Wednesday, 9 March 2011

(9.30 am)

THE CHAIRMAN: Good morning.

MS DUNLOP: Sir, the first witness this morning is Dr Myrtle Peterkin.

DR MYRTLE PETERKIN (sworn)

Questions by MS DUNLOP

MS DUNLOP: Good morning, Dr Peterkin.

A. Good morning.

Q. I need to begin by asking you some details about yourself. You are retired now. Is that correct?

A. Yes, I am.

Q. Before you retired, what position did you occupy?

A. I was clinical services consultant at the Glasgow and West of Scotland Blood Transfusion Service.

Q. And you are a haematologist by trade?

A. I am a haematologist, yes.

Q. When did you do your medical training?

A. I qualified as a medical doctor in 1974. My training was done at the University of the West Indies in Jamaica and I then came to the United Kingdom in 1978 to do my postgraduate studies in haematology and was persuaded to stay at the end of those studies.

Q. And did you work in haematology from then until retirement?

A. Yes, I worked in haematology throughout my time having graduated as a doctor. My time in Glasgow, first of all, was spent at the Glasgow Royal Infirmary, where I was a registrar in haematology and then I moved to the West of Scotland Blood Transfusion Service in 1984. Initially as a registrar and then in 1985 I was appointed senior registrar at the West of Scotland Blood Transfusion Service and in 1989 I was appointed consultant with the service.

Q. Thank you.

A. You are welcome.

Q. In that role, I gather that you carried out some investigations into blood transfusions given to a Mr Victor Tamburrini. Is that correct?

A. I certainly did.

Q. I should ask you to have a look, if you could, first, at [TAM0012463]. Can you tell us what this is, please?

A. I wonder if I can make clear how the blood transfusion service operates first of all.

Q. Yes.

A. The blood transfusion service here and throughout the United Kingdom operates wholesale blood banking. Just to explain that in a little detail. We supply to our regional hospitals on a daily basis, sometimes more often, units of blood to the hospital blood banks, so we

send out a bulk shipping, as it were, in response to a request from the hospital blood bank. So, as we speak at this moment, vans, refrigerated vans are going out to hospitals around the country delivering anything up to 100 units of blood to these hospital blood banks.

The hospital blood banks then cross match specific units of blood to patients who require blood and this, that I'm looking at here, would be one such record of blood that was transfused for this patient. So the regional blood transfusion service really has no idea of which units of blood sent out on a daily basis are transfused to individual patients. It is only when we come to do an investigation of this kind of nature that the hospital blood bank, the consultant in charge, notifies us which units were transfused to a specific patient.

Q. Yes.

A. So I would not have seen this document. I would have been told by Lorna McLintock, who was the SPR at the Royal Infirmary at the time in 2001, that four units of blood, which we had supplied from the West of Scotland blood transfusion centre had been transfused to this patient.

Q. Yes, but this document is in fact part of a trail that you followed. Is that correct?

A. The unit numbers?
Q. Yes.
A. I would not have seen this document at all.
Q. Right. Well, if we look at it, some of it is self-explanatory. We can see that the patient with whom this document is dealing is Victor Tamburrini.
A. That's right.
Q. His date of birth is 27 April 1957?
A. Yes.
Q. And that the date and time of the request for the blood has been 13 December 1998.
A. Yes.
Q. We can also see that he was blood group AB, rhesus positive, and if we scroll down, we can see that there has been noted on the form some information about the blood which was actually given to him. It looks from this as though what was given was red cells.
A. That's right.
Q. That is different from whole blood. Is that correct?
A. Well, most of the blood that we supply is supplied as red cell concentrate.
Q. Yes.
A. Because what we try to do is make best use of every donation given by a donor to us and this is standard, modern transfusion practice because the plasma from

these donations can be used in a specific way to treat patients. So it is wasteful to actually transfuse whole blood to patients.

Q. So really out of one donation of blood, one can treat several people?

A. That is absolutely correct.

Q. So if we can just perhaps go back up a little bit so that we can see the three records which are noted there. I think for today's purposes, the important numbers to look at are the ones in the middle, under the heading "pack number" or "batch numbers". I don't think we are going to be able to hold these numbers in our head. If we look at them for a moment, we can see that they are, what, six-digit and then a letter and then either another letter or another number. So these are reference numbers for the packs of red cells. Is that correct?

A. Yes.

Q. Right, we can see that they have quite a short expiry date. The packs of red cells from the point at which the transfusion service sends them out to a hospital blood bank, how long can they be kept?

A. For 35 days.

Q. There is another page, which we should look at. It is [TAM0012464]. Can we look at that? We can just see

that this record of red cells given to Mr Tamburrini goes on to the following page and we can see a fourth pack number or batch number there in the middle, 631627X1. In fact there is other record-keeping on these forms so that the person who prescribes the red cells -- that is the doctor who decides that the patient needs red cells -- is that correct?

A. That's correct.

Q. So he signs in "prescribed by", and then the "given by" and "checked by" are likely to be nursing staff.

A. Nursing staff, yes.

Q. So the form is signed by a number of individuals and other details are noted, including the time at which the infusion is commenced. So that's one part of the trail.

If we could then look at [TAM0012918], this is further record-keeping in relation to the units of packed cells and we can see the four of them there but there is an additional piece of information recorded in relation to C, which says that the bag was pierced in error and that it was discarded. Do you see that?

A. Yes.

Q. Right. So that gives us some information about the four units. It looks as though, so far, we know that three of them were used and one of them was discarded. Can I ask you next to look at [TAM0013029]. I should

probably have started here because this is a piece of narrative for which you are responsible and this is you really beginning the detective work.

So you are saying that there are these four donations and you want this person, Ian McVarish, to whom you are writing, to start a file on a case of alleged transfusion transmitted Hepatitis C infection and to arrange for archive samples from the donations to be tested. You are taking these steps, as I understand it, because at this point there is concern that this episode of transfusion in 1998 may have transmitted Hepatitis C to Mr Tamburrini. Is that correct?

A. Lorna McLintock had written. She had telephoned initially asking me -- well, informing me that this patient, whom she had been consulting about, had been found to have markers of Hepatitis C infection. And it was clear that he had received some blood, which the West of Scotland Blood Transfusion Service had supplied, and therefore when we get this kind of information, it is imperative that we follow it up.

So this is how the process starts, with notification of the unit numbers of the donations supplied and we start an X file, so that all the investigative detail is held in one secure place so that the whole trail is absolutely transparent.

Q. I see. With any luck the next part of the jigsaw should appear, if we look at [TAM0012396]. This is your letter. We are not looking at the end of it yet but you can take it from me that you have signed it and indeed we can see your reference at the top. "MAP", that's you, isn't it?

A. Yes, that's me.

Q. You are writing to Dr Walker to give her information about, the detective work you have carried out. Is that correct?

A. Yes, I am.

Q. Who is Dr Walker?

A. Dr Walker was the consultant in charge of the department of haematology at the Royal Infirmary at the time. Lorna McLintock was her specialist registrar. So my role as consultant was to respond to the consultant in charge of the department and this is why I have said I have mentioned that Lorna is the person who has notified me about this but to give her her place as head of the department, I was writing to her.

Q. I see. And the letter, we can read for ourselves, it is pretty self-explanatory, but you are focusing on transfusions in December 1998 and this is in view of the fact that in September 2001 Mr Tamburrini has tested positive for Hepatitis C?

A. That is correct, yes.
Q. If we look at the box at the bottom, we can see that -- well, firstly, what this represents is one of the four numbers that we looked at on the sheets from his records. Is that correct?
A. That is correct, yes.
Q. Sir, I should say that I have checked to make sure the numbers were transposed correctly but if anyone else wants to reassure themselves that that has been done ...
So the first donation we are talking about is 631627X1, and that's one with the reference numbers from the patient's treatment sheet.
A. Yes.
Q. That has been traced to having been given by a donor with a seven-digit reference number, and the particular donation concerned, we see, was given on 11 November 1998. Is that correct?
A. That is correct, yes.
Q. Right. That donor's donating history has been examined and perhaps you can tell us what has been discovered when that exercise has been carried out.
A. It is important in cases like this that we don't just focus on the one donation; that is really critical. The index donation, which is why I highlighted it in bold, so that you can refer back to that -- but as it were, to

make assurance doubly sure that we are not missing any marker of infectivity, we look at the entire donating record. We actually retrieve archive samples from all the donations given and probe these donations as well for the specific markers that relate to the case in point.

So in this case we are talking about a possible Hepatitis C transmission and this is why we look at all those donations with specific references to the Hepatitis C virus, and as you will see from the record here, all of the donations which were checked are Hepatitis C PCR negative, including the one that was given to the patient, and this donor had given two donations prior to November 1998, and so this is the full record of this donor that we have looked at.

Q. It is possible for the third column to be filled in because, by 1998, there was screening of donated blood for Hepatitis C?

A. That's right and that screening -- that's why we were able to do that.

Q. Yes. We need to turn the page, please. In short, the same exercise has been carried out for all four packs?

A. Yes, the same exercise. I should say that, even though we had been notified that one of the donations had been pierced, I had no way of knowing whether any of that

blood had been transfused to this patient and I felt that it was imperative that that investigation should also be undertaken. So we looked at all four donations and not just three.

Q. I see. So in relation, in fact, to all four of these donors, they are all people who have given blood more than once.

A. Yes, that is a very important point to stress, yes.

Q. So it was possible; I think most donations -- this is in fact the second donor?

A. The second donor, yes.

Q. It is possible to look at a high number of donations, that nine, including the donation which you were investigating, and check that the results of screening every time the donor had given blood had been negative?

A. Yes, that's right.

Q. I should clarify with you that a blood donor who gives regularly -- and we can see this person is giving about every few months in fact in 1999, but they are checked each time.

A. They are checked each time so this is why I said that, really, this is belt and braces, but within the Scottish National Blood Transfusion Service, we feel that it is important to undertake this sort of testing, even though we know that the donations are tested at the

time of donation. We still repeat the investigation, to make assurance doubly sure, as it were.

Q. Yes. Can we scroll back up to the top of the page, please. If we look at TAM0012398, the following page, this is the conclusion of your letter.

A. Yes.

Q. And again I think it is really the first paragraph we are interested in:

"In light of the repeated testing with HCV PCR negative results given by donors of the four units of blood transfusion, I do not consider this to be the route by which he acquired his Hepatitis C infection."

Is that your view?

A. That's my view, yes.

Q. It remains your view?

A. It certainly remains my view, yes.

Q. You've looked again at this material prior to coming here today, I expect?

A. Yes, I have.

THE CHAIRMAN: Dr Peterkin, just a little bit of clarification. When the blood was taken, it would have been screened?

A. Yes, it would have been screened.

THE CHAIRMAN: Would that have been a HCV PCR.

A. It would not have been.

THE CHAIRMAN: At that time it would be anti-HCV?
A. Yes, it would have been.
THE CHAIRMAN: So this is not only a second test, it is a different test?
A. It is a different test, yes.
THE CHAIRMAN: And this one is specific for the virus.
A. This is specific for virus. It is looking for viral RNA in the blood sample, so it is really very specific.
MS DUNLOP: Sorry, doctor, my attention has been drawn to the transcript. I think you said it is looking for viral RNA. Is that correct?
A. Yes.
Q. Viral RNA. Thank you Dr Peterkin. I don't have any further.
THE CHAIRMAN: Mr Di Rollo, do you have any questions for Dr Peterkin?
MR DI ROLLO: No, sir.
THE CHAIRMAN: Mr Sheldon?
MR ANDERSON: No, sir.
MR SHELDON: No, sir.
THE CHAIRMAN: Dr Peterkin, thank you very much.
A. Thank you very much.
THE CHAIRMAN: Yes, Ms Dunlop.
MS DUNLOP: The next witness for the Inquiry is Professor van Aken.

PROFESSOR WILLEM GERARD VAN AKEN (sworn)

Questions by MS DUNLOP

MS DUNLOP: Good morning, Professor. You have come here from the Netherlands to assist us at the Inquiry and before we ask you about the specific matters that you have examined on behalf of the Inquiry, I should take some details from you biographical details.

We have a curriculum vitae, which I think is PEN0020647. That should appear on the screen in front of you in a moment.

This is, Professor, something of an abbreviated curriculum vitae, I am sure, because we can see from this synopsis that you have had a long career in the field of blood transfusion. Is that correct?

A. That's correct.

Q. You studied medicine in Nijmegen. Is that correct?

A. Yes.

Q. When did you finish your undergraduate training?

A. The undergraduate training was finished two years before. So that was in 1964.

Q. And then you went on to do an MD in Nijmegen?

A. Yes.

Q. And you have also done a PhD in Amsterdam and worked in University Hospital in Amsterdam, and in fact, you are also a FRCP, a fellow of the Royal College of Physicians

of Edinburgh. We see a number of awards, and you have also listed your current activities, although nominally you are retired. Is that correct?

A. That's correct, yes.

Q. What position did you occupy immediately before retirement?

A. Before I retired, I was the director, a member of the board of the central laboratory of the Netherlands Red Cross Blood Transfusion Service, which, after I left, is changed; the organisation is now called Sanguine, Sanguine Blood Supply of the Netherlands.

Q. Can you tell us just a little bit about how the organisation works in the Netherlands. You referred to the Red Cross?

A. Yes. You see, the history of the transfusion organisation in the Netherlands goes back until the situation after the Second World War. Then the Red Cross was asked by the government to take responsibility for the organisation of the blood transfusion in Holland and they started to, with two big centres, one in Rotterdam and one in Amsterdam, which were taking care for fractionation of albumin, and then at the same time, hospitals were asked to start local transfusion services.

Gradually this proved to be not an efficient system

and so the decision was taken to concentrate the various hospital blood banks in regional centres. So we got 29 regional blood banks, which were independent, which were in fact foundations in which the Red Cross was represented together with somebody from the government or from local authorities, and there was one organisation in Amsterdam, the central laboratory, which took care for the fractionation of plasma and also for certain diagnostic services as well as for research.

But again, this proved to be a very inefficient organisation because of there were always discussions and disputes among the various centres and the central organisation. So it was decided by the minister in 1998 to restructure and to create one organisation in which all these various partners which existed were, in fact, merged and which was one central board.

So that is the present system. There are now currently four blood centres, which collect blood and distribute blood, and there is one organisation in Amsterdam, which takes care for most of the viral testing, the PCR, things like that, and also for the production of plasma products.

Q. In common with the United Kingdom, the Netherlands is operating on a voluntary donor system. Is that correct?

A. Indeed, sorry, not just voluntary but also not

remunerated. Voluntary means you are not --

Q. Yes, thank you for correcting. Voluntary, non-remunerated donor system. Again, in common with the United Kingdom and in particular in common with Scotland, the service in the Netherlands is responsible both for collection of blood and supply of blood, and presumably red cells for transfusion, and also for manufacture of blood products from plasma. Is that correct?

A. That's correct.

Q. And in the description you have given, that has been so for a long period of time.

A. That's correct.

Q. And continues to be so.

A. Yes.

Q. And in your particular position were you overseeing all of that activity?

A. No, I was overseeing medical affairs and production.

Q. And is that in relation both to transfusion and manufacturing?

A. Yes, with production -- I mean, production of plasma components, so of albumin, Factor VIII, Factor IX, immunoglobulins and also products prepared for plasma but -- and also responsible for the collection of red cells by the central board itself.

Q. We are still looking at your curriculum vitae and we can see that after a list of a number of honours, which you have been awarded, your current activities, we can see this for ourselves, that you are an emeritus professor of medicine and that you are involved in a number of different initiatives, in fact, in a number of different countries, Switzerland, France and the People's Republic of China as well. I see, too, from the following page that you have been a non-executive member of the board of the National Blood Transfusion Service in England?

A. That's correct.

Q. An eight year period between 1998 and 2006. You have also been involved in the French Blood Agency and then you list other positions you held within the Netherlands, and then at the bottom you can see Canada as well. You have also listed special activities: reports for the European Commission. I'm not sure, I did see from the Internet that you had been responsible for a Council of Europe report entitled "The collection and use of human blood and plasma in Europe" in 1993. I'm not sure if that's listed under one of the activities. In which role were you responsible for that?

A. You see, the first item on the special activities

mentions reports for European Commission regarding blood supplies. So just a year before the Council of Europe asked me to do -- to start that report, which was taken over later by the European Commission. So that is why I haven't specified that.

Q. I see. But it obviously relates --

A. But it is the same, yes.

Q. Yes. And finally from this short summary, we see that you have had involvement as an expert witness in litigation concerning blood safety and HIV, and again that has involved you in considerable international travel.

You can put that to one side and I ask you to look at a report you have prepared for today's proceedings. That report is [PEN0010306]. We have it before us.

This report was finally received at the Inquiry on 11 January of this year, sir, so although it doesn't bear a date, it should be treated as being dated 11 January 2011.

We can see that the query you have been asked to address is whether or not stable plasma protein solution could have been the source of Mr Tamburrini's Hepatitis C infection. Is that correct?

A. That's correct.

Q. You have given a brief resume of Mr Tamburrini's medical

history. You noted that he had had an appendicectomy in 1968. At that time he would have been a child, he would have been 11. We did have some discussion yesterday as to whether someone might ever receive a transfusion during an appendicectomy. What would be your answer to that possibility?

A. In my experience it would be a rarity. It would be very seldom, only when there is a complication and major bleeding, but I would not have expected most appendicectomy's would have required the transfusion of blood.

Q. So not in the ordinary course of events but it can't be ruled out. Would that be a fair summary?

A. Indeed.

Q. Then you have noted the episode with which we are now familiar, in September 1984, when Mr Tamburrini sustained burns and he received stable plasma protein solution. Could you explain for us, please, what function the plasma protein solution will have fulfilled for somebody who had just sustained burns?

A. Very briefly, if you have such severe burns, you lose a lot of fluid which is normally in the blood circulation. So the blood vessels in the burn area are dilated, are leaky, and so a lot of fluid is disappearing there and so the threat is that patients

with severe blood loss go into shock. So the blood pressure drops and there is not enough concentration any more. So one of the first policies, in fact, of burn treatment, is to restore that loss of volume by adding a fluid which in fact not just restores the water content but also what we call the osmotic/oncotic pressure, which is a composite of the protein content in the blood and the resistance provided by the tissue.

So if you -- if that balance between these two forces is disturbed, then you need to add also protein to the circulation, and that is what SPPS, stable plasma protein solution does; it restores the protein content and thereby helps to decrease the loss of -- the first loss of volume.

THE CHAIRMAN: What is the nature of the liquid that is lost?

A. The nature of the liquid that is lost is quite complex. It is not just only fluid but it also is protein, which protein are notably albumin but also other proteins, which are present in the circulating blood.

THE CHAIRMAN: Does the SPPS in some way compensate him specifically for that or is it just a general --

A. Well, it is specific insofar as in some -- certainly in severe patients with burns, you see that the albumin level in the blood drops and that -- so in that respect

it is specific indeed. But -- because that's why you could argue: why not give whole plasma? Because you supply everything. And that is not a policy because, first of all, this albumin, you can, so to say, take from the bench. It doesn't require a whole logistics of supplying and having a donor and things like that. So you can start immediately and on top of that it is far safer than plasma.

MS DUNLOP: Just from our own experience, Professor, I suppose, we have probably all seen when you sustain a burn, it tends to weep. I don't know if you would use that term but you can see for yourself that burned skin tends to lose fluid. The fluid loss comes from the surface area of the burn.

A. From the area of where the burn -- where the skin is burnt. That area is leaky.

Q. Yes. Under a heading "Manufacturing of SPPS by SNBTS" you tell us firstly that the units of plasma protein solution Mr Tamburrini received came from the same lot or batch, which was 1194. We are all aware of that now, which was manufactured in March 1983. The source material consisted of a pool of liquid plasma collected from blood donated by human subjects.

Just to clarify, Professor, you heard Dr Peterkin. She was talking about the use of red cells and this is,

in a sense, the other half of the donation, so that one is almost getting two products for the price of one. The patient who needs red cells can be treated from the same donation as someone else can receive plasma, which is a different component of the donation of whole blood. Is that the way it works?

A. Well, it is not precise to say it is the other half because you see --

Q. It is a crude simplistic analogy.

A. Because if you look at the whole blood unit, you can put it in the centrifuge and after 10 minutes centrifuging, you get two parts. You get a top part, which is yellow, which is plasma, and the bottom part is red cells and you separate that. But only a portion of that yellow part of the plasma is SPPS. So it is not everything in plasma, it is only one component, albumin.

Q. We heard yesterday that there is a difference between something which is correctly called "albumin" and something which is called "SPPS", in that to be termed "albumin" it needs to be 95 per cent or more albumin. Is that correct?

A. That's correct.

Q. Whereas SPPS will be over 90 per cent but presumably not over 95 per cent?

A. That's correct.

Q. Taking it stage by stage, you explain that albumin was extracted from the plasma through cold ethanol fractionation according to the method described by Cohn and others. It is fair to say that Edwin Cohn in this area was a pioneer, is it not?

A. That's absolutely true, yes, he is the pioneer.

Q. Perhaps you could just give us a very brief explanation of the process which he pioneered.

A. What Dr Cohn, in fact, found out is that if you submit human plasma to alcohol at a certain pH and certain -- yes, pH, I should say, that you get a precipitate and you get a supernatant. So you can precipitate certain proteins by adding ethanol. And by choosing the proper concentration of ethanol and the right pH, you can, in stepwise, you can create precipitates which are composed of certain proteins and leave in the supernatant some other proteins.

So in this stepwise process, you can separate various plasma proteins in a very elegant way. So this is what is done.

To make a large volume of material, of starting material, of plasma, put it in a big container, add concentration of alcohol at a certain pH. This is incubated for a certain period of time, then the precipitate is separated from the supernatant, put in

a different chain of events in fact, and the supernatant goes on to be added to a new concentration of ethanol and pH and the subsequent protein is precipitated. So this in various fractions which are obtained, then you can locate various proteins.

Before this is done, there is one step ahead of that in which the whole plasma is frozen and thawed slowly so that you get, again, a precipitate, which is factor 8 predominantly, but that is a separate chapter. So after precipitation, the supernatant is in fact used for alcohol fractionation.

Q. In this section of your report you describe what seems a very flexible option, that either one can precipitate out something one doesn't want and leave the desired protein in solution.

A. Yes.

Q. So in a liquid form, or you can precipitate out, in a solid form, something you do want and leave everything else in solution.

A. Yes.

Q. After your description of the use of ethanol at different concentrations, you say that the plasma fractions which are precipitated are harvested by centrifugation or filtration, and then finally the ethanol is removed. And that gives, as it were, the

albumin product, which can then be submitted to this form of heat treating.

A. Yes.

Q. In our particular case, the heat treating method used is pasteurisation for ten hours at 60 degrees Celsius.

A. Right.

Q. You have also referred to the British Pharmacopeia. I think you are familiar with the one-page extract from the British Pharmacopeia explaining how the albumin is processed, are you?

A. Indeed.

Q. I think the extract from the publication was sent to you in the course of preparing your report. But it is no doubt something you had seen before?

A. Yes.

Q. Next you have a heading "The heating procedure of SPPS used by SNBTS". Did you see, Professor, in your preparation of this report, the actual batch processing records for batch 1194?

A. Yes, indeed.

Q. Yes. That's a printout from a microfiche record and we looked at it yesterday; not entirely easy to read, but still available. Just for the record, perhaps we could see it and confirm that we are talking about the same thing, [PEN0010260]. Is that the record that you have

seen?

A. Yes.

Q. Thank you. You tell us that, having looked at this batch, manufacturing records show that the temperature was measured and recorded and confirm that the heat treatment process was controlled at around 60 degrees Celsius for a minimum of ten hours.

According to the British Pharmacopeia:

"The approved conditions of heat treatment were to heat in the final containers at this temperature so as to prevent the transmission of hepatitis."

The point was made yesterday that the use of the word "prevent" is quite strong for a pharmaceutical preparation, that the publication appears to be saying if this is followed, transmission of hepatitis will be prevented. Is that, in your view, an unusual word to use?

A. Well, of course, this is not my mother language, so you can always criticise me that I'm not aware of what the various interpretations of "prevent" can be, but I think for me it was quite logical to use it in the context of this procedure here. So I have not had any doubt about, or uncertainty about, whether that word was correct or incorrect or should have been changed by another term.

Q. Right. So making allowances for this not being your

mother tongue, and obviously we are very grateful that you are able to converse in this as you are, but making allowances for that, you don't argue with the use of the term "prevent"; you think it is justified?

A. Yes, well, what in fact is happening is -- in the way it is done, is that, as I think I have indicated later on in the report -- or maybe I'm going ahead now -- is that this particular procedure, where the heating procedure is done in the final container, is essential because it has been shown previously that if you don't do it in that way, you can come across certain transmission of infections going to be Hepatitis B. Not Hepatitis C because that also -- but Hepatitis B. This is the publication of Dr Pattison, which is also quoted in my report.

Q. And we will come to that.

A. So in the context of that I think "prevent" is, for me, not a term which I have difficulty with.

Q. You say there are two ways to vet the virus safety of plasma products such as albumin -- sorry, we should go back to Professor van Aken's report at PEN.001.0307. Thank you. And you say:

"There are two-ways to investigate ..."

The two ways you have selected are a way which is used technically, as it were, to see how effective the

viral inactivation procedures are, and also one can do scientific research to see if there are any reports of transmission of viruses by plasma treated in this way.

To take the first, the description that you give of the use of model viruses is again, for lay people, rather difficult to understand but it might help if you could explain to us the concept of a model virus.

A. Okay, thank you. Well, Hepatitis C is one of the viruses which is transmitted by blood which is not yet completely isolated. We have evidence about the composition, the genomic composition, which allows us to test for Hepatitis C but the virus as such is not isolated. So you cannot use that virus to see what I have described here for spiking. You cannot add it to plasma and then submit it to inactivation and see how much virus is destroyed.

Q. I'm sorry to interrupt you but this is important for our whole Inquiry. The virus has not been isolated. By that you mean no one has succeeded in culturing the virus?

A. Indeed, that's a term which is very appropriate here.

Q. Sorry, carry on.

A. Yes. So only --

Q. I should ask what do we mean by "culturing"?

A. Culturing means that if you isolate a virus from, let's

say, blood, you get a very small quantity, minute quantities, which are not sufficient to be used for experiments. So you need to expand that -- those particles by putting appropriate culturing -- appropriate fluids to it where the virus feels very well and can propagate and can multiply, and thereby, after a certain time, you can have sufficient. That technique we call "culturing", multiplying the quantity of the virus by adding proper nutrient substances. Yes? And appropriate conditions like 37 degrees and sufficient time. Is that sufficient?

Q. Can we contrast it then with another virus that we have done a lot of reading on, which is HIV?

A. Yes, HIV is a virus which is one of the best known viruses now because we know almost everything about HIV and that can be cultured.

Q. Yes, and indeed that was possible really from the mid 1980s, it was possible to culture HIV.

A. Whether -- well, the virus was in fact -- became known in 1984 and indeed, Montagnier and Gallo were able to culture that virus some time later but around 1984, yes.

Q. Professor, plainly we have a long journey to travel in our Inquiry and we will be looking at the Hepatitis C virus in a great deal more detail, but it is perhaps sufficient at the moment just to record that Hepatitis C

proved very elusive for a long time, it was very difficult, really, to find any part of the virus until 1988/1989. Is that correct?

A. Sorry, I didn't catch that question correctly.

Q. It has been very difficult to find Hepatitis C --

A. Yes.

Q. -- as a virus. And the actual virus, no part of it had been isolated until the late 1980s. Is that correct?

A. Yes, that's correct.

Q. And the position today, as you have explained to us, is that even yet it is not possible to grow, to culture, the Hepatitis C virus and work with it in that way.

A. Hm-mm.

Q. Perhaps I won't go into this too far but in fact, the scientific breakthrough that occurred at the end of the 1980s was really based on genetic technology, on cloning?

A. Yes.

Q. And that's how it was possible to find at least a part of the virus and enable tests to be drawn up or tests to be created?

A. Yes, that's correct.

Q. So we were at the notion of model viruses and you were explaining that, because you are not able to grow the Hepatitis C virus, you have to use something else

instead, and if you could explain further where the model virus notion then comes in.

A. Yes. So the genomic part of the Hepatitis C virus has been identified, at least I think, almost 100 per cent of the genomic composition of the virus, and that has been used not just to develop a test but also to compare with other viruses, like, for instance, so-called "pestiviruses", which show -- and that investigation has shown that the genomic part of the Hepatitis C, it looks very similar to certain pestiviruses, like bovine diarrhoea virus but also togavirus.

So there are a number of viruses which have a similarity in the genomic part. And also the density of the virus and -- yes. Those two characteristics looks quite similar to Hepatitis C.

Q. I think for the transcript, Professor, I should ask you to confirm the name of the second virus. I got the name of the bovine diarrhoea virus and that's in your report, but was the second virus "togavirus"?

A. Togavirus. T-O-G-A.

Q. And that's essentially an animal virus as well, is it?

A. Yes.

Q. So the theory is, trying to put it in layman's terms, because you don't have the actual Hepatitis C virus, you do the best you can to use a virus which appears to

share characteristics with Hepatitis C and you measure the inactivation of that virus by the process. Is that a reasonable summary?

A. Yes, instead of model viruses, also the term "indicator virus" is used, just to illustrate also what its purpose is.

Q. Right.

THE CHAIRMAN: Is one looking for a proxy --

A. Yes, for a proxy, that is the term, yes.

MS DUNLOP: When did the use of a model virus for Hepatitis C begin? When did people start doing that, just roughly?

A. Well, a good question. I have not in mind exactly which publication -- at what time the first publication about this was done. But I --

Q. Perhaps an easier question would be whether the use of a model virus would be something that was being practised in 1983?

A. No, not in 1983.

Q. So in fact --

A. Absolutely not.

Q. -- what you are describing here is information that we have about the process, which is based on research that's accumulated over recent decades?

A. Yes, indeed.

Q. So it is the position as at today, but not necessarily everything that would have been done in 1983?
A. No, I think -- the earliest I would judge is 2000 or thereabouts.
Q. Right. But one can still look, even though it is a step which is being taken now and which would not have been taken in 1983. We can still use this information because it gives us more detail about the process and whether it works. Is that reasonable?
A. Yes.
Q. You say that the process of cold ethanol fractionation significantly reduces the concentration of viruses in plasma fractions. Is that because ethanol is to some extent viricidal?
A. No, the major -- there are two effects here. There is one effect that the ethanol itself -- but that is not very significant viricidal. It is mostly the partitioning, the separation that the virus is in certain fractions and less in other fractions.
Q. And indeed, some of the articles that you have drawn our attention to deal with the partitioning. Perhaps we could look at some of those articles. In fact it is probably better that we look briefly at all of them, although they are, if I may say so, quite technical, but you mentioned partitioning, so could we perhaps look at

the reference [LIT0013218]. I think this must be PEN.001.3218. This is an article which you have provided by the authors Yei -- is that a reasonable pronunciation, Yei, Y-E-I and Tankersley. Actually, the second reference in your list in italics; about the partitioning of Hepatitis C.

I don't want to go too far into material which we might all struggle with, Professor, but by partitioning, are we really just talking about where the virus goes when the fractionation process is carried out?

A. Yes.

Q. And perhaps even just looking at the summary, can you give us a brief overview of what has been discovered about that?

A. What they also have done is they have used a sort of smaller design of the Cohn fractionation procedure and they have -- let me see. So they have looked at the plasma pool of anti-Hepatitis C reactive donors. So there you would expect that there is at least some Hepatitis C present. Then they have used an assay to quantify that and looked in the various fractions what is the quantity of Hepatitis C which you can detect in certain fractions; yes? And it appears that most of the Hepatitis C RNA -- that's not the whole virus but just the RNA -- was found in the first fraction as a

cryoprecipitate.

So there's the first step, as I explained earlier, where you start to separate the various proteins, as well as in Cohn fractions 1 and 3, and these are used for products like fibrinogen and coagulation factors, not for albumin. Then they go on; they found out that in fraction 2 there is also a major quantity and that fraction is used for immunoglobulin preparation and that was the reason, in fact, why this investigation was done, because there has been an incident where one producer noticed that his product caused a lot of Hepatitis C in recipients.

So this study, in fact, shows that it is logical that this product is more risky when it comes to Hepatitis C transmission, and what they conclude in fact, is that the partitioning of the various fractions leads to various proteins which are more at risk of contributing and transmitting Hepatitis C than others.

Q. Yes. So for our purposes in looking at Mr Tamburrini's illness, what we should take from this is that albumin is not one of the products which you would expect to be found to contain a lot of Hepatitis C after the fractionation process?

A. Indeed.

Q. Is that correct?

A. Indeed, I would even go further than a lot. I would say a minute quantity.

THE CHAIRMAN: Ms Dunlop, do you think that's going to communicate itself to everyone or shall we try a little bit of clarification? I think it is important that everyone who listens gets the idea of what's happening in Cohn fractionation. Should I try a little or are you going to come back to it?

MS DUNLOP: I'm trying as I go along, sir, to summarise what the witness is saying in what I hope is comprehensible shorter sentences, but I'm happy to check how that's working.

THE CHAIRMAN: I think, at the moment, the picture will be clearer to someone who has read a lot about Cohn fractionation than it will be to someone who is hearing the terms "fractions" and "factors" and "precipitates" and things of that kind, perhaps for the first time.

MS DUNLOP: Perhaps if I go back a little bit and try to summarise what we have established so far, Professor. One of the difficulties is that we are all lay, so we all struggle with this. Some of us have the advantage of discussing this with you before and we have obviously also been able to do a bit of background reading and that's not possible for everybody. So if I could perhaps try to summarise the point we have arrived at

and you, please, correct me if I'm getting this wrong because it is very difficult for us all.

A. Okay.

Q. From a donation of whole blood, it is possible to extract the material -- it is not, as you pointed out, half and half -- but it is possible to extract red cells which can go for transfusion to patients and it is also possible to use what is the non-red cell part to make plasma products, and there is a range of plasma products which serve different functions, and can be used in the treatment of different illnesses or for different conditions.

The product we are examining in this case is known generally as "albumin". That is not entirely accurate because the product that we are particularly looking at is called stable plasma protein solution, but most of that is albumin. So if we can call it "albumin" for the moment.

The way in which that is taken out of the plasma is by a process called "fractionation". Is that correct? Perhaps all we need to know about that is that scientists have discovered that by use of ethanol, alcohol, in fact, at different strengths, it is possible to remove from the plasma these various different products for the raw material to make these various

different products. Is that a reasonable summary?
A. You gave a perfect summary.
MS DUNLOP: I don't know, sir, whether you feel that helps.
THE CHAIRMAN: I think it does, sometimes just repeating it, helps to get it over.
MS DUNLOP: Advocates always have the experience of being able to grasp it one day and losing it within the next few days, so I can confidently predict that will happen.
THE CHAIRMAN: It is not a skill one loses with age.
MS DUNLOP: It is difficult stuff. I'm very aware of that.
Perhaps we don't need to know much about partitions. That's really at the outer edges of what I think we maybe need to know about in the context of Mr Tamburrini's illness, but all I think I was trying to take from you was that, when this separation process is being carried out with the use of the ethanol, the virus will not be spread equally among the various products. Is that correct?
A. That's correct.
Q. So you are more likely to find more of it in some products and less of it in others?
A. Yes.
Q. Albumin is one of those in which you would expect to find a much smaller quantity of virus?
A. Correct.

Q. So if you are setting out to treat albumin against Hepatitis C, your task may not be as difficult as it would be with one of the products which would have a high concentration of the virus?

A. That's correct.

Q. Is that correct?

A. Yes.

Q. Good. Can we just look at the foot of page 4 of that article, please? This is interesting for our purposes because if we look at the paragraph at the bottom of the page on the right-hand side, the authors are talking about, as I said at the start, where the virus goes and really you have already explained that to us, but what's interesting for our purposes is what is said at the bottom in the sentence beginning "products":

"Products derived by further fractionation of supernatant 2 and 3 include a list in which we see albumin ..."

Then the authors go on to say:

"... all of which are subjected to heating for ten hours at 60 degrees centigrade. The fact that these products do not transmit HCV ..."

You understand that was a sentence in this article which jumped out at me and I was looking at it and the authors are saying, in fact, these products do not

transmit HCV, maybe due more -- can we turn the page, please -- to virus inactivation by the heating step than to physical removal of virus by the fractionation process.

Perhaps another article that we should only look at very briefly, just to see if there is anything in it which sheds light on the examination we are carrying out, is the one by, I think it is Scheiblauer. The reference is [LIT0013131], and we can see the names of the authors. This is a German article and perhaps you could explain to us what these authors are looking at particularly.

A. They are in fact, like the previous publication that you discussed, also looking at the various fractions where the Hepatitis C may end up.

Q. Yes.

A. And again, with the purpose: why is it that immunoglobulins have transmitted Hepatitis C?

Q. And it looked as though this article was really saying that the actual fractionation process, the ethanol fractionation process, did not itself inactivate virus.

A. Yes, well, I think it goes too far to say it does not inactivate hepatitis. It does not activate Hepatitis C to the same extent as other things.

Q. And actually if we look through the article, I think we

can see that the virus that these researchers were using was bovine diarrhoea virus?

A. Yes.

Q. So that's the concept that we identified earlier on: if you do not have the virus in question, you have to use it, as his Lordship put it, a surrogate or a proxy, something that you think is as good as, or nearly as good as having the virus itself?

A. Yes.

Q. Then also look at the first article that you referred to, which is the Erstad one, [LIT0013117]. That is perhaps a more straightforward article for us all to try to grasp, but this is really looking at the very question, the exact question, that we are trying to examine today. Would that be reasonable? It is looking at the viral infectivity of albumin and plasma protein fraction?

A. This article is not a research paper. It is more of a review.

Q. So it is not original research?

A. No, it is not original.

Q. It is looking at other people's?

A. Yes.

Q. Right. Perhaps it is enough for our purposes just to look at that summary, to see what it was the author set

out to do. He set out to examine other people's research on the viral infectivity of albumin and plasma protein fraction. He looked at a number of different aspects which might contribute to whether virus could be successfully inactivated and then he says, in the summary, that:

"Both human serum albumin and PPF are manufactured ..."

This is reading from about half way down the summary:

"... with pasteurisation procedures that have led to an excellent viral safety record based on 50 years of clinical use. One outbreak of Hepatitis B was associated with PPF as a result of an unreliable manufacturing process which has been corrected. Pasteurisation process is effective in eradicating known viral pathogens when good manufacturing practices are followed."

I know the incident that he is referring to there is in fact one that you mention yourself in the next part of your report, and, perhaps, we should go on to that now.

A. What is important, I think, to emphasise, if I may, is that this paper does not talk as much about fractionation itself as about a pasteurisation step. So

it concentrates -- and that is what is clearly said -- the pasteurisation process is affecting, and so it doesn't spend too much attention to either partitioning or pH or ethanol as responsible for the decrease in Hepatitis C transmissibility.

Q. So although this is not original research, it is a very useful article for us in the task in which we are engaged --

A. Yes.

Q. -- because it is exactly the same point?

A. Yes.

Q. You say in your report, after you have mentioned these different articles at which we have looked:

"These studies have shown that heating of albumin for ten minutes at 60 degrees Celsius results in a virus reduction of greater than 16.3 of bovine diarrhoea virus, as compared to more than 17.8 of HIV and 16.4 of pseudorabies, which is a model virus for Hepatitis B."

So again, that is, I think, for lay people, quite complex to understand but the numbers that you are quoting represent a large reduction in the amount of virus. Is that correct?

A. Yes. These data I have also from a document which is published by the WHO. The WHO expert committee on plasma products in fact has addressed this issue in

a very extensive report in which all these papers here are included, and one of the conclusions is in fact that ten minutes at 60 degrees Celsius results in a virus reduction of more than 16 logs, which means that -- again, it is difficult for lay people to understand what does that figure mean, but it means in fact that it is about a risk of one in 16 millions that still a virus is not inactivated. So it goes well beyond our imagination that there is still some virus left after that period of time.

Q. Thank you. You have emphasised -- and this is slightly easier maths for us all -- that ten hours is 60 times longer than ten minutes. I think we can follow that.

A. Yes.

Q. So to do the pasteurisation for ten hours is 60 times longer than is needed to inactivate hepatitis viruses.

Sir, I'm conscious it is 11 o'clock. This is heavy going so perhaps it would be a good time for a break?

THE CHAIRMAN: I think it probably is. I'm not sure how far we really need to know what these figures mean. I have to say that I'm sometimes slightly concerned that the extrapolation of data by multiplication gives rather an odd feeling of unreality to things, Professor van Aken. Do we just need to know that it is a tiny, tiny risk that remains, or do we need to know that it is 16.3 on

a log 10 basis?

A. Well, for people in the business, so to say, in medicine, when you start to compare the risks of blood and plasma product, yes, you want to be sure that the inactivation goes beyond a certain degree.

THE CHAIRMAN: So it is a reference level that gives comfort?

A. Yes, that's why it is important. So the figure itself is not the most important. It goes beyond a certain reference.

THE CHAIRMAN: I think that's very helpful. Thank you very much.

(11.02 am)

(Short break)

(11.33 am)

THE CHAIRMAN: Yes, Ms Dunlop?

MS DUNLOP: Professor, just before we stopped for our break, we had, I think, finished the first of your two ways of investigating the virus safety of plasma products, which you outline on the second page of your report. So we need to have your report in front of us again and that is [PEN0010306], and if we could have page 2, so in fact 0307.

At the end of the first section you tell us, as SPPS is essentially composed of albumin, it is allowed to

apply any evidence of safety as published for albumin into SPPS. So it is a legitimate exercise to take this data and apply it to SPPS, is what you are saying?

A. Yes.

Q. The second way, you say, is -- and you have alluded to this earlier -- to look at published material, to see if there have been reports of patients treated with albumin going on to develop Hepatitis C. It is correct to say that you have also conducted that research, is it?

A. Yes, I have looked at the literature to find what is available in evidence, to either support or just to deny that there is a link between the transmission of Hepatitis C by albumin or SPPS.

Q. Right. You refer to another article and I think we should have that in front of us: [LIT0013122]. We had Dr Cuthbertson from the blood transfusion service giving evidence yesterday and he made brief mention of this incident but it might help us all if you could summarise what happened.

A. What happened was that in the United States somewhere around 1973, one hospital using PPF, which is in fact similar to SPPS, found that there were a number of recipients who had developed an illness which was compatible with hepatitis and they found out that it was a Hepatitis B infection which, after excluding a number

of other reasons, was attributed to the administration of PPF.

Then they went to the manufacturer of this product and they found out that it was related to two lots, which in fact were prepared from plasma, one of which was in fact associated to a high prevalence of Hepatitis B sero-positivity in the recipients. So the study was in fact showing that there was indeed a batch which was clearly related to the transmission of Hepatitis B and when they went to the manufacturing conditions, they found out that it was the pasteurisation, the way the pasteurisation was performed, which they found was in fact responsible for incomplete inactivation of Hepatitis B.

Q. Would it be correct to say that the way in which the plasma was being treated was in one big tank?

A. Yes.

Q. If I can put it like that?

A. Yes.

Q. Rather than in individual containers?

A. Yes, and therefore, if you do that in one big tank -- and you have to imagine that these are really big tanks of more than 800 to 10,000 litres -- there can be sort of what you may call "islands" of product, of material, which are not behaving in the same way as all the source

material around it. Yes?

Q. I think we might say "pockets", would that be another word?

A. Yes, pockets. That's the word which I was trying to find, "pockets".

Q. So there might be pockets where the treatment hasn't worked or hasn't reached, as it were?

A. Yes.

Q. As I understand it, the solution to that problem -- which is an actual problem because it has happened, it is not just a theoretical problem -- is to pasteurise the material in individual containers?

A. Yes.

Q. From your understanding of the process at the Protein Fractionation Centre in Edinburgh that was what was done there?

A. Yes.

Q. You go on to mention in your report -- and if we could go back, please, to 0307 -- reports of healthcare authorities, and this is at the bottom of the page. We can scroll right down. You say:

"The hepatitis safety of albumin is addressed in the reports of several healthcare authorities. British Pharmacopeia requests heating in the final containers to inactivate hepatitis viruses."

Then you go on to talk about WHO:

"The expert committee on biological standardisation of the World Health Organisation ..."

Does WHO have a number of standing committees? Is that the way it works?

A. That's correct.

Q. And this is one of them?

A. Yes, this is the committee which meets every year and discusses all the items related to safety of blood product, blood and plasma products and vaccines.

Q. Roughly how big is this committee?

A. There are about 25 people in attendance.

Q. Are they drawn from all over the world?

A. They come from all the regions of the world, yes.

Q. And you say they look at issues like the safety of blood products and the various methods used:

"In 2001 this committee adopted an extensive report."

Perhaps people won't be surprised to learn that you have given us that as well to look at. We should, I think, so that we don't miss anything out, look at the section that you have provided for us, which is a section from a World Health Organisation technical report. First of all, look at the next page of your own report, where we see the reference for that publication:

"WHO Technical Report Series 924, Annex 4."

And that is [LIT0013143], if we could have that first, please.

We see that this is Annex 4. We can see from the copyright section at the top, the copyright declaration, that this is a WHO publication and this is their technical report. This is Annex 4:

"Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products."

If we could go to page 3160, please, we should see the paragraph to which you refer, 4.1.1, and there isn't, at least to me there doesn't seem to be anything in this paragraph which is new to us. This all seems to be what you have described in your report.

A. This was just added to show that such a broadly composed committee -- because there are representations from regulatory authorities and from manufacturers in that committee which develops these guidelines -- to show that this is not an issue which is in the margin but has been discussed, really, severely and intensively to know for sure that we can give this recommendations, these guideline, to the world, so to say.

Q. Right. You see in the middle of that paragraph that safety, with respect to hepatitis viruses and HIV, has

been demonstrated for decades with few exceptions. Then there is a reference, which is reference 11. You tell us in your report that reference 11 is the Pattison article from the American Journal of Epidemiology and that's the article we looked at a moment ago, which described the Hepatitis B outbreak you told us about.

A. Yes.

Q. And that was the problem which arose because the material was being heated in bulk rather than in individual containers.

A. Indeed.

Q. So if we could return to your report, please -- and we are now at page 8, so 0308 -- your conclusion is:

"The batch of SPPS administered to Mr Tamburrini was manufactured using methods which were at the time (and still are) widely recognised as being capable of eliminating any risk of virus transmission."

You have looked at the records and you say that:

"The records indicate that the manufacture, including the pasteurisation, was carried out according to recognised industry and pharmacopeia standards."

Then you say:

"The answer to the query is that the transmission of Hepatitis C by SPPS is most unlikely."

I think really in this paragraph you are reverting

to your two ways of approaching the task you have set out in your report: one, by looking at the science and two, by looking at the published literature because you are saying that the method has been found to work and that the literature doesn't report transmission of Hepatitis C by material treated in this way. But, Professor, why do you say the transmission is most unlikely? You are not saying it is impossible.

A. Well, "impossible" is a word which I use only very rarely because I have learned through my career that some events you can judge to be highly unlikely or even further, but you have to be cautious, so I cannot oversee the whole chain of events which was related to this incident because it is a chain of events; it doesn't stop with the manufacturing. It is also what happened during the administration, what happened in the hospital, which I cannot oversee, which I have no reports about, which I have no data about. So that's why I thought it would be more accurate to say "highly unlikely".

Q. Yes.

THE CHAIRMAN: Is there also something about the scientific method, Professor, that means that absolutes, positive or negative, have to be avoided generally?

A. Yes.

THE CHAIRMAN: Because a single positive proposition can undermine an universal negative and vice versa.

A. Absolutely.

THE CHAIRMAN: And therefore, when we read all these articles, I think we will find that throughout the expressions are less than absolute.

A. Yes.

THE CHAIRMAN: And that's the scientific method.

A. Yes.

THE CHAIRMAN: Yes, I can't resist the logic, as you know.

MS DUNLOP: Thank you.

Professor, you have prepared also a supplementary report, and I should ask you a bit about that. Your supplementary report is [PEN0110001], and we can see that this is actually a letter which you sent on 1 March and it is addressed to a member of the Inquiry team in response to questions posed to you.

First of all, you say that you have been referred to some reports from the medicines inspectorate in which a number of deficiencies regarding buildings and facilities were identified in 1981, and good manufacturing practice related issues in 1988 were found.

In the second paragraph, when interpreting these findings, you make a point that this really seems to

have been an ongoing process, the process of implementing good manufacturing practices at the beginning of the 1980s. Is that what you were telling us? And you say that the process takes considerable time, especially if one is working in buildings and with facilities that were constructed before the statement of manufacturing practice was written; in other words, it is easier to design your facility if you have a statement of manufacturing practice than it is to make it fit something that already exists.

A. Yes. What I attempted here was to give some context of the situation in the 1980s because it is easily forgotten that at that stage the whole issue about safety and quality was different from now and the introduction of good manufacturing practice was a major change in, not just the pharmaceutical industry, but also in this type of sector of plasma fractionation.

So it required, on the one hand, that facilities were adapted and that equipment was changed but also that personnel were trained in a completely different way, and that is the sort of cultural change which had to happen. You can't do that overnight, you need some time to do that. So I thought it could perhaps be useful for people who were reading this inspectorate's report to have this background information.

Q. Right. But applying that sort of background to the situation we are looking at, which is Mr Tamburrini's illness, you set out for us the first question posed -- and I'm reading now from the third paragraph, the passage that's in quotes:

"Whether there is any potential link between the documented unsatisfactory state of affairs at Liberton in the 1980s and the possible infection of Mr Tamburrini with Hepatitis C as a result of the transfusion in September 1984."

You assume correctly that the term "transfusion" is used for the administration of SPPS.

You go on to say that you can't completely discount the proposition that he was treated with unsafe SPPS but your view is that that would be unlikely, highly unlikely; and then you also address, in the following paragraph, the likelihood of mislabeling products and mixed heated and non-heated products.

If I could stop there and just say to you: since you wrote this, have you seen a further statement of clarification from Dr Cuthbertson?

A. Yes.

Q. And did that help you to develop your understanding of the process that was used in 1983?

A. In a number of aspects, certainly. As I have written in

my report, some of the conditions which you would expect, studying virus inactivation methods and manufacturing, that is normally done in separate environments, in separate rooms, and so the question would almost suggest that there is some relationship in that facility there, which could cause that; and from the report I got later on, it became much clearer to me what they had done to avoid that this could occur.

So I found that Dr Cuthbertson did a really very nice job to formulate it and just to go through line by line and indicate which measures had been taken to minimise or to either reduce or completely avoid that risk.

Q. Right. So I think what you alluded at the start of your answer to the separation between the manufacturing and the study of virus inactivation, and did Dr Cuthbertson's additional information help you to feel reassured that that separation had been maintained.

A. Yes, for me that was -- from the description I got, yes, indeed.

Q. You say:

"The likelihood of mislabelling of products and mixing heated and non-heated products ..."

Again, once you read Dr Cuthbertson's further explanation, did that improve your understanding on that

point?

A. Yes, well, what he had told in his report was in fact that they have, I think, included a number of situations where -- which I hadn't thought about, that they had done it in that way. I mean, when you look at the -- just looking at where in the report he was -- oh, yes, so what he said is:

"The filling area and -- "

Q. Sorry, Professor, can you tell us what page that is?

A. Sorry, that is page 7 of the report of Dr Cuthbertson.

Q. Yes. I think we should all have that so we can see what it is you are reading. Just give me the number of that. Statement of clarification. It is [PEN0110048].

Would it be possible to look at that alongside Professor van Aken's supplementary report? So if we could keep what we have currently got and have Dr Cuthbertson's statement beside it.

The page you were reading from was page ...?

A. 7.

Q. 7. Is that 54? Thank you.

A. So on the top of that page.

Q. Right.

A. It says:

"Prior to pasteurisation ..."

Et cetera, yes?

Q. Yes.
A. That sentence. So what he shows there is that the SPPS is not stored in manufacturing areas. That is to summarise briefly what is said quite extensively. So that means that mix-up from the point of the fact that it is stored in different areas is already clear, but again also the total number of bottles -- that is further down the line -- that is the total number -- even further down the page. The total number of bottles inspected and packaged is recorded.

So that should also give you an idea about whether or not a mix-up has occurred.

Q. Yes.
A. So those two. And then there is a further safeguard, which is even lower on that page, about seven or eight lines from the bottom; that is, the presence of abnormal characteristics which, on visual inspection or later on, chemically would be detected. So I feel that this evidence in fact would give me a good feeling that there is no question of mix-up between material which was pasteurised and material which was not pasteurised.
Q. Dr Cuthbertson gave us quite a vivid description of the different appearances of unpasteurised product and pasteurised product. That's correct, isn't it?
A. That's absolutely correct. In manufacturing facilities

all these bottles are inspected visually against a special light and you can see from the nature, from the colour, but also from the general appearance of the product that there is a difference between pasteurised and non-pasteurised material.

Q. Thank you. Now, to return to your document, to the final paragraph on the first page, with regard to another question, namely batches being contaminated by staff movement:

"My answer is that such trials are normally done in separate facilities."

So you were saying at this point that generally you expected that when the viricidal efficiency trials were carried out, they were carried out in a different room from the rooms in which the plasma was being manufactured or processed. That was your expectation when you wrote your report?

A. Yes.

Q. And has that been confirmed?

A. Well, I must say that I'm not quite sure where in the report of Dr Cuthbertson this is dealt with.

Q. Right. Look back at Dr Cuthbertson's paper and go to page 10. So can we go on from page 7 to page 10, please?

A. You mean the last paragraph?

Q. Yes.
A. Yes, indeed. So, I'm sorry, I see now that that I have read. Indeed. So he first started by saying Hepatitis C has never been used, so it could not contaminate any bottle and, secondly, the validation studies were carefully controlled to prevent cross-contamination and the heating was carried out in a separate, purpose-built microbiological containment.

So I think the last sentence for me is quite convincing, that the proposal that contamination could have occurred by these virus inactivation studies is very, very, very unlikely.

Q. Right, you make two points in your paragraph, as I understand it, Professor. Firstly, you are making a point about a physical separation between the carrying out of virus-killing testing and the actual processing of the material -- so that's the physical separation -- and then you also make a point that no one was doing virus-killing tests using Hepatitis C virus at that time anyway. Is that a reasonable summary of what you are saying?
A. I'm not quite sure if we have the same interpretation here. What I tried to say is that first of all there was no Hepatitis C used for the validation.
Q. Yes.

A. And the whole issue is gone in fact because how can you then use this as an argument, that this was the reason why the material was contaminated, yes, and then, secondly, the separation in the various rooms was an argument. But there, of course, I can only read what I see here. I haven't seen it myself.
Q. Indeed. I think I was only going to make what I think was quite a short point, that if you compare, Dr Cuthbertson's two bullets on his page --
A. On the last page?
Q. -- seem to be the same two points that you are making but just the other way round. I think his first point is about Hepatitis C virus not being used at all, which, as you said, renders the whole of the rest of the argument really irrelevant?
A. Yes, I found it very difficult to see how it would have occurred.
Q. Yes, and then he also makes the physical separation point.
A. Yes.
Q. Yes. Then the last point you deal with -- and we need to go on to the final page, the second page, of your supplementary report, which presumably is PEN.011.0002.
THE CHAIRMAN: I don't think that can be so. The sentence just stop in mid-air.

MS DUNLOP: Yes. We all have the second page, so an irregularity has occurred. But --

A. I have it here.

Q. You have your own hard copy, do you? Do you think you can find it?

There it is, yes. It was my mistake in calling it 0002, is it?

Then you also consider the possibility of contamination of batches due to the reuse of pH probes by using virus-spiked samples. It seems what you are really saying, I think, Professor, is that in 1983 that couldn't have been done because they didn't have the virus.

A. Yes.

Q. So they weren't using the virus on probes, so there couldn't have been contamination from probes which were carrying the virus.

A. Yes.

Q. And in fact, looking at Dr Cuthbertson's description, would it also be relevant to take into account that bottles which went for patient use were sealed and the seal was "crimped", we would call it. So there was an additional seal round the top of the bottle. So in fact the bottles which made their way to Mr Tamburrini wouldn't have had probes stuck in them anyway. Is that

correct?

A. That's correct, and it is, I think, forbidden even to add anything or to put anything in bottles which you are going to (inaudible) on.

Q. Yes. Just, as we say, for completeness, go back to Dr Cuthbertson's document, page 10, which we still have, and go up to the page, please:

"No manipulation such as pH measurements are made on the finished bottles, which remain sealed with tamper-evident overseals until required for patient treatment and if the tamper-evident overseal was not seen to be secure on any bottle during inspection, it would have been rejected."

So he is really making the same point here --

A. That's correct, what he says.

Q. Now, we understand, Professor, that you weren't there, so you have to go on the basis of the written descriptions of the process that you have seen, but with that reservation, is it reasonable to say that you have considered the possibilities for some sort of mix-up or contamination and you haven't identified one that you think was a real possibility -- sorry, that's not a very well expressed question, but from the evidence you have seen, if you assume that what you have read accurately describes the processes carried out and the way in which

the facility was operated, it is possible to exclude the suggestions of some sort of irregularity which have been made?

A. Well, as I said earlier, I have used the word "likely" with a certain background. But I must say that when I read what Dr Cuthbertson has provided here on information, this is not a logical or even a way I would have thought that it could happen put this way.

So I found it at some points irrelevant, yes, when it comes to the fact that the Hepatitis C virus was not used. Of course we had no Hepatitis C virus at that time, so from that point of view I can say I cannot follow the reasoning any more. So I stopped there and I thought, "This is impossible."

Q. Thank you very much, Professor. No further questions.

THE CHAIRMAN: Mr Di Rollo, do you have any questions?

MR DI ROLLO: Just one or two points I just wanted to ask.

Questions by MR DI ROLLO

MR DI ROLLO: Professor, I just want to be clear that you have seen the inspection reports from October 1981 and May/June 1988 concerning the Protein Fractionation Centre in Edinburgh.

A. Yes.

Q. And obviously there are certain criticisms that are made in those reports about the Protein Fractionation Centre,

which you are obviously fully aware of, having read those reports?

A. Yes.

Q. And as I understand your evidence today, what you are saying is that there is nothing in those reports, having regard to the other information that you have, that makes you think that there is any connection between anything that was going on at the Protein Fractionation Centre in Edinburgh and any possible contamination or infection through the SPPS sample that Mr Tamburrini was given. I know that was a long question but is it clear? Do you understand what I'm asking you?

A. If I'm correct, you are repeating the question which you put earlier in one of your letters, I think. Is that correct?

Q. The question -- and I want to make it clear it has not been put in the form of an argument; this is an Inquiry. The question was: is there any potential link, and that is the question that really -- I am understanding your evidence is that you are saying there is no, as far as one can be clear, potential link between the Protein Fractionation Centre and Mr Tamburrini's SPPS batch?

A. Well, I would like to answer that question as follows: first of all, I cannot disregard the inspector's report. That would not be good. I mean, there is an inspector's

report. These people have looked in the facility and I have not seen that, so they have an advantage over my opinion, in fact when it comes to the inspection of the Liberton Fractionation Centre. Yes? So what I have noticed clearly shows that there is still a way to go before GMP is really introduced and I think that the people in SNBTS would realise that.

However, if you look at this particular product, albumin, which is the most stable protein which we have, yes? Which is the only stable protein which can be heated, pasteurised, in the wet state, as we call it, yes, so in fluids, before (inaudible) becoming denatured and therefore not efficient.

So this product for (inaudible) purposes is far more robust than what other products in the same area do and therefore I think, even though some of the circumstances may not be completely ideal and certainly not to the standard of now, yes? -- I would still consider it highly unlikely that there is a link between that circumstances and the infection.

Q. And that's because of the nature of the product and the process to which it was subjected?

A. Not just that but also some of the conditions which Dr Cuthbertson has outlined in his paper.

MR DI ROLLO: Right. Thank you.

THE CHAIRMAN: Mr Anderson?
MR ANDERSON: I have no questions, sir.
THE CHAIRMAN: Thank you. Mr Sheldon?
MR SHELDON: No, thank you.
THE CHAIRMAN: Professor van Aken, thank you very much.
A. Thank you.
MS DUNLOP: Sir, there are no more witnesses coming to speak about Mr Tamburrini's situation, any more witnesses on our list, and the next person whose circumstances we propose to investigate or in relation to whom we propose to lead evidence is the Reverend David Black. I don't know, sir, if you are content just to move straight to that or if you want any short break.
THE CHAIRMAN: I think that it might help the participants to refocus, as it were, if we have a short break, and if anyone needs to speak to you or find out where we are going, it might help to make progress later.
MS DUNLOP: By all means.
THE CHAIRMAN: So I think a little bit of reassessment would do us no harm.
(12.12 pm)
(Short break)
(12.35 pm)
MS DUNLOP: We should explain at the outset that we don't have Mrs Black as a witness. Mrs Black, I gather, is

rather frail and I think it would have been too much of an ordeal for her to come and give evidence at the Inquiry. With that in mind, I would like to begin by looking at her statement, which is [PEN0010011].

This is the statement which a member of our team has taken from Mrs Black, sir, and I might mention at the outset that I gather that Mrs Black is a retired nurse, so she is more familiar than many of us with some of the terminology and indeed some of the aspects of hepatitis.

Some of the points to which I would draw attention, as we look at this statement, is that Mrs Black is in her 70s, that the Reverend Black was born on 1 May 1937 and died on 31 October 2003. The cause of death was hepatocellular cancer in a transplanted liver, Hepatitis C, transfusion of blood products and haemophilia. She says she doesn't know the genotype. Perhaps, just as a matter of interest -- and we will see this in the correspondence later -- we could note at the moment that it was actually genotype 3.

Mr and Mrs Black met in 1961 and married and had a family. She speaks a little bit about Mr Black's haemophilia and mentions some treatment in his youth for tooth extraction for accidental injury. She refers to treatment at Glasgow Royal Infirmary. She describes his consultant in relation to his haemophilia being Dr Lowe.

I think actually, if one goes further back into the history of the Royal Infirmary, we can see him being treated at Professor Douglas's clinic and also at various times by Dr Davies and Dr Prentice. But certainly Dr Lowe became the director of the Haemophilia Centre in Glasgow.

There is reference to the fact that the family, I think, travelled a lot, and you can see that on the second page. The Reverend Black was a baptist minister and worked, I think, both in America and indeed in developing countries, and there is a reference in the records to his having worked for Oxfam at one point.

He requested, in 1985, an HIV test, which Mrs Black says was, fortunately, negative. He became ill in 1987 in Florida. We will look at some correspondence relating to that. Paragraph 7. I did ask for some clarification of the word "sclerosis", where it occurs, because it doesn't read entirely fluently. It says:

"David was informed that the virus could have caused the diseased liver to become sclerosis."

As a result of communication with Mrs Black, her view is that that word should be "cirrhosed", so can I simply indicate that as a change which has Mrs Black's authority?

If we move to the next page, she refers to learning

that Mr Black had Hepatitis C, the fact that treatment, pharmaceutical treatment, was discussed, and then a gradual deterioration in his symptoms.

Paragraph 13, attendance at the liver transplant unit at Edinburgh Royal Infirmary, and then the undergoing of a transplant operation in April 1996.

Then Mrs Black says, on the following page, at the top of the page:

"The projections were that his new liver would last his lifetime before the Hepatitis C would have the chance to affect it."

But we can obviously work out that it was in fact a period of seven years between the transplant and his death.

Then Mrs Black herself has undergone testing for Hepatitis C, which has been negative, and then she describes Mr Black's final illness, that he had cancer in his transplanted liver and that he died in fact ultimately in Strathcarron hospice.

Mrs Black says in paragraph 19 that it has come as a shock to the family to learn, as a result of the investigations initiated by the Inquiry, that Mr Black's own liver in 1996 was affected by cancer, that Mr Black was not aware of that and the family weren't aware of that either.

I should say just at this point, sir, that we will come to that, and further enquiry has been made with Edinburgh Royal Infirmary as to how that might have happened, and both a letter and a report have been received from the transplant unit on this topic, which we will look at this afternoon.

In conclusion, Mrs Black to refers to just some of the difficulties of Mr Black having had Hepatitis C, to the problems with insurance, which I'm sure will be familiar to anybody who is listening or reading this and who themselves has Hepatitis C, and she also refers to an awareness of stigma and she refers to having had payments from the Skipton fund.

In conclusion, she expresses her appreciation of the medical care which her husband received.

THE CHAIRMAN: Now, gentlemen, I don't imagine that anyone could have any concern with the approach that has been adopted but since Ms Dunlop has been selective, if there are any other parts of the statement that you think ought to be referred to in the transcript, this would be an opportunity, I think, to draw attention to them. But if you are content, we can just proceed.

Content to proceed? Fine. Thank you very much, Ms Dunlop.

MS DUNLOP: My first, witness, sir, is Dr Brian Colvin, who

is here, I think. Yes.

DR BRIAN COLVIN (sworn)

Questions by MS DUNLOP

MS DUNLOP: Good afternoon, Dr Colvin.

A. Good afternoon.

Q. We are beginning by looking at people's CVs and we do, of course, have a curriculum vitae for you. Right at the moment, I'm sorry, I don't have the number for it. It is an omission on my part. It doesn't have a number on it.

Just while we look for it, doctor, I can't resist asking you, did you at one time begin the study of law?

A. I did, more as a way of educating myself in my last year at Cambridge rather than an initial desire to become a lawyer. I used to listen to the works of Edgar Lustgarten on the radio, when I was a child, and admired Lord Birkett, and then at the end of my time at Cambridge, having taken the part 2 law Tripos, I had a long discussion with Judge Ormerod, who I think was a gynaecologist as well as a lawyer, and he advised me to take a safer path by going into medicine rather than going to the bar.

Q. Some would be grateful that you considered it and then you did something useful. But anyway, I'm not sure if we have yet located your CV.

THE CHAIRMAN: Certainly if you thought that Birkett was the standards you were after, your prospects were perhaps less than good. But I suppose one should aim for the best.

A. I suppose later, when I was reading law, Lord Denning was regarded as the new god of the legal process.

THE CHAIRMAN: For different reasons.

A. For different reasons.

Q. And HLA Hart was very much admired in Oxford at an academic level.

THE CHAIRMAN: Have I used enough time for you?

MS DUNLOP: We can come back to this after lunch. I think that's probably best. We can just explore some of the more general aspects of what Dr Colvin has told us and we can come back after lunch and ask you some more detail about yourself, but in short, you were the director of the haemophilia centre at Barts and The London for over 30 years, and you say your principal interests have been:

> "... the development of haemophilia care, home treatment and the management of HIV and hepatitis infection in this community."

A. It is fair to say that for the first 20 years of my directorship, The London was alone but then the government decided on a regimental merger between Barts

and The London. So it was only from the early 1990s onwards that Barts came into the equation.

Q. You started at The London?

A. Yes, I came down from Cambridge to The London in 1966 and rightly or wrongly remained there for my 40-year sentence.

Q. There is a bit of a divide between haemophilia care south and north of the Thames. Is that the case?

A. That's extremely true. I don't think it is true any more but it was very true during my directorship, and I looked always to the Royal Free for sustenance and advice. Because at The London I was really the only haemophilia specialist and I think it is always very important to discuss cases and policy with colleagues, and I tried very hard to make sure that in north London the Royal Free and the Royal London worked together and in parallel.

Q. You have prepared a report on the Reverend Black and that report is [BLA0012281]. We can see it there. I wanted, before we look at the detail of your report, doctor, to ask you one or two general questions about haemophilia, particularly because, of the four individuals whose lives and illnesses we are looking at this week, the Reverend Black was the only person who was affected by haemophilia. Before we examine your

report, if we look at 001.2164.

THE CHAIRMAN: Prefix, Ms Dunlop?

MS DUNLOP: It is [BLA0012164]. This is, I think, a slightly elderly record of an assessment of somebody for haemophilia and allied disorders. I think the patient's age is noted on the top right, 18 and a half, so we are talking about maybe 1955.

If we scroll down, we can see the first haemorrhagic episode that the person who has been speaking to the Reverend Black, presumably a doctor, has noted was when Mr Black was five. Do you see that?

A. Yes.

Q. Indeed, it says:

"He was in hospital for scarlet fever and he was tested and found to be ..."

I think that's "a haemophiliac".

THE CHAIRMAN: Is it "a haemophiliac".

MS DUNLOP: Maybe it is meant to be "Haemophilia A". I think it could be.

A. I think the text, if you would like me to try and clarify that, is that he is actually writing "found to be a haemophilia". I don't think, certainly in the 1950s, there was any distinction really between Haemophilia A and Haemophilia B because Factor IX hadn't really been described -- or it was about to be

described. And it may be that he might have wanted to use the word "haemophiliac" but didn't find the time to write the "C" on the piece of paper. But I think this just means that they found him to have haemophilia.

Q. Then, the form provides for questions to be posed about dentition. So I take it this is the loss of the milk teeth, primary dentition. Is that what a doctor would be asking about? Is that correct?

A. In general, dental health is very important for children with haemophilia, and perhaps the most likely beginning of abnormal bleeding related to the teeth will be at the time of shedding the milk teeth, although quite often milk teeth are shed without any real difficulty, but child dental health is very critically important in haemophilia care.

Q. Yes. In this instance, we noticed that these were shed without undue bleeding, except one, which was taken out in the Western Infirmary in Glasgow. If we can go a little bit further down, we can see secondary dentition is referred to. If we can scroll down the page, please, the line that seems to lead from secondary dentition, I don't think we can see what is or was written there. But in any event, we can see that he was found to have haemophilia in the early 1940s. Can we look also at [BLA0011740]. This is a much later note of

information provided by Mr Black but if we could go down that page, please, we can see that in 1996 someone has taken quite a full history from him in hospital and he has told the doctor that he required transfusions from age 7 but has had no haemarthrosis. What is haemarthrosis?

A. That just means bleeding into a joint; "haem", blood, "arthrosis", within a joint.

Q. And that is something which people with haemophilia can suffer?

A. It is one of the cardinal findings of a person with haemophilia. I can explain a little bit about the difference between mild or moderate and severe haemophilia at some point if you wish.

Q. Please do. This is as good a time as any.

A. Children with severe haemophilia usually present, in the first 18 months of life, particularly at the time when they begin to get up and run around or crawl around and bump into things. So the little child with severe haemophilia gets bruises on the shins and may develop haemarthrosis, particularly in the knees and ankles, or when they are trying to put toy soldiers into their mouths, they may cut the mouth and get bleeding from the mouth.

So many children with severe haemophilia who don't

have a family history may find -- or their parents may find -- that they are accused of non-accidental injury, which of course is extremely upsetting for someone who later proves to have a significant blood disorder. But when you are dealing with children with mild or moderate haemophilia -- and this, I think, comes under the category of moderate haemophilia in the Reverend Black's case -- spontaneous bleeding or bleeding after minor injury is not quite so common, so that you may need quite a significant injury in order to cause bleeding. For example a dental extraction, a classical injury which would cause trouble, or if there is a more important injury, where, you know, there is a twisted ankle or a twisted knee that may lead to bleeding or at the time of a major contusion like falling off your bicycle or having an operation.

So the person with mild to moderate haemophilia may remain undiagnosed for quite a long time, and being diagnosed at the age of 5 or 6 or 7 years is pretty routine and I have seen patients being diagnosed with mild haemophilia in their 60s and 70s. So it just depends on the level of trauma to which you are subjected. But in the Reverend Black's case, to be diagnosed with haemophilia perhaps after dental extraction at the age of 7 is absolutely typical of the

condition.

Q. The terms you are using, "mild", "moderate" and "severe", they have correlations in terms of percentage of the relevant factor in the person's blood. Is that correct?

A. Yes, and the World Federation has set that in tablets of stone, so: for less than 1 per cent Factor VIII or Factor IX is severe haemophilia, from 1 per cent to 5 per cent is moderate haemophilia and 5 per cent and above is mild haemophilia. And in the Reverend Black's case we have values for resting Factor VIII may be between 3 and 7 per cent. So he is, if you like, on the cusp of mild to moderate haemophilia. So the moderate side of mild, I would say.

Q. Obviously, there is an upper limit to mild. I mean, at what point does mild haemophilia stop and normal clotting begin? We have heard it suggested as 30 per cent or 50 per cent?

A. The normal range for Factor VIII is a technical term and the value will be two standard deviations away, using a mathematical terminology, from 100 per cent because 100 per cent is defined as the normal amount of Factor VIII in the blood, which translates into more modern definitions as one unit per millilitre or 100 units per decilitre. So normality is defined as what

the average person's level of Factor VIII will be, which is 100 per cent or 100 units per decilitre. The normal range of Factor VIII is, generally speaking, between about 50 and 150 or 200 per cent, and the way to work this out is to take a population of normal people and measure their Factor VIII level and then work out mathematically what the normal range is.

So that's the sort of scientific definition. Now, the truth of the matter is that in the area around 50 per cent or below, it is quite possible to have a less efficient haemostatic mechanism, a less efficient blood clotting mechanism. So if you look at women who are carriers of haemophilia, they will generally have a level of Factor VIII around 50 per cent, and in this area below 50 per cent you occasionally find a degree of abnormal bleeding, particularly after injury. It is very difficult in this area to define exactly what is happening and I will try and explain that in more detail if that's what you would like me to do.

Q. No. No offence, doctor, but just for a guideline, would it be reasonable to say that mild is between 5 and roughly 50 per cent?

A. Mild is between 5 and 50 per cent because some people with a demonstrable genetic defect -- we now have the genetic capacity to work out the precise genetic

defect -- have a level of around 50 per cent. And just one brief explanation I think I should give is that you only really have to climb the stairs or go for a run, or for something to happen in your life, for the level of Factor VIII to rise physiologically.

So if you are going to really make a precise diagnosis of an abnormal Factor VIII level, you need really to be in the resting state and if you get taken by your mother to the doctor and somebody presents you with a needle, the chances are that you may become less than calm. And once that has happened, then the level of Factor VIII may rise. So the diagnosis at the edges of normality can be quite difficult.

Q. Yes.

A. But in this case, with the Reverend Black, 3 to 7 per cent is easy to diagnose once you know what you are looking for.

Q. You have partly answered my next question, which was that: looking through the records, the levels do seem to fluctuate so that you yourself have given a range of between 3 and 7 per cent. Actually, I think there is one measurement which is in double figures.

A. Yes.

Q. So that happens, does it?

A. Absolutely acceptable. There are a whole range of

reasons why the levels might be different. One might have a patient who is not so well or a patient who has had a tooth out and the levels have risen as a result. One might also have some discrepancy of the standard used to measure the Factor VIII. Certainly in the time of the 1940s and the 1950s, there were no standards for measuring the Factor VIII by. So if you were using a normal standard to measure the Factor VIII in the 40s and 50s, it is quite possible that the normal standard might not really be normal, and then you would be measuring your test against something which wasn't truly normal. So there is a whole range of possibilities for this fluctuation.

Q. I understand. The other potential complication to which Mr Black has referred when he has been talking to this doctor, is spontaneous bleeding. Take from that that people with, I think, severe haemophilia, may experience bleeding without a trigger. So they don't need to fall or have a dental extraction or something, the bleeding just happens.

A. That's true, although the majority of bleeding in severe haemophilia takes place into the joints and muscles, which are the moving parts. However, it is the case that people with haemophilia, particularly severe haemophilia, may have spontaneous -- intracranial

haemorrhage is the best example -- where there is clearly no discernable trigger. Maybe somebody might have bumped their head, but there is no doubt that some people with haemophilia, particularly severe haemophilia, have truly spontaneous bleeding. Of course, it is still possible that there might have been some minor defect in the circulation within the brain that pre-disposes to this spontaneous bleeding. So the word "spontaneous" is certainly valid in everyday speech; whether it is completely valid at a scientific level is less clear.

Q. Can we just look at the second page of this entry, which is 1741. We just see that that is the conclusion really of the doctors' interview. Can we just scroll right down, please, and this is an entry which has been made by a registrar, in fact, taking these details from the Reverend Black, who has obviously been quite a good historian of his own --

A. Yes.

Q. I think, sir, before we go on to look at some other details of the Reverend Black's earlier life, it might be as well just to stop because it is five past one?

THE CHAIRMAN: Do you recognise the initials there? Dr Bathgate?

A. No, I don't know Dr Bathgate.

MS DUNLOP: Thank you, sir, it is Dr Bathgate.

THE CHAIRMAN: We will break.

(1.04 pm)

(The short adjournment)

(2.10 pm)

MS DUNLOP: Dr Colvin, we have found your CV and we should put it before the Inquiry. It is PEN.001.2017.

I think we will maybe not scroll down to the bottom because it has more information than I think we would want for Dr Colvin's sake to be disclosing.

It tells us about your work as a haematologist, and you have been the founder director and company secretary of the European Association for Haemophilia. First author of the European principles of haemophilia care.

And you have also worked for Wyeth and Pfizer. Is that correct?

A. Wyeth were taken over by Pfizer in October 2009.

Q. Then if we look at page 2, you have documented for us your education, university education and medical education. Then page 3 is your positions held. We have mentioned this morning the Royal London Hospital and then, as you said, you joined St Bartholomew's. And then you have also had academic responsibilities. You have been a lecturer and, indeed, then a senior lecturer. Moving on to the following page, we see --

that's presumably a university in Rome, is it?

A. Yes, it is.

Q. You had an appointment as a visiting professor in Rome in 2005. Your teaching activities, and then your examining your committee activities, societies, then some commercial connections from 2002. This is on page 6. Then finally a very long list of publications where you have had to go into a much smaller font to get them all in. So 59 articles. Is that right? 59 papers and 14 books and chapters. All of them about haematology essentially?

A. Mostly, yes.

Q. If we could go back, please, to where we were just before lunch, looking at some of the information that is apparent from Mr Black's medical records about the history of his haemophilia.

I want also to look at 2121. This is [BLA0012121] and we're going to rotate that right, please. This is a document which comes from a set of records marked as "Glasgow Royal Infirmary records" but I think it would be fair to say we are not actually terribly sure at the moment that that is actually true. Anyway, it is interesting, I think, to those of us who are learning about haemophilia, because it is the family tree and we can see Mr Black there in the middle, David Black, and

what's particularly interesting to us, because it features or it recurs throughout his medical records, are the two uncles. There is one uncle on the left and then one uncle on the right and the uncle on the left, who is described as having gastrointestinal bleeding and his joints are affected, and the uncle on the right is described as having died at 15 or 16, a question mark saying that was because of haemophilia. May we take it then, Dr Colvin, that people may have been more seriously affected than Mr Black himself?

A. Generally speaking, haemophilia breeds true within a family, which means that those who are affected within the family are affected to a similar degree. However, characters do differ and so people who sit in front of a computer screen all day in the modern world are less likely to bleed than those who go out on their bikes, and of course, it is also the case that if you have a particular event, like, say, falling off your bike, then that may lead to more trouble than for your sibling or cousin who is sitting at home. So I think it is difficult really to say that these people were affected to a different degree. Probably the level of Factor VIII was rather similar. But they may have had different characters or different life experiences.

Q. Yes. If this is an account that came from Mr Black

himself, we can see that he seems to have said -- or someone has said at the bottom -- that he is very mild compared to his uncle. So that may have been his own view of the position. If we look at [BLA0012167], we can actually see -- and this is again rather an elderly sheet, I think from Glasgow Royal Infirmary -- at this point he is 17, so again in the 1950s, and appears to be working in a CA's office at this point. If we go down to the little family tree on that page, it looks from that as though he said that the uncle has died after a tonsillectomy. But perhaps that's something that decades ago, may have been the unfortunate consequence of what would be a relatively minor operation.

A. That really illustrates the point that I was making, and it is very important to appreciate that mild haemophilia doesn't mean mild bleeding. Once someone who has mild haemophilia or moderate haemophilia begins to bleed after an event such as a tonsillectomy, they will go on bleeding until something is done. And a tonsillectomy is a very good example of something which could be life threatening because a large amount of material is removed from the throat during a tonsillectomy and it is in a very difficult area where the airway is critical and where death from bleeding could very easily take place.

THE CHAIRMAN: Would treatment have been readily available at this time if the uncle had died?
A. We are talking about 1950 odd. No, it wouldn't. No serious treatment available for haemophilia until 1965.
THE CHAIRMAN: I think it may, in fact, if you think of the generations, have been rather before 1950.
A. Quite. No serious treatment available for haemophilia before 1965.
PROFESSOR JAMES: And before the war, no blood transfusion available.
A. No, indeed. And there must have been some early experience of treatment of haemophilia with blood transfusion, although I'm probably a little bit too young to have experienced it. But if you look at the experience of the Tsarevich in the 19th century and early 20th century, rather, with the influence of Rasputin, it is clear that the physicians were desperate to know what to do with the unfortunate child and that the influence of Rasputin was that the Tsarina believed in his capacity to stop the bleeding.
MS DUNLOP: I have taken you to some entries in the records, really because they give a bit of background about haemophilia more generally, particularly in times earlier in the 20th century, but I need to take you back to your report so that we can look in more detail at

what happened to Mr Black.

So if we could have your report up again, please, [BLA0012281]. On page 3 of your pagination -- if we could just go to the next page, the page headed "introduction". You have a summary but do not look at the summary just now but look at the substance of the report, and go to the next page where you start with the facts.

You say that Mr Black was born on 1 May. He seems to have been first treated in the 1960s. I take it you would accept that that reference we looked at earlier about requiring transfusions from age 7, in fact -- I should say, I'm not sure that these records were sent to you. We have rather a large collection of medical records in relation to Mr Black. If he was being transfused from age 7, then we are talking about the 1940s, actually.

A. It depends what you mean by treatment for haemophilia, I guess. He would have been treated for his condition but not with factor concentrates which we, perhaps in modern times, regard as the treatment for haemophilia itself. So there may have been some ambiguity around my statement.

Q. I see. Then if you could look, please, at [BLA0012204], this is just to understand some of what you say in your

report by looking at the actual pages from medical records. It is not very easy to see but we can make out that this is an admission in 1965. He seems to have been in hospital between 20 October and 29 October and the reason was a dental extraction. If we look also at [BLA0012200], looking at that in slightly greater detail, it says:

"Haemophiliac for tooth extraction."

I think there is a reference to his having received -- I'm not sure if it is actually on this page, maybe on [BLA0012157] -- four flasks of AHG. Can we look at [BLA0012157], please? There is a reference to four flasks of AHG and this is the letter which says that during his admission in October 1965 he has had dental extraction under AHG. What was AHG?

A. That is a very interesting question from 1965. I think what must have happened was that in Scotland, as in England at the time, early concentrates of Factor VIII were being prepared before cryoprecipitate had been discovered. These were in tiny quantities and I think they would have been derived either from single donor units or possibly from very small pools, and what we are looking at, I think, is an extremely early example of the use of a Factor VIII concentrate. And the importance of this is that the treatment begins in terms

of haemophilia care proper in 1965. I think there are others -- experts, possibly even in this room -- who might be able to enlighten you more about exactly what AHG was in Glasgow in 1965 but that's my interpretation.

Q. Thank you. Then after [BLA0012157], can we look at [BLA0012154]. This is another 1960s letter but this time referring to a dental extraction in 1969. And not just my own perusal of the records, which would be unreliable, but I think others who have been through the records haven't actually been able to find details of administration of any product in connection with this dental extraction but one can surmise perhaps that that dental extraction will also have been covered by some form the treatment.

A. I think most likely cryoprecipitate, because the amount of antihaemophilic globulin, AHG, that was available in 1965, would have been very, very small indeed. There were small amounts being prepared in Oxford, also bovine and porcine Factor VIII in Oxford, derived from cows and pigs, and it may be there was some means of preparing these products in Scotland or it may be that they were being obtained from Professor Macfarlane's unit in Oxford. But I think that by 1969 we have entered the period of general treatment with cryoprecipitate, which was a single donor unit frozen product of plasma, and

I would be surprised if this extraction in 1969 was not covered with cryoprecipitate rather than a very early antihaemophilic globulin concentrate.

Q. Sorry, doctor -- and I'm sorry, sir -- but just as lawyers say, for completeness, the reference to four flasks of AHG is on [BLA0012204]. I think I just couldn't see it. But if we could go back to [BLA0012204] so we are sure what it is we are noting.

A. From my understanding of the period when I was at university, it was the case that a flask would not have contained cryoprecipitate. Two reasons: the cryoprecipitate wasn't described by then and it wasn't prepared in flasks in my experience.

Q. Right, okay. Thank you for taking me back to that. I think I just failed to spot it earlier. It is actually quite obvious now. It is under "Progress and treatment". It says:

"Patient was given four flask of AHG preceded by phenergan and cortisone."

Phenergan to make him a bit drowsy?

A. Possibly it would have made him a bit drowsy but the real purpose is to avoid the allergic reactions that would be liable to occur when you give a crude plasma product, as this was, to a patient. That's the design of the phenergan and cortisone: to reduce or eliminate

an allergic reaction.

Q. Thank you. Just to go back again to around about this time, [BLA0012149], and you will be interested, sir, to see that Mr Black had been treated by Dr Judith Pool in Stanford. Dr Pool is a well-known name in this area, Dr Colvin. Why is she so famous?

A. Because it was she really who described the preparation of cryoprecipitate. I think others had in fact been aware of the fact that a cryoprecipitating process led to a concentration of Factor VIII but Judith Pool in California is certainly regarded as the sort of founding mother, if you like, of haemophilia care by her description of the preparation of cryoprecipitate as a therapeutic product in 65 and 66.

Q. The trail then goes a little bit cold until [BLA0012146], we are looking at Mr Black's treatment at around this time. We see from this letter -- can we scroll a little bit further down, please. This is 1973. The reference CDF I think may, in fact, be Dr Forbes, Charles Forbes -- in any event, that somebody has been looking through the files of the haemophilia centre and noticing that he hasn't been reviewed for four years, perhaps because, as the writer says, it is an example of no news being good news, "I presume this is because you had no major bleeding problems."

Anyway, he is to come back and have a review. And then on [BLA0012142] there is another dental extraction:

"I understand he is likely to require a dental extraction in the near future. I would be pleased to admit him for replacement therapy at the time."

That was Dr Davidson, a haemophilia clinician.

A. I know John very well.

Q. Then [BLA0012137]. A reference to a problem, a knee problem, in 1975. I think, understandably, from the description you gave us earlier of the sorts of problems people with haemophilia have, someone has been wondering whether this was a haemarthrosis, but the letter tells us that he had replacement therapy as an outpatient in June 1975 as well.

A. So it can be difficult to distinguish between a haemarthrosis and a haematoma in the area of the knee but it doesn't make much difference to what treatment one might offer, and I refer to this particular event in my facts 3.2 when I say that he had Factor VIII replacement. And the way that has been written, bearing in mind it is 1975, suggests to me that this was a large pool freeze dried concentrate rather than cryoprecipitate, although it might have been cryoprecipitate.

Q. Then we can link back to your report, if we look at

[BLA0012231], where you say:

"There is a record dated 25 May 1978."

If we could look at the top of that, that's much clearer. Thank you. I think this is the sheet you must have been looking at when you wrote 3.2 because we can see "25/5/78" at the top. I think that's "pre-extraction", so we are back to dental problems. Then:

"Blood products type, Edinburgh, units 800."

And that's the reference you make in your report. You say:

"It is very likely that this was a large pool Factor VIII concentrate prepared in Edinburgh. Even if he had not already been infected with hepatitis C by then, the infection would almost certainly have been transmitted on this date."

In summary, Dr Colvin -- and obviously we are going to hear a lot more about this in the course of the Inquiry -- around about this time, the late 1970s, for people receiving concentrates for the first time, the rates of infection with non-A non-B hepatitis were very high, whether the product was commercial or NHS; is that correct?

A. That's absolutely correct and a very important point.

Q. Yes. I would like you to look next, please, at

[BLA0012232] and I think this is perhaps what you were looking at when you wrote 3.3. You say:

"The first abnormal liver function test I have been able to find is dated 14 December 1979 and the transaminase GOT."

What does that stand for, please?

A. I am afraid that I have temporarily forgotten the exact nomenclature of GOT. It is glutamine something or other, but it is a long while since I was at medical school, but basically it is a transaminase result, and the normal amount of transaminase, the SGOT, will be up to 40. So that 97 is twice what it ought to be, or a little over twice what it ought to be. The SGPT is another transaminase in the liver and that also is abnormal. Again, it should be up to about 40. So these are measures of the inflammation of the liver because of the enzymes detected that have been derived from the liver and are present in a greater amount than they should be.

Q. Just to take you further into the story or further along the story, can we look at [BLA0010869], please? I have mentioned this already. But what's interesting about [BLA0010869] is that the writer of this letter is referring to mild haemophilia. This is line 2 of the letter:

"Mild haemophilia, base line levels around 15 per cent."

So that really illustrates the point you made earlier about fluctuating levels, doesn't it?

A. It certainly does, or indeed fluctuating assays or assay methods. There is no doubt there are many different ways of measuring Factor VIII, or at least three, and some of them produce rather different results, and particularly they can produce different results in the mild/moderate category. So at a technical level, whether one is dealing with a one-stage assay or a two-stage assay, or whether one is dealing with a particular assay system or another or a particular standard or another, can make big differences in the levels. So this is not a surprise.

I think that the clinical picture of bleeding after injury, with some bleeding that seems to take place after not very much injury -- for instance the knee haematoma, which we don't have a record of a particular piece of damage to the knee -- suggests to me that the range of 3 to 7 per cent that I put in my report and which appears elsewhere in the text or the notes, is not far away from the truth.

Q. So the 15 per cent may be an aberration of some sort?

A. I think it is probably a bit higher than one might have

expected. Interestingly enough, this sentence says:

"I reviewed your patient. As you know, he is 44 years old with mild haemophilia, who recently has had a bleed into his tibial muscles of the right leg."

So it is just possible that this level, which they call a base line level, might not be truly base line. It might be following some kind of event.

Q. I see. So the level would be artificially high because of blood loss, would it?

A. Because of the pain and suffering of the process and of the blood loss, and even conceivably it is not all that uncommon for somebody to take a sample, thinking it is a base line sample, when actually the patient has been treated within the past 48 hours. So it is quite hard, looking back to 1981, to know quite what that means.

Q. [BLA0010867] takes us to 1984. We are back at 3 per cent here. Interestingly, there is a description of the liver function tests as being normal. So I suppose, for all the reasons you have given in relation to the measurement of Factor VIII, the liver function tests may vary from attendance to attendance as well?

A. It is very typical of non-A non-B hepatitis as it was then, and Hepatitis C as it is now, for the transaminase results to fluctuate. So it is not just a question of

the sort of variation that I was talking about in relation to the level of Factor VIII. When one is dealing with liver function tests, and particularly the transaminases, I think what seems to happen is that the amount of inflammation in the liver actually does vary from time to time. And it is typical of Hepatitis C that one day you will have normal liver function tests and the next they will be abnormal. So this is absolutely typical and it may well be that when Dr Greer saw this patient on this particular day, he or she may have taken a blood sample, had an SGOT SGPT level, and noted that the result was normal. But you need to look at a sequence of transaminases to tell whether your patient truly has an increase in transaminases in terms of liver function.

It is also important to appreciate that the transaminase levels themselves don't tell you how well the liver is functioning, they only tell you that there is evidence of inflammation within the liver. So they tell you nothing about liver function itself, even though they are called liver function tests.

Q. Can we look at [BLA0010863], please, as well.

This is 1985. There is a little bit about Mr Black's travels. He was going to Kenya and Uganda. I don't imagine it was particularly easy to do this much

travel when he had this medical problem. I see that there are a number of occasions in the records on which he has asked for letters to take with him, presumably to explain to doctors in other parts of the world what the problem is.

Then this is showing us a level back at 3 per cent and then, if we look at the bottom, bilirubin and alkaline phosphatise were slightly elevated and transaminases were markedly elevated this time."

A. The AST is the aspartate transaminase, the ALT is the alanine transaminase. These are other ways of saying the same thing.

Q. Yes.

A. Both quite clearly abnormal.

Q. Yes.

A. The gamma GT, the gamma glutamyl transferase is an another transaminase which is thought particularly to reflect the liver function in a way which -- the others are a bit less specific. So the gamma GT is particularly associated with liver dysfunction.

Q. What should it be?

A. Well, the AST, 40; the ALT, 40 and the gamma GT, different laboratories have different upper limits but probably not more than 50.

Q. So 250 is quite a significant elevation?

A. Yes, but it is difficult to make much of the level of increase. So when there is quite a lot of inflammation in the liver, you may have values of thousands for the transaminase. So the exact figure is not that helpful.

Q. Can we look at [BLA0010861] and BLA0010862. Another letter. This is taking us to 1987 and this comes from the United States. I think it actually comes from Florida. Can we go to the top, is it the Lawnwood Medical Centre which, certainly in the records, everybody seems to know is in Florida but I couldn't myself see something on it showing it was in Florida. I don't think that really matters. Because we can see that he has required some medical treatment in the United States and that there has been a problem, he has basically had some gastrointestinal bleeding, and to take it shortly, this was the beginning of an episode which led to the diagnosis of varices. Perhaps we can look at the next page.

Can you see that? So he had grade 1 oesophageal varices. And we had some discussion of this yesterday, doctor, and our working understanding of what this means is it is almost like internal varicose veins and that these are the result of Hepatitis C.

A. The result of a build-up of pressure in the portal venous system due to liver damage, which could be of any

cause. It isn't specifically related to Hepatitis C itself, it is related to the pressure within the portal venous system due to liver damage.

THE CHAIRMAN: I think Ms Dunlop, yesterday the suggestion was that with the restriction of flow through the liver due to cirrhosis, there was a back-up into the other systems.

MS DUNLOP: Yes, I'm taking it a bit short. In retrospect one could say that is very probably a consequence of having the hepatitis, but I take your point, doctor, that it is not specific for that.

A. Yes, but this is 1987 so this is nearly 20 years, possibly 20 years from the date of first infection with Hepatitis C, we assume.

Q. Yes, and that doesn't surprise you, does it, that that length of time afterwards he is having problems like this?

A. If you look at the work from Sheffield and other places, it looks as though by the time 20 years have passed, about 20 per cent of those infected with Hepatitis C will have got into some kind of clinical trouble. So as I say in my report, this is a little bit earlier than average but not surprisingly so.

Q. I think this is really what you are saying in 3.4, just to link back to your report:

"By 1987 the liver and spleen were palpable. There was evidence of chronic liver disease."

You go on to tell us:

"Portal hypertension and oesophageal varices were treated in a conventional way."

I think if we look at [BLA0010859] and BLA0010860, this appears to be Mr Black back home and being treated for his oesophageal varices. I wonder, doctor, if we could go back up the page, please, if we could scroll back up, what is a Mallory Weiss Tear?

A. When people are unfortunate enough to vomit to a great degree -- I'm not sure whether this was associated with vomiting itself but normally when associated with vomiting, it is possible to tear the oesophagus as part of the process of throwing up. Who Mallory and Weiss were, I am afraid I don't know.

I do have a book at home of eponymous nomenclature of medical conditions. I am afraid they are not nowadays very popular although it is quite romantic to talk about these names. But the Mallory Weiss Tear is specifically related to tearing the oesophagus usually as a result of vomiting.

Q. Thank you for explaining that. It certainly wasn't a term that I had ever seen. So that's why I thought I would ask you. Then we can go down, please. We see

the description of what has happened, that he had had an dental extraction, treated with cryoprecipitate, gone to the United States. Perhaps we should also note in passing that tranexamic acid is another basically coagulant medication. Is that correct?

A. I can explain it in a few words, if I may.

Q. A few words, please?

A. Tranexamic acid is a chemical which acts as an opponent of the natural means by which blood clots are dissolved. So-called fibrinolysis. So tranexamic acid is an anti-fibrinolytic agent, and the idea is that particularly after gastrointestinal bleeding, if you have managed to get a blood clot forming by the action of adequate amounts of Factor VIII, then to give an anti-fibrinolytic agent like tranexamic acid will prevent the dissolution of the clot, and the same applies after dental extraction. And it is particularly important because the mouth and the gastrointestinal tract are particularly rich sources of fibrinolytic activity. So to neutralise that activity gives you a better chance of an effective use of your clotting agent.

Q. Thank you. Can we look at the second page of that, please, 857 and we see that looks like a very low base line Factor VIII level. Base line Factor VIII level of

1 1 per cent.
2 A. It is possible this was a two-stage clotting assay and
3 you find at the lower end, in my experience, that the
4 two-stage clotting assay often produces levels of
5 1 per cent or less when you would have a measurable
6 level with a one-stage clotting assay, just to give you
7 an example.
8 Q. I see. But it looks as though in view of that, someone
9 has decided he should have some cryoprecipitate. Is
10 that likely to have been the train of thought?
11 A. It is just a question of -- he was having an endoscopy,
12 wasn't he.
13 Q. Yes.
14 A. So he would have had an endoscopy covered by
15 a therapeutic dose of Factor VIII in the shape of
16 cryoprecipitate in order to prevent the bleeding at the
17 end of the endoscopy if that was what was happening on
18 the previous page.
19 Q. Yes, it is. Can we just go back and look at
20 [BLA0010859] again. Yes, it says:
21 "Upper GI endoscopy done."
22 And that that had shown grade 1 varices.
23 A. You would want to get the level of Factor VIII up at
24 least to 50 per cent before an upper gastrointestinal
25 endoscopy, and getting it to 100 per cent is fine.

Q. Can we just look at [BLA0010303] in the records? We can see that in 1991 there is a reference to Mr Black's having varices, and perhaps we can just -- without going to the records -- see that he is treated for these varices, or for the symptoms of his viruses, in 1988, 1989 and 1990, and then in 1991, someone is saying that his hepatic derangement is presumably secondary to Hepatitis C. And indeed so it proved. If we could go to [BLA0010533] and look at that. This is a specimen taken on 24 September 1991, the result, 14 October 1991, he is positive for the antibody to Hepatitis C virus.

So the diagnosis of Hepatitis C coming in the autumn of 1991. You tell us in 3.5 -- just to go back to your report, if we could, please, at BLA.001.2284. Down a little bit to 3.5 -- that from reading the records it is evident that there was a lot of discussion about the possibility of interferon therapy but that in 1996, because of the deterioration in Mr Black's liver function, he actually underwent a transplant. And then in the ensuing years, again there is a lot of discussion about the possibility of interferon treatment which finally commenced in 2002, but his condition continued to deteriorate and in fact he ultimately died of hepatocellular carcinoma.

Dr Colvin, if we could go to the next page, you have

given us your opinion and this opinion is really based on your experience as a haemophilia clinician, although in that role you have obviously had a lot of contact with people who have Hepatitis C as well. So you are in a position to comment, and have commented on some of the abnormal liver tests, and indeed on the treatment he received for Hepatitis C. But in your opinion, you tell us firstly, at 4.1:

"On the balance of probabilities, he was first treated with the large pool concentrate by 25 May 1978."

In fact, depending on what some of the other products were, it may have been quite a bit before that. We don't really know about the AHG, for example. But you say:

"It is now known that virtually all those treated with large pool Factor VIII concentrates before 1985 or 1986 became infected with Hepatitis C."

You refer to being surprised that he was still being given cryoprecipitate in 1987 or 1988 but that that is clinically irrelevant because on any view, I think the likelihood is that he had been infected by that point and he did not acquire HIV:

"The course of HCV infection was relatively rapid but it took nearly 20 years to progress to transplantation."

You do not think -- and this is perhaps going more into the territory of a hepatologist -- that there was anything lost by delaying referral to a hepatologist until 1994? There is good evidence of chronic liver disease by that date and it seems Mr Black is not keen on the treatment.

A. I was one of the authors of a paper from the Royal Free which addressed the treatment of people with haemophilia with interferon alone in the early 1990s. So I think I am in a position, despite the fact that I'm not a hepatologist, to give a view that treatment with interferon alone was largely ineffective in the early 1990s.

Q. You then tell us in 4 that:

"Transplantation would have cured Mr Black's haemophilia but reinfection of the liver by Hepatitis C was inevitable. It is not surprising to me that modern antiviral treatment was ineffective."

Then he developed hepatocellular carcinoma as a direct result of HCV. Then finally you say you have been unable to find that his treatment was unreasonable or inappropriate at any stage of his illness or care. You make a small comment about the use of cryoprecipitate as late as 1987 but you think that had no effect on the outcome of the case, and that, I take

it, is still your view, Dr Colvin?

A. Yes, indeed.

Q. And then on the last page you have set out your conclusion, which I think is really in similar terms, that the treatment of his haemophilia was appropriate and that infection with Hepatitis C was not avoidable and specific antiviral therapy for Hepatitis C was generally ineffective, certainly at the point in the early 1990s when he might have been considered for that:

"It isn't surprising that he needed transplantation about 20 years after infection or indeed that the liver became infected and fibrotic or that carcinoma developed."

Then your final view at 5.5:

"Found no evidence of unreasonable or inappropriate treatment in the case."

That remains your conclusion?

A. It does.

Q. Yes, thank you very much, Dr Colvin.

THE CHAIRMAN: Professor, if, in fact, there had been treatment with a Scottish AHG derived from Johnson technology before the date that you have identified, that would merely extend the period, would it?

A. It depends a bit whether this was a large pool concentrate or whether it was an antihaemophilic

globulin prepared from individual bags -- or bottles, as it would have been then -- of plasma. Because if they were individual bottles of plasma that had been used to produce antihaemophilic globulin -- which is clearly not cryoprecipitate because it hadn't been discovered by that time -- then the risk of Hepatitis C from individual bottles of individually prepared antihaemophilic globulin would have had the same risk of Hepatitis C as cryoprecipitate.

In your report you calculate, I think, that the donor population in Scotland had a prevalence of Hepatitis C of about 0.1 per cent. When I was working in this field some years ago in England, the figure we were using, I think, was around 0.3 per cent but I think it is quite uncertain what the true figure is and indeed it will vary between one place and another. So that one can therefore say that -- and I am afraid I'm not a mathematician or indeed a person who understands betting odds -- the more bags or bottles of an individual donor unit product you are exposed to on a random basis, the greater the chance is that eventually you are going to get one that has got Hepatitis C in it.

In the Reverend Black's case, by the time he was being treated with a large pool concentrate, assuming

that this bottle from 1965 was single donor rather than large pool, by the time we get to 1975 and he begins to be treated with a large pool product, he has probably had enough single donor unit products to make him somebody who has had a high risk of having already contracted Hepatitis C from single donor unit products.

It is just that once you get to the large pool products -- we are talking about tens of thousands of donations -- we know from the work of Peter Kernoff in the Royal Free and the Oxford group, that once you were treated for the first time with an unheated or non-virally inactivated concentrate, then Hepatitis C inevitably followed, whether there were symptoms or not and whether the product was American or British.

THE CHAIRMAN: That's quite a lot of information in that answer but there is one point I would just like to make sure that I understand.

I can understand that the prevalence in the population is 0.1 -- and of course we have done a lot more work since then and other figures do keep emerging -- then a single treatment from a single donor will reflect that prevalence, but is it the position that a person on regular therapy has an accumulated exposure every time he goes back, as it were, and so the 0.01 would not be a measure that would apply after

a course of treatment?

A. With respect, I think it is 0.01 -- I think it is a tenth of 1 per cent, isn't it? That's the figure I think we are looking at.

THE CHAIRMAN: Yes.

A. But every time you are treated, the risks are the same. And eventually -- I mean, it is Russian roulette, really. If you go on firing the gun long enough, eventually you will hit one with a bullet in the chamber.

THE CHAIRMAN: Yes. Thank you for the colourful illustration.

Mr Di Rollo, do you have questions for Dr Colvin?

Questions by MR DI ROLLO

MR DI ROLLO: Just one point that I wanted to ask you about. The use of cryoprecipitate, I realise it is irrelevant in terms of the actual cause of death, but I just wanted to ask a question, if I may. You say at paragraph 4.2 of your report, it is perhaps surprising that Mr Black was being given cryoprecipitate treatment in 1987/88, and then you echo that comment in your conclusion about treatment. Can I just ask you to explain why it is unusual and what is the significance of pooled cryoprecipitate at that time?

A. This is partly related to the HIV risk. But I will

explain it because I think it is an important point to clarify.

The position is this, that in the early 1980s, before HIV was identified, the advice was -- or at least it was accepted -- that it was a good idea to use cryoprecipitate, particularly perhaps for children who needed very little material, in order to reduce the risk of infection. And that applied probably to Hepatitis C and to HIV. Then in 1985/86 viral activation became well understood and it eventually turned out that proper viral inactivation -- not the early viral inactivation but proper viral inactivation -- would protect people against both Hepatitis C and HIV infection. And therefore, in the period towards the end of the 1980s, the advice from UKHCDO, the national organisation, was that probably it was better not to use cryoprecipitate because cryoprecipitate was not a virally inactivated product. So that by 87/88 the use of cryoprecipitate in this context had really ceased. Now, as it happened, the Reverend Black did not have HIV infection and was not exposed to it and had already been exposed to Hepatitis C infection.

Had it been the case that he had been free of HIV infection in the early 80s and had then developed HIV infection from a cryoprecipitate dose in late 87/88,

then that would have been unsatisfactory medication. The situation was that by the middle of the 80s, 87/88, the feeling was that the virally inactivated concentrates were safer than the non-virally inactivated cryoprecipitate.

One sees all the time in this very difficult period of the 80s, that the balance of opinion kept changing between different products and so it was quite difficult to know at any particular moment which was the best or the safest product to use, and the point that I'm trying to make is that by 87/88, it is a little bit surprising that cryoprecipitate was still being used I think, but it makes no difference to this situation at all.

MR DI ROLLO: To this specific case?

A. Yes.

MR DI ROLLO: But you do think that it is surprising that cryoprecipitate was being used at that time; is that right?

A. That's my opinion. I haven't really given you a view on whether or not at a sort of Bolam level it was a breach of duty of care. I could be pressed on that but I would prefer not to be because I think it makes no difference to the individual case of the Reverend Black.

THE CHAIRMAN: I can console you, I'm not competent to judge, in this context, on breach of duty of care.

Mr Anderson.

MR ANDERSON: I'm obliged.

Questions by MR ANDERSON

Q. Good afternoon, my name is Anderson and I'm instructed on behalf of the SNBTS and the various Scottish health boards. Can I just raise two matters with you. The first is the one my learned friend, Mr Di Rollo, raised with you, and that is the use of cryoprecipitate in 87/88. I'm advised that it was, in fact, common practice to prefer cryoprecipitate to Factor VIII for patients with moderate severity haemophilia A. Is that not the case?

A. It was in the early 80s. Just to give an example from my own practice, I had a children's department, I had children with haemophilia and I tried to treat them with cryoprecipitate up until the spring/summer of 1985, when the 8Y became available in England, when we switched them over to the heat treated NHS product.

So, yes, cryoprecipitate had a very good record. The problem with cryoprecipitate was that if you gave somebody who didn't have Hepatitis C -- or for that matter, HIV -- a dose of cryoprecipitate, then if that dose was infected with HIV or Hepatitis C, they would develop HIV or Hepatitis C. So that if you are looking at a person who is not infected with HIV or Hepatitis C

in 87/88 and they develop Hepatitis C or HIV from a dose of cryoprecipitate in 87/88, then I think that's a problem.

Q. Would it not be a matter of clinical judgment.

A. It would be a matter of clinical judgment, which I think is why I was reluctant to give a view on breach of duty of care.

Q. Is it not the case that the first guidelines that came out in relation to this came out in 1988?

A. Are we talking about the UKHCDO guidelines?

Q. Yes.

A. I think that the UKHCDO guidelines inevitably reflected opinion, perhaps more than they led it. And again I think we are get into a difficult area over what a reasonable haematologist would do.

Q. Perhaps we can cut it short. Again, does it simply come to this, that it is then a matter of clinical judgment as we agreed earlier?

A. Yes, I think it is and I'm not really critical and I tried to make clear in my report that I wasn't really critical of what happened but I was asked specifically, I think, in making my report; my letters of instruction were:

"Whether or not the treatment and management of Mr Black's haemophilia was reasonable and appropriate."

And that was the only area where I found myself in some doubt as to whether this was the best treatment for him.

Q. I'm obliged to you. Can we turn then to a second and final matter, Dr Colvin. You told us earlier that the varices that were identified in 1987 would be consistent with the first infection of Hepatitis C about 28 years earlier. Do you remember that?

A. Hm-mm.

Q. As a matter of plain arithmetic, even I can work out that that would take us back to about 1967 or so.

Can I ask you this: have you seen the statement by the Reverend Black's widow, Mrs Jean Black, in this case?

A. I think I saw it on the screen very briefly before lunch.

Q. Without going to the bother of putting it up in front of us, there is simply one aspect of that I would like to raise with you. She says in paragraph 4, this:

"I do not know how often he was treated with cryoprecipitate or when he was treated with Factor VIII. He did receive blood products in San Jose, California in 1970 due to a kidney stone."

Were you aware of that?

A. I wasn't. In 1970, I had just started really treating

people with haemophilia at The London and we were just beginning to use the large pool concentrates which certainly transmitted hepatitis. So if it were to be the case that the Reverend Black was treated with a large pool concentrate in the United States of America in 1970, we can confidently put the date of his infection back to 1970.

Q. The question I was going to ask you was really quite a simple one. If he had not already been infected by then, that is to say in 1970, would you accept that he would almost certainly have been infected by that transfusion in 1970?

A. Assuming it was a large pool concentrate. It depends slightly on the wording of what was said. One can often tell from the wording of what is written down in a clinical note, whether one is dealing with a large pool concentrate or not. But the Americans were in the vanguard of preparation of these large pool concentrates and we had started to use them around 1970. So this was the very earliest date that at The London we were using large pool concentrates. But the Americans would have been a bit ahead of us. So I think it is entirely possible that if he was treated in the United States in 1970, that he would have been given an American large pool concentrate. And that would have transmitted HCV,

had he not been previously infected.

MR ANDERSON: I'm very much obliged to you, thank you Dr Colvin.

THE CHAIRMAN: Mr Sheldon?

MR SHELDON: I have no questions.

THE CHAIRMAN: Anything you want to follow up?

MS DUNLOP: Save to say that I think perhaps the American reference may be the treatment by Dr Pool. If necessary we can look back at that particular section in the records but not at the moment.

THE CHAIRMAN: Very well. Thank you very much.

MS DUNLOP: Sir, I do want now to go to Birmingham and to Dr Mutimer, who is waiting. On the other hand, I don't know if we can just carry on without stopping for five minutes.

(3.12 pm)

(Short break)

(3.24 pm)

DR DAVID MUTIMER (continued)

Questions by MS DUNLOP

MS DUNLOP: Good afternoon, Dr Mutimer. Welcome back.

A. Good afternoon.

Q. We are today discussing the case of the Reverend David Black. I should have shared with everybody before this, I think, that what I have been

planning to do is to discuss with Dr Colvin, who has just given evidence and who is a haemophilia specialist, the Reverend Black's haemophilia treatment. We have looked at some material to do with his earlier experiences in his childhood and his teenage years, and with Dr Colvin we have looked at the records and looked at some emerging abnormalities in his liver function tests and we have arrived at a point where, in 1991, he has been diagnosed as having Hepatitis C.

So this is really the point at which I would like to start with you. If we could go to [BLA0010287].

A. I don't have that yet.

Q. No, while we are waiting, I should say that -- I don't know, do you have a hard copy of your report?

A. Yes, I do.

Q. Right. Well, that's handy because, to link into your report, we are on the page 2 of your report, where you have a paragraph that begins:

"In 1994 ..."

A. Yes.

Q. Just to orientate you, that's where we are, and [BLA0010287], when it appears, will be Dr Lowe, haemophilia centre at Glasgow Royal Infirmary, arranging for Dr Mackenzie, the gastroenterologist, to become involved in the care of the Reverend Black.

A. I have my hard copy and I have got document 0245 on the screen.

Q. We should be at 0287.

A. It is changing page.

Q. Oh, right.

THE CHAIRMAN: We don't have anything. We don't have anything on our screens.

MS DUNLOP: I don't either. Here we are.

Sorry, I should also have said, sir that, Dr Mutimer's report is [BLA0012277]. I think we have all the reference numbers we need.

This is 27 January 1994 and this is Dr Lowe, Gordon Lowe, who is writing to Mr Black's general practitioner saying that he has seen Mr Black and his wife in January 1994. If we go down, this is a letter giving a little bit of explanation. His vascular spiders. I have forgotten the pronunciation. Is it naevi?

A. Naevi.

Q. And a trace of ascites:

"As you know, Mr Black has chronic Hepatitis C. We reviewed precautions against Hepatitis C transmission and explained that he has progression."

And then a bit about his liver function tests, and then at the end he says:

"I have asked our gastroenterologist to review him."

And also Mr Anderson is going to be arranging regular endoscopic review in case he develops recurrent varices. I should say that by this point from the records, it appears that the varices had been successfully treated.

So that is the beginning of some care which is more directly related to the liver disease and the next document I wanted you to look at is 283 and --

A. I'm not getting any of those documents.

Q. You are not getting that, right. It may just be a question of waiting a moment and hoping it will appear.

A. It keeps bringing up the same document, 0245.

Q. Can you press "published view" on the left-hand side, please?

A. Yes, I have done it.

Q. Is anything changing?

A. It changed then. It reverted to 0245. I will do it again. It did the same. It very quickly had a view of a letter that seems to say:

"Dear Dr Lowe ..."

Then it reverted to 0245.

Q. I think that 0245 is the first page of that particular batch of records. Oh, do you want me to scroll through.

What page number?

Q. Page 39, please.

A. Yes, that has done it.

Q. You have got it? Good.

A. Yes.

Q. This is reporting back to Professor Lowe of the haemophilia unit. I think a Dr George has seen Mr Black and he has also discussed Mr Black with Dr Mackenzie, and in short this is really to do with the possibility of interferon treatment, and you yourself discussed this in a paragraph in your report that we looked at. We can see that there was a long conversation about the pros and cons and Professor Lowe also had such a conversation:

"Dr Mackenzie was of the opinion interferon therapy should be tried, and Mr Black himself would prefer to think over things further."

Obviously there has been some explanation to the patient about what would be involved and Mr Black has been concerned about how it would impact on his life, given that he is travelling abroad a lot.

Just flip over and look at the next page. I don't think there is much on it. Yes. There really isn't anything which we need to look at, but whether there was any other potential cause for the cirrhosis but I think

that's really a blind alley for us.

The next document in this course of events is [BLA0010279]. So if you can go back five pages from where you are.

A. What page number exactly?

Q. Page 35. We can see that in 1994 he had developed gross ascites while on a visit to America and then he had been seen in the clinic, again Dr George, and he still had gross ascites and pitting oedema. What is the cause of the pitting oedema?

A. The ascites and the oedema are both due to salt and water retention. So almost certainly they are both due to his liver failure.

Q. He has been told, in fact, he is not going to be well enough to go to Italy in a fortnight's time. Then [BLA0010274] is actually a letter from Reverend Black, if we look at that.

A. Do you have a page number?

Q. That's page 30. We can see that he has been prompted to write because he has had an insurance claim turned down, and we can see that he is in dispute with the insurance company about whether he should or shouldn't have separately told them about his chronic liver disease and so on, but he is wanting to know how long he has had it. He says:

"I would be grateful if, from the blood samples, an estimated date could be given for the first likely appearance of Hepatitis C. It would be helpful to know how longstanding the condition and the number of years degeneration of the liver has been taking place."

I haven't succeeded in finding a written response to that but it may be that there is some discussion of that at his next clinic visit or something like that.

A. Possibly a document from the insurance company, which would have been sent directly back to them.

Q. Maybe. [BLA0010263], which is 19, please. This is back to Dr Mackenzie, so back at the gastroenterologist, and Dr Mackenzie is recording to Professor Lowe that there has been very slow deterioration in liver function. Halfway through the letter we see that Reverend Black remains unkeen on any medication:

"I suggested to him that hepatic transplant may become an option within the next few years."

And that there is going to be discussion with the unit in Edinburgh. You say this yourself in your report, that:

"During 1994 and 1995 there is further evidence of hepatic decompensation. The patient was referred to the Edinburgh liver transplant unit."

And if we look quickly at [BLA0010260], which will be

page 16, we can see that there has already been a telephone discussion with Dr MacGilchrist from the transplant unit about Mr Black, and this is the follow-up letter and Mr Black is wanting to come to Edinburgh and discuss the issue. Indeed, if we look at [BLA0011675]. This is a new challenge, I suspect, Dr Mutimer, finding this but we will do our best. If the technology were consistent, you would be looking at the first page of 339; are you?

A. Not yet, no. Yes.

Q. Is it the first page of 339?

A. Yes, it is.

Q. You need to go to page 211. This letter is from --

A. Page number?

Q. It was 211. Yes, that's it. That's the other half of the correspondence. That's Dr MacGilchrist writing back to Dr Mackenzie. He has by this time seen Reverend Black and he has got a clear idea of the history. Reverend Black's symptoms are that he has developed significant fatigue. He has to spend the occasional day in bed and he can't concentrate for more than an hour or two at a time. He has, however, lost no time off work:

"He is a minister whose involvement with the prayer movement involves a lot of travelling and he is

encountering problems getting medical insurance cover when he goes abroad."

Can we go a little bit further down, please. His varices, we are told, are checked, or are checked every year to make sure he is not showing any recurrence of his varices:

"No major bleeding from his haemophilia for many years and does not suffer from any joint problems."

Can we go to the next page, please? Dr MacGilchrist is saying:

"Reverend Black is a good candidate for liver transplantation. Clearly it will be a major undertaking for the blood transfusion service to supply sufficient quantities of Factor VIII to cover the procedure."

Quite an interesting sentence, I suppose, to those who can get sidetracked into the semantics of it. On the one hand it is a major undertaking but it is not a major problem. It says:

"Transplantation has been undertaken successfully with patients with haemophilia elsewhere."

I take it, Dr Mutimer, that a liver transplant for somebody who has haemophilia, is quite a major undertaking.

A. With appropriate Factor VIII replacement and haematology expertise, the results are very good. I don't think

they are any different from transplantation with patients who don't have haemophilia.

Q. Right. Then if we could go back to the last set of records that we were looking at, [BLA0010253]. If you bear with us doctor, we will be able to give you a page number.

A. I'm not sure who is turning the pages at the moment. Whether I'm meant to be doing it or your colleagues.

Q. I think we will tell you what to look at. Are we back at page 1 or something?

A. I have been trying to locate the pages myself but there seems to be more than one person operating my screen at the moment.

Q. What are you looking at on your screen?

A. I have to answer quickly because it keeps changing. I'm on page 1 of 592 at the moment.

Q. Well, we are in the right area. Can you go to page 9, please.

A. I won't touch it.

Q. Right, this is a report back to Mr Black's general practitioner, Dr Hill. Have you got that?

A. I'm having to do it myself. So page 9.

Q. Page 9, yes.

A. From the Royal Infirmary of Edinburgh.

Q. Yes, to the GP.

A. September 1995.

Q. Yes. So he has been back to the transplant clinic in Edinburgh, September 1995, and he was giving rather mixed messages. He has been researching his own condition but is finding it difficult. I'm looking at the bottom of the page:

"... finding it difficult to obtain statistics regarding haemophiliacs who have been transplanted."

Then perhaps quite a sensitive assessment of what the Reverend Black's concerns are. This is a Dr Ruth Gillespie:

"He is terrified his condition is going to deteriorate suddenly to the extent it would preclude transplantation. I have tried to emphasise to him that that is not the natural course of events."

Can we go to the following page, please. We can see Dr Gillespie thinks he should come in for assessment. Then we find that assessment and that's at [BLA0010249] and BLA0010250. So page 5, not much further back. There is a discharge summary of a three-night stay at the end of October 1995 and if we perhaps go down, he was admitted for liver transplant assessment. There seems to be a comprehensive recital of the problems so far, except that I don't think he had two daughters, as far as I understand. He has a son and a daughter.

Anyway. He is a minister involved in the Third World.

Then can we look at the following page, please. Quite a detailed recital of the results of investigations and a conclusion that he was discussed for assessment by the multidisciplinary team. It is felt currently his liver function and quality of life are such he does not require liver transplantation.

Perhaps we can skip forward to [BLA0011664] because, as you say, he did undergo transplant in the spring of 1996.

A. What page number is that?

Q. For us it is [BLA0011664] but I think you may need a different number, 200. 200 of 339.

It is a letter to the GP, 7 March 1996, and this is Dr MacGilchrist again. He was seen in the clinic and he is less well. There has been a deterioration in his liver function, it is time again to consider transplantation and he is going to be coming in for a few days to set this in motion and then as you say, the transplant was carried out in April 1996. I don't want to go to it because I don't want to take up time but [BLA0011657], which is a letter dated 1 April just repeating the point about worsening condition, that he has had to have paracentesis and that he has been listed for transplant. Then if we go to [BLA0011422] and

again, without taking up time, sir, by going to it perhaps we should note in passing that on [BLA0011461], we can see that Dr Ludlam had to be involved, obviously to provide the sort of cover that Dr Mutimer was referring to a moment ago. So there had to be involvement from the haemophilia centre at Edinburgh Royal Infirmary to cover the surgery.

At [BLA0011422] and BLA0011423. [BLA0011422] should be page 23 of 65 for you, Dr Mutimer.

A. I'm still on the 339 page document. It is changing. 1065?

Q. Yes. It should be 23.

A. A letter from the Royal Infirmary?

Q. Yes. To the general practitioner. It just tells us that he has had his liver transplant. He has been in hospital from 20 April until 13 May and there has been some fluid retention. He has had to have some antibiotics for spontaneous bacterial peritonitis but by the time of discharge he looked well with no pallor or jaundice and no leg swelling.

Then if we could go to the following page, we see he is going to be reviewed in May and we have heard already from Dr Bathgate that obviously the review is pretty intensive after someone has recently undergone a liver transplant.

A. Yes.
Q. Obviously that's not controversial. Could we look at [BLA0011453], please. This should be for you page 54 of 65.
A. 30 October.
Q. Yes. In relation to an examination or an attendance on 24 October. We can see here that there has been a discussion about the long-term impacts. This is the third paragraph:

"Long-term impact of Hepatitis C recurrence and chances of developing cirrhosis. Hard to predict his long-term prognosis although it is reasonable to predict that his quality of life should be fairly good for the next ten years."

He is obviously aware of the fact that the transplant doesn't cure the Hepatitis C and indeed over the next period, we can see quite a lot of discussion about the possibility of starting antiviral treatment. That was October 1996. [BLA0011451] should be 52 of 65.
A. 18 December?
Q. Yes. Dr MacGilchrist has seen Reverend Black in December, 11 December 1997. He is keeping extremely well and working as hard as ever but his liver function tests are a little concerning. His liver function tests never returned completely to normal and we can see --

this is the third paragraph -- that his ALT is quite significantly raised, is it, at 153?

A. Yes, that's raised.

Q. And you would have agreed perhaps that this is most likely to represent recurrent hepatitis?

A. Yes.

Q. And then the doctor is saying:

"I couldn't bring myself to spoil his Christmas by worrying him too much and I have therefore simply told him the liver tests are slightly abnormal."

[BLA0011416]. That's page 17 of 65.

A. 16 February?

Q. Yes. We are now into 1999 in fact, but this is another example of discussions about the possibility of treatment. It says:

"He was informed his liver biopsy showed recurrence of Hepatitis C. We would probably consider treating him for Hepatitis C. He himself is not quite sure if that would be the best option for him at this present time, as he felt the side effects of interferon would be too much for him."

I should say, doctor, that you have rehearsed all of that period in your report, on the second page that we were looking at earlier. You have told us that over this period, 1996 to really 2002, there is a lot of

discussion when he attends hospital about the possibility of going on to drug treatment.

A. Yes.

Q. And --

A. It was obvious from the notes.

Q. Yes. And perhaps understandably, a degree of uncertainty on the part of the patient.

A. I think so. It probably reflected some uncertainty on the side of the physicians as well. They are aware that the treatment is associated with significant side effects and the chances of success are fairly low, so I think that the decision the patient took is quite understandable.

Q. Right. Now, can we look at [BLA0010117]. I suspect this is in another batch of records. So will you bear with us, please, doctor?

A. 244?

Q. Yes, actually it is just page 117. This is the very first batch of records, so that's a little bit easier. It is page 117. You can see that by April 2001, if we look at the letter, there has been another discussion, a long discussion, with Mr Black about treatment for his Hepatitis C. If we could go slightly further down the page, please, the doctor is telling Mr Black that

treatment has improved with the introduction of combination interferon and ribavirin:

"He seems much more receptive to the idea of treatments and has gone away to think about it."

But if we look at page [BLA0010111] -- so 0111 -- he has been at the clinic on 27 September, and if we go down that letter, please, he is not going to go for it. This is the letter which tells us that he was genotype 3, and I think we can recall from yesterday that that will have offered the chance of a shorter period of treatment than if you were genotype 1, to get rid of the virus. Is that correct?

A. That's certainly the case in the non-transplant setting but the appropriate duration for the post-transplant settings is not really certain. There are a number of units which would still suggest 12 months of treatment.

Q. I see, and by this time Mr Black is feeling he would be happier to wait in view of potential side effects which he might find disruptive to his life:

"He is currently very busy at work."

Then can we go over to the second page, 112 --

A. What page are you on, sorry?

Q. I just went to the next page to see --

A. Is it 112?

Q. Yes, just that his tacrolimus is being reduced. That's

his antirejection medication. Right, [BLA0010108]. This is Dr Bathgate. Dr Bathgate has seen Mr Black in 2002, February 2002, and found him doing very well. Again slightly raised liver enzymes, Dr Mutimer?

A. I have lost that page. It has disappeared. What page was it?

Q. Sorry, it is 108.

A. AL is 127, does that say?

Q. Yes.

A. Yes, it is elevated.

Q. Yes. And GTT?

A. It is elevated as well.

Q. Yes.

A. That would be fairly typical of Hepatitis C infection in this setting. So they are not terribly high, but it doesn't give you a very good idea about the severity of damage.

Q. I see. Can we also look at [BLA0010106], to two pages before this. There was an annual biopsy in April 2002. Ultrasound scan was satisfactory. That is perhaps something that we should note at the moment because we might come back to that.

Then page [BLA0010102]. He is still wondering about treatment. The appearance at this point short of cirrhosis but more advanced as compared to last year.

Appearances consistent with HCV fibrosis in the transplanted liver.

Finally, Reverend Black did commence treatment in December 2002, and that's [BLA0011234]. You cover this in your report, Dr Mutimer, on the following page. I think this is page 3 in your report.

What page is this for Dr Mutimer?

This is page 3 of 167, doctor.

A. Yes.

Q. And --

A. The December.

Q. And he has commenced interferon and ribavirin and I think we remember from yesterday that interferon is something the patient injects and ribavirin is a tablet?

A. Yes.

Q. Right. This didn't run very smoothly, this treatment. You say in your report:

"Unfortunately he experienced severe anaemia and treatment was abandoned."

We can see that from [BLA0010090]. So that will be page 90 of 244. Dr Simpson is telling us that Mr Black has had quite a time with the interferon and ribavirin for the recurrent Hepatitis C. It is, I understand, generally, Dr Mutimer, not pleasant treatment. Is that correct?

A. That's correct. The problem with the anaemia is due to the ribavirin component of his treatment, and the main problem is that the dose needs to be adjusted very carefully and frequently in patients if they have any degree of kidney dysfunction, which is quite common in the transplant patient. So I suspect the severe anaemia was because the level of the ribavirin was too high for the patient. But there are no useful published guidelines on picking the right dose.

Q. And the anaemia has been bad enough to necessitate a transfusion, we can see as well?

A. Yes.

Q. Matters changed in May. Can we look at page 79, [BLA0010079]?

A. 79 of 244?

Q. Yes. We can see that he was admitted -- if we look at the top, he was admitted in May. He had ultrasound-guided liver biopsy:

"It is felt from scans there was a possible focal lesion."

Two cores of tissue were taken and unfortunately pathology had confirmed hepatocellular carcinoma. If we look at the letter before, [BLA0010078], we find that it is Dr Bathgate who has had to tell Mr Black that this has happened:

"It is clear from the imaging that it is multifocal."

Can you explain that for us, please, Dr Mutimer?

A. In this setting it means that, instead of being a single, isolated tumour, it has spread, with multiple nodules throughout the liver usually.

Q. Right, and the letter is really saying that it can't be treated. Is that correct?

A. The page has disappeared. Could you tell me the page number again?

Q. Right. It was page 78. Dr Bathgate is saying it is multifocal and therefore would not be appropriate for any form of intervention.

A. Yes.

Q. You would agree with that?

A. Yes, I would.

Q. Now, I would like also to look at page [BLA0010064].

A. It is a letter from the hospice.

Q. Yes, I'm not asking you to comment on it, doctor, I'm really just drawing it to the chairman's attention that this is Strathcarron hospice. Mr Black has been referred to Strathcarron hospice and Dr Fiona Downs has been to see him at home and has noted his symptoms as they then were, and if we can look at the following page, she thanks the doctor for referring this

remarkable man.

So at this point arrangements are being made, I think, really for palliative care, and Mr Black, we can see, had a poor prognosis but he had been sustained by his strong faith.

Then, finally, can we look at [BLA0011471]?

THE CHAIRMAN: We must be in a new group of documents now.

MS DUNLOP: 1471. It will come, I think.

THE CHAIRMAN: It can't be 1 of 339.

MS DUNLOP: Page 7 of 339 is Dr Downs again and Mr Black has died in Strathcarron hospice. Perhaps we should just look at the following page as well.

Now, Dr Mutimer, can you also please look at the death certificate which was ultimately issued. There were certain requirements, I think, given that the death was from Hepatitis C, and there was a post mortem, as a result of which the death certificate was completed in a particular way, as set out by the pathologist. Look at [BLA0012118].

A. Page number of 339?

Q. It should be 1 of 1. I'm hoping it will come, 2118.

A. Yes.

Q. Can we see that the death certificate has four conditions in section 1? Now, Dr Mutimer, I am told that one can actually read these in reverse order, as it

were, and say that he suffered from haemophilia, which led to the transfusion of blood products, which caused Hepatitis C, which caused hepatocellular carcinoma in his transplanted liver. Is that a reasonable way of looking at events?

A. Yes, it is.

Q. And I think, as I understand it, what's in section 1 on a death certificate is the list of conditions which contributed to the person's death. Does that --

A. Yes.

Q. -- accord with your understanding?

A. Yes, it does.

Q. Right. I should go back to your report. This is [BLA0012277] but at, I think, page 79, 2279.

A. I have got the hard copy in front of me.

Q. Fine. You see at the very end of your report:

"I have no concerns at all about the treatment given. From the time that he developed complications of liver disease, his medical management in Glasgow and Edinburgh seems entirely appropriate."

With one caveat, which I'm coming on to, and that is the matter that you have looked at more recently in relation to the pathology reports from 1996 -- with that caveat, can we take it that your conclusion remains the same in relation to the actual treatment that Mr Black

received?

A. Yes, I think I see what you mean. I think his treatment was entirely appropriate. If you include in his management that appropriate information should have been given to him after the liver transplantation, then we are unable to find any record that that information was given. So I guess that is a concern about his overall management.

Q. Thank you, Dr Mutimer.

Sir, for this last section, perhaps if I can draw to your attention that the pathology reports on the explanted liver, the removed liver, in 1996 seem to have come to light towards the end of last year, and the Inquiry team realised from the pathology reports -- I should give the number, sir, of the batch of pathology reports, which are [BLA0012289]. I'm hoping that will appear. Yes. That's page 1 of 9, Dr Mutimer.

A. I have probably got the hard copies here. This is from the pathology directorate, Royal Infirmary of Edinburgh?

Q. Yes. I think we probably gain most information by looking at the third of those pages, which I see already in front. 2291, is it?

A. Yes, I'm looking at that.

Q. Sorry, it was actually the page we just had. I'm not sure if I have the pages in the same order. It is 2289.

In fact it transpired that there was quite significant tumour in the explanted liver. Is that correct?

A. That's correct.

Q. Yes, and you have actually prepared a supplementary report on this aspect of matters. The supplementary report, if I can just find my inventory, is [BLA0012287]. So can we perhaps put these side by side? Yes, that's your supplementary report, and then the pathology page that we had a moment ago, 2289.

A. What am I meant to be looking at?

Q. I was just going to say firstly in your supplementary report you have covered --

A. My supplementary report? Sorry.

Q. Yes, 2287. You have dealt firstly with the post mortem report, which is plainly the examination of the second liver, the transplanted liver, and --

A. Yes.

Q. -- indeed that revealed multiple focal hepatocellular carcinoma, but really the point which you were asked to consider with greater prominence in the supplementary report was what you deal with at the bottom of that page, the histology reports from the pathology directorate at the Royal Infirmary of Edinburgh, and this is the report that you should be seeing on the right of the screen -- or you will have the hard copy --

with the heading, "Macro report". The date of this is 22/4/1996.

A. Yes, I'm looking at that.

Q. Yes. Can you just tell us in brief, Dr Mutimer, what was apparent from the explanted liver?

A. Well, just from my own report:

"The explanted liver showed extensive primary liver cancer. The microscopic report defined at least five nodules in the left lobe and three in the right lobe. The largest tumour was 4 by 3 by 3 centimetres. There was no evidence of spread outside the liver. Some lymph nodes were examined and showed no evidence of tumour."

Q. Now, it is fair to say, Dr Mutimer, that it was very difficult to work out from the records what, if anything, had been done with this information. Perhaps I can tell you that members of the Inquiry team looked in the records and could find really no reference to how extensive this tumour was and only, I think, a few brief references to five small hepatocellular carcinomas in the explanted liver. I don't know if you have seen a further letter and report from the Royal Infirmary, which is dated 1 March 2011. That's something the Inquiry team only received yesterday.

A. Dr MacGilchrist?

Q. Yes. You have that?

A. I have seen that letter, yes.

Q. That's [PEN0131091]. If we can just go down that page, really in a nutshell Dr MacGilchrist is summarising his view on really the second of two questions that could be said to arise from this. If the first question is what happened to the information and if the second question is seen as whether any oversight made a difference, I think Dr MacGilchrist in this letter is really answering the second question and saying that he doesn't think that any oversight has made a difference.

I think that really appears more fully from his report but, more importantly perhaps for the family, he is offering that either he or Dr Bathgate would be happy to meet the family to discuss all of this; that is the surprising finding that there was quite extensive tumour in the explanted liver in 1996.

We noticed, sir, when we looked at Mrs Black's statement, that that had been a shock to the family. So we have tried to take that forward and have received this really very full report.

If one looks at the next couple of pages, so 1092 and 1093, there is a report, but just to look quickly at the fourth paragraph, Dr MacGilchrist is saying that he would speculate the finding was somehow overlooked by the medical team, which would explain why it was not

discussed with the Reverend Black's family and, by implication, with the Reverend Black himself.

So you said, doctor, if we could go back to your own supplementary report, that it would have been appropriate to share this information with the patient?

A. Yes, I said that.

Q. For some reason, which probably we won't discover, that didn't happen, but what I was describing as the second question is important and that is whether, if that finding had been fully appreciated by the members of the medical team who saw Mr Black at all his review appointments, the outcome would have been different, and I think you have a view on that. Is that correct?

A. Yes, I think the histology should have been discussed with the patient, and when I reviewed the files, there is no way that I could know whether or not it had been discussed. It is only since I reviewed the files that we have had the information that this was not discussed with the family or with the patient.

Concerning the second point about whether or not alternative management strategies could have changed the eventual outcome, I don't think that they would have. I think that when transplantation is undertaken in the presence of cancer, we know that there is a proportion of cases where the cancer will recur following

transplantation and there are no established strategies which will prevent that and, once recurrence does occur, if it is recurrence, then there are no proven therapies to prolong life.

Q. There is also, is there, Dr Mutimer, an unanswered question, which is whether the cancer which was detected in 2003 was a recurrence of the previous cancer or was a development of a new tumour. Is that right?

A. Yes, that's the other possibility, that this is a new tumour. We know that when there is cirrhosis, there is a risk for cancer, and cirrhosis had developed in the graft, so it is possible that the cancer arose merely in the graft rather than representing cancer which had been lurking for seven years and then recurred as a form of recurrent cancer.

Q. I took from your supplementary report, doctor -- and please correct me if I am wrong -- that there was a significant risk of recurrence from the extent of the cancer that existed in 1996. Is that really what you are saying on --

A. Yes.

Q. -- page 2?

A. -- I think Dr MacGilchrist later agrees with that as well, that the risk of recurrence is proportional to the number of tumours and to the size of the tumours, and

with this particular case there was a significant risk of recurrence.

It is a risk, it is not inevitable, and there are patients who have single, small tumours who unfortunately suffer recurrence. There are patients with extensive cancer like this who are lucky and do not suffer a recurrent cancer. So it is the magnitude of the risk; it does not predict inevitably that the patient was going to get recurrent disease.

Q. But the other point I took from your supplementary report was that this would have been a long period of time for it to be recurrence. We are talking about seven years, which, from the last paragraph of your supplementary report, seems to be unusual in epidemiological terms. Is that right?

A. Yes, it is, it is unusual, as cancer that recurs after transplantation does within two years. I can hardly remember recurrence beyond five years, although it can happen, and this patient appears to have relapsed at seven years. So it is unusual but it doesn't help us to know whether it is a new cancer or a recurrent cancer.

Q. Actually, you had suggested one possible investigation, which would only have been helpful if the donor had been female, that there could have been --

A. That would be one way of showing, or trying to

demonstrate, whether this was recurrent cancer or new cancer. There are alternative scientific techniques which might be applied and those might be discussed perhaps with your own pathologists, your own forensic pathologists, as to whether or not they could distinguish the origin of the cancer in the patient's transplanted liver.

Q. The suggestion about making some use of a gender difference seems to be unprofitable because Dr MacGilchrist tells us that the donor was also male, so that wouldn't work.

A. That would have been the simple way to do it but there may be other ways that your forensic pathologists could approach this. You might consider that.

Q. Well, doctor, I should ask you firstly, if the extent of the tumour had been detected in 1996, is it possible that that would have altered the management of Reverend Black's disease in 1996?

A. It wouldn't have affected his management.

Q. Right. And what about in the interval between 1996 and 2003? I think you have really covered this.

A. The knowledge that there was cancer in his explant would not have determined any difference in his management following transplantation.

Q. In short, was there anything that could have been done

to prevent recurrence?

A. Not to prevent recurrence.

Q. And that's against the background that we don't actually know whether it was recurrence or the development of a new tumour?

A. That's correct. If it was a new tumour, then prevention of the progression to cirrhosis would probably have prevented a new tumour from developing.

Q. Right, and that takes us back to the debates about whether or not he was going to begin the antiviral treatment in the late 1990s, does it?

A. Yes. I think the only way that things could have been different for this patient would be if it was a new cancer that was developing in the liver, and if he had had successful antiviral therapy after transplantation to eradicate the virus, then things might have been different.

Q. Right. The only other thing I wanted to ask you, doctor, was whether -- when we looked earlier at the annual ultrasound that was carried out in 2002, the fact that that was normal, is that an indicator that the tumour perhaps wasn't -- the second cancer perhaps wasn't present in 2002?

A. Yes, it is. I can't find the document but if the ultrasound early in 2002 showed no evidence of cancer,

then it tells you that any cancer, if present, was extremely small, probably less than 1 centimetre in size, but possibly the cancer had not yet developed.

Q. Sir, just to give the reference for that again, that was [BLA0010106], and that's April 2002.

Thank you, Dr Mutimer, I don't have any further questions for you.

THE CHAIRMAN: Nothing from you, Mr Di Rollo?

MR DI ROLLO: No, thank you.

THE CHAIRMAN: Mr Anderson, do you have questions and are they extensive?

MR ANDERSON: One question only. I don't know if I need the microphone.

A. I can hear you.

Questions by MR ANDERSON

Q. Good afternoon to you. My name is Anderson. I'm instructed on behalf of the SNBTS and the Scottish Health Boards.

Can I just discuss with you briefly this question of whether or not the Reverend Black was told about the existence of the cancer in his original liver?

You see from the penultimate paragraph of Dr MacGilchrist's report that I think, strictly speaking, it was not known whether he was told or not but it appears that he might not have been told. Is

that a fair assessment?

A. I don't have doctor's letter -- I have got page 1 but I don't have the ability to turn the pages.

Q. The second page is 1093.

A. What you are saying is true. You know what has happened by what people document in the file but if something is not documented, you cannot know whether it was discussed with the patient or not.

Q. You see, in your supplementary report you say that it would have been appropriate to share this information with the patient. I just wondered what the benefit would be of discussing this matter with Reverend Black, and I ask you that in the knowledge that we see him referred to as obviously quite an anxious man. Your attention has already been drawn to that. So what would be the benefit of telling the Reverend Black that he had cancer in his original liver?

A. I think it is honesty really. It is providing the patient with information that will be of interest to him and it may actually determine his attitude to his illness and his recovery. So I think it's appropriate to discuss it with him. You are quite right that it may have unfortunate consequences in causing anxiety and the cancer may never recur, in which case in retrospect you might look back and say, "I wish we had never told him,"

but I don't think we are in a position to manage patients like that. This is important information that should have been shared with the patient.

Q. Is that an absolute or again is that possibly a clinical judgment that the doctor makes, given his relationship with and knowledge of the patient?

A. I think there are circumstances in medicine where it might be suggested that it is in everyone's interest, including the patient's, for information to be withheld, but I don't see that in this case.

Q. All right, thank you for that, but we do know, I think, at least in this case, that Reverend Black had seven years' life without knowledge of cancer in his original liver. Is that right?

A. I believe that's the case.

MR ANDERSON: Right. I'm much obliged to you. Thank you, sir.

THE CHAIRMAN: Mr Sheldon?

MR SHELDON: Nothing from me, thank you.

THE CHAIRMAN: Thank you very much, Dr Mutimer.

A. Okay, thank you.

MS DUNLOP: We will see you tomorrow.

THE CHAIRMAN: Yes. Very well, ladies and gentlemen, until tomorrow.

(4.36 pm)

(The Inquiry adjourned until 9.30 pm the following day)