Wednesday, 14 December 2011

(9.30 am)

MR DUNCAN MACNIVEN (continued)

THE CHAIRMAN: Good morning, Mr Macniven.

MR MACKENZIE: Good morning, sir, thank you. We interject the hearings today to finish off the topic C2 on surrogate testing. Mr Duncan Macniven has kindly returned. I have no further questions for Mr Macniven but my colleagues do.

THE CHAIRMAN: Mr Di Rollo?

MR DI ROLLO: This is C2 and Mr Dawson is taking the witness.

Questions by MR DAWSON

MR DAWSON: Thank you, sir.

Good morning, Mr Macniven. Thank you very much for coming back to finish off this topic with us. You explained the last time that you were here that in your role as assistant secretary, you were ultimately involved in giving advice to the minister on matters which fell within your remit, including, between 1986 and 1987, blood transfusion matters. That's right, isn't it?

A. Not quite. My interest in blood transfusion matters continued until 1989. So it was 1986 to 1989. I had other responsibilities besides but it included -- my

remit included blood transfusion matters.

Q. But between 1986 and 1987, you were in that role?

A. Indeed.

Q. Can you tell me what the role of the SNBTS directors was in the process of you providing advice to the minister on blood transfusion matters?

A. The SNBTS directors, and particularly John Cash, the national medical director, was one of the -- were one of the sources of advice on which we relied in putting advice to the minister.

Q. We have seen a good deal of evidence throughout this section and indeed other sections showing the position of a number of expert advisory groups, which were set up to give advice to the government nationally. Would it be fair to say that the SNBTS directors' group really was a ready-made expert committee on blood transfusion matters in Scotland?

A. It wasn't -- I wouldn't describe it as an "expert committee". It wasn't constituted in that way. But it was certainly a source of advice, and the meeting, the periodic meetings of the directors, were attended by John Forrester, Dr John Forrester from the department -- from whom you have already taken evidence.

Q. In Dr McClelland's evidence on this subject, he was asked what kind of advice would require to be given to

ministers to persuade them to do something like introducing surrogate testing, and three of the adjectives that he used were "strong", "clear" and "well argued". I'm sure you would agree with Dr McClelland that that's the kind of advice you would have to give them for such a measure to be taken?

A. Yes, I do.

Q. Thank you. You talked the last time you were here in some detail about your involvement in the financial implications of a process such as surrogate testing. Am I right in saying that the application for funding for surrogate testing came via the public expenditure survey documents that we looked at?

A. Yes, that was simply the bureaucratic vehicle by which such bids were made.

Q. Could we possibly have a brief look at your evidence from the last time you were here, which is on page 152 of the transcript from Day 65, 17 November 2011.

I just wanted to remind you of a passage. This is a passage where Professor James was asking you about the process of dialogue between yourselves and the SNBTS in relation to the public expenditure survey applications. Could we just scroll down a little bit further than that. It's page 152 I'm looking for, please.

Professor James asked you:

"Was the bidding process iterative in any way?

"Answer: Yes, it was. My memory is that the SNBTS submission was quite brief and was sometimes a little hard to understand. So we would have certainly gone back -- if we had been in any doubt what was underlying it, we would certainly have gone back to the SNBTS and asked questions. My memory, which may be faulty, is that the submission was also discussed at the periodic meetings we had John Cash."

Does that encapsulate the kind of approach that you would generally take to these applications?

A. Yes, indeed. We would certainly not want there to be any risk of misunderstanding lying between us and the BTS.

Q. Could we just have a look at the public expenditure survey documents? I think the relevant ones are 1986 and 1987, as far as surrogate testing is concerned. The first is [SNB0112637]. You can see there this is the PES document 1986 programme narrative. If we could just have a look at page 2640, please, we see there, set out under table 1, projections for various costings for various things.

I think Professor Cash told us that this document would have been likely to have been drafted around about May 1986 and it's projecting forward for the

1987/1988 year. So we see figures there, and in particular under 5(g), we see in the column entitled "1987/1988 ":

"Non-A non-B Hepatitis testing, 810."

And then for the following year, 836, which is the projection for those years.

A. That's correct.

Q. Could we look at page 2649, please. At the bottom of that page you see the passage entitled "NANB":

"Despite the absence of a specific test to detect donations which transmit non-A non-B Hepatitis, there is increasing evidence that both in Europe and North America formal moves will be made within the next 12-18 months to introduce surrogate testing of all donations (liver function and anti-HBsAg core tests). Current studies in the States have costed this exercise at $7 per donation. For the SNBTS this would be approximately £1.5 million ..."

Is that million pounds per annum?

A. I think so.

Q. "... using current exchange rates. There would be additional capital monies required and the US costings do not include a significant revenue cost for subsequent counselling of donors. Provision has been made for this development to commence in 1987-88 (part year)."

Before asking you any specific questions, I will just take you to the next document, which is [SNB0113743]. This is the similar PES document for the following year. I think, again, Professor Cash told us but one can see the reference at the bottom right-hand corner and that probably suggests that this was drafted in around about June 1987 for the following year?

A. That fits in with my recollection of the financial cycles, I'm sure he is right.

Q. Good. If we go to page 3750, please. Again, we have a similar table there. Obviously a year later time, and under 5(f) this time, we have a reference for non-A non-B Hepatitis testing, and the references there under the 1988/89 and 1989/90 year, and I think we have had some evidence already explaining why those figures are lower than the ones before, so I do not want to go into that in any detail. Could we look at page 3755, please? There we have a similar passage to the one that we saw in the previous PES document:

"NANB surrogate donation testing.

"The SNBTS directors have now decided that in the light of the advent of new product liability laws in 1988 and an emerging unchecked private sector blood collection services, it would be prudent to plan to commence this programme in the financial year 1988/89.

The costings are estimates only and it is proposed that we plan to ensure the financial burden covers two financial years but begins in July 1988 (the date new product liability legislation will be introduced)."

So there we have the basis upon which it would appear the application ultimately, to you for funding, is being made. Is that correct?

A. That's correct, yes.

Q. Did you, when you received these documents in 1986 and 1987, find the reasoning behind the proposal that surrogate testing should be introduced and funding provided for it, in your own words, "a little hard to understand"?

A. Yes, if one was relying on these documents alone. They have been drafted more to explain the arithmetic, if you like, than to justify the introduction of the testing that was proposed. But, of course, that was supplemented by the very frequent contact that we had with the BTS on this and on all the other matters that were covered by the public expenditure survey bid that they were making. So we weren't left reliant on that seven lines in the second document alone.

Q. Okay. I follow that. Could we just take those two things separately: the reasoning and the arithmetic. Did you go back to the SNBTS directors after receiving

either of these documents to ask any further questions about their reasoning for proposing this?

A. I can't remember specifically having done so. We are talking about something half a lifetime ago.

Q. Of course.

A. But I certainly would have done either after the document was received, or before the document was received, because of course, the public expenditure survey bid was a point in time but the dialogue that we had with the SNBTS was constant. It would have been to John Cash that I would have turned for elucidation rather than to the directors corporately. It was really John with whom I had the contact.

Q. Okay. But your position on whether you went back, after either of these documents, specifically to seek further elucidation from Professor Cash on surrogate testing is that you do not specifically remember doing it?

A. I don't remember doing it but we would have certainly elucidated it. I just can't remember the means by which we did so.

Q. Obviously there are a number of other things that you need to take into account. It's not just surrogate testing in this document. There are a number of other things that they are looking for funding for.

A. Indeed.

Q. And on the arithmetic -- you said that the document was predominantly for finding a basis on the arithmetic. Did you find that the arithmetic that had been used to arrive at the figures sought was clear or did you find it a little hard to understand?

A. I don't remember but my impression now is that I would have found the first document easier to understand than the second document, the 1987 document, because it at least explained where the figures came from, whereas this one doesn't. We would have certainly asked them -- not necessarily I but we would certainly have asked them, "Run us through the calculation a wee bit further".

Q. Would it be fair to say that the calculation in both these documents is a little bit rough and ready?

A. Indeed, yes, and I don't know that that is surprising because they were looking in the first document 12 to 18 months ahead; they were estimating in conditions of considerable uncertainty. So I don't think that I would have felt that they were falling down on the job --

Q. Okay.

A. -- when I looked at that at the time. I would have understood the uncertainty around their estimate.

Q. Okay. What information was available to you from the SNBTS in 1986/1987 about how the directors thought that

surrogate testing would work in practice?

A. I don't recall in detail but, looking at the papers which you have kindly provided, there is mention of the topic because of the concern about the effect on donors, the need for counselling for the many donors who would have been highlighted by any testing that was introduced. But the mechanics of how that was done was very much the preserve of the SNBTS. That was a matter of day-to-day management that we would have been happy to leave in their hands. They had huge expertise -- have huge expertise -- in communication with donors like myself and we did not.

Q. Okay. I think you have mentioned there donor counselling, which is obviously an important practical matter. We have heard evidence from other witnesses that there would be other practical matters that would require to be considered, including training, the provision of appropriate equipment, efforts to replace blood lost to the donor system, and making decisions about practical matters such as where the cut-off in any ALT testing would be.

Would it not have been important for you to know about what proposals were being made about these practical matters in order properly to assess the likely costs of surrogate testing?

A. Yes, that would have been what we would have probed when we were asking about costs in the way that I described a moment ago. That's the sort of questions that we would have asked. But really the experts, in answering these questions, were the BTS. We didn't have in-house expertise at the level of detail necessary to be certain that their estimates were right. So there was, as you will imagine, an element of trust lying behind our relationship.

Q. Okay. I think you said there that these are the kinds of matters upon which you would have probed further but is the position that you remember or don't remember probing further in relation to these specific matters at the time?

A. I don't remember but it's very much the sort of thing that we would have done, so I'm sure we would have done it. I don't remember and the papers don't recall -- don't record -- or the ones that I have seen anyway -- don't record meetings with the BTS and details -- detailed questioning about these calculations, but undoubtedly that process would have been gone through. We were talking about relatively large sums of money.

Q. Indeed. You will remember last time being taken to the minute of the meeting of the SNBTS directors in which, effectively, a decision is taken for a recommendation to

be made. It might be useful just to have that up although I don't want to look at it in any great detail, [SGH0016653]. I'm looking in particular at page 6658.

This is the 3 March 1987 meeting, which I think you were probably taken to the last time that you were here, Mr Macniven.

A. I was, yes.

Q. You will recall there in bold that we have record of the recommendation that surrogate testing be implemented with effect from 1 April 1988. You will recall, as I think we see in the "Action" column on the right-hand side, that Dr Forrester attended that meeting in the normal way?

A. Yes.

Q. I just wanted to ask you a little bit further about how it was that the information about the recommendation made at that time was conveyed to you, to the best of your recollection?

A. I can't remember.

Q. I think maybe the last time you made reference to the possibility of there being a note by Dr Forrester, and we have certainly seen that that was his practice.

A. Yes.

Q. But I don't think we have actually managed to uncover that note, but I just wanted to ask if you could

remember anything specific about it.

A. No, I can't but that was indeed his practice and what was at that time a surprising turnaround in the position of the regional directors would have undoubtedly got to me quickly, perhaps orally, from John Forrester.

Q. I think you said the last time that the reaction certainly of Dr Forrester to this recommendation being made at this time, against the background of what had gone before, was that he was very surprised that they had come to this conclusion. Was that accurate?

A. Yes, that's an accurate reflection of my reading of the papers now. I don't remember it at the time.

Q. At the time when that recommendation was made, as far as you were concerned, on the basis of the information available to you, would you say that the reasoning behind the recommendation being made was clear to you or was it a little hard to understand?

A. I don't remember and again, I'm reliant on re-reading the papers. I think that I could have understood why they came to that view, which reasons are reflected in the public expenditure survey 1987 document that we looked at a moment ago.

Q. The reference there was to the impending product liability legislation. Was that your understanding of why they were making the recommendation?

A. And what they referred to, broadly speaking, as the continuing free access by the private sector to blood.
Q. Okay. At the time when the recommendation was made, did you or anyone else within SHHD, to your knowledge, seek any further information over and above what was available at that time and what appears here about the reasoning why the recommendation was being made?
A. I can't recall that. We would have certainly done so if we had felt doubtful about our understanding because, as I explained a moment ago, we were very keen, as a matter of good governance really, to avoid any misunderstanding between the BTS and the department.
Q. Against the background of there apparently having been a change and Dr Forrester's surprise, would it be fair to say that as a group you were doubtful about their reasoning, or is that inaccurate?
A. It depends what you mean by "doubtful".
Q. It's a word you use.
A. Yes, well, I was perhaps -- there are two elements that we might have -- that there might have been doubt in our mind. Doubt about why they had made the recommendation, why they had changed their minds, and I think that was the doubt that I was referring to. The other doubt is whether they were right or not.
Q. Right. So are you saying, just to be clear, that there

was a doubt about why they had changed their mind on this topic?

A. If there was any doubt, we would have clarified it, was the point that I was trying to make. I can't remember whether at that time we were in any doubt or whether John Forrester's account of the meeting was sufficiently full that we said, "Yes, we do understand".

Q. Were you, in your important administrative role, confident at this time that Dr Forrester, who was attending these meetings, was conveying to you accurately and fully the information and opinions that had been conveyed to him on this subject?

A. So far as I can recall, yes.

Q. I don't want to go into them in detail, and I hope you recall this, but after this -- I think you were taken to them the last time you were here -- there is a series of memos which starts off with one from Dr McIntyre, setting out his position on this, and then I think just about everybody else in the team replies, supportive of his opinion on the matter, and I think one of them is from you?

A. Indeed.

Q. I hope you remember that.

A. I do remember that, yes.

Q. At the time of the exchange which went on over the next

month or so after this, are you aware of anyone else within SHHD going back to seek further clarification of the reasoning for the recommendation at that time?

A. Remind me when "that time" was. I think it was very shortly afterwards, a month or so after.

Q. Yes, indeed, April/May I think would be correct.

A. I can't remember and the papers don't help my memory whether there was clarification sought at that time. If there had been any doubt in anyone's mind, such clarification would have been sought. And before Archie McIntyre wrote the memo that you are referring to, he would have personally been very clear in his mind why the directors were making the recommendation that they were.

Q. Okay. Thank you. Could I just move on to a slightly separate topic, and that's to do with your knowledge at that time of non-A non-B Hepatitis. You explained in great detail the last time your role and the role of the medical officers in ultimately making recommendations to the minister.

Could you tell me, as far as your recollection permits you, what your understanding, around about this period, 1986/1987, was about the potential severity of non-A non-B Hepatitis?

A. Yes, I can't remember from the time.

Q. Okay.
A. From the papers, I think the position is quite clear. Our understanding, voiced in a couple of notes by John Forrester at important points in the process, and I think perhaps that note from Archie McIntyre as well, was that non-A non-B was not serious, indeed not symptomatic, in a great many cases. But in some cases, particularly for pregnant women, it was a very serious matter indeed, and it could lead to cirrhosis of the liver, which even as a non-medical person I regard as a very serious condition.

So it could lead, could lead, in a small number of cases, to very serious conditions.

Q. You referred there to documents that are floating around. They are, obviously, as you have explained before, your knowledge of this would be coming through the medical advisers?
A. Yes.
Q. And you have made that clear. Could we just have a look, just for the sake of clarity, at [SGH0031657]? This is a document entitled "Material for the PMO Report". If we scroll down to the bottom, we can see that it's written by Dr Forrester and really at about this time, 26 January 1987, which, would it be fair to say, this is forming the backdrop to the recommendation

being made in the March?

A. Yes, but one has to bear in mind the length and purpose of this document. This is John Forrester contributing to a periodic -- was it monthly or quarterly? -- report that went to a meeting of the senior medics in the department. He was boiling down issues to a minimum and he was talking to a particularly well informed audience. That wasn't one of the documents that I'm recalling. I'm recalling a document -- a two-page document -- from John Forrester, earlier than this, when the issue first came up, and I'm recalling a single-page document, perhaps from Archie McIntyre, which was the one that you have just alluded to. This document is -- the one that you have on the screen in front of us -- is a fairly shorthand summary.

Q. I see. I selected this document really because of the timing of it but the particular passage that I was looking at is under number 2, where it says:

"Blood Transfusion and non-A non-B Hepatitis (Dr Forrester).

"This 'hepatitis' is a residual rag-bag when Hepatitis B and Hepatitis A are excluded, and consequently no specific tests can detect it."

And it says there:

"It is relatively benign."

What I would like to ask you about that, although you have explained what the purpose of this document is, is whether that statement, "it is relatively benign", is consistent or not with the information that you had at that time from the medical advisers about the severity of the disease?

A. This is four words. There are longer and more complete sets of -- pieces of advice from the medical advisers on which we would have relied.

Q. Okay. Did the understanding, as you have described it -- and obviously you are saying it goes a little bit further than is here -- influence the decision-making process within SHHD as to whether or not surrogate testing should be recommended?

A. These four words that you have quoted didn't. It would very much surprise me. Because behind them lay the longer analysis that I summarised a moment ago and that would have been one of the factors that affected us. Another factor was the incidence of non-A non-B Hepatitis, so far as we could tell, among the recipients of blood products, which, particularly in relation to the levels in the US, was low.

Q. Okay.

A. There were few patients treated with SNBTS blood products caught non-A non-B Hepatitis, so far as the

blood transfusion service was able to advise us at that time.

Q. You told us the last time you were here that part of your role was to appraise advice received from the medical officers and to assess it critically. I think that was the shorthand way you put it, and you explained in more detail what that might involve.

A. Correct.

Q. Would that process or that responsibility have involved looking into the literature behind the advice that you were being given from people like Dr Forrester about the severity of the disease or would your responsibility not go that far?

A. No, I would have relied on John Forrester to go through that process with, behind him, the people to whom he spoke in the SNBTS. The only kind of literature, of the kind that you are describing, that I would have looked at would have been The Lancet letters, which I was reminded of in the run-up to this -- to my appearance here, about the differences of opinion in the various blood transfusion services in the UK about what exactly should be done about the problem of non-A non-B Hepatitis. So that, because these were relatively short and non-technical, my non-medical mind could grasp. Otherwise, as your question implies, I would have relied

on the experts within the department.

Q. Right. So you looked at The Lancet correspondence. I think there were a number of letters we have looked at from Dr Contreras, Dr Gillon, Dr Dow and then, of course, as we may get to later, the letter from Professor Cash and others, on the subject of surrogate testing.

A. Yes.

Q. Would you have looked at Lancet articles relating to the severity of the disease, specifically?

A. Probably not, no. I don't think so. I would have relied, because my technical knowledge was limited, on the experts within the department.

Q. Just to be clear as to what your understanding was, can I take you very briefly to a passage in the preliminary report, which one can find at page 250. You will be familiar with the Inquiry's preliminary report, Mr Macniven?

A. Yes.

Q. I just want to take you to a short passage which seems to summarise the literature relating to the severity of the condition. You have told me that your understanding in around 1987/1987 went beyond the phrase "it is relatively benign". In paragraph 9.1, it says under reference to a number of articles, which one can see at

the bottom:

"From about 1985 onwards, there appears to have been a growing awareness that non-A non-B Hepatitis was a potentially serious and progressive disease which could lead over time to cirrhosis of the liver, hepatocellular cancer and death."

Does that accord with your understanding as at 1986/1987?

A. Yes, as recorded in the papers at the time that I alluded to a moment ago.

Q. Hm-mm. So rather than the short phrase I referred you to earlier, you think this would be a more accurate summary of the state of your knowledge in 1986?

A. I think the best summary of my knowledge at that stage would be in one of these papers that I was referring to a moment ago, but my recollection of them is that the essence of them is the same as paragraph 9.1 of the Inquiry's report.

Q. Thank you. I just want --

THE CHAIRMAN: In particular are you referring to Dr McIntyre's paper?

A. I can't remember. I have the papers in front of me and I can quickly discover if that's --

THE CHAIRMAN: Could you just do that?

A. Okay.

MR DAWSON: I think, just to be clear, I referred to a memo by Dr McIntyre, and I think Mr Macniven thought we were talking about the same one. That's [SGH0028127].

THE CHAIRMAN: That's the one I have in mind.

MR DAWSON: This is the one that I described as starting the chain of correspondence between the members of the team.

A. Yes.

Q. Perhaps we could have that one up?

A. That's Archie McIntyre's minute of 6 April, 1987.

Q. Yes, that one. Could you just tell us which passage it is that you were referring to in that, which summarises accurately your understanding?

A. I suspect then that it was a different document. The document from John Forrester that I was alluding to a moment ago is his note of 12 June 1986, where it says:

"The condition is not, as a rule, serious".

Q. I think we have it up on the screen there.

A. Yes, that's correct. Paragraph 5 there is what -- is one of the two documents that I'm recollecting. The other document is not the note from Dr McIntyre that you were referring to and I thought it was, but there is another contemporaneous document, as distinct from the interim report of the Inquiry.

Q. So it's paragraph 5 there that you are referring to. There is another later document. I wonder if this might

be perhaps the one that you are referring to. That's SGH0024673. This again emanates, I think, from Dr Forrester. I apologise, I think I have referred to the second page. [SGH0024672] is the document.

Can we just flip over the page to 4673, just to verify the date of that?

A. I don't think that's the document that I was recollecting.

Q. Oh, right. I just thought it might be because of the reference there to the last passage, which goes slightly further, I think.

A. No, it's not that one that I'm recollecting.

Q. If you are happy that your position is accurately summarised by the document that we looked at immediately before this, I'm quite content to leave it at that, unless, of course, the chairman wishes me to probe this further?

THE CHAIRMAN: At the moment, Mr Dawson, I don't know where you are going. I don't know what the purpose of the questioning is and therefore I can't help you.

MR DAWSON: I'm trying to establish, sir, what Mr Macniven's understanding of the severity of the condition was. I think he has agreed with the passage in the previous document as being his understanding.

THE CHAIRMAN: He has also made it clear that there were

other documents that contributed to it and really, in fairness to Mr Macniven, who is not a medic, my intervention is related only to making sure that if you are going to follow that, you have to put to him the material that you think is relevant.

MR DAWSON: Yes, okay.

THE CHAIRMAN: I don't think that's unfair.

MR DAWSON: I appreciate that entirely, sir, and I am satisfied that I have explored it to the extent that I wish and so I will move on.

A. Yes, if it's material, I'm sure that given a more convenient moment to leaf through documents, I can identify the second document that I'm very clearly remembering but don't have to hand at the moment.

THE CHAIRMAN: You mustn't let yourself be put at a disadvantage, Mr Macniven. If you want to draw attention to a particular document, then when you get the chance just do that.

MR DAWSON: Thank you, sir.

Just moving on to slightly different topic, we discussed earlier that ultimately the purpose of this entire exercise was to consider whether or not a recommendation should be made to the minister to go down the route of surrogate testing. As I think you told us the last time, the factual position was that we

didn't get to that stage and it was your view, along with the advice of others, that it was not appropriate for the matter to go to the ministerial level. Is that accurate?

A. Yes, it is.

Q. Okay, thank you. My understanding is that in your role as assistant secretary, you were succeeded by Mr Tucker. Is that right?

A. Yes, it is.

Q. Could I just briefly take you to a passage in a report that he has provided for the Inquiry, which is [PEN0172060]? I'm looking in particular at page 2063. This is a report which he has provided for a separate section, the C4 section, which is to do with anti-HCV testing. Is this a document that you have seen before?

A. No, it isn't.

Q. I'll just take you through roughly what's being discussed here. This is a question that was put to him on the topic of anti-HCV testing, in which he is asked:

"A civil servant, Mr Tucker, himself sent a memo to Michael Forsyth, at the time Minister rather than Secretary of State, on 23 August 1989. The memo was prompted by an article in The Guardian regarding the Hepatitis C test. At the end of the memo it is stated that this was a UK issue and the Department of Health

was taking the lead. This appears slightly different from a position that the health departments were working together to appraise, and if appropriate, introduce the tests simultaneously. There is also the penultimate paragraph of page 3 of a certain document, which seems to suggest the Scottish decision would be taken in its own right on a recommendation from ACVSB. What was the position? Were the health departments for Scotland, England, Wales and Northern Ireland working jointly on the decision or was it an issue on which Scotland would follow whatever decision was taken in England? Was the formal position that the decision for Scotland would be taken in Scotland independently from the decision in England."

You will be pleased to hear I don't want to ask you anything specific about anti-HCV testing but I wanted just to refer you to a passage, which appears further below, about the procedure which was followed at this time. It was about half of the way down. You will see there is a passage starting:

"I am asked whether Scotland ..."

Do you have that?

A. Yes, indeed.

Q. He said:

"I'm asked whether Scotland would simply follow

England. The answer to this is yes and no. We would follow England if it was sensible to do so, for example in relation to the introduction of national testing where there was clear expert advice that this was the correct thing to do. We would not necessarily have followed England, if, for example, the ACVSB's recommendation had not been unanimous and had decided not to introduce testing. If we had contradictory Scottish expert advice, then ministers would have been consulted first."

It's really that last statement that I wanted to ask you about, because it seems on my reading that in relation, of course, to a separate issue at a different time, Mr Tucker is saying that where there was contradictory advice, in this case between the position in England and the position on expert advice in Scotland, if there were supportive expert advice for a certain course, although the English position was against that, the matter would be put to the minister.

As I understand it, the position in relation to surrogate testing was that you had a position in England that was essentially against it and there was a recommendation in Scotland in favour of it. What I wanted to ask you was whether the practice at your time was different from the practice that Mr Tucker has

pointed out, on the basis that you did not make a recommendation to the minister in those circumstances?

A. Yes, it's broadly speaking the same. As I explained the last time I was sitting in this seat, the task of deciding when to put an issue to ministers wasn't an absolute black and white one, which is why George Tucker is saying the answer to this is yes and no. But I agree with the thrust of what he is saying.

Q. I may not have made myself exactly clear. What he appears to be saying there is when there is contradictory supportive Scottish evidence for a particular course, that matter would be put to the minister. In your situation, that basic set of circumstances appear to exist but the matter was not put to the minister, so there appears to be an inconsistency in practice. I just wanted to explore that with you a little bit further.

A. No, with respect, this is a different situation.

Q. Okay.

A. He is talking about the -- is he not? -- the hypothetical question of an advisory council, the national advisory council -- covering Scotland as well as the rest of the UK -- the advisory committee coming up with a positive recommendation and Scotland finding reason to dissent. I was facing the opposite position,

that the constituted advisory body was recommending -- or was not recommending surrogate testing; by implication was against it -- was not recommending it.

Q. I think the advisory body that you were referring to is the Working Party On Transfusion-associated Hepatitis. Is that right?

A. I don't recall the precise title but there was a constituted body that covered the whole of the UK, which was advising both us and DHSS --

Q. Okay.

A. -- on this topic.

Q. Right. So you don't see any difference between the position being advocated there, which is the matter would go to the minister if a different position were being taken in Scotland, and the position with which you were faced?

A. There are two hypothetical questions there, I think, and as I have explained, the decision on whether or not to put a matter to ministers was a matter of degree, which wasn't black and white in quite the absolute way that you are seeking for. I'm sorry but there just weren't absolute rules that guided you in when to put a matter to ministers.

Q. Okay, thank you. Could I just ask you about a document which you wrote, which is [SGH00028076], please? I'm

sure this is a document you have been referred to before?

A. Yes, it is.

Q. I just wanted to look at it in a bit more detail with you. You see it's a document by yourself dated 2 October 1987. If we just scroll up to the top, we can see that it's going to Dr Forrester, Dr McIntyre and Dr Forbes, and if we could just read through it, it says:

"SNBTS: screening donations for non-A non-B Hepatitis:

"1. Thank you very much for your helpful minute of 1 October. Your final paragraph concerns timing. The PES timetable really requires us to reach a decision very soon on whether to earmark funds for the SNBTS for this purpose. I have, however, taken steps to get round this problem by registering with finance division that a need for NANB testing may emerge but (and this is the key point) it would be premature to allocate money to the SNBTS for the purpose at the moment.

"2. But I'm a little anxious about the timescale implied by your minute. I am very anxious indeed for our decision (on whether or not to put resources into NANB testing) should be properly informed by research evidence. If that evidence justifies testing, then it

is very important that we should be able to find the money to start it quickly. If it does not justify testing, it is equally important that we should not have allocated money to the SNBTS for the purpose, thereby sterilising it for other uses, but I think the worst of all possible worlds is that research cannot get off the ground. I fear that in those circumstances we would be subjected to increasingly irresistible pressure to spend the money in any case, for the sake of improving (at any price) the safety of blood and blood products.

"3. With that in mind, is it possible to expedite the feedback to SNBTS? I absolutely agree that we should not give feedback until DHSS has come to a view, but what is the timescale for that? What prospect is there for the biochemical research committee's feedback being given, perhaps on the basis of an informal meeting in the first place, very soon thereafter? I can well understand the general CSO disinclination to repair research proposals, but I hope that too much stress does not need to be placed on that principle in this case, because of the substantial patient safety/expenditure issues which are at stake."

So this is a little bit later in the timescale and obviously, as I think you described the last time, your concern at this stage was whether funding would be

earmarked for surrogate testing or not?
A. Yes, I was very keen to make sure that funding should not be the limiting factor if the scientific/technical light turned to green.
Q. Okay. So would I be correct in saying that at this stage the SHHD view was that research was required before surrogate testing should be introduced?
A. That there were problems with surrogate testing on which research could throw light.
Q. Okay. You say in this document that it would be the worst of all possible worlds if research could not get off the ground. What was your understanding of the nature of the research that was being proposed at this stage by the blood transfusion services?
A. I don't remember from the time but from reading the papers -- but you can read them as well and what I'm about to say may be a slightly inaccurate recollection of them. From the papers it was a study of donors who tested positive to ALT to see why -- to overcome or try to overcome the false positive/false negative problem, that the ALT test both ruled out the use or indicated against the use of blood which was in fact safe, and failed to pick up blood which was in fact infected.
Q. Did you think at that time -- I think this is probably inherent in what you are saying here -- that the

research would be likely to tell you whether or not surrogate testing would be of value or not?

A. It would give an indication. It wouldn't of itself overcome some of the problems that we saw around surrogate testing. But it would be a very helpful factor, as the tenor of my document at the time shows.

Q. Okay. At the beginning of paragraph 2 you point out that you are anxious that the decision should be properly informed by research evidence, and you say:

"If that evidence justifies testing, then it is very important that we should be able to find the money to start it quickly. If it does not justify testing, it is equally important that we should not have allocated money to the SNBTS for the purpose ... "

Are you asking Dr Forrester to give some sort of prediction as to what the research will show?

A. No, I'm asking him to unblock an obstacle to the funding of that research.

Q. Okay, and you then go on to say that:

"The worst of all possible worlds is that research cannot get off the ground."

Because in those circumstances you would be subjected to increasingly irresistible pressures to spend the money in any case for the sake of improving, at any price, the safety of blood and blood products.

Why would it be "the worst of all possible worlds" if research could not get off the ground at that time?

A. Because we would be taking the decision on information which was not properly informed by research evidence.

Q. Okay. From whom would the increasingly irresistible pressure come to spend the money on surrogate testing?

A. I think, as far as I can recollect, I would have been reflecting there the same kind of pressure that had led the directors earlier -- the SNBTS directors earlier in the year to change their tune.

Q. Is it the position that at this stage your view was that research was the number one priority, no matter what the nature of that research, because if you didn't have research, then you would have to make a decision and that decision would, because of the irresistible pressure, be to introduce surrogate testing?

A. No, not any research, research that threw light on the question that I described a moment ago.

Q. Okay. Thank you very much indeed, Mr Macniven.

Thank you, sir.

THE CHAIRMAN: Mr Anderson?

MR DAWSON: Excuse me, sir, Mr Di Rollo has just pointed out to me that he has located a document which may or may not be the one that Mr Macniven referred to earlier, which may save him some further research. It's

[SGH0028142].

A. This is one of the two documents but it's the one that I have already identified.

MR DAWSON: This is the one where you accepted the content of paragraph 5, I think.

A. That's right. That was one of the two documents I'm remembering. I'm very grateful to Mr Di Rollo for his researches but I am afraid I will have to continue them myself.

MR DAWSON: My apologies, sir.

Thank you Mr Macniven.

THE CHAIRMAN: A polite civil servant's way of dismissing the effort --

A. At least it was polite.

THE CHAIRMAN: Mr Anderson?

MR ANDERSON: I have no questions.

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: I have no questions.

MR MACKENZIE: I have no further questions for Mr Macniven but I would like to spend five minutes just tidying up the topic.

THE CHAIRMAN: Mr Macniven, thank you very much.

A. Glad to help.

Final matters on topic C2

MR MACKENZIE: Could I just have five minutes to finish the

topic by referring to various documents, particularly statements from witnesses who have not been asked to attend the hearings and also one of the ancillary documents as well.

THE CHAIRMAN: Take it reasonably gently, please, since this is taking us back quite a way. Take it reasonably gently, please.

MR MACKENZIE: I think it's helpful to do it with reference to the inventory for this topic, which we find at [PEN0172637]. This is a very full and helpful inventory prepared by Miss Marsh for us. If we just go through firstly, sir, Dr McClelland, we will see there is a shaded document, a response to request for data on ALT threshold. We won't have to go to it.

THE CHAIRMAN: Could you just stop because my copy of the inventory, hard copy, has got a blank against this --

MR MACKENZIE: I see, it's [PEN0172667].

THE CHAIRMAN: Thank you.

MR MACKENZIE: In short, this is a series of emails between Dr McClelland and a colleague in Germany on the question of the ALT thresholds in Germany. I refer to the documentation for completeness but I don't think it does actually materially add to the existing evidence.

As regards Professor Cash, the last document under his listing, "Comment on ALT Testing of Plasma", the

document is [PEN0172635]. That relates to Professor Cash's supplementary statement. He had raised the potential issue of proposals made in England in 1990 and again in 1994, to test plasma sent to BPL for ALT, and we asked a number of witnesses: was that proposal given effect to, did that in fact happen? That document is Professor Cash's response. He thinks it may not have but, like the other witnesses, he simply can't say definitively. It's a "for completeness" question.

Under Dr Ruthven Mitchell, Dr Mitchell voluntarily provided us with a statement on shortages of donor blood. It's [PEN0172805].

THE CHAIRMAN: 2806 or 2805?

MR MACKENZIE: 2806, I'm grateful.

I don't propose going to that document. It's again in the "for completeness" category.

Dr Eddie Follett has provided a short commentary at [PEN0171860] on both the C2 and the C4 topics. I say "commentary", it's really short comments. Again, I don't propose going to it.

THE CHAIRMAN: It's very short indeed.

MR MACKENZIE: It's very short.

And then returning to the inventory at the bottom of page 1, on the question raised by Professor Cash in his supplementary statement of the proposed ALT testing of

plasma sent to BPL in England in 1990 and 1994, we also asked Dr Foster and Dr Perry for their recollections as to whether that in fact happened. In short, they think it may not but can't say definitely, and their respective statements on that are [PEN0172636] and [PEN0172777]. Over the page there are some more substantive documents, albeit still, I think, secondary to the evidence that has been led at hearings.

Firstly Dr Forrester. He has provided voluntarily an email of 3 December 2011 of what he understands by the word "benign". I think that may not in fact yet have a court book reference number, and I think in fact it is being treated as a new application, which I think is still outstanding.

So I refer to this email here for completeness but one will have to wait and see what the outcome of that application is. I think it has been circulated to the other parties and I think we are perhaps waiting to hear if anybody objects to that being received as evidence. And if it is received, then it would be of course under the category of untested evidence. It would be there for what weight it can be given. We can provide a court book reference for that once we have it in due course.

Dr Scott, sir, has provided a principal statement, [PEN0171850] and a supplementary statement,

[PEN0171854]. They are worth looking at. I won't take you to them now, sir, but they are reasonably short documents setting out Dr Scott's recollection, such as it is, on the question of surrogate testing. But I think the better or the fuller evidence has been given by Dr MacDonald, who of course attended in person and was in fact the CMO.

Then Mr Murray provided a statement, [PEN0171755]. He didn't attend but we did go over his statement in some detail with Mr Macniven, so we are aware of the contents of that, and it's quite helpful, setting out the procedure for the PES bids and how they were dealt with.

Dr McIntyre is unable to attend but he did provide two short statements, [PEN0171856] and [PEN0171858]. Again, useful to look at but I think the better evidence has been led at the hearings. So the fuller evidence has been led at the hearings.

Then, sir, Dr Moir was in the chief scientist's office at the time and his statement, [PEN0171941], is in respect of the refusal of the Gillon/McClelland application in 1987 for funding to take part in the UK study on surrogate testing. This statement is worth looking at for some of the general background but I don't think it materially adds to what we have heard

in evidence about the reasons for the refusal of the application.

Then Dr Moir produced a further response, [PEN0172489], in response to a separate point raised by Professor Cash, namely the reasons for the disbanding of the MRC blood transfusion committee, and Professor Cash has suggested Dr Moir might be able to help in that regard. In short, Dr Moir isn't able to help us.

Then, sir, three final matters, which aren't in the inventory. Firstly, if we can go, please, to [PEN0172803], sir, you may recall the question of the precedence book.

THE CHAIRMAN: Yes.

MR MACKENZIE: Thank you. We will see that the Scottish Government had helpfully provided us with an emailed response of 29 November 2011. I think we can just read for ourselves what is said there.

THE CHAIRMAN: Yes.

MR MACKENZIE: It may still raise various questions, sir, but I'm not sure we can take that any further.

THE CHAIRMAN: No, if it was the sort of document that was used on a temporary basis and then discarded, there is not very much we can do about it, although it might have been interesting if we had been able to have it in its original form. At least it removes the suspicion that

I had that it might be some sort of style book that could be drawn on by others who were trying to prepare submissions of one kind or another.

MR MACKENZIE: Thank you. Then another email, please, [PEN0172805]. This is an unprompted email from Professor Leikola, clearing up one minor point of detail in his evidence. It's 2 December 2011 and it's not the first paragraph. We can see the return trip went uneventfully and the same wind and rain welcomed him in Helsinki. It's not that, it's the next paragraph, the question of Vox Sanguinis and his attendances.

THE CHAIRMAN: Yes.

MR MACKENZIE: The final matter, sir, to conclude this topic: I felt I ought to return to the question of positive predictive value. That was something I side stepped at the time but I have now had the chance to go and look in a dictionary, in particular the Cambridge Dictionary of Statistics in the Medical Sciences. It's the first edition in 1995. It provides this definition. I think the term is really self-explanatory, namely:

"The probability that a person having a positive result on a diagnostic test actually has a particular disease."

PROFESSOR JAMES: That's very crisp.

MR MACKENZIE: Sir, that now concludes the topic C2 and we

return, perhaps after a break, with Professor Hayes on C6.

THE CHAIRMAN: Thank you very much. I think that's an appropriate time to break, even though it's a little bit early.

(10.42 am)

(Short break)

(11.14 am)

PROFESSOR HAYES (sworn)

Questions by MS PATRICK

THE CHAIRMAN: Yes Ms Patrick?

MS PATRICK: Sir, Professor Hayes this morning is speaking to the topic C6.

I would like to start, Professor Hayes, with your CV. Unfortunately the fuller version, which we were discussing earlier, has not made it into our court book system. You did provide us with a much abbreviated version, which is [PEN0180237].

Sir, I'll make sure the extended version is lodged into court book and provide the reference for everybody, when I can.

This confirms that you are professor of hepatology and honorary consultant gastroenterologist at Edinburgh Royal Infirmary. When did you become a consultant there?

A. In 1990.
Q. Right. A professor?
A. In 1998.
Q. Previously you obtained your medical degree in Dundee?
A. I did, yes.
Q. And MD and PhD, was that based in Dundee?
A. The MD was based in Dundee and the PhD in Edinburgh.
Q. Right. You tell us that your responsibilities as consultant hepatologist are both in the centre for liver and digestive disorders and in the Scottish liver transplant unit.
A. Yes.
Q. You are lead clinician for Hepatitis C management in Lothian and the designated hepatologist for the Edinburgh haemophilia unit.
A. The second part of that is true. I share the lead responsibility now with a Dr Bathgate.
Q. When did you first start working with the Edinburgh haemophilia unit?
A. I suspect in the early 1990s. I can't remember exactly when. I was appointed in 1990 as a consultant and I should think slowly became more involved with the activity of the haemophilia centre in the early 1990s.
Q. You say there "recent president of the British Society for the Study of Liver"; how recent is that?

A. I demitted office in September this year. So it was a two-year post.
Q. You are also very actively involved in research. How much of your time is taken up with research?
A. It's supposed to be 50/50 in my contract. The research -- very little of it over time has been in the laboratory. The vast majority is involving patients. So in fact my research and clinical activity overlap quite a lot. It varies considerably as the years have gone by. I remain research active.
Q. And your main research interests, what are they?
A. Primarily portal hypertension, which is a complication of cirrhosis that leads to problems in patients who have cirrhosis, but I have been interested in many other aspects of liver disease, including Hepatitis C and liver transplantation.
Q. Yes. With regard to Hepatitis C, having started as a consultant in 1990, presumably you have been involved in the treatment of Hepatitis C since, really, the early days of it?
A. Absolutely, yes.
Q. You have provided the Inquiry with a report. The reference for that is [PEN0180240], and this report was in response to questions which the Inquiry posed to you, and the reference for these questions, which I don't

need to look at just now, is [PEN0180238].

So we are looking firstly at the what treatment might have been available for patients before the Hepatitis C virus was discovered?

A. Yes.

Q. And you point out that at this time the obvious difficulty was that it was an unspecific diagnosis?

A. Yes.

Q. And so patients who presented with jaundice or had abnormal liver tests might be diagnosed as suffering from non-A non-B Hepatitis. Was that usually the case if a patient presented --

A. No, many people have abnormal liver function tests, for example, nowadays probably one of the commonest would be obesity. That was less of an issue in the 1980s but it wasn't really appreciated that things like obesity and diabetes could cause abnormal liver tests. So there were many, many causes -- there remain many, many causes -- of abnormal liver tests that are not viral, such as alcohol.

So a diagnosis of non-A non-B wasn't really considered in patients where an alternative explanation could be found and it tended to be triggered -- or it's likely that it would have been triggered if somebody had had a blood transfusion and then had abnormal liver

tests, and that's really where the concept of non-A non-B being a virus came from. So if somebody just had abnormal liver function tests, it's relatively unlikely that a putative viral diagnosis would be made, but on the other hand, if somebody had had abnormal liver function tests following a blood transfusion, then that's more likely.

But my understanding is it was not a very common diagnosis.

Q. No.

A. No.

Q. And you tell us further down that not all those who were at that time thought to have non-A non-B Hepatitis represented Hepatitis C?

A. Absolutely. The term "non-A non-B" was not well defined and you can find references for "enteric", which means GI-tract-related or acquired by the oral route. Non-A non-B, I mean, clearly that's not Hepatitis C. So many people who had non-A non-B wouldn't have had Hepatitis C and many more who had Hepatitis C wouldn't have been labelled as "non-A non-B". For example, a lot of people were found to have a combination of alcoholic liver disease and Hepatitis C. Before the discovery of the virus, they would be labelled as "alcoholic liver disease" alone, whereas, you know, to have two risk

factors would now be recognised.

So it was a woolly diagnosis.

Q. And presumably that made treatment of it difficult at that point?

A. Well, a lack of certainty that there might be a virus; how you pick them up with abnormal liver function tests; what you would be monitoring if you were to treat them and the lack of proven effective treatment. And it wasn't really until around 1986, when there were suggestions that interferon might be successful; but these earlier reports were small and they were inconclusive in the sense that were we really doing long-term good.

Q. If a patient presented with jaundice, how was that treated?

A. If somebody presented with jaundice after a blood transfusion, then -- we now know that actually that's a very unusual presentation for Hepatitis C. The vast majority don't get jaundice. But if somebody became jaundiced some weeks after a blood transfusion, people would say this is likely to be non-A non-B and they would be monitored and no specific treatment would be given, as there wasn't anything proven to be effective, and this is likely -- I actually cannot remember a case in that situation.

Q. Was there a time when somebody with jaundice was seen as infectious?
A. People who are jaundiced are considered at the present time and in the past as potentially infectious, depending on what the cause of the jaundice was. So if they were found to be Hepatitis B, they would be considered infectious. If it was after a blood transfusion and non-A non-B was considered, then being a virus, it is likely they would be considered infectious. But the natural history of that infectivity and the risk factors really didn't become clear, other than related to blood transfusion, until Hepatitis C virus was discovered.
Q. You tell us in the second paragraph that the first treatment that was found to be successful in some cases was human Alpha interferon?
A. Hm-mm.
Q. Were other treatments tried before then that were unsuccessful?
A. There are reports in that paper of people trying things like steroids, but it's remarkably difficult to treat a condition if you don't have the cause. You are likely to be treating people who didn't have the virus. So I think it would be fair to say that Alpha interferon was the first drug that looked promising but, although

it was in a very famous medical journal, the New England Journal of Medicine, if you were to try and prove nowadays with a study of ten people, that a treatment was effective, you wouldn't persuade many people, and in that study they took ten pairs where they had a diagnosis or a putative diagnosis of non-A non-B viral infection and gave them Alpha interferon, and all they could monitor to see if it was being effective was their liver function tests and they found that these tests improved in some.

When they stopped the interferon, they would deteriorate in some, and they did some liver biopsies before and after treating some of the patients and suggested there might have been some improvement, but it was not conclusive proof that interferon was an effective treatment, which is, in hindsight, what we would expect once there had been far bigger studies, once the virus had been identified.

Q. What had interferon been used to treat before this study?

A. Interferon is a drug that had been produced recombinant with technological methods. The interferon is a natural substance the body makes to fight viruses, so it was developed with the idea that it might be used for viruses. I'm unaware in 1989, around that time, there

was -- it was a standard treatment for anything. Subsequently, variations have been used in MS conditions, yes.

Q. Thank you. The article that Professor Hayes was referring to, sir, is [LIT0013806].

You say that you have no personal recollection of using interferon treatment in the setting of non-A non-B Hepatitis.

A. No, I have used it around -- it must have been around that time -- for Hepatitis B, a different liver viral infection, which was being considered at that time but I have no recollection of ever treating somebody with interferon before 1991 or something like that. I was only a consultant in 1990, so it would be unlikely that I would be leading treatment before.

Q. Moving on to the next section of your report, if we could scroll over to page 3, you tell us in the second paragraph there that once the virus could be identified, drug trials showed in turn that firstly Alpha interferon alone, three times weekly, appeared effective in clearing the virus in a minority of patients. And further down, if we could scroll down, please, under the paragraph 3, you tell us that this was really introduced in clinical practice around 1991 and 1992.

Then in 1995/1996 ribavirin was added.

A. These would be the times when there were reports coming out they might be successful, publications, being introduced into clinical practice, outwith trials would be a little bit later than that. So reports with ribavirin. So pretty soon after the virus was discovered, because of the early suggestion that interferon might work, it didn't take long for interferon to be used in the patients shown to have Hepatitis C. As you say, it was not particularly effective, probably around 20 per cent of people were cured and the haemophiliacs, probably that number was quite a lot less.

One of the difficulties at the time was to know if and how you had cured somebody. What was the definition of "cure"? We knew that after treatment, this condition would relapse. So if somebody was negative for the virus after it had been treated, how long did you have to monitor them before you could be certain that they weren't going to relapse later on? And the figure of six months appeared.

Obviously these things take time but very few people who are still negative for the virus six months after finishing treatment will relapse, whereas quite a number who were negative at the end of treatment would relapse within the first six months.

So the idea of curing people took some time to be accepted.

Q. You mention a six-month figure?

A. Yes.

Q. When did that figure start to be used?

A. I think that figure was probably being used between 1992/1995. There would be debate and dispute about these things but we certainly recognised well that people relapsed after stopping treatment, and one of the advantages of ribavirin, probably, was that it reduced the risk of relapse.

So many people would show some response to interferon but it became clear that actually only 10 to 20 per cent would maintain this clearance of the virus. When ribavirin -- I think the suggestion that ribavirin might be useful probably was appearing around 1994/1995/1996, but it wasn't introduced into standard clinical practice for some years after that. The bigger trials were required to show effects there and they were in the late 1990s.

Q. Right. So to recap, these dates you have given us for the introductions of the treatment, is this when patients might have received these treatments as part of a clinical trial?

A. Yes. So the requirement for drugs to be licensed and go

through regulatory approval and local formal approval evolved over the last 20 years. So interferon was probably used locally in Edinburgh early on, around 1991/1992/1993. Ribavirin was probably introduced locally later than I have down there as 1995, 1996, when it was used in trials, and pegylated interferon, the slow acting, the longer acting, interferon would be well into 2000s.

Q. So as a patient, if you wanted to receive treatment with these, your first opportunity to do that would be to take part in a clinical trial?

A. Not all areas or patients would have access to clinical trials. The clinical trials tended to be dominated by a small number of companies and they would run trials really for regulatory authorities in the US and Europe, and you might be "lucky" enough to be in a centre where they were recruiting for clinical trials or you might not.

And access to that newer treatment wouldn't be available outwith clinical trials until it had been approved and licensed. That process is now far more vigorous than it was going back 20, nearly 30 years. Nearly all the clinical trials at that time would require the patient to undergo a liver biopsy before treatment and after treatment, and we didn't consider

that that was likely to be in the patient's best interest in people with haemophilia. So the haemophiliac group of patients we didn't feel would be particularly suitable to be going into trials.

Q. So patients with haemophilia were less likely to benefit from the trial of these treatments?

A. They were less likely to be exposed to the trial situation. Some trials -- I mean, the trials we are talking about here were successful. Not all clinical trials show benefits. So I don't think not being in trials was a major disadvantage. The standard trials would have a standard treatment in half the patients generally and the new treatment in half and compare them. So even if you went into a clinical trial, you were just as likely to have the standard treatment as the new treatment.

Q. And the time between trying to be part of a clinical trial and not and then eventually getting the treatment --

A. Would be some years.

Q. -- would be some years, and the effect of that on the virus?

A. It's generally believed the earlier you have treatment, if you have Hepatitis C, the better the potential outcome, but since the natural history of the infection

or the natural history of the condition from the time of infection until it causes problems is measured in decades rather than years and some people will have the infection for 60 years and not have cirrhosis at the end. So to wait one, two, three, four, years, I don't think would be considered a major disadvantage.

Q. But it does mean that there is a difference in treatment which a patient receives, depending on where they live. For example, if they are not living near a centre --

A. Absolutely. Absolutely. And whether they were prepared to have a liver biopsy, which is a potentially dangerous and not very pleasant procedure, and in a trial you would have two of those, one at the beginning and one at the end, and that's not without risk.

Q. Would you tell us about liver biopsies? What do they involve?

A. A liver biopsy -- generally the standard method for doing a liver biopsy is to anaesthetise an area of skin between your ribs overlying the liver, and once that's numb, then to put a needle down into the liver and remove a small piece of liver tissue. That's the standard way of doing that. That can be done at the bedside. There are other ways that are adopted that can be done with ultrasound examination, and there is also ways of doing it through the neck, where you put a long

needle down through veins in the neck, down to the liver. The reason that's done is that, not unexpected, if you stick a needle into an organ, it can bleed afterwards and it needs to stop of its own accord. If you do it from inside a vein, it bleeds back into a vein.

So that, some would consider, a safer but still quite unpleasant procedure. So the standard way of doing it is at the bedside, under local anaesthetic, taking a small sliver of tissue but it's not without complications of haemorrhage and even death.

Q. Right. I was going to ask you the risks. So they are of haemorrhage --

A. Haemorrhage requiring a blood transfusion. To have pain afterwards would almost be the norm. So that's --

Q. How painful is it?

A. It can be extremely painful. It seems to be very variable, whether it's to do with the patient or the amount you are bleeding afterwards. Everybody will bleed a little bit after a liver biopsy ends. Whether that stops on its own or doesn't. Transfusion is unusual and deaths would range from round about 1 in 10,000, that sort of case. But the haemophiliacs -- this was considered not to be a sensible risk to be taking unless it was required for clinical practice.

Q. And what is the position about that now?
A. Things have changed quite a lot, the requirement for liver biopsy. The method that we adopted locally was we like to see the liver as we did it, and we put a very small telescope into the abdomen and put gas to give you a view and then we would do the biopsy, seeing directly the liver and where the biopsy went into, and when we did this in patients with haemophilia under very close monitoring from the haemophilia doctors -- we originally did do biopsies and latterly we didn't do the biopsy, we just inspected the liver and gained information from inspecting rather than increasing the potential risk by taking a biopsy.

So in trials, clinical trials, you were mentioning, liver biopsy was an important end point: did the liver look better compared with before? In trials it's still quite common they will want biopsies. It's a good, objective outcome.

For a clinical practice, when it came to treating individual patients, in the early days it was thought that a liver biopsy was important and some people would consider that a means of selecting patients who needed the treatment more at the time we were introducing the treatment and those who could wait, and that was certainly how I would interpret the NICE guidelines for

1 treating Hepatitis C.
2 Q. Which we are going to come on to.
3 A. Which we will come on to.
4 Q. Yes.
5 THE CHAIRMAN: Your method was the laparoscopic approach.
6 When did you start doing that? Was it always the
7 approach?
8 A. No, I would say it's still a relatively uncommon way of
9 doing it. It wasn't unique. There was a literature on
10 it. I would be guessing, I think it was probably before
11 I was a consultant we started. So I suspect in the late
12 80s, that we did locally; other people had a large
13 experience of doing that before.
14 THE CHAIRMAN: I suspect that Professor James has got more
15 interesting questions to ask.
16 PROFESSOR JAMES: They are really just a couple of
17 clarifications. Concerning those trials, particularly
18 let's say, from 1991 to the late 90s, just for
19 clarification, the need to have the biopsy before and
20 after, it wasn't some kind of whim. I mean, it was that
21 the regulatory authorities felt at that time that this
22 was perhaps the best way of demonstrating the efficacy
23 of the trial?
24 A. Yes.
25 PROFESSOR JAMES: And that's why it was very important. You

will appreciate that there are a number of people, you know, who are involved in this Inquiry who may feel that they "missed out on treatment" because they weren't in a trial and so on.

A. Yes.

PROFESSOR JAMES: I just wanted to ask -- and perhaps you would confirm -- that that was the case. The point about the biopsies was, you know, that that was done for good regulatory reasons at that time. It may well not be so important now for --

A. Absolutely. To go into clinical trials, there were strict criteria and one of them was that there was a biopsy before and after treatment.

Biopsies are unpleasant and potentially dangerous and some people, who may have had a liver biopsy, could go into a trial later because they had had a baseline biopsy within, say, six months. But that's splitting hairs a little bit.

So to go into a trial, you usually require two liver biopsies with all the risks and problems. As I said, by definition you wouldn't do a trial if you knew the treatment is going to be successful. So not all trials -- I mean, these trials led to improvement but it would be true to say that taking part in a clinical trial does not guarantee you better treatment.

I mean, there is a learning curve associated with treatments and going into a trial. You will be earlier in the learning curve if there are going to be complications. So I don't think there was an awful lot of delay for the interferon but once trials were required really for guidelines and change in management, then there would be a delay from setting up the trials, because some of the trials would require treatment for a year and then you would have to follow the patients, so there is necessarily a delay from when the trial is conceived to it being published and accepted of some years.

PROFESSOR JAMES: The second point: you implied, and I obviously very strongly agree with you, that actually, you know, no real definite knowledge that even interferon on its own, which after all was probably only really effective in 10 to 20 per cent of patients -- there was no real knowledge that it was proven to work in this minority of patients until there was good ability to quantitatively measure the HCV RNA, sort of before and after, and that really we regard now as very commonplace but actually that methodology took a number of years after the measurements of anti-HCV and so on, didn't it?

A. With hindsight it's easy to look back and say these

people were cured or not. But going forward at the time, I mean, I was involved in the publication which sadly, I suspect, is now incorrect, but we thought and reported that we could identify virus in the liver, still in the liver, in people in whom the virus couldn't be detected in the blood, and if that were true, then this raises big doubt about whether you are actually curing anybody or whether you are providing a holiday period from the virus.

So I agree, it's easy to tell patients the risks, chances of cure, et cetera, but it certainly wasn't --

PROFESSOR JAMES: And my final tiny point, really for clarification, is that in those years, in the early 90s, there were terrible complexities about you were in a trial, then the drug had to be licensed by the Committee on the Safety of Medicines, then it had to be in the British National Formulary, and then it had to be adopted by your area in the local formulary, and then there was the question of funding, whether that would be provided by your hospital or by your region and so on, or whether exceptions could be made to this, and these were a very difficult thing for a clinician and their patient to sort of find their way through sometimes, weren't they?

A. Yes, absolutely. I think that we are so used to the

idea of drug approval and regulation and guidelines that we think that they will always have been there but actually, the first set of guidelines about treatment, I think, was round about 1998, which was the NIH, National Institute of Health, in America, giving consensus views about how to treat it. So for 1991 up until that time, there would be considerable variation in treatment and there would be undoubtedly less homogeneity in the pattern of treatment across the country than there is now.

PROFESSOR JAMES: Thank you very much, sir.

MS PATRICK: I wonder if you could clarify for us what the BNF and the local formulary --

A. BNF is the British National Formulary, which is the tome of drugs that doctors receive at regular intervals, that will give you backgrounds of how to prescribe and what are the risks, how much they cost --

Q. Who is responsible for that? Who provides the information for that?

A. I can't answer that question. It's a publication that has been around for a long time. It will be a regulatory authority and it will be related to the licensing authority.

PROFESSOR JAMES: Yes.

MS PATRICK: And the local --

A. Local formularies are relatively more recent and when a drug now appears in journals that it looks as though it might be successful, that will be submitted by the pharmaceutical company generally to the regulatory authorities, and that will either be licensed or not licensed and that means it can appear in the British National Formulary.

However, there are a number of hurdles now that need to be jumped over before you can prescribe it to an individual patient and that will be in England, whether it's approved by NICE, and in Scotland by the Scottish Medicines Consortium.

You are not really allowed to prescribe it until it has been through that and then once it's nationally approved, then the local authority, the formulary, will have a view on who should it be prescribed to and fundamental questions of who is going to pay for it.

So it's quite a different situation that we have now, where it really looks fairly standardised, albeit slow, compared with the situation 20 years ago.

THE CHAIRMAN: At local level, will an individual hospital have a particular formulary or will it be an area?

A. It will be an area, generally an area.

MS PATRICK: Having done some research here, the BNF is a joint publication of the BMA and the Royal

Pharmaceutical Society.

A. Google is great.

Q. It is indeed. I would like to move over to page 4 of your statement and look at other aspects of care and treatment of patients with Hepatitis C.

You speak in the first line about counselling for patients and I wonder in what way you mean "counselling". Are you meaning counselling in the way of providing information --

A. Yes, and support. So it's perhaps not a very specific title. Locally, for example, in the early days, when it was clear that this led to liver disorder with potentially serious complications and there might be a treatment, it was thought sensible that a hepatologist or a liver specialist should be involved with seeing the haemophilia patients rather than just the haemophilia specialists.

Rather than asking the patients to come to extra clinics locally, I would go along to the haemophilia centre and see the patients generally, at the same time as the haemophilia specialists, usually Professor Ludlam, and we would go through the process, depending on whether the individual knew they had Hepatitis C.

If they hadn't and this was the first time they were

being told, we would try and give them the information that was available about the natural history and the problems that they may or may not have, what symptoms perhaps could be explainable about the condition, how they may transmit it, what are the risks to the family, and then go on to discussing any treatments that might be available and whether they wish to be considered for treatment or whether they wish to defer it until there were better treatments. And not everybody wanted to go into treatment particularly, when they had heard about the relatively poor success rates and side effects.

People will often ask other questions there, such as about alcohol and whatever. So we would try and give information in a fairly standardised way to each of the patients on a one-to-one basis, when they came through the centre. And as time went on, and they may or may not have opted for treatment with the standard interferon, which was given three times a week by injection, when treatment had improved and a second line of treatment, which would be that same drug but with oral ribavirin, and then five years later or so when pegylated interferon, the slower acting interferon, which is just once weekly injection -- each of these had an improved outcome, more people were cured, and we would discuss with the patients, you know, at subsequent

visits. So the counselling would be different and we would have more information that we could give them.

So over the years, that counselling will have changed. It's more advice and answering questions.

Q. I'm wondering more about emotional support in dealing with a diagnosis like this, "counselling" can imply to people a more touchy feely, looking after your psychological wellbeing. Was that given to patients in the early days?

A. I think you would have to ask patients whether I was touchy feely. I like to think that we provided a reasonable level of support and I believe that we did. I'm not sure not everybody would agree with that. There was around this time discussion about HIV testing and whether there needed to be pre-testing counselling, whether you need to discuss with somebody before you did the test what the consequences were. And there was discussion whether this same should apply for Hepatitis C. Should you ask people's permission and give them counselling, what the implications might be before testing for the Hepatitis C. And it was thought that that level of counselling wasn't necessary, that if somebody had abnormal liver tests or a risk that it was good clinical practice, that you should find out what was wrong with the liver, which would mean measuring

Hepatitis C.

But I'm sure that the haemophilia group compared with many other patients who had Hepatitis C will have had far more counselling.

Q. Yes. And you are obviously talking about your experience in providing this service in Edinburgh Royal Infirmary.

A. Yes.

Q. You do point out that the question of counselling and other holistic care will have varied from unit to unit. Do you know anything about what counselling and such care might have been given in other areas?

A. No, I can't really comment on that from personal experience, no. But I'm sure it would vary with different doctors within a hospital, and it was relatively standardised that I was the individual that would, with the haemophilia doctor, give the counselling.

For example, a lot of patients were interested in alternative medicine. There are medicines that are sold and purported to have beneficial effects on the liver and they would often ask that and I would try and give them an answer that I thought was scientific, and that was that if they were shown to be beneficial, then I would be prescribing them but if they wished to

purchase them themselves -- so that's holistic.

More recently, issues -- and at that time people would ask about alcohol: was it reasonable for them to continue to take alcohol, and more recently obesity. We give people advice and then even more recently we might mention to them coffee.

So I think that over the years the level of counselling will have changed and many of the patients will have been unfortunate enough to have numerous sessions with me.

Q. And in the earlier days, what would the advice about alcohol have been?

A. I think our advice about alcohol probably hadn't changed very much, and that was people who had Hepatitis C that were short of cirrhosis, did not have cirrhosis, they could drink within sensible limits, 21 units for men and 14 for women. And I can't recall telling people at that time -- but we certainly do now if they have cirrhosis of any cause -- that they should drink no alcohol.

But in the early days, when relatively few would have cirrhosis, then it was generally discussions about did they have to be tee-total or could they drink small amounts, and if they clearly -- this is -- again, the population of people with Hepatitis C overall tend to have a higher prevalence of alcohol abuse than the

haemophiliac population.

It was quite a big issue to discuss alcohol abuse with the Hepatitis C patients who may have acquired it from drug misuse, for example.

Q. Does the practice in relation to the advice given about alcohol vary from place to place?

A. I suspect it's fairly standardised. There were documents written which Professor Ludlam would be involved with, that I have seen, that would suggest that it was fairly homogeneous that the less the better, I think was said, but that 21 units for men and 14 units for women in a week would be unlikely to have a significant effect on the progression of their liver disease. But we certainly now -- people who have cirrhosis -- would recommend that they are tee-total and I suspect we have said that for many years.

Q. Sorry, bear with me a minute. (Pause)

Sorry, I would just like to take you back to something you said earlier in relation to the counselling matter. You said that there wasn't pre-test counselling in respect of the Hepatitis C virus. Does that mean that the test was carried out without the patient's knowledge? Or could it have been?

A. In many cases the test for Hepatitis C would be undertaken in patients with abnormal liver tests. I'm

not talking about the haemophiliacs specifically because I'm not in the best position to tell you, in the haemophilia centre, exactly what was happening in 1989/1990, when this was an issue. But many patients, probably the majority of patients with Hepatitis C, would have had that test done, either specifically, because there was a risk factor such as having a blood transfusion or injecting drugs, et cetera, and that would now be considered part of good practice to test people, or it was done because they had abnormal liver tests, when we would undertake what is generally called a liver screen, where you measure or test for anything in a standardised way that can cause liver disease. So you would test for other viruses, such as Hepatitis B, you would check Hepatitis C, you would check they didn't have genetic liver disorder, you would check for immune disorders, as part of good care. And if you were to omit that, that would be considered not good clinical practice.

So the majority of patients now with Hepatitis C testing, unless it has been done specifically for Hepatitis C screening, will have this done as part of a liver screen. And it would be nice when people have these tests done that it is explained to them what tests are being undertaken and detail about that. I would

say, for example, "I'm going to test for viruses in the liver," I wouldn't specifically go through individual ones.

It does not seem to have been a major issue but I know in the early days in the haemophilia centres, there was discussion about consent, should it be obtained in the same way that it was for HIV beforehand, and I'm led to believe that that was considered not good practice. But I'm sure that in the early days, when the haemophilia patients were being screened for this, there was a lot of discussion about this but, as things have evolved, to test for Hepatitis C is generally part of a liver screen, rather than specific.

PROFESSOR JAMES: Could I perhaps just add to that?

I thoroughly support, obviously, what Professor Hayes has said but the other side of the coin for the liver screen -- and we are in a position where, whether people did give their permission for a test is a live issue in the Inquiry, but you have got to look at the other side.

Professor Hayes sees people with abnormal liver tests and if he took them through the ten most likely possibilities for the cause of their abnormal tests, a number of patients would be extremely frightened by those possibilities. So good practice is to do the

tests and then try and tell the patient about what's wrong with them, not the other nine conditions that might be wrong with them.

I think that would be fair, wouldn't it, Professor Hayes?

A. In practice it does not seem to cause many problems.

PROFESSOR JAMES: No. Thank you, sir.

MS PATRICK: In practice, if you tested a patient and the test result came back positive, when would you convey that information to the patient?

A. That will vary, I am afraid, considerably, on the clinical circumstance. For example, the commonest situation I would have had would be a general practitioner will write into me at the hospital and say, "I have tested Hepatitis C in this person, abnormal liver test. It has come back positive. Will you see and advise?" So it may well be that weeks and months will go between the test and being seen and the explanation given.

The haemophilia cohort is somewhat different to the practice that we would generally be exposed to now, in that it's likely that the vast majority of them were screened early on and given that information. It would be unusual now to find somebody with haemophilia whose Hepatitis C has not been checked and is positive --

very, very unusual.

Q. Thank you. I just want to go back briefly. We were discussing the impact of alcohol.

The Inquiry has heard evidence that acceleration from fibrosis to cirrhosis can be increased if alcohol is consumed, which would tend to suggest it might be better to resist alcohol altogether at an earlier stage than cirrhosis?

A. I'm sure it would be advisable for the whole population not to drink ever again, but the evidence that we had, and we generated some locally, is that people who drunk -- I actually think in the early days we took 50 as a cut-off when we were looking at cohorts and what people report they drink and what they don't. But the concept that is generally given of these sensible limits, I'm unaware that it was ever teased out that there was a dose response that meant we should limit the amount of alcohol.

We say for patients with cirrhosis, they shouldn't drink any alcohol, not because we know that to be true but we do not know of a safe limit. So it's believed that if you, as a man, drink 21 units or less than 21 units in a week, you will not develop alcoholic liver disease, you may lose brain cells and whatever but you won't have alcoholic liver disease. Clearly, if you

drink 22 or 30 or 40, there will be a small risk and that will increase.

So in cirrhosis it may be that we are giving advice that's not particularly fair. There may be a small amount of alcohol that we can take but that has never been dissected out -- and I suspect that that study will never be done -- to allow people with cirrhosis to take five units of alcohol.

So it does seem, I would accept, rather all or nothing, that if you have Hep C and you are drinking within sensible limits, that's probably okay, and that if you, a year or so later or two years later, have cirrhosis, you are told you must be tee-total. But that's the information that we gave, and I don't believe that it has been shown to be incorrect: that drinking within sensible limits does not appear to accelerate the disease.

THE CHAIRMAN: It all seems very, very general tests and criteria. Do you give anybody any advice as to the extent to which the coffee offset --

A. Perhaps I shouldn't have put the coffee in this statement. But the information about coffee -- and it's interesting because coffee has never really made health claims, unlike green tea -- that became apparent some years ago from large epidemiological studies, that

people who drank coffee tended to have more normal liver tests, compared to those who didn't, and that it did appear that people who drank coffee had less cirrhosis and it did appear that people who drank coffee had less liver cancer. And if you drank five cups of coffee a day that the liver cancer risk was reduced, I believe, 60 per cent.

So this may be a surrogate marker for diet, middle class, I don't know. We do not know that it is correct. It's very difficult to do a trial. I would like to do a trial, randomising people to coffee and no coffee. But it would be very difficult to do. People who like it are not going to stop it and people who don't like it, won't. But I think the evidence is strong enough to mention it to patients, and I do nowadays, and I suspect it happens quite a bit, whereas ten years ago that level of counselling wouldn't be there.

We don't know if it's the caffeine but in relation to Hepatitis C in particular, there was one American study where they looked at people who drank coffee and looked at the amount of fibrosis in the liver and the people that drank coffee, the fibrosis was less over a period of time.

So I think there is some evidence. But in answer your question about offset, it's difficult to be

certain.

THE CHAIRMAN: I'm just thinking of a sliding scale. As one moves towards a full bottle of spirits a day, how much coffee there has to be taken to balance it out.

PROFESSOR JAMES: This is in the days of the carbon offset that Lord Penrose is applying.

THE CHAIRMAN: I'm not suggesting that somebody else should drink the coffee for the alcohol consumed.

PROFESSOR JAMES: That's a really good idea.

THE CHAIRMAN: It's just very, very difficult to generalise, I imagine, because each individual who might become a party to your extended test would be so different in experience, in physical characteristics and make-up and so on.

A. And people's response to being told something. I mean, there are people who have had Hepatitis C who have cleared it, who remain deeply troubled by the fact they have had it, could they have infected people. It has major effects. Whereas in a medical model, we would say, the virus has gone, move on.

But people are very different and contrary-wise, there are people who have it who feel well, want no treatment, very happy to come along once a year, year after year, say that they are feeling fine and don't want treatment; very different and very difficult to

predict, and that's why a standard sort of patient information sheet or website will not replace what I should have put in inverted commas, "counselling".

MS PATRICK: Moving on down to the next paragraph of your statement, you tell us there how your understanding of the natural history of the condition obviously changed and how this impacted on the patient selection for treatments. One of the changes in knowledge, if you like, in respect of the condition is the one you refer to there, and you have touched earlier on how in the early days, as you say, the figure of 20 per cent becoming cirrhotic after 20 years.

When you say "early days", what timescale are you referring to there?

A. You will be talking about in the 90s. I think that there was -- and perhaps still is -- a considerable debate on how aggressive this condition is. We didn't know.

What happened was that when a test for Hepatitis C became available, instead of just identifying, confirming a relatively small number of people that we had labelled as non-A non-B Hepatitis, we found masses of people who were unsuspected of having non-A non-B Hepatitis. This is not particularly relevant to the haemophilia population but suddenly we went from

thinking that this test would identify a very small number of people to recognising that lots of the people that we were seeing in the clinic labelled as something else had Hepatitis C. And I'm sure this had a major effect in other countries. We have a prevalence that is low, less than 1 per cent. In many countries it's 2 per cent. In Egypt 20 per cent of the population.

So we didn't know whether these people, who were identified as being Hepatitis C-positive, how that was going to impact on their life over the next ten or 20 years, and it ranged from a cohort of mothers who were given rhesus injections in Ireland, which was Hepatitis C contaminated, who over many years of follow-up, very few developed significant liver disease. And if you were quoting that literature, you would say in many people this was very benign.

On the other hand, 20 per cent was a figure that came along but it's difficult to know, when you haven't got years of follow-up, actually what the natural history is, and the paper that I mentioned there from Foster in London, where he identified 70/71 per cent of patients who developed cirrhosis over 60 years, was a retrospective guess that those Asian patients had been infected either at birth or as children.

So I would say the natural history is still unclear

and is complicated by other factors, major factors, such as alcohol and obesity.

Q. Yes. So that obviously impacts on the treatment of patients?

A. It impacted very much on the counselling you gave to patients, whether you gave them a story that this was a fairly benign condition in most people and NICE guidelines suggested that people didn't need treatment or weren't eligible for treatment unless their liver biopsy showed significant disease. So if it was a benign disease and the doctor said you don't need treatment for it, then, you know, people would expect it to be benign and not requiring treatment. But that has changed.

So I think our appreciation of the natural history, how aggressive this condition was, has definitely changed significantly over the years from thinking that in the majority it was fairly benign to now feeling that a large number of patients will go on to major complications, including cirrhosis and it's complications.

Q. And the reference to the document you refer to there is [PEN0180255], which is in fact an editorial discussing the study which was carried out in 2005.

So this impact in relation to, as you say, the

funding treatment, and NICE recommended that only those patients with severe disease should be treated and that this should be based on a liver biopsy.

A. Yes.

Q. These recommendations, did they apply to Scotland and were they followed in Scotland?

A. I suspect people chose to follow them or not to follow them, depending on their interpretation of how useful it was in practice. I did not think that liver biopsies were a particularly fair way of allocating treatment. If somebody was very upset about having the Hepatitis C, they were very symptomatic, it didn't seem to me to be particularly fair to make them have a liver biopsy and tell them that it looks fairly mild and you do not need treatment now but I'll repeat the liver biopsy in another three or four years and see whether you have progressed. That didn't seem to me to be particularly fair.

And in Scotland it was agreed at a consensus conference, I think in 2005, for the first time that liver biopsy was not a prerequisite to getting treatment. I have to say that in the haemophiliac population, we had pretty much stopped doing liver biopsies earlier than that consensus meeting and many of them will have had treatment without having liver

biopsy, and I think the NICE document almost certainly mentions haemophiliacs being an exclusion group.

Q. And you say that it was only those with severe disease, what do you mean by that?

A. It was defined by the pathologist. I did not think that mild, moderate and severe was a very clever way of classifying things that I tended to look upon it as early, medium and late disease, and that if you had mild disease, it didn't necessarily suggest it was going to stay mild. But those were the terms that were used and the pathologist would look at the liver biopsy and decide on the basis of the amount of inflammation, damage that was being done was ongoing and the amount of scar tissue that had already taken place, whether this was considered mild or early disease, or whether it was more advanced and justified treatment.

So it was treatment based on the liver histology, which was, I think, a rational way to look at allocating treatment right at the beginning, when there were a lot more patients known to have the infection than there was the capacity to treat everybody at once.

PROFESSOR JAMES: Effectively, what Professor Hayes said near the beginning of his remarks was that there is no enormous hurry about treating people who have got the relatively early stage. It was measured on a scoring

system for the scarring and for the inflammation. And you know, if your score was less than 4, you were thought to be relatively early and therefore if there is a limit of resource, as there was then, then it was thought reasonable, as Professor Hayes has said, that those people could, if you like, take a rain check for three or four years.

But I also would like to support what Professor Hayes is saying about the current, modern lack of absolute necessity for a liver biopsy, partly also because there are other ways of assessing the severity and also even the degree of scarring in the liver now, apart from the liver biopsy. These proxy methods, which I know are very much used on Professor Hayes' unit, are also very kind of helpful in this respect really.

MS PATRICK: Over the page. In the first paragraph at the end, you tell us that it was the realisation of the seriousness of the condition once cirrhosis was established and presumably the irreversibility of cirrhosis?

A. Yes, cirrhosis is generally considered to be irreversible. Cirrhosis means that there is scarring in the liver and lumps. So a liver that has scarring is not necessarily cirrhotic. So lumps and scarring, and it is a recognised stage in progression from

inflammation in the early years or mild, through inflammation and scarring, through to more scarring, cirrhosis and then complications. The complications of cirrhosis, which include liver cancer, liver failure and things like bleeding from varicose veins in your gullet, these are extremely unlikely to occur in patients who don't have cirrhosis.

So preventing cirrhosis prevents the complications. So preventing cirrhosis has been an important goal and similarly identifying patients with cirrhosis. And we rely, as Professor James was saying, less on biopsies now. We have better imaging techniques and we have blood tests and we have other devices to see how much scarring is present, whether they have cirrhosis or not.

Q. And over what period did the thinking change in relation to this and come to the conclusion that we have just been talking about?

A. The consensus meeting about the importance of liver biopsy was a fairly active discussion at that time. So that's 2005. So it's not that long ago that we have changed, six years ago.

At that time, I think we were pushing against an open door and there was discussion and recognition of the importance of treatment and money was available. So, for example, in Scotland the action plan, it was

thought that one of the most important criteria was to treat as many people as possible and targets were set to treat as many people, rather than tailoring the treatment to those patients who we believe might need it most.

So there was a sea change really that was brought about by a combination of better treatments -- better treatment responses anyway -- the treatments remain unpleasant -- but better treatment responses and more recognition of the seriousness of the complications of Hepatitis C and the lack of a requirement for liver biopsies.

So I think that round about the middle of 2000 probably, there was a change in the concept that the more people we treat, the better, rather than just concentrating on the severity. But in the early days I think it was entirely justifiable to treat the people who needed it most, and liver biopsy was one way of doing that.

Q. Yes. Moving on down this page, you refer to the guidelines for treatment, which you have touched on earlier. I think you mentioned the earliest one in 1998 was an American one?

A. Published in Hepatology in 1998, which was the NIH -- I think was the first consensus view. So again, that

was eight years -- seven years or so after people had been using interferon. Then really every time there was a change in treatment efficacy, each time there was a new treatment that looked as though it was better, then guidelines needed to change. So there really have been a plethora of guidelines over the years, starting with that one.

Individual countries and societies wanted to have them and many of them were basically the same, but they encapsulated the most recent advance with consensus views. So, when interferon was replaced by interferon and ribavirin, then guidelines could be produced and then, when pegylated interferon came out, then guidelines changed. And there were a new set of guidelines that are going to be produced about the newest drugs, telaprevir and boceprevir.

And in fact, I suspect within two or three years, there will be a new set of guidelines as even newer treatments come out. So there has been a concertinaing of guidelines relating to the necessity of keeping up-to-date with new treatments. So I think in the 90s, there really weren't consensus guidelines, partly because we didn't practise medicine that way so much then, and partly because the evidence base was a lot smaller than it is now for treatment.

Q. Yes. For the record, the guidelines referred to in your report, the European Association for the Study of Liver consensus conference statement, is [PEN0180249], and the guidelines that you refer to published December 2006 are [PEN0180298].

I just wanted to ask you about treatment once a patient has had cirrhosis confirmed, and what treatment is given to such a patient at that time?

A. If somebody has cirrhosis from Hepatitis C, they may or they may not have had treatment before. They might be diagnosed -- I mean, this is not likely in the haemophiliac population, as they will have had the diagnosis almost certainly made many years before, but generally speaking, if somebody is found to have Hepatitis C and they have cirrhosis, then we know that at the present time they are relatively unlikely to be cured of the Hepatitis C with treatment, partly because the condition is likely to have been there quite a long time and partly because they don't tolerate the treatment complications in conjunction with the problems with cirrhosis. So we would try, if it's appropriate, to cure the Hepatitis C, to stop the disease progressing, but in many cases that's not going to be successful.

However, once a diagnosis of cirrhosis is made, it's

our responsiblility, we believe, to monitor those patients carefully for complications of cirrhosis. Many patients with cirrhosis don't know they have cirrhosis. They are completely asymptomatic, whether it's Hepatitis C or non-Hepatitis C; many people walking around the streets here will have cirrhosis and not know it. You do not know -- even though it's a serious complication -- that you have it.

So the two major complications that we need to look out for in patients who would appear otherwise quite well, are liver tumour, liver cancer. These are tumours of the liver and not tumours that have spread from somewhere else, which is sometimes referred to as "liver cancer", but this is cancer of the liver. And if you have cirrhosis of any cause, the risk of developing a tumour is around 2 to 3 per cent per year.

So if we ultrasound and do a blood test, called "alphafetoprotein", every six months we are reasonably successful in identifying tumours when they are small, when they are curable, either by resection or targeted treatment or transplant. So it's very important that we identify people who have cirrhosis and we screen for tumours.

The other complication that can occur out of the blue are varicose veins in the gullet. As the cirrhotic

liver affects blood flow through the liver, the scarring and distortion restricts the amount of blood that can pass through the liver. That blood bypasses the liver and channels can open up in the veins in the gullet and if they bleed, that's a very serious complication indeed and life-threatening.

So, if somebody has cirrhosis, we will check to see whether they have varicose veins or not and if they don't, they can be reassured. If they do and they reach certain criteria of size, then we would institute treatment to reduce the risk of bleeding, which is either a tablet or an endscopic treatment with a camera to put little bands on. So identifying whether people have cirrhosis or not is a very important part of the hepatologist's role, whether it's Hepatitis C or not.

The other complications that can develop tend to be more obvious to the individual. We don't need to screen for them. And that is signs of liver failure, which is where people become encephalopathic, which means they become drowsy and confused, or ascites, which is a collection of a lot of fluid in the abdomen. Those two features indicate that the liver is beginning to fail and that you should be considering transplant.

Q. And treatment for hepatocellular carcinoma, when this develops in a patient for Hepatitis C, mainly liver

transplant?

A. Then liver transplant is certainly an indication -- or certainly indicated in some patients. It has the advantage that it gets rid of a cirrhotic liver. Once you have started to form one tumour in the liver, we believe that you are likely to form more. There is what we call a field change, and it's not uncommon that if you find a tumour, you actually find two or three.

So if you target a treatment, if you just ask a surgeon to remove the segment that has got tumour in it, you are leaving behind a liver that's pretty prone to developing tumours, and they may develop another one within two/three years.

So a liver transplant is certainly an attractive option to get rid of that cancerous or pre-cancerous -- the tumour and the pre-cancerous change in the liver, and liver transplant, in the haemophilia setting, has the added attraction of curing the haemophilia, not because the transplanted liver cells make the Factor VIII but the blood vessels that go in within the liver produce enough Factor VIII for the haemophilia not to be a clinical problem.

So it has an attraction from that point of view. But the Hepatitis C will always infect the new liver and the natural history from infection to cirrhosis is

considerably accelerated in the transplanted liver and you can go from a new liver to a cirrhotic liver within a couple of years. So it's not a cure-all in all people, and obviously there is a shortage of organs ...

Q. And are there any other treatments for hepatocellular carcinoma?

A. If they are small then, as I mentioned, surgery just to remove a segment of liver rather than transplanting it. There is a way of putting a needle in and killing the tumour under x-ray screening, to try and kill a small section of liver. That's called radiofrequency ablation, and you can also introduce, via the blood supply to the liver, poisons, which is called chemoembolisation. So you can kill off segments of the liver.

So there are a number of alternative treatments, all of which are really only likely to be beneficial in people that have tumours that are identified when they are small. If tumours are over 5 centimetres, there really is no curative treatment.

Q. If you treat a patient with tumours in that way, are they likely to develop new tumours after that treatment?

A. Yes.

PROFESSOR JAMES: Could you just amplify a little, Professor Hayes. As a matter of fact, the proportion of

individuals who are with liver cancers. And by chance we saw yesterday a witness, who is a patient, who kindly came, witness Gordon, who had a liver transplant for five tiny little tumours in their liver -- done outwith Scotland, actually, just so you are not racking your brains. It was because he moved, it wasn't that he had any lack of faith in the Scottish transplant centre. But actually, the proportion of individuals who are suitable for a transplant is really overall, rather small, isn't it?

A. Yes.

PROFESSOR JAMES: Sadly.

A. I don't have the exact figures of the number of haemophiliacs who have been transplanted in Scotland over the past 20 years but it's small.

PROFESSOR JAMES: Apart from haemophiliacs. The Inquiry is dealing with people with post-transfusion Hepatitis C, for example, and so on and as a treatment. Your centre probably gets referred five possible patients for consideration of transplant with a liver tumour for every one that it's technically possible to carry out sort of thing. That kind of figure would be fair, wouldn't it?

A. I think that with the realisation that patients with cirrhosis can develop tumours, there is a lot more

screening, or surveillance that goes ahead, and we will get referred more people --

PROFESSOR JAMES: At an early stage.

A. -- at an earlier stage, but clearly it is phenomenally expensive and risky treatment and it's far, far better to try and prevent cirrhosis than try and tame the complications.

MS PATRICK: Moving over to page 6, looking at the effectiveness of treatment -- and we are discussing here the interferon and ribavirin -- you quote figures there of interferon monotherapy of probably around 10 to 20 per cent, and it improved with the addition of ribavirin to around 30 to 40 per cent, and with pegylated interferon and ribavirin to around 50 per cent in genotype 1 patients, and over 70 per cent in genotype 3.

A. Yes.

Q. Was there a variation in the success rate of interferon monotherapy depending on the genotype?

A. I don't think that was really appreciated at the time. The standardisation -- because of the lack of trials and trial data, originally it was thought the interferon -- and we didn't know really whether it was six months or 12 months, but at the time that ribavirin was introduced, it became recognised that genotype 1 was

a less responsive genotype than the others, and it was recommended that, along with other factors, such as being over 40 and male and obese and having cirrhosis, these were all things that had a negative impact on treatment success rate. And it became -- over time -- it was introduced into guidelines that people with a genotype 1 infection should have twice as long treatment, have 12 months' treatment rather than the individuals with non-1 genotype, who could get away with six months' treatment without reducing the effectiveness.

So knowing the genotype of the patient was important and we would discuss with people the consequences of having genotype 1 or not 1. It would, nevertheless, impact on both the successfulness of the treatment and the longevity that they had to take the treatment.

Q. You have touched on earlier that one of the most important determinants in considering treatment is whether the patient wishes to be treated or not?

A. Yes.

Q. And this is obviously an important factor that a patient would be trying to take account of in reaching that decision, along, presumably, with what the side effects might be --

A. Absolutely, I think there is considerable -- I mean, it

was not that long ago that, you know, individual help groups would say to patients or word would pass round that Hepatitis C was for life, it wasn't curable, at the time when we were telling people that they can be cured.

So I think there was the potential for quite a lot of confusion. Was everybody being fair, up front; how awful the side effects were. You can imagine that side effects that are bad are more likely to be passed round and people hear about them more than side effects that are minimal.

So I think there was a lot of potential for different ways of interpreting the data and patient choice and it remains that there are some patients who, despite the fact we think the treatment is getting better and better, are perfectly happy to have no treatment and seem to have fairly benign disease; otherwise we would encourage them to have treatment, and others in whom, irrespective of the success rate of treatment and how unpleasant it was, were extremely keen to do all they could to get rid of the virus, and some people will have been through -- I can't think of an individual offhand -- but who may well have gone through all three treatment regimes, with five year intervals.

Q. Yes. Do these figures take account of people who may have dropped out of treatment during it?

A. These studies tend to be quoting intention to treat. So you look at the group of people who start on treatment and then look at the final success, and one of the reasons that people may well not be successful in treatment is because they can't tolerate it. And these figures actually have been borne out in clinical practice.

I think there is a feeling that trial results that are published with selected patients, sometimes quite carefully, may give better results than actually applying it in real life. I think these figures are probably what we see in real life. So we would encourage people who don't have genotype 1, very strongly now, that they should go for treatment, six months, and are likely to be cured, compared with patients with genotype 1, who have 12 months' treatment.

We now have what we call "stopping rules". So monitoring the patient. So if somebody was genotype 1 and they still had virus in the blood that hadn't responded after 12 weeks, we wouldn't continue for the full year because we know that they are extremely unlikely to be cured and they will just suffer from the complications and side effects. So there are starting rules and stopping rules, which have become more and more refined over the years.

Q. Can you give us a rough idea of the proportion of patients who don't manage to complete treatment?
A. I would reckon that -- it will depend from centre to centre and trials. Trials. People are far more likely, I think, to go through than somebody not in a trial.

I suspect that those figures -- I'm guessing here -- would be around 20 per cent, something like that. It will depend on the level of support you can give them. For example, some people with ribavirin can have quite severe anaemia. So if you are very determined and we have given people transfusions to support them through that, and you can give them erythropoietin, which is a drug to stimulate marrow. If people's white count falls, you can use expensive agents like G-CSF to try and support that. So it will vary depending on centre to centre and how enthusiastic and keen the patient is to support, and the side effects.

Q. And if we go over the page, you were asked about treating a patient with more than one genotype of the virus, and you tell us that while theoretically patients may be infected by more than one genotype, in clinical practice it's very rare to find a patient with more than one genotype. Is that right?
A. Yes. You can imagine in batched -- blood that has been pooled from a large number of donors, that you could

have more than one genotype, but it would appear in practice, I can't think of an individual where we have done genotyping and we have come up with two genotypes. It's not uncommon for the individual virus to have what's called quasispecies -- that's mild variations of one genotype -- but to have more than one genotype is extremely rare. But I suspect that the virology specialist would be better able to give you answers on that.

Q. And in the next section on that page you tell us about the effect on treatment of a person having haemophilia and while initially it might have been thought that their response to treatment was less, that has not been borne out by more recent --

A. The haemophilia per se -- again, the haemophiliac doctors who concentrate on the literature may give you better information but it would appear that from our experience in the early days of interferon monotherapy that our results were not up at the 20 per cent cure rate but more likely to be 10 per cent, and we wondered whether the haemophiliacs might not respond so well to treatment. But I don't believe that that has been borne out with the subsequent treatments, and there is some evidence for that, a publication there, that the results in the haemophiliac population of 51 per cent is

remarkably similar to the non-haemophilic patient. I don't think the haemophilia per se with modern treatment has a major effect on a treatment response.

Q. For the record that publication you refer to is [PEN0180258]. Does treatment for Hepatitis C virus have any effect on a person's haemophilia?

A. Other than transplant, I don't think it does.

Q. Moving on, you discuss under 6 the effect of co-infection with HIV and tell us that the response to treatment in such co-infected patients is generally believed to be reduced.

A. The co-infected patients tended to be looked after locally, and I suspect that this may be true in a number of centres, by doctors who were more specialist in HIV therapies.

So the patients that we had, that were co-infected, would be looked after more by people like Professor Leen, who have an interest and expertise in this area, rather than myself. But it would appear that the patients who were HIV-infected -- and perhaps not a surprise, since your ability to clear the virus is related to your immune competence. And that's one of the reasons post-transplant, when you are immuno-compromised, that the disease is probably so much more aggressive, that your immune system is important in

clearing the virus, and after all interferon is an immune stimulant.

Q. Do those patients co-infected tend to have higher Hepatitis C viral loads?

A. I couldn't answer that accurately.

Q. Over the page you summarise for us the side effects of treatment for the Hepatitis C virus which you describe as significant. You mention the ones in relation to interferon and ribavirin. Interferon alone, what were the side effects of that?

A. Mainly flu-like symptoms, which, when you are unlucky enough to get flu, you feel fluey because of the body's production of interferon. So it's not surprising if you took a syringe-full three times a week, then you would feel pretty lousy after the injections, and we used to tell people to take it at night and take a paracetamol with it.

It was a predictable side effect which we believed would get less with time and that's probably the advantage with pegylated interferon, once a week, a flu-like problem. So it was reasonably predictable. Some people found it very debilitating. Again, there seems to be a lot of variation. The side effect that concerned us most actually was probably depression and occasionally suicidal ideation, and that was something

that we were aware of fairly early on, I believe. And fortunately it is not common but it can be potentially a major side effect, depression. And if the drug is stopped and people are started on anti-depressants -- it seems to be a chemical effect -- they can restart treatment.

I think it would be true to say it's a bit smug of doctors to outline just a list of complications. I think the people that know the complications best would be the patients, and they varied remarkably in their tolerance to them. Some people would find the treatment not awkward at all and others, it was absolutely debilitating, they could not complete treatment no matter how much they tried.

Q. So the impact on a patient's day-to-day living could range from not much of an impact to being unable to work?

A. Yes.

Q. Being unable to leave bed?

A. People often suggest that they start it on holiday, so that it didn't affect work but it was very, very considerable and, you know, people who were very mild-mannered would suddenly say that they became intolerable and angry and so, you know -- things that are not personally easy to just put down as a rash or

something like that, but the effect on patients' lives was considerable, and each of the treatments that's interferon-based is not likely to have significantly less side effects.

So we start with interferon, then you add another drug that has its own side effects, ribavirin, particularly anaemia, and then we add in boceprevir or telaprevir, that's the next stage, which has its own side effects. So we are expanding the cocktail of side effects at the same time that we are getting better cure rates and hopefully shorter and shorter treatment.

But the treatment, it would be fair to say, is generally unpleasant.

Q. And the way of managing the side effects, I take it, included reducing doses?

A. Yes. The drugs can have the doses reduced but this tends to impact, nevertheless, on the success rate. So, for example, with the ribavirin, we know that the more ribavirin you can get in -- or at least this was what was believed until very recently when we have these newer drugs -- that if you reduce the ribavirin you affect the success of treatment and that it was better to use drugs like erythropoietin and keep the haemoglobin up, rather than reducing drugs.

I suppose that's not a particular surprise. If you

have an effective treatment, you should try and keep the doses up. So we tried, by mentioning potential side effects so people are forewarned, to give them support. We may change the dose and give them support if medication and support overall -- but the tolerance that people displayed was very, very considerable and I'm not sure it's absolutely true but it would seem to be an impression that the people who had least side effects actually responded less well.

Q. If you had maybe been treated with interferon or interferon and ribavirin and had suffered extreme side effects, and you moved on to pegylated interferon and ribavirin --

A. You would have very similar side effects.

Q. -- it would be likely to follow the pattern set previously?

A. Absolutely. Many people where they couldn't tolerate, they would just not contemplate going on to trying it again, unless they could be guaranteed the treatment was going to be for a far shorter period.

So the side effects, ribavirin, reasonably well-known; the side effects of pegylated interferon were pretty similar to the standard interferon, the advantage being that it was just given once a week. And we can anticipate with the new drugs that the side

effects, since we are still using the two previous drugs, will be exactly the same plus extra.

Q. Yes. Could I just ask you about the stigma associated with the Hepatitis C virus? We have heard from some patients who feel that assumptions were made about them in respect of their alcohol consumption. What do you have to say about that?

A. I think there is a number of areas of stigma that have arisen and I suspect it will depend a little bit from centre to centre. For example, we tend to see our haemophiliacs in the haemophilia centre, whereas the majority of patients with Hepatitis C have acquired this from drug misuse, and they are a very different population indeed. And if you had a centre where you had joint clinics and they were mixed together and treated the same way, then it's entirely reasonable that people would feel stigmatised about this.

I think that people who had abnormal liver function tests -- it still remains common that people who have abnormal liver tests are referred up to the clinic and they have had a good telling off from their GP about drinking too much alcohol when they insist that they are almost tee-total. It's just because alcohol is such a common cause of abnormal liver tests that it's statistically accurate in many cases for the GP to

assume that that's the case.

So I'm sure that lots of patients with liver disease per se, as opposed to just Hepatitis C, can feel stigmatised about things, but I think that the haemophiliac population and those who acquired it from blood transfusion, compared with those who have acquired it from intravenous drug misuse, are very, very different populations and have the potential, therefore, for a lot of misunderstanding and stigmatisation.

Q. Finally, you have touched on it a few times throughout, the prospect of new treatment for the Hepatitis C virus. Could you tell us about this, please?

A. You will see in the report there there are two drugs that have, over the past couple of months, been licensed. These are drugs that are taken orally, and both seem to be considerably more effective, a quantum improvement. This is in genotype 1 only. So the group of people who need a better treatment, these are what they are targeted for and indicated for.

It's difficult, until we have used them both and compared them in the wider practice, to know whether one is going to be better than the other. They seem generally similar in effectiveness, and we will take the genotype 1 patients, who at the present time only 50 per cent will be cured with 12 months' treatment --

that will take that up to 70 per cent or so, with shorter treatment, we hope.

So they have been licensed and they are in the process of going through local formulary approval and are likely to start being used, I would think -- well, they are already used in some centres in Scotland.

So they are definite improvements and we need to inform Hepatitis C patients about this improvement, bearing in mind this is just genotype 1. So people who have never had treatment before or people who have had previous treatment and relapsed need to know about these new treatments and be given counsel and advice about that.

On a final note, just to be positive, it does appear that it's not going to be that far off that we have drug treatments that don't rely on interferon injections as a baseline but just oral tablets, that have the potential, it would appear, at the present time, to be remarkably effective and may well cure, hopefully, all patients, with relatively short courses. In this month's "Hepatology", there is a publication about these regimes of just three oral tablets that look remarkably effective. So I suspect it will take another five years for it to get into the last set of guidelines but it does appear to be promising.

Q. Thank you very much.

THE CHAIRMAN: It's 1 o'clock, Mr Di Rollo.

(1.03 pm)

(Short break)

(2.00 pm)

Questions by MR DI ROLLO

THE CHAIRMAN: Mr Di Rollo?

MR DI ROLLO: Professor, I just wanted to revisit some of your evidence about advice in relation to alcohol, if I may.

A. Okay.

Q. One of the documents that has been lodged, accompanying this section, is the Scottish Intercollegiate Guidelines Network document, the management of Hepatitis C, and you have referred to that in your statement.

A. Right.

Q. I think in your evidence this morning you told us -- and in your statement indeed you have indicated -- that you wouldn't advise a patient to abstain from alcohol short of cirrhosis but once it get to cirrhosis you would advise to abstain at that point.

A. Hm-mm.

Q. So as I say, your evidence this morning was that short of cirrhosis, you wouldn't advise a patient to abstain but once cirrhosis was diagnosed, you would.

A. Yes.
Q. What I wanted to ask you is, looking at the guidelines, chronic hepatitis is given a definition at page 2 of that document, which is [PEN0180298]?
A. Right.
Q. The actual page I'm looking for is the second page of the actual document, which I think will be about page 7 or 8. Page 6 of [PEN0180298].

Chronic hepatitis there is divided up into the three categories, I think you mentioned; there is mild, moderate and severe, and we see that:

"Mild disease is present when inflammation of the liver tissue is absent or largely confined to the portal tracts with no evidence of fibrous tissue extending between the portal tracts."

Then:

"Moderate liver disease is described when there is significant inflammation and/or liver cell damage associated with increased fibrous tissue extending beyond the portal tracts but not resulting in nodule formation.

"Severe disease occurs when the patients have developed bridging fibrosis or cirrhosis, (histologically proven or otherwise) of the liver, whether there are clinical signs of liver dysfunction or

not."

So I suppose the mild and moderate categories of chronic Hepatitis C don't involve cirrhosis; the severe does, according to this definition, involve cirrhosis. Is that right?

A. Yes, I mean, this is a categorisation which is no better or worse than others. There are different ways of staging liver disease, depending on the cause. The most important and the type that's thought to be irreversible and is the one that's associated with the implications, is cirrhosis. So we tend in liver disease, irrespective of the cause, to talk about pre-cirrhotic and cirrhotic. But this was, I think, particularly used because the NICE definitions had suggested that people with early disease didn't need treatment, and that's why perhaps there are three here, rather than two.

But for alcoholic liver disease and non-alcoholic fatty liver disease due to obesity, they are divided up into stage 1, a stage which is pretty reversible and benign, and then an intermediate stage and then a cirrhotic stage.

Q. The mild and moderate states can be diagnosed on the basis of clinical findings presumably?

A. No, these mild and moderate -- one of the biggest questions in hepatology is, you know, can you really

know what's going on in a liver from liver tests, and you can't really. That's why biopsy, until relatively recently, the last five years or so, was such a central part of the treatment algorithm.

You can't really tell, looking at the patient and looking at the liver tests, whether they have -- actually you can't tell whether they have mild disease, moderate disease or even early cirrhosis. The liver biopsy, until relatively recently, when we have other ways of not trying to look at the activity of disease but how much scarring there is -- there is a device called a "Fibroscan", which is like an ultrasound machine, which we use a lot now, which, just by putting on the side of somebody's liver, you can get a test result there and then, which will tell you how much scarring is in the liver, whereas that wasn't available, you know, five years ago.

If you could tell exactly where people were on the pathway without biopsies, you could wonder why you might not say, you could see take X amount of alcohol there but as you move down, you should take less.

Q. What I was wondering was, as we come to the guidance about alcohol, it doesn't differentiate between any of the categories. If we come to it, page 20 of [PEN0180298], I hope. Under "Alcohol" -- this is under

section 8 --

A. 4, yes.

Q. Section 8.4. This guidance deals with progression of untreated disease, and this is 8.4, in relation to the alcohol, and the headnote, if you like, under B there is:

"Patients with CHC ..."

Which is chronic Hepatitis C:

"... should be advised that drinking alcohol (even in moderation) can accelerate progression of liver disease."

Is it correct to say that even with mild or moderate hepatitis, chronic Hepatitis C, drinking alcohol, even in moderation, can accelerate progression of liver disease?

A. The problem with this whole issue is accurate identification of the amount of alcohol and duration.

I mean, if you drink more than the recommended amount and do so for five years, it's extremely unlikely to give you significant liver disease. If you do that, however, for 80 years, then you can accumulate the risk.

So the average alcohol intake at more than six units a day -- so that's the 50 units -- and we did some work on this. The people drinking that, which is essentially 50 units a week, they did have more rapid progression of

liver disease than the people who drank within recommended limits.

The statement after that:

"Even moderate amounts of alcohol (within government recommended guidelines) have been associated with increased ... fibrosis compared to those who abstain."

I'm unaware of that data, and it's not what has generally been advised, that people should be tee-total. And the documents that were given out to patients from haemophilia centres, which I think -- the documents are here -- in 1994/1995 there was a working group, whatever. My understanding was that was pretty much in line with what I have been saying, that people didn't have to be tee-total, drinking within recommended limits.

Q. This guidance is obviously produced in December 2006.

A. December 2006, yes.

Q. So my questioning wasn't really designed to ask you about guidance at a particular point in time; what I was really trying to ask you is whether or not somebody who has chronic hepatitis, leaving aside cirrhosis -- I'm really interested in the mild and moderate categories for the purposes of this discussion -- whether in that situation one is at risk, even if you drink alcohol in moderation, of progressing the disease?

A. I think that is debatable. I think that when people are talking about moderate amounts of alcohol, general consensus for that is more than you should be.

There is heavy, moderate and there is within recommended limits, and the recommended limits -- 21 units of alcohol and 14 units of alcohol -- is relatively small amounts of alcohol, and I have never been persuaded by the evidence, nor has it been drawn to my attention that that small amount of alcohol will accelerate liver disease.

When you talk about a moderate amount of alcohol, I would tend to use that term for between the recommended upper limits and 50 units, and 50 units being heavy. But I take your point that even government recommended guidelines is in that statement.

Q. It does looks as though, from what you are telling us just now, you are not agreeing with what is contained in the guidance here. It doesn't sound as though you are.

A. I think it will -- I would like to -- those two references that are there, I would like to review the data. Certainly it is not widely advocated in any condition, irrespective of Hepatitis C, that patients should be tee-total, both in transplant circles. It has always been the patients who are cirrhotic should abstain from alcohol irrespective of the cause, and

people with liver disease of any cause other than alcohol -- I mean, obviously if you have liver disease due to alcohol, it may well be best for you to be tee-total because of the alcohol problem, but other causes of liver disease, not due to Hepatitis C or alcohol, it is general recommendations that drinking within sensible limits is reasonable.

Q. Obviously there is a distinction in relation to what advice you might give someone in terms of how they might follow it and managing the patient. That's one sort of possible way of looking at the problem, and another aspect of the matter is whether in fact, as a matter of scientific fact, there is actually a risk of progression of the disease. The two aren't necessarily the same thing. Is that fair?

A. That's fair.

Q. All right.

THE CHAIRMAN: Before you leave it, I'm not quite sure that I see what this is saying:

"Average alcohol intake of more than six UK units per day."

That's 42 units a week. So that starts by being twice the recommended level?

A. Yes.

THE CHAIRMAN: I take it just --

A. And I would categorise that as moderate alcohol intake, or heavy. It's certainly above recommended limits and potentially harmful drinking, and that amount of alcohol has been shown in Hepatitis C -- as I suspect it would be in people without Hepatitis C -- to increase your risk of fibrosis of the liver.

The debate really is whether drinking within the recommended limits, in patients with Hepatitis C or other causes of liver disease, can accelerate the liver disease, and I have to say that I'm unaware of that data being widely supported.

THE CHAIRMAN: At the moment I'm just trying to understand this paragraph. That middle sentence is one that appears relatively easy to populate with figures. The other sentence that is causing the trouble is that:

"Even moderate amounts of alcohol ..."

That's even moderate amounts, an expression that comes after talking about 42 units a week, and at the moment I'm not sure that I can populate that with any value. So I don't know whether the answer may lie in the two references, professor, but I'm not sure how far you can go, if you do not know what the data is that's being referred to.

But if you look at it just as an expression, it says:

"Even moderate amounts of alcohol have been associated with increased liver fibrosis compared to those who abstain."

So the basic hypothesis is that you have got two people with fibrosis, and you have got a progression, and it's saying that even moderate amounts of alcohol have been associated with increased progression in the case of those who drink as compared with those who abstain. Would that be a surprising proposition to you?

A. Yes, I think that -- as I said, I'm unaware of the data that's quoted or the reliability or the source of those references, and it is certainly not accepted hepatological practice that we tell people with liver disease of any severity that they must be tee-total. Interestingly, nor is that what this recommendation, if they believe the data, suggests, or reports. If this data were believable, the recommendation surely should be that patients with Hepatitis C should be tee-total.

THE CHAIRMAN: Yes.

Mr Di Rollo, I think I understand why you are interested in the topic but if you care to get the references, we might get some data that Professor James could help us understand.

MR DI ROLLO: Well, obviously, I know what the references are, I can give the references. I don't remember copies

of them.

PROFESSOR JAMES: Can you kindly turn to them, and perhaps Professor Hayes and I could just eyeball the references, and they may be helpful.

A. Reference 86 is a retrospective follow-up study of 384 patients. So a retrospective study scientifically is always open to debate. The other one is 98.

MR DI ROLLO: It's 88 and 98, not 86.

A. Sorry --

Q. As I understand it, 88 is the Zarski, McHutchison, "Rate of natural disease progression ... "

A. It is, I apologise.

Q. And then 98 is "Impact of Moderate Alcohol ... ", Hezode et al.

A. "Impact of Moderate Alcohol Consumption on Activity in Hep C: Elementary pharmacology and therapeutics."

PROFESSOR JAMES: Both of those are respectable groups of authors and journals which might well publish respectable data. So they will certainly be worth proper examination. That would be fair, wouldn't it, professor?

A. It would, yes.

THE CHAIRMAN: So if you are happy with that, Mr Di Rollo?

MR DI ROLLO: Certainly.

THE CHAIRMAN: Professor James can look it up and see

whether there is something that can be fed into our understanding of these things.

MR DI ROLLO: Certainly. It just struck me that your evidence this morning wasn't quite in keeping with what, on the face of it at least, the guidelines indicate in terms of what has been said.

A. A set of guidelines; there are many.

Q. Right. The other thing I wanted to ask you was about liver biopsies, and it relates to the problem of diagnosis. I think you were telling us earlier in your evidence this afternoon, in the course of your answers to the questions that I have been asking, that it has been a problem historically, making up a diagnosis. You have told us, I think, fairly clearly, that you can be walking around with cirrhosis and be unaware of it?

A. Hm-mm.

Q. One way of carrying out a diagnosis is to carry out a liver biopsy, and you have told us about that and how unpleasant and risky that can be.

The situation with someone with haemophilia is obviously that there is a serious risk there with the haemophiliac in carrying out a liver biopsy, which isn't there with a normal person, which is because of the risk of bleeding. It wasn't until relatively recently -- am I right in thinking -- that liver biopsies were carried

out on haemophiliacs? Is that right? There was a reluctance to carry out --

A. There was a reluctance to carry it out at all. I'm not sure that the data would say that the risk is considerably high but it seems counter-intuitive not to think that doing a liver biopsy in somebody with a bleeding tendency has increased risk.

So when did liver biopsies in haemophiliacs, we tried to do it in the safest way possible and replacing clotting factors, and it was probably because of our exposure in practice with them that we realised that actually knowing what the liver biopsy result was wasn't so important to the treatment algorithm that we were using, accepting that it was different to what had been proposed by NICE, which said that liver biopsy was central in the algorithm. Although I'm pretty certain that document excludes haemophiliacs from that.

Q. When was there less reluctance to carry out a liver biopsy on haemophiliacs?

A. I wouldn't have said there was less. I would have said now there is probably even more. So in the early 90s, I would be doing laparoscopic liver biopsies, or laparoscopy without biopsies on haemophiliacs, and I can't remember when we last did one in a haemophiliac, and actually we do far, far less liver biopsies overall

now because of the advent of newer tests.

Q. Can you just give me an approximate timeframe as to when the newer tests that allow you to achieve a result in terms of making a diagnosis, making it less necessary to do a biopsy, became available?

A. I think the data has been available for decades. It has really been a point of principle in some ways in hepatology that you need a liver biopsy to know exactly where you are in the conditions.

So if you were to look at surrogate markers of cirrhosis, the Skipton Fund criteria, which is the APRI and the AST to ALT ratios, were used and accepted 10/15 years ago. There were other tests that were brought in with the Fibrotest, which was again blood tests. These were all attempts to stage liver disease accurately, without a liver biopsy.

There are some that are very simple at the bedside, with, you know, using platelet counts, but I think that in liver hepatology circles practice, everyday practice, liver biopsies have gradually reduced, other than post-transplant situation to diagnose rejection, over the last ten years.

Q. Right.

THE CHAIRMAN: You described a sort of echosounder approach.

A. Yes.

THE CHAIRMAN: When did that technology become available?
A. The Fibroscan, which fires a little sound wave through the liver and measures the speed with which it goes through, I think, was commercially available probably around five years ago and became commonly introduced into hospitals in the UK over the last two to three years.
THE CHAIRMAN: So very, very modern technology that we are talking about.
A. Yes.
MR DI ROLLO: Thank you.
Thank you, sir.
THE CHAIRMAN: Should I be amazed, Mr Di Rollo?
MR DI ROLLO: Certainly. I wasn't particularly brief.
THE CHAIRMAN: Mr Anderson?
MR ANDERSON: Sir, I am sure I can live up to this expectation, if I may.

Questions by MR ANDERSON

MR ANDERSON: Good afternoon, professor. The short heading of our topic is the effects of infection with Hepatitis C on patients, and in your report you deal with the effectiveness of treatment but you don't say anything about life expectancy, and I would just like to discuss that, if I may, very briefly with you just now.
Could we look together, please, at a paper with the

reference [LIT0011263]? It should come up on the screen in front of you.

I think we see this as a paper published in the American Society of Haematology, Blood, with a date of April 2007. Is that correct?

A. Yes, I see.

Q. And the lead author appears to be Sarah Darby, and we see a number of names, one or two of which are familiar to us, for the UK haemophilia doctors organisation. Is that correct?

A. Yes.

Q. Can we turn to the next page? That's 1264. We will come back to the resume, as it were, of the results but do we see under "Introduction" that it tells us:

"In the late 1960s, the UKHCDO initiated a nationwide database for planning the care of people with congenital blood coagulation defect. From 1976 to 1988, it included details of all males diagnosed with Haemophilia A or Haemophilia B, regardless of whether they required treatment and it was updated each year adding newly diagnosed individuals. The information held on the database has been used to carry out a study of mortality in the complete haemophilia population in the United Kingdom over a period of 23 years. This paper presents information on people with Hemophilia A

or B, who were not infected with human immunodeficiency virus."

So this is one which excludes HIV. It might be convenient next to go to the study design, which we will find on page 1270, in the right-hand column, we will see:

"Discussion.

"Study design.

"This is the largest follow-up study ever performed of people with haemophilia and it covers the longest period of follow-up. The study includes the complete population of United Kingdom residents diagnosed with Haemophilia A or B during a period of more than 20 years, thus eliminating the possibility of bias that is present in studies based on cross-sectional surveys of haemophilia populations, where there are inevitably a number of non-respondents and in which children who die in the first three years of life tend to be under-represented, leading to estimates of life expectancy from birth that are higher than the true value. Additionally, the study has made use of the nationwide flagging system, available in the United Kingdom via the NHS central registers, to eliminate duplicate records for individuals who attended many haemophilia centres or who changed their name. This

central system of flagging has also enabled ascertainment of the appreciable number of deaths that occur in people with haemophilia but without the knowledge of any haemophilia centre."

I think on the final two pages -- that is to say 1272 and 1273 -- we see the UK haemophilia centres contributing data and on the face of it it appears to be just about every haemophilia centre. Is that right, do you think?

A. I am afraid I'm not in a good position to give you the answer to that, not being a haemophilia centre doctor.

Q. It seems to be a very lengthy list.

A. Right.

Q. All right.

If we turn to page 1272, the concluding remarks, we see there that the authors say this:

"This study has made use of the UKHCDO nationwide database, together with the ability to ascertain vital status on a nationwide basis via the NHS central registers and, for those who have died, the certified cause of death. It has for the first time characterised life expectancy and cause of specific mortality in a large haemophilia population that was not infected with HIV. The results showed that, despite the advances that took place in the treatment of haemophilia during

the last two decades of the 20th century, mortality from intracranial haemorrhage changed little in the absence of factor inhibitors. They also show that life expectancy in severe haemophilia was still 15 years lower than that of men in the general population at the end of the 20th century, while in moderate/mild disease was three years lower."

It goes on to say:

"The prospects for the future are good. The study confirms that there is a substantial reduction in mortality from ischemic heart disease in people with haemophilia compared with the general population and, more importantly, the results are consistent with a substantial reduction in mortality from intracranial haemorrhage among those receiving prophylaxis."

If we now turn to the resume at the start of this paper at page 1264, we see there a summation of the results:

"Since the 1970s, mortality in the haemophilia population has been dominated by HIV and few reports have described the mortality in uninfected individuals. This study presents mortality in 6018 people with Haemophilia A or B in the UK during 1977 to 1998 who were not infected with HIV, with follow-up until January 1, 2000. Given disease severity and

factor inhibitor status, all-cause mortality did not differ significantly between Haemophilia A and Haemophilia B. In severe haemophilia all-cause mortality did not change significantly during 1977 to 1999. During this period, it exceeded mortality in the general population by a factor of 2.69 ... and median life expectancy in severe haemophilia was 63 years. In moderate/mild haemophilia all-cause mortality did not change significantly during 1985 to 1999, and median life expectancy was 75 years. Compared with mortality in the general population, mortality from bleeding and its consequences and from liver diseases and Hodgkin disease was increased but for ischemic heart disease it was lower, at only 62 per cent of general proportion rates, and for 14 other specific causes it did not differ significantly from general population rates. There was no evidence of any death from variant CJD or from conditions that could be confused with it."

So I think, without going to the bodies of the paper, professor, it would appear that what we can take from it is that life expectancy of people with severe haemophilia in the period 1977 to 1999 was 63. Is that correct?

A. Yes.

Q. Can we turn now to an earlier paper perhaps, which is

[LIT0010159]. This is a paper by Rosemary Biggs, who I think was with the Oxford Haemophilia Centre at the Churchill Hospital in Oxford, and this is an earlier paper from the British Journal of Haematology in 1977. If we look at the summary, we see that:

"A study has been made by the haemophilia centre directors of the United Kingdom and Northern Ireland. From 1969 to 1974 2600 patients with Haemophilia A and 388 with Haemophilia B attended haemophilia centres for treatment.

"Of these patients, 71 are known to have died in the survey period. A record is presented of the amounts and types of therapeutic materials used each year during this time."

If we go simply to page 0162 and we look at table 2, you see there in quite simple form set out the age at death of patients having Haemophilia A or B, and we see in all cases the average age at death was 42.3: second column. Is that right?

A. Yes.

Q. Now, would I be right in thinking in this earlier paper -- that's to say the Biggs paper -- in the period 1969 to 1974 this group would have been treated predominantly with cryoprecipitate? Would that be right?

A. I'm not the right person to ask that question. I don't know about the specifics of haemophilia treatment.
Q. All right. Can we, for the purposes of this discussion, assume that they were treated with cryoprecipitate?
A. Okay.
Q. And again say, if it's the case: in relation to the first paper we looked at -- that is to say the period 1977 to 1999 -- they would be predominantly treated with concentrate. Would that be correct?
A. I'll have to take your advice on that.
Q. All right. We may manage to cut this short, professor, but if it were the case that the former group -- that is to say the Biggs cohort -- were treated with cryoprecipitate and the later group were treated predominantly with concentrates, would it be over simplistic to suggest that the increased life expectancy would be due to the use of concentrates?
A. That's not how I would interpret that data. I would need to read the detail of the first paper but the average age at death is not the same as average life expectancy. That's the average age at which the people who died, died. There may be a lot of people who are not dead who are a lot older than that. So we would need to know what the average life expectancy, rather than the average age of death in that first cohort, was.

I didn't see that in the summary.
Q. All right.
THE CHAIRMAN: The age at death is not necessarily representative of the distribution of ages among the whole population.
MR ANDERSON: All right. Thank you very much, professor.
THE CHAIRMAN: So far as the first paper you were shown was concerned, I have one concern about that, that it appears to deal with people who did not have HIV. Do you know whether it dealt with people who were co-infected but who died of the complications of Hepatitis C?
A. I don't know the details of that publication but I would assume that the co-infected patients would be excluded, in that, whether this was mono-infection with HIV or co-infected with HIV and Hep C, I presume they would have excluded them because HIV has such a dominant influence there.
THE CHAIRMAN: But it might have been a complication of Hepatitis C that was the cause of death.
A. It could be, but the conclusion -- I mean, people within that span of 20-odd years, some of them may have died of complications of Hepatitis C, but the conclusion from that paper really was that the all-cause mortality hadn't changed over that period of time, which might be

reassuring that over that period of time there weren't a lot of deaths from complications of Hepatitis C.

But when you are dealing with a disorder with a natural history that may have 30/40/50 years, that period of time is still relatively short and may include a large number of people with Hepatitis C early on in their disease course, and if they were followed for ten years, you may suddenly see an increase in liver-related deaths.

THE CHAIRMAN: That was the next point for which I was grateful to Professor James: a period ending in 1999 is really relatively short to base general conclusions on. Yes.

Anything you want to follow, Mr Anderson?

MR ANDERSON: No, thank you, sir.

THE CHAIRMAN: Mr Johnston?

Questions by MR JOHNSTON

MR JOHNSTON: Thank you, sir. I just have one short point, Professor Hayes, in relation to the new treatments that you touch on at the end of your statement. At the time you wrote your statement you quite rightly said that telaprovir is now licensed but has not been SMC-approved. However, I --

A. Two days ago.

Q. Two days ago, yes. I simply wanted to draw that to your

attention in case there was any comment you wanted to make about it.

A. I think that it is to be welcomed. I think that to have two buses come along at the same time is interesting and it will allow us to compare and contrast the two drugs and which are more suitable. They are both, I'm led to believe, going to be extremely expensive, at £20,000 to £30,000 a treatment course for an individual, which is a lot of money, and that may be a factor that comes into place.

But it may be that one of the drugs, the telaprevir, can be used for quite a short period of time, whereas the boceprevir may be for a longer period of time and spread out. So I think it's nice to have a choice of drugs and we will be able to see which is going to be best in this population.

Q. I see. Thank you very much.

A. Thank you.

THE CHAIRMAN: Thank you very much.

MR JOHNSTON: Thank you, sir.

THE CHAIRMAN: Numbers of buses approaching at the same time entertained Wendy Cope. I don't know if you know her. It sometimes suggests that too much choice merely causes trouble. Yes. Have you any further --

MS PATRICK: I have nothing further.

THE CHAIRMAN: Professor, thank you very much indeed.

A. Thank you.

THE CHAIRMAN: Now, Ms Patrick.

MS PATRICK: There are no further witnesses today.

THE CHAIRMAN: Until tomorrow.

(2.48 pm)

(The Inquiry adjourned until 9.30 am the following day)