975, certainly well into the mid 1980s.

A. I think he is a great credit to his endeavours and to studying hepatitis in a systematic way, which, as far as I know, was hardly happening anywhere else in the world. This was sort of world-leading research.

Q. Could we go back, please, to [PEN0150375].

You are talking here about home treatment, and we can see about halfway through this paragraph reference to the delay in introduction of home treatment for many

eligible patients.

Just on that point, professor, we have seen some references from the early 1970s, particularly at the point where the commercial concentrates are arriving in Britain, to ideas of home treatment being confined to people who lived a long way away from the haemophilia centre. Even if that was someone's expectation or someone's hope, it doesn't appear that that was ever translated into practical policy. Do you remember that being a sort of caveat about home treatment, that it was only for a small group of patients who couldn't get to the centre?

A. No, each patient was considered individually. There were patients who travelled very long distances and who had severe haemophilia, and I can think of one or two patients that I tried to help, because they were coming so frequently, by putting them on to home treatment. But home treatment, when there is a plentiful supply of Factor VIII, is for anyone who is competent to give it to themselves and bleeds sufficiently frequently that they need it.

Q. I suppose it would have been a way of limiting expenditure when the commercial concentrates became available in the early 1970s?

A. I see -- I don't think it was ever a way of rationing

treatment.

Q. When you arrived at Edinburgh Royal in 1980, what was the system for patients who realised that they were having a bleed? We had Dr Forbes on Thursday describing the system in Glasgow and he laid out for us a sort of open-access policy. I wonder if you can describe what the system was in Edinburgh around this time?

A. Certainly. This is for a patient who needs to come into hospital for treatment?

Q. Yes.

A. Yes. They would phone up in the morning, usually the morning, to order an ambulance to bring them to the haemophilia centre. So the patient would wait for an ambulance. The ambulance would bring them, sometimes a considerable distance, from West Lothian or Fife or down in the borders. They would come to our haemophilia centre, which in those days was a single room attached to ward 23 in the hospital. One of us, either myself or my registrar, would go and see them and by the time we went to see them, often several patients had accumulated so we would go round with our notebook, noting what was the trouble, where the bleeds were and we would order up the cryoprecipitate, although we did encourage patients, when they phoned in advance, to say they were coming, to let us know, so we could get the

cryoprecipitate sort of thawed out in advance. We then had to put the request to the blood transfusion who were 50 yards down the corridor. They conveyed the cryoprecipitate up to our haemophilia room. The infusion would have to be set up. Some patients could set their own infusions up. Others had to wait for a doctor to come and do it. The infusion would take about half an hour/three quarters of an hour to run through, at which point the patient was free to go. The only thing was that they often had a bleed in their knee or elbow, so it was difficult for them to get around and they would wait for an ambulance to take them home.

The ambulance might come at the end of the morning or the early afternoon and they would be home by about four o'clock.

Q. Did that system operate well during working hours? Was that a kind of nine-to-five system?

A. That's how it worked during the working day. Patients could come up at any time of the day or night. It was an open-access service. So we had to respond to patients whenever they came.

Q. So what about a patient who felt they were starting a bleed at nine o'clock at night or on a Sunday at 11 am. What would happen to them? Would they have to go to casualty?

A. No, they came up to the haemophilia room and usually the doctor on call for the ward would see them and ring one of us up and we would make some recommendations about their treatment, and the ward doctor would give the treatment and the patient would go away again.

Q. So help was available really 24/7?

A. Absolutely.

Q. Just moving through this part of the statement, professor, you refer to the driver for collection of plasma being obviously the need to produce more Factor VIII concentrate. You say:

"One of the disadvantages of Factor VIII concentrate was the yield of Factor VIII from starting plasma is substantially lower compared to plasma being converted to cryoprecipitate. The demand rose sharply in Edinburgh after 1980 because I wished to use more Factor VIII concentrate to treat the patients."

Then an interesting paragraph about patients having a card. You say that:

"Patients were individually told to request either cryoprecipitate or an NHS concentrate and to avoid a commercial concentrate if possible. To emphasise the importance of this, each patient was supplied with a small statement to this effect which was placed in their haemophilia card, which could they could show to

get treatment at another centre."

When did you initiate this system, or was it something Dr Davies had done?

A. I think I initiated it, very shortly after I arrived. Because patients would obviously travel and they might go down to England and, as you know, in England there was much more commercial Factor VIII used. So if a patient turned up as a visitor there was a possibility they might get an injection of commercial concentrate.

Q. Right. So did every patient with haemophilia have a little card like a sort of bank card or a little cardholder?

A. Every patient we diagnosed with haemophilia or other congenital bleeding disorder is given a card stating what the condition is, what is the level of severity of the condition, which haemophilia centre they are registered with, where to phone in an emergency.

Q. Right.

A. They are invited to carry these with them wherever they go.

Q. Has that been the system for as long as you have worked in haemophilia care?

A. It has been the system since the 1970s.

Q. This issue of patients needing treatment in another place, or indeed even when they are in Edinburgh, being

on home therapy, I wanted to ask you how they actually physically got the product, the medicine. I suppose people who arrive at hospital because they think they are having a bleed, that's all done from the hospital pharmacy, is it?

A. With the Factor VIII concentrate.

Q. Yes.

A. No. The Factor VIII concentrate was stored by a blood bank in the hospital and the blood bank was overseen/managed by the Blood Transfusion Service.

Q. So it doesn't form part of the pharmacy set-up in the hospital at all in fact at this point?

A. Not at this point, no.

Q. Right. And for patients on home therapy, how did they get their material?

A. They would phone up and say that their stocks were running low, could they have some more. We would phone the blood bank and ask them to make up a package which the patient would come and collect, often in the early evening on their way home from work or a relative would come.

Q. I see. You go on to say that:

"Because of the relative scarcity of NHS Factor VIII concentrate during 1981 and 1982, a small amount of commercial concentrate was purchased but it was

purchased for treating a small number of patients with specific haemostatic therapeutic difficulties."

There are really two propositions rolled into that, professor. I wasn't sure whether you were saying that some commercial concentrate was purchased in 1981 and 1982 because there wasn't enough NHS concentrate, or some commercial concentrate was purchased because it was necessary for patients for whom NHS concentrate wasn't suitable?

A. Mostly the latter.

Q. Mostly the latter, right. So there were occasions when you had to supplement your NHS concentrate with commercial material just because there wasn't enough NHS?

A. I have set out in one of the documents -- I don't know your number --

Q. We are going to that later.

A. Okay.

Q. You have set out a very detailed account of the individual patients for whom commercial concentrate was used and why.

A. Yes.

Q. You have. So if I say that we will come back to that, but this point about relative scarcity, perhaps it is just very difficult to remember, and we appreciate it's

30 years ago, but do you think there was ever a time when you had to buy commercial because there just wasn't enough?

A. There was at least one patient who I put on to home therapy with commercial because of the distance he lived from the hospital and because his brother was also going to go on to it because he had started, if I can call it, for clotting reasons.

No. If I had been anywhere else in the UK in these circumstances and had not inherited this situation where commercial concentrate had never been used, then I would have been going to my health authority and saying, "Look, we need much more commercial concentrate to allow these people to go on to home treatment". Because that is what had happened five years earlier or four years earlier, in England. So a lot of my patients couldn't get home therapy because there wasn't an adequate supply of concentrate. And I wasn't prepared to take the risk of giving patients cryoprecipitate at home.

Q. You see, that was interesting, professor, because you are saying that really the reason why you didn't try to get a large number of patients or a large increase in the number of patients on home therapy by going to commercial product, to make up any shortfall, was that you wanted to maintain Dr Davies' policy but you

yourself must have reached a clinical judgment as to whether it was a good policy or not.

A. It was very difficult. As you see, there is much more literature. A great deal of interest and concern about hepatitis, non-A non-B hepatitis and what it was and what it meant, and I took the view that here are a group of patients who had not been exposed to commercial concentrate and maybe it was worth trying to preserve that in these very difficult times of supply, so that at least we had a group of patients that we could see what happened with NHS concentrates because the majority of patients being treated in England were treated with a mixture of NHS and commercial.

Q. So there was at least, to some extent, an interest in monitoring what was going to happen if you had this group of patients treated purely with NHS product. You are nodding?

A. Yes.

Q. The last paragraph on that page, you talk about a batch dedication system -- and I appreciate we are jumping into 1984 but just because it is there. I think if we look at a letter, which is [SNB0074755], this is actually from Dr Perry to Dr McClelland, and if we go down to paragraph 2. It takes a minute but when you first see this letter you don't appreciate the

difference but there is a difference between dedicating a batch to a patient and dedicating a patient to a batch and it looks as if it was mooted, certainly in 1984, that each patient would have, as it were, their own batch but because that would have led, as I understand it from this letter, to a degree of wastage because the batch would outdate perhaps before the patient had got through it, the system that was introduced was actually the other way round, so that the batches were dedicated to the patients. I think that's when you describe in your statement?

A. Yes.

Q. If we go back to that then, please, that's [PEN0150375] at the bottom. You say:

"There were three parallel batches of Factor VIII concentrate. Patients received from a particular batch based on their surname."

Do you know if that operated elsewhere in Scotland or indeed in Britain?

A. Yes, it was a Scottish initiative, as part of our collective activities. I think it operated in Glasgow. It was started at about the same time. The reason why it came in rather later than it might have done is because you need to have a larger stock of Factor VIII available actually to run a system like this. You have,

in a sense, to have three times the stock level. Where there was a paucity of Factor VIII concentrate, then it made it difficult to run a system like this. So this became available -- or we did this when there was more Factor VIII available.

Q. I see. Then on to the following page, you actually talk about heat-treated product being issued in December 1984. But we don't need to go into that just now.

I would like to move from here to page 8 of this document. If we look at the first paragraph you talk about:

"In the 1980s commercial fractionators moved towards manufacturing clotting factor concentrates of higher purity, which is more units of Factor VIII per milligramme of protein in the final vial."

You say:

"This was important for the treatment of babies in whom it can be difficult to give injections of clotting factor concentrate because of the small veins buried in chubby arms. Higher purity products were also less likely to give rise to allergic reactions ..."

We are going to go on to look at purity and potency but just because you mentioned children here, I wanted to ask you in general terms, from your arrival in 1980,

how children were cared for, children with haemophilia, particularly were they on home treatment and so on?

A. When I arrived, there weren't actually many very small children with haemophilia but I was responsible for looking after them as well. Previously, some of them had been looked after by paediatricians in other hospitals in the city, and they continued to be so even after I arrived for a spell and so I would find myself advising about their treatment, as it were, by proxy. But eventually, as part of the "centralisation of services" I became responsible for about a 13-year period.

Q. Right. Did you move to introduce home treatment for children?

A. Yes.

Q. From what sort of age of child?

A. Oh, it is very variable. It depends on the child and the parents. It could be done from the age of four/five/six/seven. It very much depends on the child.

Q. The reference to babies; do babies tend to need much treatment for haemophilia or is it really only once a child is ambulant that they are more at risk of bleeding problems?

A. A child with severe haemophilia usually starts to bleed about the age of nine months when they start to crawl

around and walk and fall over. And so to begin with, they only get occasional bleeds, perhaps every month or so, and so they need treatment and the baby is distressed from the pain of the bleed and that makes their veins constrict a bit. They have very small veins, they may have chubby arms, and it is not easy to treat small babies, give them an intravenous infusion of anything. The clotting factor concentrate is of some volume and therefore it can be very traumatic for everybody, treating very small babies.

Q. Nonetheless, you managed to maintain Dr Davies' policy of using NHS material, even though you had a constituency of children in your haemophilia patients in Edinburgh. Is that right?

A. Yes, I did not have, as I say, many small babies when I arrived, actually. I don't know why that was, except that one or two of them were looked after by paediatricians, who would have done some of the therapy.

Q. What about school age children? Did you have a group of them?

A. Yes.

Q. And so notwithstanding the difficulties of possibly having to use quite a large infusion -- we discussed earlier about maybe 200 or 300 mls -- you did manage to treat the children as well without resorting to

commercial product?

A. Yes.

Q. I suppose for the home therapy, you had some sort of training programme for parents, did you?

A. Yes.

Q. The rest of that statement, I think we can put to one side, save perhaps to notice that I think on the following page it says "iron" when it should say "ion". I just wanted to correct that one in case we became confused. You see in line 3:

"It was agreed to develop a high purity iron exchange concentrate."

I think that should read "ion"?

A. The "R" should be removed.

Q. The rest of this section is dealing with events rather later than we are focusing on, at least in this topic.

Can we go next, please, to [PEN0150445] at page 15? This is, as promised, purity and potency. Just to be sure that we understand this, professor, looking firstly at paragraph 51 you say:

"Purity is defined as unit clotting factor per milligramme of total protein in the reconstituted vial."

Then:

"Potency is the concentration of clotting factor in the reconstituted vial, international units per

millilitre."

Given that the former one is international units per milligramme, would we be losing anything if we thought of your definition of "purity" as being units of clotting factor per milligramme of the solid, as it were? I appreciate, the solid is dissolved but ...?

A. You would need to ask the protein fractionators. That is milligramme of protein. In the freeze-dried keg in the bottle, there may be some salts solution and stabilisers. So they will be, if you like, additional weight and are not part of the purity definition.

Q. Yes. I suppose there is the water as well. This is an international or a conventional understanding, is it?

A. Yes.

Q. Well, we should probably stick with that. So purity is unit clotting factor per milligramme of total protein in the reconstituted vial and potency is the concentration of clotting factor in the reconstituted vial and the former is expressed in international units per milligramme and the latter in international units per millilitre. Then we have a definition of purity. That's another one that has three gradations, and you say:

"The definition of purity changed in the 1980s but for the purposes of this statement the above categories

are used."

It is interesting to note that -- and this is line 4 of that paragraph beginning "Factor VIII" -- that:

"Factor VIII protein represents about 1 to 2 per cent of the protein in the concentrate."

So there is an awful lot of other stuff in there as well?

A. It is probably less than 1 per cent, actually. Yes, most of the protein is not Factor VIII in these low and intermediate purity concentrates.

Q. Then you explain that:

"From a manufacturer's perspective, a low purity product usually maximises the yield of Factor VIII. It is highly relevant when trying to reach self-sufficiency. But purity is important to a physician and patient for the following reasons: one, lower purity products are usually slower to dissolve. There is a greater chance of aggregates remaining in the solution."

I was wondering -- obviously the answer to this must be that it does matter but if you were trying to dissolve and there is other stuff there that you don't want, it doesn't just sink to the bottom. It is not as simple as that?

A. Well, you want to make sure that you have dissolved, if

you like, all the Factor VIII.

Q. Yes.

A. So we teach people that they should wait until the whole of the keg is dissolved. It is actually drawn up out of the bottle through a filter needle, which filters out big aggregates of proteins -- probably non-Factor VIII proteins, like immunoglobulins and fibronectin -- so that when the solution is injected into the patient, they don't actually get aggregates, or as many aggregates, as they might otherwise.

Q. Then the second point you make is that:

"Lower purity products are more likely to result in 'allergic' reactions because there are more 'contaminant' proteins ..."

Then over on to the next page:

"Lower purity concentrates may contain anti-blood group A and B antibodies, which can react with the recipient's red cells ..."

Then fourthly:

"The contaminant proteins may accumulate in the recipient pre-disposed to a haemorrhagic state."

So it does look, professor, as though there is an inevitable tension between the manufacturer, who wants as big a yield as he can, for which there may be a purity cost, and the physician and patient, who would

like as pure a product as possible but for which there would be a yield cost. Is that accurate?

A. Yes, at that time.

Q. At that time.

A. What transpired -- and I'm sure Dr Foster will be able to speak much more eloquently to this than I can -- is that when we came to develop, or they developed the high purity Factor VIII concentrate in the early 1990s, the yield in making that was actually quite high, and I remember during the 1980s there was -- because of events in protein fractionation technique -- the ability actually to increase the yield at a higher purity.

Q. Right. Pleasing both sides of the tension?

A. Absolutely.

Q. Then reading on, paragraph 54:

"Purity became a particular issue in the 1980s."

And you explain that. You say:

"In the early days of AIDS it was considered that a large amount of these proteins might pre-dispose to or be the cause of AIDS."

Were the commercial products at that time not much more pure?

A. Yes.

Q. Right.

A. In general. It was an evolving scene, and can I draw

your attention, if I may, to Peter Foster's witness statement, in which he gives a table of many of the commercial concentrates prepared in the 1970s and the 1980s, and he gives their physical characteristics including their purity.

Q. Right. Thank you. But then you say:

"There was a possibility that the contaminant proteins might be beneficial. Beneficial by modulating the immune system and reducing the development of antibodies to the transfused Factor VIII."

Then:

"Anti-Factor VIII antibodies arise in about 25 per cent of small children with severe haemophilia and are currently the most feared and severe complication of haemophilia."

Anti-Factor VIII antibodies are much more of a problem for young children than for older people, I suppose, because they have come through the stage of being exposed to the other products. Is that right?

A. Having an inhibitor at whatever age greatly influences what treatment you give and the response to it. Whether you are a child or an adult, if you have an inhibitor, it is much harder to treat the bleeds. But the inhibitors mostly -- not exclusively at all -- arise in children with severe haemophilia within the first ten or

20 injections of concentrate. So by the time the child is two or three, a quarter of them have these inhibitors.

Q. If you were able to extract a sample of pure Factor VIII from everybody in this room, would it be the same substance?

A. Probably not completely identical because there are some polymorphisms in it.

Q. I just wondered why, if people have a small amount of Factor VIII circulating in their body, they would develop an antibody to Factor VIII?

A. Oh, but individuals with severe haemophilia don't have any Factor VIII.

Q. Right. I understand you mention elsewhere that you can get a gene deletion. So that would be an example of somebody who wouldn't have any Factor VIII. Is that right?

A. Yes, but you can get other genetic abnormalities resulting in no production of Factor VIII.

Q. Right.

A. So those individuals see Factor VIII as a foreign protein, like a flu virus, and they make an antibody against it. There are other people who have a Factor VIII with reduced activity, in mild haemophilia, say 10 per cent activity of Factor VIII.

If they receive large doses of Factor VIII, particularly under particular circumstances, they are actually only tolerant to their own Factor VIII. They recognise their slightly abnormal molecule as their own. So when you transfuse them with Factor VIII to treat their bleed, that Factor VIII is structurally slightly different from their own Factor VIII. They then may make an antibody against that so it neutralises the transfused Factor VIII. And to complicate matters further, that antibody may then cross react with the patient's own Factor VIII and reduce the basal level to nought. So a mild haemophiliac suddenly turns into an individual with severe haemophilia and severe haemophilia with an inhibitor.

Q. Right. So it is not just people with no Factor VIII who can develop inhibitors?

A. That's correct.

Q. Yes, it is people with abnormal Factor VIII. Is there any other group of people who can develop inhibitors?

A. They can arise spontaneously. It tends to be in older people, with an instance of about 1 in 1 million. We see about one patient a year with acquired haemophilia and they can be very difficult to treat.

Q. So when a patient has developed inhibitors, is that it as far as concentrate treatment is concerned? You have

to think of something different?

A. There are two things. One is how we treat a bleed in someone who has an inhibitor, and that depends on the level of the inhibitor. If it is a very low level inhibitor then you can give large doses of Factor VIII and as it were, neutralise the inhibitor. If it is what we call a high level inhibitor, then however much Factor VIII you give, it is immediately neutralised.

So we use currently two other medicines. One is called FEIBA and one is called Recombinant 7A. Both those are effective in stopping bleeding in inhibitor patients. It is not as good as treating a patient with haemophilia who doesn't have an inhibitor with Factor VIII but --

Q. FEIBA has been around a long time.

A. FEIBA has been around for a long time but you are then left with the other problem in a child who has an inhibitor, of trying to get rid of that inhibitor, and what emerged from studies in the Bonn haemophilia centre is that if you treat these children with huge doses of Factor VIII, sort of industrial doses of Factor VIII each day, after about a year or two, in about 80 per cent of children the inhibitor actually disappears and the patient then responds to Factor VIII normally.

Q. Right. If I'm following -- this is a dangerous question because I may not be -- this description of inhibitor formation would make it seem as though inhibitors are as likely to develop, or were as likely to develop whether the concentrate used was commercial or NHS.
A. That's correct.
Q. Right. But of course, there are other immune responses which might happen in a recipient which are due to the material other than the Factor VIII, and that would depend, I suppose, on how pure the product was.
A. That's also correct. I should perhaps qualify my previous answer, when you asked the difference between NHS and commercial. Commercial includes recombinant Factor VIII these days, and there is an important question before the haemophilia community at the moment as to whether inhibitors arise more frequently in patients treated with recombinant Factor VIII.
Q. All right.
A. The supposition being that maybe some of the contaminant proteins, the non-Factor VIII containing proteins in plasma-derived concentrates, may actually be beneficial and suppress the development of inhibitors.
Q. And that's the point I think you make in the second bullet there, is it?
A. The one that ends with the Sippet.org.

Q. Yes?
A. That's the study that's being mounted by Professor Mannucci in Milan.
Q. I guess that's a current major "trial" rather than a current major "trail", is it?
A. Trial, yes.
Q. Going on to the next page, you talk about potency. And there is obviously a huge difference between the early Factor VIII concentrates and currently available products?
A. Yes.
Q. The corollary being that you need very much less in your syringe with the modern product?
A. Yes.
Q. And you say that purity and potency are bound up together because lower purity concentrate requires a larger volume of diluent for a reconstitution and that gives you a lower potency product. Then you go on to instance a particular difficulty and we will come back to that because it links in with your use of commercial product.

Having looked at purity and potency, can we move to page 14 of this same document, please. "Home therapy". Again you give us quite a lot of information, professor, and a table showing the UK as a whole in 1980 and then

Edinburgh in 1979 and 1980. Large use of commercial. Edinburgh in 1979 under Dr Davies' stewardship, no commercial product. Then 5 per cent of the product used in 1980 was commercial. We worked it out to be slightly higher than that but I'm not going to get bogged down in single figure percentages. You refer back to the historical policy. At the beginning of 1980, this is reading from this paragraph, you say:

"There were only six patients on home treatment out of a population of 187 patients registered with Haemophilia A."

Do you think the patients felt that they were in a very backwards centre because they heard of people in the rest of Britain on home treatment and they weren't?

A. There was a lot of enthusiasm for home treatment and I was being continually asked about it.

Q. And we have heard that there are weekends organised by the Haemophilia Society. That must have been a big topic for discussion when patients met people with haemophilia from other parts of Britain?

A. Indeed.

Q. You have set out for us how the number on home treatment increased from 1976.

Can we go to [PEN0150385] at page 11 and also [PEN0150468] at page 1. Maybe if we could juxtapose

them.

This document that's coming, Professor Ludlam, is really more of a timeline or a chronology, and we see that you drafted it in about 1988. So we accept that it's not a recent piece of work. Your timeline begins in June 1981, like many we have seen, with that reference to the MMWR. I don't need to go to it but I did want to ask, when you move into 1982, about a symposium that took place in Stirling in June 1982. Its full title is:

"The second international symposium on infections in the immuno-compromised host."

We have been told that it actually occurred in Stirling in June 1982. Were you at that?

A. No.

Q. No. Does it ring any bells? Do you remember --

A. No.

Q. No, right. It was actually Professor Hann who drew our attention to it. So I think we will save that for him.

Then you refer to the publication in July 1982 in MMWR, three patients with haemophilia who had pneumocystis pneumonia. And you paraphrase that for us.

There is also perhaps to be inserted in 1982 -- and I suppose we should have put it above the July reference -- a reference [LIT0010566]. This is another

MMWR. It's 11 June. This one we refer to in the preliminary report but you will see from the first paragraph, Professor Ludlam, that:

"Of the 355 reports that had been received at CDC, 79 per cent were homosexual or bisexual men, 12 per cent were heterosexual men, 6 per cent were men of unknown sexual orientation and 4 per cent were heterosexual women. This proportion of heterosexuals is higher than previously described."

So we can see that even by June 1982 it was evident that people who were heterosexual were being affected. I suppose we can see that there has been a search for the best way in which to classify people who were getting this new disorder and one approach seems to have been in terms of sexuality, and that's reflected here. But I suppose there was no one obvious way in which to classify people. When you are looking for the aetiology of a new syndrome, it may depend on all sorts of things and the classification you choose may be completely misconceived, I suppose. Is that right?

A. I think so, yes.

Q. But nonetheless it's evident that by this stage it has been noted that some people who are getting this, whatever it is, are heterosexual. So it is not confined to those of homosexual orientation. The other thing

that we can see from this particular report, if we go down, is that in the mind of the writer or writers the question of intravenous drug use is featuring. So is it reasonable to say that even by June 1982, those in the CDC were very much thinking about transmission and possible roots of transmission? So that would be why, looking at intravenous drug use would be of interest?

A. Yes.

Q. Yes. Can we go back to that statement, please? That's [PEN0150468]. We can close down the MMWR for just now.

You say that:

"During 1982 it became apparent that fatal Pneumocystis and Kaposi's sarcoma were spreading epidemically in homosexual populations. Homosexuals were also noted to be at risk of a syndrome of Persistent Generalised Lymphadenopathy."

Then you mention non-Hodgkin's lymphoma. It looks in fact as though it was a particular form of non-Hodgkin's. It was diffuse undifferentiated non-Hodgkin's lymphoma that was particularly striking people. I don't know if you recall that, but that's what's mentioned in the MMWR you refer to.

A. Yes, okay.

Q. Right. It seems that the syndrome at that point was being described, at least by some people, as KSOI

syndrome. So that would be Kaposi's sarcoma opportunistic infection syndrome, would it?

A. Yes.

Q. In fact I had hoped that we had the 4 June 1982. We do have it in hard copy, the MMWR, but we don't have it on the screen. But, sir, I think we will arrange for it to be available in the court book. Simply, at least, note that what it seems to be saying, as a kind of conclusion, is that these particular patients are suffering from very unusual tumours and opportunistic infections. I suppose that fits with calling it KSOI syndrome.

Then going back to that timeline, if we go down a little bit further, you say:

"September 1982 AIDS diagnosed in drug addicts."

First date. At this point, because we are in September 1982, I just wanted to mention the UKHCDO meeting on 13 September 1982. We have a note -- and I'm not going to go to it because we looked at it last week -- that was prepared at that meeting by Dr Boulton who was one of those who attended from Scotland, and he has written down in his note that the cases in the people with haemophilia -- that is the three people whose cases are reported in the July 1982 edition -- were possibly associated with parenteral drug abuse. We

have looked at the MMWR and not only is there no reference to these patients using intravenous drugs, it actually says there is no history of intravenous drug use. I just wondered, do you have any idea how it could be being said in September 1982 that there might be this association?

A. I wonder whether Dr Boulton misheard what was being said.

Q. The other point I suppose that strikes us when we look at the actual minutes of the meeting is that what's referred to as a possibility that blood products may be involved in the MMWR report in July becomes a remote possibility in the minutes of the UKHCDO meeting. What do you think would be the explanation for that?

A. Only that this was three out of 20,000 people with haemophilia.

Q. Right. Do you think it is possible that the tone of the discussion in September 1982 led to a sort of understatement of the possible connection because haemophilia clinicians would very much not want there to be a connection?

A. No, I don't think so. I have vague recollections of the meeting and it was brought up towards the end of the meeting, as I recall, and possibly even "under any other business", and it was, "There has been this report.

What should we be doing about it? What do people know about it?" This was only two months or so after the MMWR report. I should say that the MMWR report is not something that we all read every week, or took. It's a minor publication that most of us had never seen until HIV and AIDS came over the horizon. It was filed away in a discrete part of the library. It really didn't cross our horizons at all because we weren't, apart from hepatitis, in the infectious diseases business and that's what a lot of the MMWR reports are about.

Q. So I suppose, even though it is American, people in the United Kingdom in the infectious diseases world would be much more interested --

A. I'm sure they would read it. It would also have to come by airmail so although it is dated, whenever it is in July -- 16 July -- it would take a month or so to come.

Q. I think our impression is that PFC also took the MMWR, but we can certainly ask them.

Then you mention December:

"An additional four cases of AIDS in haemophilia. No common batches identified."

Common batches of concentrate were identified and then the first case of transfusion-associated AIDS in California, in a 20-month old infant after multiple

transfusions. We can look in more detail at that shortly.

Then, January 1982, first reports of two cases of AIDS in female sexual partners of IV drug addicts with AIDS. So just that last reference, the January 1983 one about AIDS in female sexual partners of IV drug addicts, that points clearly in the direction of something that's sexually transmissible, does it?

A. It is suggestive, although I presume that there was absolutely no evidence of even a single injection in either of these women from their partner.

Q. Right. Can we look at the other side, the left-hand side, please? We see the same reference to the report in June 1981, a reference to non-Hodgkin's, and if we just go slowly down that, we see you discuss, a little bit, PGL. You say:

"It was difficult to reconcile this evidence indicating an apparent active immune state with the subsequent development of clinically profound immune deficiency."

Over on to the next page, please:

"The aetiology of AIDS was unknown and was the subject of much speculation."

We are going to come to look at that in a little more detail, all of that paragraph. You say:

"During 1982 it also became apparent that AIDS was occurring with increasing prevalence in intravenous drug abusers in the USA."

That's another MMWR reference. You have a table, which we will come to look at later. You say:

"It is pertinent to note the relatively high prevalence of AIDS in the USA, compared with most countries in western Europe in 1982 to 1984. Although the first AIDS cases were reported in the USA in 1981, it was not until 1983 that a small number in England were identified."

There is, of course, the case that was mentioned in the Lancet in 1981. We discuss that in our preliminary report, paragraph 8.8. Perhaps we could just have a look at that briefly, if we could. That's page 188 in the hard copy and [LIT0012479], page 3. Towards the end of paragraph 8.8 there is this reference to the person who had been treated at the Brompton Hospital in London and the hospital in Bournemouth. Actually, Dr Winter was working in London at the time. He could recall this being a talking point.

So there was that one in the UK, and then we also noted, if we could just look at the following page, please, paragraph 8.13, that the BMJ of 3 July 1982 had an article about severe Acquired Immuno-deficiency in

European homosexual men, and that was describing four Danish men with KS or opportunistic infections. Three of them had never been to the United States of America.

So I take your point, Professor Ludlam, that the numbers are very different as between western Europe and the United States, but it had happened in Britain and it had happened in Denmark as well in individuals, three of whom had never been to America.

Can we go now, please, to [PEN0150445]? This is back to your statement. So, having dipped into the chronology up to a certain point, we now look at this section in your statement on page 2 entitled, "Potential causes of AIDS".

Actually, I wonder, sir, this is quite a big chunk. Maybe it would be better to start it after lunch.

THE CHAIRMAN: I think so. Are you going to raise with the professor the history given by Professor Forbes?

MS DUNLOP: You mean the Ratnoff and Menitove paper?

THE CHAIRMAN: Yes.

MS DUNLOP: Professor Ludlam has a copy of it, which I gave him this morning, sir, and I have said to him that I'll give him time and I'll ask him about it tomorrow. Is that adequate?

THE CHAIRMAN: That's adequate. What I'm interested in, of course, is not just the paper but whether, within the

haemophilia doctors circle, if I can call it that, there was any dissemination of the information that Professor Forbes had, so if you could cover that as well. I'm happy to leave it.

MS DUNLOP: Thank you.

(12.54 pm)

(The short adjournment)

(2.00 pm)

THE CHAIRMAN: Yes?

MS DUNLOP: Yes, sir.

Professor Ludlam, although we were at a certain point in your statement, when we stopped for lunch, before we go back to that, I think it is probably useful to ask you a couple of questions, which relate to 1981 and I'm going to ask you to have a look at a couple of documents.

The first is a minute of the meeting of the directors of SNBTS and the haemophilia directors in St Andrew's House on 30 January 1981, and actually you mention this in your evidence, that there was one of these larger meetings in January 1981. The reference for it is [SNB0015055].

For what it's worth there is quite long paragraph in this about recognition of Glasgow and Edinburgh as reference centres. That's paragraph 9. But that wasn't

why I wanted you to look at it. It was because of the reference to commercial purchases of Factor VIII. You see at the bottom of the first page -- this is really paragraph 3(c) -- it says that:

"Data provided for 1979 and 1980 showed that a significant and apparently increasing quantity of commercially produced Factor VIII was being used. The reasons for this were discussed. Sometimes only a commercial product was available."

Said somebody:

"There were also occasions when, for clinical reasons, a high purity product was required."

If we could just go back to the first page of that again. This is during Dr Willoughby's time at Yorkhill but we can see from the minutes of that meeting that Dr Pettigrew, actually, subbed for him at that meeting. And you were there.

Then at more or less the same time, March 1981, if we go to another document, please, [SNB0015064]. This is the working group, which is meeting on 4 March 1981. So really only about five weeks after the meeting we just looked at, and you were on the working group at that point as well.

Paragraph 6, which is on the second page:

"Concern was expressed at the level of commercial

material being purchased. It was agreed that the aim must be for the NHS in Scotland to be self-sufficient."

I suppose it is very unlikely you remember either of these meetings as meetings, Professor Ludlam, do you?

A. Just a little bit. Not very much.

Q. Right. Do you remember round about the spring of 1981, quite a focus on how much commercial material was being bought and why?

A. I don't think I can answer that question actually. From my recollection of the discussion, I obviously read here ...

Q. It looks, professor, as though around about that time, the explanation for the large amounts of commercial material being purchased must have been largely The Royal Hospital for Sick Children in Glasgow. Do you remember that?

A. Well, I remember that but I also remember there was a substantial shortage of NHS Factor VIII concentrate.

Q. You see, I just wondered, Professor Ludlam, in light of what you were saying this morning about the patients in Edinburgh using only NHS material and about how your group included some children, there was obviously a difference of practice between Glasgow and Edinburgh at that time, and Dr Willoughby, in particular, as far as we can make out, seems to have been very keen to

introduce home therapy and to use commercial product. What can you tell us about that?

A. I can tell you that he was a very good, enthusiastic paediatric haematologist and he was, I think, wanting to treat his patients almost certainly more aggressively that I was able to. I read recently that he was introducing prophylactic treatment. That was very go-ahead for the UK at that time. Clearly, the type of therapy he was wanting to give needed to be concentrate rather than cryoprecipitate, and I imagine he had had difficulties in getting sufficient supply of NHS concentrate that he thought was of a suitable quality to give to small babies, small children.

Q. Did you ever have any conversations with him about it?

A. No.

Q. What was the atmosphere of the time? I don't mean to be disrespectful but was everybody really doing their own thing, as between Glasgow Royal Infirmary, Edinburgh Royal Infirmary, Yorkhill?

A. We were working much more independently as separate units than we did from, shall we say, the mid 1980s, onwards, where the directors of all the centres would meet regularly to promote the service in a unified way across Scotland. Before that, they were more separate institutional activities.

Q. Do you have any knowledge about the establishment of Yorkhill as a separate haemophilia centre?

A. No.

Q. Right. Just the other thing before we leave these minutes that we see in front of us, to look at paragraph 7 onwards, the chairman, and that was Dr George McDonald, who was from Glasgow Royal Infirmary:

"The chairman invited Dr Cash to comment on the proposal that freeze-dried cryoprecipitate be produced with a view to studying, on a multi-centre basis, its role in home therapy."

Then Dr Cash appears to have gone on to speak in favour of cryoprecipitate, paragraph 8. Interestingly perhaps in light of what we have recently seen, the last sentence of paragraph 8:

"The majority of home therapy patients had no problems when using cryoprecipitate and in Belgium it was used extensively. The chairman suggested it could be an R and D project, research and development. Dr Foster said PFC didn't have resources. There was a study being undertaken in the West of Scotland ... which was being extended to include children with the help of Dr Willoughby. Dr Ludlam expressed his interest in the treatment of children, particularly the need to

protect them from the problems of liver disease and hepatitis."

So should we take it from your evidence this morning that you would not have been at all enthusiastic in this discussion about the proposals to consider more cryoprecipitate use?

A. There was a project -- I'm just seeing whether it was referred to here -- in the West of Scotland to produce small pool cryoprecipitate and that never really got the resources to get off the ground, and it is not an approach that has received much support elsewhere. I think I was, as you see, interested in the use of small pool treatment if it was convenient and suitable for children. There was a number of different ways actually of making cryoprecipitate which would alter the purity of it and therefore the propensity to reactions.

Q. Right.

A. I accept that there is a spectrum of opinion, both in how children should be treated and in whether or not cryoprecipitate is suitable to use at home, and you have seen some of the spectrum from me today.

THE CHAIRMAN: Professor, were you aware of any particular preference for the use of cryoprecipitate in the West of Scotland, leaving Yorkhill aside?

A. No.

THE CHAIRMAN: That never came to your notice?
A. A preference for cryoprecipitate?
THE CHAIRMAN: Yes.
A. I can't recall it and at one of these meetings we considered the Council of Europe recommendations on self-sufficiency, and in that one of the recommendations is that cryoprecipitate should only be used if a concentrate is not available.
MS DUNLOP: To reassure you I should let you see the next page, to show that that was the end of that particular discussion.

There doesn't really seem to be anything else about cryoprecipitate use, at least in those minutes.

Right. We can put the 1981-minutes aside now, thank you, and go back to your statement, [PEN0150445]. If we could go to page 2, please. Just at that numbered heading, "Two potential causes of AIDS". You say:

"In the earlier 1980s there were many potential aetiological agents which were considered to be possible causes of AIDS."

Then you list the groups of individuals in whom the occurrence of the syndrome had been noted. Then you list some possible aetiological agents:

"1. An AIDS-causing virus."

Which I take to mean a new virus, in essence,

compared to what you go on to say?

A. Yes, I think so.

Q. So an AIDS-causing virus:

"What was it and where had it come from? If so, why had no haemophiliacs in Germany, where large amounts of US commercial concentrates were used, developed AIDS by 1983.

"2. A previously known virus which had mutated to a virus which caused immune suppression, for example Hepatitis B.

"3. A virus known to cause immune suppression, for example CMV or EBV, cytomegalovirus."

What's EBV again?

A. Epstein Barr virus.

Q. That's a glandular fever type illness?

A. Yes.

Q. Which may have become more virulent. Just at that point, professor, having noted that the first three suggestions are all viruses in the early 1980s, when patients with haemophilia were receiving concentrates, whether NHS or commercial, does it follow that as well as hepatitis, which we know a bit about, there must have been quite a lot of other viruses being transmitted in the concentrates as well?

A. Yes.

Q. Right. And you have mentioned CMV, EBV and in your curriculum vitae you mention other viruses that you have researched. So I suppose some of these viruses, the only reason we are not having an Inquiry about them is that they didn't really cause much by way of symptoms?

A. There were some that were transmitted that appeared to cause no harm. There were some that we appear all to have and to live happily with. There are some, and one in particular is parvovirus, which is a small DNA virus that in small children causes a mild erythematous condition, sometimes called slap cheek condition, which about a third of children get at nursery school when they come into contact with other small children.

But a goodly number of people do not get infected as children and this virus is not really susceptible to the solvent detergent technique or heat treatment, and therefore can be transmitted by plasma-derived concentrates.

Into adults, who are susceptible, that can cause quite an unpleasant condition of arthropathy, generalised arthritis. It can cause the death of a foetus in pregnancy and it can cause the bone marrow problems in someone who has what we call a haemolytic anemia.

That's all well-known. The reason that I think it's

an important virus is not for the damage that it does at the moment, but we know it can be transmitted by plasma-derived concentrates. Were that virus or one like it to come into the plasma supply, then we might have an outbreak of some other infection. West Nile fever has been in the news and has been considered in relation to blood safety. It was very fortunate that that was a lipid-coated virus that was sensitive to the solvent detergent technique and heat treatment. Had it not have been, then it might well have been spread by plasma-derived concentrates.

So parvovirus is a very valuable, in one sense, model virus. I mean, it has mutated in dogs to a more virulent form and caused an outbreak around the world of a dog infection porcine infection, that was much more fatal.

So that is why there is an interest in small DNA viruses.

Q. The fourth --

A. And one of these could have caused, obviously, immune suppression.

Q. The fourth candidate cause, if we go on to the next page, we can see is antigen overload. You say by way of example, semen in the rectum of homosexual men and non-Factor VIII or IX proteins in clotting factor

concentrates used to treat haemophilia. I just wondered, professor, I hadn't actually seen antigen overload advanced as a possible explanation for the immunodeficiency in homosexual men. Was that actually a theory that had much currency in the early 1980s?

A. I think it had some and potentially exposure to white cells and their antigens in the rectum of men, particularly if there was any mucosal injury and these could be antigenic.

Q. Your fifth suggested cause is recreational drugs. For example, amyl nitrate and isobutyl nitrate. But both number 4 and number 5, professor, are surely much less likely, particularly as soon as you had, on the one hand, the three people with haemophilia reported in July 1982, who were all reported as heterosexual individuals, they were 62, 59 and 27 in terms of their age, and also in the December of 1982 the report of AIDS in an infant. Surely both of number 4 and number 5 are much less likely as soon as those events had occurred?

A. That is making the assumption that the AIDS in people with haemophilia was of similar aetiology to the AIDS in the other groups, and we know that clinically they were different and so we considered the possibility that actually they had arisen simultaneously, or nearly simultaneously, but were of different aetiologies.

Q. I think we will come on to look at how different they were, but you go on to say that:

"Even after there was general agreement that HTLV-III was the probable cause of AIDS, there was very considerable uncertainty as to how to interpret an anti-HTLV positive and negative result in an individual person."

Then you say:

"There was also doubt as to whether this virus was the sole cause. Even up to 1996, reputable scientific and medical journals were giving publication space to non-viral pathogenesis for AIDS."

I wanted just to carry on with this theme by looking at [PEN0150385] at page 13, if we could, please. Just looking down through that you mention in this statement as well the report in July 1982 in the MMWR. You say:

"These haemophiliacs denied homosexual activity or intravenous drug abuse."

If we look at the actual report. That's [LIT0010559]. You see in the very first paragraph, when talking about the three people concerned:

"All three were heterosexual males, none had an history of intravenous drug abuse."

I have seen the form of words that you used, professor Ludlam:

"These haemophiliacs denied homosexual activity or intravenous drug abuse."

Why do doctors sometimes feel it necessary to say that the patient denied drug abuse, rather than that just simply the patient didn't have a history of drug abuse?

A. Well, one is an absolute state of affairs and the other is what you are told by the patient.

Q. So do you tend to opt for the form of words that the patient denies something rather than saying -- we can see the MMWR for example, they went for the absolute form. They said:

"All three were heterosexual males and none had a history of intravenous drug abuse."

A. It's a matter of words. I'm happy with what's here but that presumably is what these individuals -- whoever took the history for this was --

Q. It is just a matter of impression, professor. It is just that where you see the words "the patient denied homosexual activity or intravenous drug abuse", and I quite accept that doctors sometimes use those words, but where you see them there is a slight suggestion of doubt which you do not get from the MMWR.

A. Well, there are instances where people will have had homosexual activity or used intravenous drugs and who

won't want to admit that to the doctor.

Q. So can we go back to the statement, please, and just go down through that page. That's 0385. Thank you.

You are making a reference to a reference centre directors' meeting on 22 September, and of course we have already looked at the UKHCDO meeting on 13 September. But the conclusion of this paragraph is that Dr Craske as chairman of the hepatitis working party had been asked at the meeting to investigate and keep directors informed, which would seem to be what was said on 13 September, but you are telling us there was also a meeting on the 22nd, was there?

A. I think it unlikely. I think this must be a mistake --

Q. All right. Then:

"Haemophilia treaters in the United States were also quick to appreciate that if AIDS was due to a virus, it might be transmitted by Factor VIII concentrates ... This body, The National Haemophilia Foundation Medical and Scientific Advisory Committee ..."

We have seen them referred to as MASAC. I suppose an acronym is always handy, isn't it?

"... recommended in January that individuals at higher risk of AIDS should be excluded from blood donation."

You presumably now know, Professor Ludlam, that

there was quite a contentious meeting in America on 4 January 1983? Yes?

A. Yes.

Q. Yes, you are nodding. Dr Evatt was there, as was Dr Aledort, and there was a bit of a difference of view there. We have, I think, already noted that it's set out in considerable detail in Douglas Starr's book "Blood". I don't know, have you read Douglas Starr's book?

A. I haven't, no.

Q. Right. Well, certainly I think those of us who are lay have found it a good read. Did you hear about this meeting at the time?

A. No.

Q. Right. If you look at an article that appeared around that time [LIT0011589], we have looked at this before. This is a piece from Science, which I understand to be an American periodical. Did you ever look at it or was it not something that you would be picking up in the Royal Infirmary?

A. Science is a reputable scientific journal, like Nature.

Q. Do you think you might have seen this at the time?

A. I think it unlikely.

Q. Right. In fact this is actually describing the meeting on 4 January 1983. Do you see firstly on the left-hand

side, Bruce Evatt is mentioned. He told the workshop that AIDS was the second leading cause of death for haemophiliacs in 1982:

"Eight haemophiliacs, who had none of the other known risk factors, died from AIDS, compared to some 40 who died of bleeding. James Curran ..."

Presumably another very well-known name, James Curran?

A. Yes.

Q. "The sense of urgency is greatest for haemophiliacs. Suspicion has been cast on blood products in addition to clotting factor, however ..."

Going on to refer to the infant -- and we will look at the situation pertaining to the infant in a moment. In the middle column we can see some easily achieved consensus about some preventative measures but the seriousness of the threat of AIDS -- and this is looking at the bottom:

"The threat of AIDS transmission by blood products and what, if anything, ought to be done in the current state of uncertainty, remain thorny issues. Not everyone agrees with the conclusion, accepted by CDC officials and many other investigators, that AIDS is caused by an infectious agent, presumably a virus, which could contaminate blood products."

And then a reference to Dr Aledort. Really, I suppose, two things that are striking, one -- and you rejected this when I put it to you earlier but I'll suggest it again -- that haemophilia clinicians found it particularly difficult to really look at the possibility that blood products were transmitting this infectious agent. I think this is an example of it here, with Dr Aledort, is it?

A. I think for Dr Aledort, yes.

Q. Right. So he was one of those in the group of haemophilia clinicians internationally who found it particularly difficult to accept?

A. I think so, yes.

Q. The other thing that's striking is the notion that haemophiliacs -- and this is reading from the last bit of the middle column:

"... because they are exposed to a great number of foreign antigens, experience a high degree of antigenic stimulation that effectively wears out their immune system."

What's striking about that is that if that were the explanation, that would not really be reassuring, would it?

A. No.

Q. Then if we turn to the next page, so LIT0011590, we can

see mention of Oscar Ratnoff who has featured in our evidence of the past day or two, a haemophilia specialist from Cleveland, proposing that patients with haemophilia might minimise their risk of AIDS by using clotting factor cryoprecipitate. You yourself do come on to mention Oscar Ratnoff and his particular practice.

Going back to your statement, please, 0385, and looking where we were, we find your reference to the infant. I think just for clarity, professor, there seem to have been the two reports, one in the MMWR in December 1982, and then it seems to have been written up in the Lancet by Ammann -- I think it's the Lancet -- in 1983, but it does appear to have been the same child.

I don't know if that has struck you since you wrote this. Perhaps if we just have a quick look first of all [LIT0010405]. That's the Lancet piece, 30 April 1983. If we look at the summary, we can see that what had happened was that this child had become ill with various different infections and because he had received multiple transfusions, some research had been done and one of the blood donors, who was well at the time of blood donation, had died 17 months later, apparently of AIDS. But just to link it to the other report, if you look at the case report, where it says the mother was 29. This is San Francisco. The infant weighed 2.85

kilos at 33 weeks gestational age. History of rhesus sensitisation.

If we look at [SGH0085105]. It is just so that we are clear. I think there was only one case, although you say an additional infant. If we look at [SGH0085105]. If we can go forward to 5108, I think we can see it's the same child, isn't it, professor? A history of rhesus sensitisation, 33 weeks gestation, the infant weighed 2.85-kilos and so on.

A. Yes, I'm interested in the title of both these. It says "possible transfusion-associated". It's not saying it's a definite, and I wonder whether, as I'm sure you are aware, children occasionally are born with congenital immune deficiency. An area I have no expertise in. But I just wonder whether there is a possibility that this child could have had a congenital deficiency of immunity, notwithstanding there was also this donor as well.

Q. Well, I guess in medicine, professor, it can be very difficult to rule anything out absolutely, but would you agree that on any view in the unfolding story of Acquired Immunodeficiency Syndrome, this was a significant event?

A. I think it's a significant event. I don't think it's a clinching event.

Q. Right. Can we go back to where we were, please. That's back to 0385 at page 14. Thank you.

Pick up the narrative in January 1983:

"Two haemophiliacs with PGL ..."

You go on to say:

"In summary, evidence accumulated from June 1982 onwards that AIDS and probably PGL were caused by an agent that could be transmitted by blood. Although it became apparent in the latter part of 1982 that haemophiliacs may have been at risk of AIDS, this did not appear to be substantial as, by January 1983, only eight cases out of a total haemophiliac population of approximately 20,000 in the USA had developed AIDS."

Then you talk about the total number of reported cases increasing in 1983?

A. Could I just interject that in the second line it says:

"Seven had received blood components other than Factor VIII concentrate."

So they might have received an infectious agent from those units of blood.

Q. Right. But certainly -- and I think this is really what you are saying yourself, aren't you -- the evidence is leading one away perhaps from possible causes 4 and 5, the antigen overload, and the recreational drugs, as far as an explanation for the syndrome in the various people

who have developed it is concerned?

A. I'm not sure that it moves us away from the -- if I can call it this -- antigenic overload theory. I think that's still on the table.

Q. All right. We will come back to that too. Then the mention of Europe. You say:

"In the UK the first suspected case was identified in May 1983."

And there is a reference again to Germany. We will develop that. But to do so we need to go to your timeline again, [PEN0150468]. And pick up the narrative at the bottom of page 1. We had gone before lunch just to that one in January 1983, which was actually the end of volume 31, I think, of the MMWR. Just because you made the point, professor, before lunch about the female sexual partners that, as you pointed out, it would be relevant to know whether these ladies, who were the partners of intravenous drug users, were themselves drug users, and we checked the MMWR over lunch and if we can go back to the context. It is the latter form of words, if you like, in that, that they are said to have denied intravenous drug use.

So it certainly looks as though, from the point of view of the CDC, that they had considered, well, was there an alternative explanation than sexual

transmission for these ladies acquiring the syndrome, and they, at least on the say-so of the ladies, could rule out that they were also drug abusers.

Two cases of PGL in haemophiliacs. This is actually a report from Margaret, is it Ragni or Ragni?

A. Ragni.

Q. You say that on the next page, if we turn over, staying in January 1983:

"There was a meeting at Heathrow Airport in January 1983 ..."

You say in your other statement you actually don't remember it but just for our narrative, could we look at the preliminary report at paragraph 8.19. This is page 191. It will be [LIT0012479], page 6. The format looks to have been, professor, arranged with Immuno, an Austrian drug company; is that right?

A. Yes.

Q. And they were keen to talk about their research into methods of reducing or eliminating the risk of transmission of NANB. So their note of the meeting didn't mention AIDS very extensively, but in the afternoon Dr Craske spoke to the assembly and we quoted what he said. So he seems to have imparted further information on 24 January 1983. There are now 800 people reported as suffering from AIDS in the

United States. With a 45 per cent mortality. 10 haemophiliacs in the United States have been infected and five have died. The youngest was aged 7. All cases have had prolonged treatment with Factor VIII. Then there is the mention of the 20-month old child as well.

Although you were there, you do not really remember this meeting, I gather?

A. I have seen the minutes from it. I can quite believe I was there but, I'm sorry, I don't remember it.

Q. So we can put the preliminary report to one side then, thank you, and go back to your timeline. [PEN0150468] at page 2. You refer to the editorial in the New England Journal of Medicine, questioning whether it would be prudent to switch to cryoprecipitate. We mentioned this last week too. I think in fact Professor James researched afterwards Dr Desforges and ascertained that she was a haematologist as well. You knew that, did you?

A. I did a little research to try and found out whether she had switched her practice and I couldn't find Ragni follow-up to this. I have to say she is not a name that I recognise as being in the haemophilia community of treaters but clearly she did have a practice and this was her suggestion, but nowhere has she, as far as I could ascertain, published how successful she had been

in changing.

PROFESSOR JAMES: She was the head of the haematology laboratory and haematology department, I think at Tufts, one of the Boston medical schools. So I don't think she ever was a treater of haemophiliac patients. She was also an associate editor of the New England Journal. So probably she had been asked as a haematologist rather than a haemophilia practitioner.

MS DUNLOP: You cover this editorial in a little more detail, Professor Ludlam, in your statement, properly so-called, which is [PEN0150445] at paragraph 15. You discuss that in a bit more detail. You say that Dr Desforges seems to have been partly basing her proposal:

> "... on the fact that the immune system of recipients of cryo appear to be normal compared to concentrate users but we now know that the immune changes are not a good reflection of the presence of infection by HIV."

Would it be correct to say, professor, if one were using immune changes as a marker for infection by HIV, that this would be a sort of marker where you would get a lot of false positives? But the false negative rate would be very low, would it not?

A. No, the false negative rate might be significant in

early HIV infections.

Q. Right, in the window period?

A. Even for the first year or two perhaps. Because these immune tests have quite large normal ranges and therefore it may be difficult. To say that a patient is outwith the normal range, they may have to be quite a long way outwith what might be their basal level. We know the levels from the studies we have done are relatively constant without HIV, and therefore if you have someone who has a high level and they get HIV infection, it may be a long time before it reaches the bottom end of the normal range.

Q. Right. Okay. We can go back, I think, to the timeline. That is 0468.

Moving through March. Also the reference to the Annals of Internal Medicine. We have looked at that as well. Perhaps we should just quickly look again at [LIT0010047]. Actually, professor, from your reference I think you are looking at an editorial which appeared on 403, whereas we looked last week at the one which began on 401, which is in front of you now. This is introducing an issue which appears -- and if you look at the third paragraph -- to have contained six articles, all of which lent further support to the transmissible agent hypothesis. Annals of Internal Medicine. Would

that be something that you would have read at the time?

A. It wasn't one of the regular ones but I could easily have had access to it if it had been referred to somewhere else.

Q. Certainly it is striking for the figures it gives about how many donors, as it were, a person with severe haemophilia might be exposed to in a year. I think actually from the figures given towards the bottom of the page, one can easily rack up a total of not just, as the editorial says, tens of thousands of donors a year but even hundreds of thousands of donors per year. And a given donor potentially exposing approximately 100 people.

Then at the bottom of the left-hand column on the second page, the comment:

"Among patients receiving blood products, those with haemophilia will continue to be at highest risk."

Unfortunately, as I say, we don't have the whole of the White reference, which is the one you make, but if we look at page 3, LIT0010049. It's the page 403 in the actual journal.

I think that must have been the particular editorial that you were referring to, Professor Ludlam. You say that the author is White:

"Had reduced surgery and switched a few patients

from Factor VIII concentrate to cryoprecipitate."

Can we go back then to the timeline, back to [PEN0150468] at the second page?

You then refer to an editorial in the Lancet in April, which itself referred to the New England Journal of Medicine and the Annals of Internal Medicine. Do you know who wrote this editorial in April 1983?

A. No.

Q. Right. And similar sorts of questions indeed to those I think you have posed yourself, about why German haemophiliacs hadn't got AIDS, they being heavy users of American concentrate:

"No strong argument for a change of treatment policy."

You refer also to this in your other statement, [PEN0150445] at paragraph 20. How did the Lancet recruit individuals to write its editorials? Was there a panel of people who wrote them or were people from the particular field invited to come?

A. I think the editor tries to find someone who is particularly knowledgeable and writes a begging letter.

Q. Right. I see.

A. I don't think they have a panel. I think it depends on the subject. They look for the best person who can provide them with an article.

Q. Right. Can we go back to the timeline? That's 0468, please, just to note the bottom of that page. We are in April 1983. Then there is a reference to an article suggesting that:

"Alloantigens in Factor VIII concentrate induce immune changes."

What's an alloantigen?

A. It is an antigen that an individual may not have but another person does have so that, when they are transfused with it, they may develop an antibody to it or at least some immune reaction.

Q. Then can we move to the next page, please? There is a reference to the work of Barre-Sinoussi and others. And further report of immune abnormalities in haemophiliacs. This is May 1983.

I thought at this point, professor, we could try to get to the bottom of the British people with haemophilia who were thought to have AIDS in 1983. Because I think it's possible to get a little confused. In the first place can we look at [DHF0014328]. Sorry, I think it has another reference. Oh, yes. First of all, do you see, if we go right to the top, I think we can get a date, yes, 2 May 1983, and if we look particularly at the Daily Mail, which is on the left, we can see:

"Government health experts have begun investigating

the possibility that Britain is importing blood products from America contaminated with the killer homosexual disease, AIDS. The action follows the discovery that two men given routine blood transfusions for haemophilia are now seriously ill, apparently suffering from the disease. Disclosure of the men's illness and their treatment at hospitals in Cardiff and London was made exclusively yesterday in the Mail On Sunday."

So that's one reference. Can we go to [PEN0150244], please? This is a CDSC report. Have you seen this before?

A. Yes, I have. But I'm not sure of the date. It has been scored out.

Q. The week ending 6 May 1983.

A. Right.

Q. We can just see that. I think there is a piece of highlighting unfortunately that goes right across the date but it's 6 May 1983.

A. Yes.

Q. We can see Acquired Immunodeficiency Syndrome, Cardiff. This is said to be the first report of AIDS in a patient with haemophilia in the United Kingdom known to CDSC. This is a 20-year old man in fact.

A. Sorry, does oral oesophageal candida put someone in the AIDS category? I'm sorry. I have forgotten from the

classification that was around at the time.

Q. I'm deferring to Dr Galbraith here, Professor Ludlam. He has certainly put this patient in the category. That's certainly a matter we can put to other witnesses.

A. It is easy enough to check up afterwards.

Q. That's a puzzle. Certainly at the time it looks as though some people at least were treating this as looking like the first report of AIDS in a patient with haemophilia in the UK.

A. I may be wrong. As you know, there are very stringent criteria for indicating that an individual had AIDS at that time.

Q. Yes. And then --

THE CHAIRMAN: Had a formal definition been developed by this stage?

A. 1983 -- May 1983? Yes. It was a clinical definition if you got an opportunistic infection like pneumocystis or Kaposi's sarcoma, for example, as a tumour. That put you in the category of having AIDS.

PROFESSOR JAMES: I think I agree with you. At that time if you just had oesophageal candidiasis, I don't think you would have been classified as having AIDS without something more than that.

A. It will be easy enough to check.

PROFESSOR JAMES: Yes.

A. -- out and the relevant literature is in your court book.

MS DUNLOP: Yes. I'm sure of that, professor, but I'm really more interested in the way that these cases were seen at the time, and certainly by CDSC, who are operating more in the realm of infectious diseases than in virology or haemophilia treatment, it looks as though they were treating this as a possible case at least of AIDS in person with haemophilia.

The other case we can see referred to on [DHF0015006]. That article "US blood caused AIDS", seems to refer to the other person. You see:

"The British haemophiliac who died from AIDS, almost certainly caught the disease from contaminated supplies of the blood clotting agent."

This looks to have been a patient treated in Bristol and this is somebody who was written up in the Lancet. I think we have worked out before that this seems to be November 1983. Just to establish, professor, that the two men referred to in the newspaper cutting appear to have been, one, a patient in Cardiff and, two, a patient in Bristol. That looks to have been the situation, doesn't it?

A. At very different times. Six months apart.

Q. Well, yes, but if the Daily Mail was able to refer to

two people, it does look as though there were people in Bristol and Cardiff. We can see that reference in the Guardian which also mentions the patient in Cardiff.

A. Yes, I mean, I think the Bristol one was diagnosed with AIDS earlier than November 1983.

Q. Right. When we look at what was said in relation to the Council of Europe report, which also gives us some information on how many patients with haemophilia in the United Kingdom seemed to be developing AIDS at this time. We can look at [DHF0014394]. I don't imagine you had seen this before, Professor Ludlam?

A. Yes, I have.

Q. You have? Right. When did you first see it? Recently?

A. Recently, yes.

Q. You see, it's a report for the committee of experts on blood transfusion and immuno-haematology for their meeting in May 1983, and the actual date of it is 28 April 1983. It is narrated as information on the present situation in Council of Europe member states and in other countries represented on the committee. But the information that appears to have been supplied for Germany in this is that there were two people with haemophilia. Could you turn to page 4, DHF0014397. You see that reference there, that the Federal Republic of Germany appeared to have sent a report that they had two

patients with haemophilia who had AIDS.

Just looking, Professor Ludlam, at all that was happening around about this time -- and there certainly seems to have been a great deal happening --

A. I'm sorry, could I interrupt?

Q. Yes.

A. Go back to this document. I think if you go on through several pages, you will find the questionnaire that John Craske had developed for investigating patients with haemophilia who might present either with AIDS or with AIDS-like -- that's it, thank you -- which I think is further evidence of the fact that Britain was well organised compared with many other countries in relation to this particular difficulty.

Q. Yes. Indeed. We can certainly see reproduced in full the UKHCDO hepatitis working party surveillance form. That, as you say, appears from page 9 onwards. It's also worth noting that actually in the entry for the United Kingdom, which is the page before that, so if we look at page 8, 4401, whenever this return was made from the UK, it certainly said there had been no reports of AIDS syndrome following the transfusion of blood or blood products.

So it looks as though, as far as we can judge after this passage of time, whenever the return was

sent, April perhaps, no one was saying that anybody with haemophilia in Britain had suspected AIDS but by May that situation looks to have been changing.

I think we should just ask you, Professor Ludlam, about the Professor Bloom letter, or the letter which has a part drafted by Professor Bloom, which is DHF0030738 [sic].

THE CHAIRMAN: Can we get it into the transcript, Ms Dunlop?

MS DUNLOP: Yes, it is [DHF0014474]. This letter is dated 4 May. We can see that from the bottom if we just quickly look at the bottom. It has a date, 4 May 1983, and then the introduction:

"In view of the unduly alarmist reports on AIDS which appeared in the press over the weekend, we are writing to reassure members of the Society. We have been in touch with Professor Bloom, chairman of the haemophilia centre directors, senior member of our own medical advisory panel and a member of the Central Blood Laboratories Authority, who has kindly written to us all as follows."

Let's take Germany first. He does say:

"Neither have any cases been reported from Germany."

I suppose it must have been very, very difficult at this time, Professor Ludlam, but, of course, no evidence that X is the case is not the same as evidence that X is

not the case?

A. I appreciate that but Professor Bloom had written round to haemophilia centres in Europe, asking about whether they had seen patients with AIDS or with AIDS-like syndromes, and he must have got reports because there is a number of large centres in Germany. When he received those replies, there weren't any cases of AIDS.

Q. Right.

A. So he had very positively attempted to find out.

Q. And do you remember then talking to Professor Bloom around about this time about the steps he had taken?

A. Yes, because I got a copy of the questionnaire as one of the many centres in Europe.

Q. Right. What about the sentence before:

"In spite of inaccurate statements in the press, we are unaware of any proven case in our own haemophilic population."

Do you think it is the word "proven" that's crucial there, Professor Ludlam?

A. I think it possibly is and, as I mentioned a few minutes ago, because there was not a laboratory diagnostic test for AIDS and because a lot of other conditions could mimic the early symptoms of AIDS -- they are very non-specific, like weight loss and sweats and, to some extent, lymphadenopathy -- the criteria for AIDS were

well circumscribed into either unusual opportunistic infections or Kaposi's sarcoma or lymphomas.

THE CHAIRMAN: Professor, I find some of this quite difficult. If the interpretation one placed on cases that some people thought were AIDS had been that, in treating haemophilia patients over a significant period of time, there was a well documented and established incidence of similar circumstances, similar signs, similar symptoms, one might have expected to see that writ large across the United Kingdom literature. I'm not sure I have.

A. No, you see, because early HIV infection is mostly asymptomatic and so people didn't present often until they got what we call an AIDS-defining illness, the PCP or the Kaposi's sarcoma, and that our patients, like other individuals in the general community, would turn up with weight loss or night sweats which could have been due to anything, we weren't seeing a lot of patients, for example, with night sweats or weight loss in our community. Does that ...?

THE CHAIRMAN: I'm not sure that helps me. You see, if the position were that in general practice these signs and symptoms were not being seen, but they then emerged, it's quite difficult to step from that point to say, oh, well, when they emerged, they might just have been

typical of other signs and symptoms and other conditions that were already well established. That doesn't seem to me to fit as a logical explanation of the response. Maybe I'm getting it wrong, professor. I'm quite capable of doing so.

A. I'm sorry, I think I have misunderstood.

THE CHAIRMAN: You see, what I had noted you as saying -- I don't want to go back to the transcript -- that the conditions were not diagnostic because other conditions could mimic the early stages in HIV infection. If there were other circumstances, other diseases, other conditions, that were producing the same range of signs and symptoms, then what appeared to me to be a possible response, when it was alleged that AIDS had been identified, was that the medical profession would say, "No, come on, now look, we know these signs and symptoms, we have seen them in the past and indeed probably before AIDS emerged, they are not diagnostic." But that seems to be missing. So why one would construe the emerging signs and symptoms as being attributable to a different condition I'm not quite understanding, but it may be, as I say, I'm not getting it right.

MS DUNLOP: It may help, Professor Ludlam, also to look at [DHF0017178]. This is another Dr Craske document and it's possible to demonstrate that it was sent to the

DHSS, presumably who wanted to know about it. It's dated March 1st 1983. It is quite interesting to look at [DHF0017183]. This is Dr Craske's survey.

Actually, Professor Ludlam, you were referring to Professor Bloom's survey. I think we will come to this but I think Professor Bloom didn't send out his survey until December 1983. But we will look at that later.

This is Dr Craske's survey and this is March 1983. He looks to be casting his net pretty wide actually. He is asking haemophilia doctors to send him a form if they see any of really quite a long list of conditions. So, rather than expecting people to go through a very specific and precise assessment of whether their patient fulfils all the criteria set down perhaps by CDC or something, Dr Craske is asking for, as it were, possibly over reporting rather than under reporting, just to be sure that he gets a complete picture. Is that not how it looks?

A. No, the heading, "1. Diseases specific for AIDS." These are what are called AIDS-defining illnesses, and I note here, going back to our discussion of ten minutes ago, that under "fungal", oesophageal thrush would appear to be an AIDS-defining illness. So, I'm sorry, I misled you earlier.

Q. It's all right, I don't carry these things in my head.

I thought it might be here.

A. This is the --

PROFESSOR JAMES: I think the point is it's a necessary but not a sufficient condition.

A. Is it not actually a sufficient condition? Can you move the screen up? It doesn't actually say whether these are AIDS-defining conditions but I think most of them are.

PROFESSOR JAMES: Yes.

THE CHAIRMAN: Could I come back to my question, which clearly wasn't terribly well expressed, against this background: one might look at the words "diseases specific for AIDS", and read it as being something that is, as Professor James said, associated with AIDS but any one of them might not of itself be diagnostic.

But if one were to dismiss it on the basis that all of these conditions are known, and particularly all known in haemophilia, then what I was suggesting was that perhaps when these were listed or when this was examined, clinicians would be saying, "Come on, we have had a long history of these conditions, we know them. They are prevalent in the haemophilia community." And it's that that I don't see anywhere.

A. No, these aren't. Yes. No, no.

THE CHAIRMAN: So the question then becomes: when they do

begin to emerge in the haemophilia community, would it be right that one couldn't say, "Oh, well, we do know them, we can dismiss the possibility of AIDS"?

A. That's right, yes.

THE CHAIRMAN: And that rather leaves one with them as being fairly diagnostic if they happen in the haemophilia community.

A. Yes.

THE CHAIRMAN: And that, I think, brings us back to --

A. I'm sorry if I have misled you.

THE CHAIRMAN: Don't worry about that. We are all capable of misleading each other here, professor.

MS DUNLOP: Yes.

A. These are all evidence of immune suppression. Part of the definition of AIDS is the appearance of one of these conditions which reflects immune suppression for which there is not another obvious cause. In other words, the patient hasn't had chemotherapy, for example, for malignancy, as perhaps the other commonest cause.

Q. I don't think the Cardiff case was written up, professor, or at least if it was, we haven't found it and we have a very big database. But I think we can perhaps just note that there were certainly two different cases being discussed at about this point in 1983 in the United Kingdom. And, you know, whether on

close examination they ticked all the right boxes at all the right times might be another exercise, but they certainly were cases that people were talking about.

Just if we go back, please, to 0468. Just read down 1983. I don't think there is anything else particularly that I want to take you to, except to say that that reference you make in November, "first UK AIDS case in haemophilia reported", I take your point that that's what, no doubt in medical circles, is a proper report, it's in the Lancet, but there certainly was mention of that case and another case in May.

December, there is a total of 21 cases of AIDS in haemophilia in the United States and then seven from outside. Can we go from there to [PEN0150385] at page 16, please -- sorry, it is being suggested to me that we should be having a break because it is 20 past three.

THE CHAIRMAN: I'm sorry, I was just far too fascinated to notice the time. We will have a break.

(3.22 pm)

(Short break)

(3.40 pm)

MS DUNLOP: Can we start with [PEN0150385] at page 16. Thank you.

Professor Ludlam, this is quite a lengthy section in

your 1990 report, and we can see it's headed "Immune studies in haemophiliacs". Just to give everybody a moment to look at that page ... (Pause)

Just a couple of points, I think, for our understanding, professor. This is a description which you are giving us of the attempts that were made to investigate these immune abnormalities, patients with AIDS, very many of whom in the early days, as we have seen, were homosexual men. The first is the ratios. It was noticed that there was a decrease in CD4 numbers. These are the helper cells. Is that right?

A. That's correct, yes.

Q. And the CD8s are the suppressor cells?

A. That's correct.

Q. In a couple of sentences can you just tell us about helpers and suppressors. It doesn't have to be two sentences. That was just a rough guide.

A. The immune system is immensely complex and I'm not an expert but it is made up of white cells, lymphocytes, some of which are called B cells, which make antibodies and some are called T cells, that regulate the process of antibody development. These cells work together in a network with other cells like dendritic cells, which take up foreign matter into them and process them and pass them to the T cells for further processing, either

activating a further set of cells called T killer cells or producing antibodies through the B cells.

My understanding, which is far from complete, is that in a sense the CD4 cells promote this activity and the CD8 cells suppress it. Having said that, it's actually immensely more complicated than that, in that I think you can nowadays get CD4 suppressor cells.

Q. Perhaps we can do a little at a time, and given that we have Professor Lever coming, he will be able to advance our understanding in a couple of weeks' time, but it was the ratios that I understand were particularly significant, and you say:

"Sometimes the reduced ratio was due to a lowered CD4 count, sometimes it was due to an increased CD8 count and yet other times it was due to both a lowered CD4 count and an increased CD8 count."

So I think we can all understand that, at least at a superficial level.

The other thing on the page was the very end, that there were other aspects of the immune system which were impaired. These included a reduction in lymphocyte response to phytohemagglutinin and other mitogens."

Can I put brackets around "a reduction in natural killer cell activity"? The reduction in lymphocyte response to phytohemagglutinin and other mitogens is

a reduction of natural killer cell activity, isn't it? I think that's the sense of the sentence?

A. No. I think not.

Q. It's the way the sentence read. It looked as though that phrase, "a reduction in natural killer cell activity", was meant to be an explanation of what had gone immediately before.

A. I'm sorry, I should perhaps have worded it differently. There was a reduction in the way in which lymphocytes responded to phytohemagglutinin. Quite separately there was a reduction in natural killer cell activity.

Q. Right, okay.

A. As well as a third thing, which was an increase in immunoglobulin levels, which is evidence of immune stimulation, because I think one of the paradoxes of HIV infection is you get both immune inhibition, if you like, and immune stimulation.

Q. I see. Go to the next page, please. It says that people with haemophilia were studied. The results that emerged during 1983 and 1984 demonstrated a range of immune disturbances. And you quote a number of those who published in this area, including yourself:

"Reduction in CD4 count, CD4/8 ratio and other immune abnormalities was observed in asymptomatic haemophiliacs. There is much speculation as to the

cause of the immune abnormalities in haemophiliacs."

You then go on to list for us some of the possibilities:

"1. A previously undescribed feature of haemophilia:"

I think you mention that so that we can now ignore that. Is that right?

A. Yes, but at the time we just wondered whether it could be.

Q. Right. Next possible cause: chronic liver disease. And then third possible cause: blood products given for the treatment of haemophilia contain large amounts of plasma proteins other than Factor VIII or IX, which constitutes less than 1 per cent of the total protein, and I think we established earlier today that that statement about large amounts of plasma proteins would be true of commercial products as well as NHS.

A. Yes, less so for most of the commercial products at this time.

Q. Then you say in a sentence at the end of 3:

"The evidence for the immune abnormality being due to blood products and not a virus are (a), many haemophiliacs exposed to blood products had abnormal immunity."

You say:

"Some studies indicated that cryoprecipitate use was associated with less immune disturbance. This was almost certainly because patients receiving cryoprecipitate were moderate and mild haemophiliacs who only required occasional treatment compared with concentrate users, who tended to be clinically severe ..."

I think we have seen this on a number of occasions but any one administration of concentrates could have been exposing a patient to approximately 1,000 times more donors than an administration of cryo?

A. Yes.

Q. Then:

"(b), recipients of Factor IX concentrates had fewer abnormalities than those treated with Factor VIII ... Studies in haemophiliacs treated exclusively in 1983 by blood products manufactured from local blood donors in AIDS-free areas, for example, Scotland, demonstrated that the patients had similar immune abnormalities, compared with patients treated with commercial concentrates manufactured in North America."

Then we are still in the paragraph dealing with why immune abnormalities in patients with haemophilia could be due to blood products and not a virus. You have said:

"(d), some haemophiliacs who had received massive doses of Factor VIII concentrate and other blood products apparently had normal immune function. If a putative AIDS virus was present in even a minority of batches of Factor VIII/IX concentrate, patients in receipt of these very large doses would have been expected to be infected."

Professor, (d) would have been a puzzle if repeated antigenic stimulation was the explanation as well, would it not?

A. Not all patients we believe respond similarly to infusion of Factor VIII concentrates. There may well be genetic differences between people in the way they respond.

Q. Right. But at the time, if you were considering the competing theories, you would have had to explain why, if antigenic stimulation was the cause, it happened to some people but didn't happen to other people who had received massive doses. You would have had to come up with an explanation for that as well, wouldn't you?

A. It could be an observation and I think some of our studies actually supported that.

Q. Right.

A. That there was a genetic element.

Q. You see, where you say:

"If a putative AIDS virus was present in even a minority of batches, patients in receipt of these very large doses would have been expected to be infected."

That could have depended on how new the virus was and really how small the minority of batches was, could it?

A. I suppose it could have done. I'm just laying out the possibilities.

Q. Right. Then (e):

"In patients who had received Factor VIII or IX concentrate, there was no relationship between the degree of CD4 concentration or CD4/CD8 ratios and the total annual use of the concentrate. This argued in favour of an all or nothing response, some patients being more susceptible to immune change following only small amounts of concentrate."

Then:

"(f), if AIDS was due to a virus transmitted by blood products, why had so few patients with haemophilia out of many tens of thousands developed AIDS in 1983? It was not proved until later, when anti-HIV testing became available, that the latency between infection and the development of AIDS could be many years."

But even in 1983, there were a number of people who suspected that, were there not, Professor Ludlam? For

example, Dr Galbraith's paper. We will have a look at that in due course. Dr Galbraith suggested that the latency period could be up to four years. So even at the time, some people were thinking there could be a very long latency period?

A. Yes.

Q. Then you say:

"The immune changes could have been due to a putative AIDS virus".

And:

"The evidence for this was ..."

You list in the same manner various factors, which we can see for ourselves.

THE CHAIRMAN: Before we go through the list, if one looks at this presentation of the possibilities, is this something that has been developed over time or are these the possibilities that a clinician in your position would have acknowledged at the time and set out in this way?

A. Very much at the time. The reason I put in this document to the Inquiry is because I was encouraged to. As you see, it was written 20 years ago. So this was written, if you like, shortly -- relatively shortly, after AIDS had arrived, and so it perhaps reflects more the way of thinking at that time, the processes we had

been through, and I fully accept that, you know, we have just been through all the non-viral possibilities that were considered and these were very real, particularly in 1982/1983/1984.

THE CHAIRMAN: If we turn to the next set, are they in the same position?

A. Yes.

THE CHAIRMAN: Yes, Ms Dunlop. Sorry for interrupting you.

MS DUNLOP: Thank you, sir.

This was actually written for a litigation in England and Wales, wasn't it?

A. It was a background document for that, yes.

Q. Was it written for any particular group? Who asked you to write it?

A. The solicitors acting for the NHS authorities, health boards.

Q. Just looking at your paragraph number 4, the same exercise, looking at the subparagraphs which are marked by letters and perhaps on to the next page, thank you. Where you say in (d):

"Other blood products, for example platelets, had been implicated in the transmission of AIDS, and by implication Factor VIII or IX concentrates might also be infectious ..."

That immediately makes us think of the infant at

whose case we looked before our break. That infant had received platelets and the donor from whom the platelets had been taken had gone on to develop AIDS. I just wondered, how would the antigen overload or the antigenic stimulation hypothesis have explained the case of the infant?

A. Well, the infant had had actually many transfusions.

Q. Right.

A. About 20 or 30 different transfusions.

Q. I think it was 19?

A. 19, all right, 19. Still a considerable number for an immune system in a baby, which is ill-formed, it is still developing.

THE CHAIRMAN: I'm sorry, but looking at the coincidence of the emergence of these things, by now, when you are writing this, or the period by reference to which you are writing it, there had in fact been a reasonable history of the use of concentrates. So patients might have been developing abnormalities. Could you have written this list, let's say, ten years earlier, sorry, with reference to a period ten years earlier, when there had been a much shorter exposure to concentrates?

A. No, I mean, I think one of the things that we were just wondering -- and it goes back to what I was trying to say earlier -- was that maybe the AIDS in people with

haemophilia was actually of a different aetiology from that in gay men; that was it possible that AIDS was arising in haemophiliacs because during the 1970s there was increasing use, massive increasing use of Factor VIII concentrates.

I mean, I calculated that at least using SNBTS concentrates, that in an average lifespan, you gave out a kilogramme of protein intravenously in an average severe haemophiliac. We are not designed to accept proteins in that magnitude intravenously. So one possibility was that actually -- as we hinted earlier -- maybe haemophilia as a whole was sliding into AIDS because of all the concentrate we were using. Quite separate from HIV or a putative virus.

THE CHAIRMAN: Just looking on AIDS almost as an end stage, as it were, in the progressive demolition of the immune system?

A. From Factor VIII concentrate per se or the proteins, the contaminant.

THE CHAIRMAN: And on any view, that would have required a significant period of time to develop and you just happened to have a coincidence in time of the two situations that required resolution.

A. Yes. And also the AIDS in haemophiliacs was clinically different.

Q. It had no Kaposi's --
A. It had no Kaposi's sarcoma which was a puzzle for a long time.
THE CHAIRMAN: I'm just trying to understand it, Ms Dunlop. Anything that can contribute is welcome.
MS DUNLOP: You have mentioned that before, Professor Ludlam, but apart from the absence of Kaposi's sarcoma, what were the other differences between AIDS in homosexual men and AIDS in patients with haemophilia?
A. I think that was the main one but a very significant one.
Q. Well, did anyone speculate then as to why Kaposi's sarcoma might be occurring in homosexual men and not in patients with haemophilia?
A. Well, we now know it's due to HHV6 or 8, but it was a puzzle for a little while.
MS DUNLOP: Yes. Professor Lever, I think, is going to explain that to us more fully, sir, about the aetiology of Kaposi's sarcoma?
THE CHAIRMAN: Right, yes.
MS DUNLOP: Which has obviously been, as Professor Ludlam says, a bit of a puzzle.
Professor, I did actually also want to take you to an article by Drs Tedder and Barbara on this whole

theme, and I take it it's an article with which you are familiar. You know the article I'm meaning? We refer to it in our preliminary report.

I'm going to take overnight because I don't have a hard copy of it with me today, and I would prefer to do it with a hard copy of it. So we will look at that tomorrow.

But just to carry on with this recital of the different reasons in favour of each hypothesis. We are still looking at pieces of evidence, if you like, that might favour a virus as the explanation. You say:

"(f), the clinical epidemiology of AIDS was very similar to Hepatitis B, a virus known to be transmitted by blood products."

Then:

"Of the four principal possible causes for immune modulation in haemophiliacs ..."

By four principal possible causes, I think we mean an incident of haemophilia, liver disease, antigenic overload; to use a shorthand, or a virus. That's what you are referring to as the four principal causes. It is the ones you have sketched, I think, earlier:

"... there was general agreement it was due, at least in part, to the extraneous non-Factor VIII proteins in the concentrates. Some of the immune

disturbance might in addition be due to the presence of a putative AIDS virus."

Then:

"The reason why it was possible that both the extraneous proteins and the virus gave rise to similar immunological changes is because the immune system only has a limited repertoire of responses when challenged by foreign substances."

Perhaps we can just read for ourselves on to the next page. (Pause)

Then you do say at the very end, professor, that as it turned out, the immune abnormalities which people had found in patients with haemophilia under their care, were not all early indicators that those individuals were going to develop AIDS. Is that correct?

A. Yes.

Q. Right. So as it turned out, this finding, immune abnormalities in people with haemophilia, in some instances was associated with the development of AIDS and in other instances was, as it were, free-standing. Is that a reasonable view?

A. Yes.

Q. Right. The analysis of all of this material is complicated, Professor Ludlam, because on any view, it must have looked around this time as though it was

certainly something about the blood products, something about the concentrates in particular, did it not?

A. Yes.

Q. Yes. I suppose lawyers are particularly interested in not necessarily going straight to getting the right answer but getting the right question first as well, because that always helps you to get the right answer if you have the right question. But if the question was seen as whether the abnormalities were due to antigen overload and only antigen overload, was there anything that pointed in the direction of antigen overload being the explanation for all the cases, including people who had gone on to develop, and in some instances, die from AIDS?

A. Could you repeat the first part of the question?

Q. Yes, sorry. I'm really trying to focus on antigen overload and only antigen overload.

A. Yes.

Q. For our purposes, I'm actually putting to one side the first two of your four possible causes; that is that it's just a complication of haemophilia per se or that it's to do with the liver disease, and I'm looking at 3 and 4 and for shorthand, if we think of 3 as antigen overload, as I have seen it referred to colloquially, and 4 as a virus, was there anything that could make

physicians examining the problem then think that antigen overload was not just a bit of the explanation but the whole explanation?

A. I think that became increasingly less tenable with the unfortunate case reports of a spouse and a child of a haemophiliac developing AIDS.

Q. Right.

A. Because that was evidence of a presumed sexually transmissible agent, furthermore, sadly being passed to the child.

Q. That's the Pitchenik article, is it?

A. I forget the author.

Q. If I'm pronouncing that correctly. We do have that in our preliminary report as well. But that would put your sense of when the antigen overload theory became less likely quite late, because I think that's not until 1984. Perhaps we can give you the reference for that tomorrow rather. Yes, January 1984. It was an article in Annals of Internal Medicine entitled "The acquired immune deficiency syndrome in the wife of a haemophiliac."

A. Yes, that's the article.

Q. That's chapter 8, paragraph 68 of the preliminary report.

A. Yes.

Q. You see, I wanted just to put to you one or two passages from Dr Winter's evidence, if I might. You might want to have it in front of you. That might be easier. Could we go to day 1 of Dr Winter's evidence, which was 26 April. Page 114. The version I have is a different page 114, I think unfortunately. It's the more fully spaced version. That's it. 114.

Yes. You see the question, Professor Ludlam, the question is posed as at July 1982 and I'll give you a minute to read the answer. (Pause)

Do you disagree with that answer, professor?

A. It is very difficult looking back 30 years, to think about the exact balance. Clearly, after the report in July 1982 in MMWR, a viral aetiology had to be a possibility.

Q. Yes. The next one, if we can do this from 27 April, so the following day, pages 7 and 8. Here I do have the four pages to a page version, if that helps. About line 9 on page 7. If we think of this report about the infant, now this question is in the context of a discussion of Koch's postulates, with which you will be very familiar, I'm sure.

Actually Koch originally was involved in research into tuberculosis. Is that right?

A. Yes.

Q. So infectious diseases research generally. But looking at line 9 and reading on right down the right-hand side of what's on the screen, if you would, please. (Pause)

You need to go down the page.

A. If you want me to comment on the 1 to 3 of Koch's postulates or ...?

Q. By all means, professor. It was suggested to Dr Winter, after his explanation of Koch's postulates, albeit that 2, the second link in a Koch chain, as it were, was missing, links 1 and 3 were there because the recipient had developed AIDS, or appeared to have developed AIDS, and the donor had developed AIDS. Did you want to say something about that?

A. Right. I wasn't quite sure in what order the three -- because in fact there were four component to Koch's postulates.

Q. What's the fourth? I think we have maybe missed the fourth.

A. I think you have to culture the organism.

Q. Right. I thought that was the second. That you could isolate the organism from a sample.

A. You have to show that an organism causes the disorder and then transmit the disorder with the organism and show that it develops the same condition. I can't remember what the fourth thing is.

Q. Right.

THE CHAIRMAN: I think Ms Dunlop, if we are having different approaches to Koch's postulates, we have to try and get the basic criteria fixed and we are getting on a bit. Perhaps, Professor Ludlam, you can think of it overnight and let us have your four criteria. I have to say, if culturing it is an essential pre-condition, then that might introduce quite a different level of test, as it were.

MS DUNLOP: I suppose another thing that's troubling me slightly, sir, is how you would ever do that, because that presupposes some sort of process in which you culture the organism and give it to someone.

THE CHAIRMAN: Or something.

MS DUNLOP: Or something. Certainly nowadays I can't quite envisage how that would happen. That was the other section, and by all means, Professor Ludlam, if you want to finish reading that whole section, that whole answer, on to page 8 and indeed on to page 9. If you want to think about that overnight and perhaps we can begin tomorrow morning by asking you if you want to make any particular response to what Dr Winter is saying.

THE CHAIRMAN: And make arrangements to get hard copies provided to cover that. Just how many pages would you like the professor to have?

MS DUNLOP: That's it. I suppose we should start with page 6 then, on to 7, 8, 9 and 10.

THE CHAIRMAN: I don't think that's too much of a challenge overnight for us.

MS DUNLOP: No, I certainly don't think we need a treatise on Koch's postulates.

THE CHAIRMAN: I don't want that. All I want to know --

MS DUNLOP: We are trying to look at the big picture here.

THE CHAIRMAN: All I want to know at the end of this is whether you are looking at the same factors that Dr Winter was looking at. Where they come in the enumeration is far less important to me, but I would be interested to know if he has omitted anything of significance that you consider to be important, for example. But otherwise, so long as you know what he is talking about, you can give us your observations on what he has said.

A. I'll try and do my best.

MS DUNLOP: Right. Thank you.

THE CHAIRMAN: How are we doing, Ms Dunlop, for progress?

MS DUNLOP: Yes, I think we are on schedule.

THE CHAIRMAN: That's fine.

(4.22 pm)

(The Inquiry adjourned until 9.30 am the following day)