Wednesday, 30 November 2011

(9.30 am)

PROFESSOR JUHANI LEIKOLA (continued)

Questions by MR MACKENZIE

MR MACKENZIE: Good morning, professor, welcome back. It has been a while since you were here. We should perhaps briefly remind ourselves of some of your biographical details. I think, in short, we have your CV. It's WIT0030004. We don't have to go to it but you were the director of laboratory services at the Finnish Red Cross Blood Transfusion Service between 1975 and 1988, albeit between 1982 and 1986 you were based in Geneva as the head of the blood programme department for the League of Red Cross and Red Crescent Societies. I think that's correct.

Then you returned to Finland and you were the director of the Finnish Red Cross Blood Transfusion Service between 1988 until you retired in 2001, and we know you sat on many international committees and organisations as set out in your CV but we note in particular that you were a member of the committee of experts on blood transfusion and immuno-haematology of the Council of Europe between 1982 and 2001. Is that correct?

A. Yes.

Q. Thank you. Could we turn now, please, to your statement on our topic C2, professor? It's [PEN0171837]. I will just go through the statement and refer you to some documents as we go along.

In paragraph 1 you refer to the two American studies, the TTV study and the NIH study, which both reported in 1981, and you explain they raised worldwide interest and showed an association between elevated donor ALT and NANBH of the recipient.

I would like to go to one document, please, [LIT0012156] that we haven't looked at before. This, I think, gives some further context to the TTV study and report. This is an excerpt from the correspondence section of the New England Journal of Medicine in 1981 and in the right-hand column we see the heading "Post-transfusion Hepatitis and Serum ALT in Blood Donors". We see a letter from Dr Blumberg of the University of Rochester Medical Centre, and we can read the letter for ourselves but in short he refers to the TTV study report, and in his final sentence he states:

"The recommendation for screening is premature."

And Dr Aach replies to that, we will see shortly, but the letter below that, the one beginning "To the editor", if we go over the page, we will see this is a letter from Dutch doctors, Dr Katchaki and others from

Arnhem, and they report on their relatively small scale prospective study and about eight lines down we will see the sentence:

"In this prospective follow-up study of 380 recipients of blood negative for HBsAg, we observed an attack rate of 3.4 per cent with no correlation with ALT levels in donor blood."

Then in the final paragraph of that letter, the Dutch doctors say:

"It appears, therefore, that although screening of bloods donors for HBsAg is of universal value in blood transfusion, the introduction of screening of blood donors for ALT should be considered on a regional basis at best. On the basis of our results, we have chosen to refrain from its introduction awaiting the development of a specific test or tests for markers of non-A non-B Hepatitis."

We will see a few lines down, at the end of the references, scroll down a few lines:

"The above letters were referred to Dr Aach ..."

Who led the TTV study who offers the following reply. So I think this letter sets out the thinking of Dr Aach at the time, and Dr Aach states:

"The TTV study group did not recommend that routine screening of blood donor ALT be initiated immediately on

the basis of their findings presented in this article. A number of questions that we believed should be answered first were listed in the discussion section of the paper."

Read on a few lines down:

"A serologic assay is clearly preferable if and when it becomes available. However, despite more than five years of intensive effort by many investigators, a confirmed reproducible serologic test was not available, and even if it were developed in a research laboratory in the very near future, three to five years would be needed to adapt the test to large-scale screening. Until that time, screening of donor ALT might provide an interim means to reduce the incidence of non-A non-B post-transfusion hepatitis in the United States."

So that, I think, perhaps sets out the position of Dr Aach and his colleagues at that time, that they didn't necessarily recommend the immediate introduction of ALT screening of donors but they did suggest that such testing might provide an interim means to reduce the incidence of non-A non-B post-transfusion hepatitis.

Professor, could we return then, please, to your statement? I'll just carry on going through it. So paragraph 2. You explain really by way of background

that:

"When an infective agent is not known, the only means of reducing the risk for disease transmission are through the selection of donors and judicious use of products."

In the last sentence in paragraph 2 you explain:

"The second possibility is to use laboratory tests (surrogate tests) that could identify donors with risk factors."

In paragraph 3 you explain:

"The use of surrogate markers to reduce post-transfusion infections has been a controversial issue."

We can read for ourselves what is then set out. You say:

"If the surrogate marker is positive in a large proportion of the donor population, it is mostly identifying wrong people. That has two consequences: it may seriously reduce the number of eligible blood donors and the donors found to be positive need to have a plausible explanation so that the test results should not raise unwarranted anxiety in the donor."

There is a need for an appropriate counselling system. Paragraph 4 you say:

"Different countries ... perceive transfusion safety

differently."

Also:

"Infection incidence varies in different populations and usually means that a careful study has to be made in a given population and in a given society before introduction of a new test, especially of an unspecific surrogate test. Much depends also on the prevalence of the marker and on the incidence of the infection."

In paragraph 5 you say:

"A third factor has to be taken into account. Once a test has been introduced to routine screening, it is psychologically and politically difficult to stop even if a specific test would have made it obsolete."

Then over the page, please. All of that was by way of background. I think we now come to look in paragraph 6 really at a chronological consideration of the use of ALT testing and the consideration given to surrogate screening. In paragraph 6 you explain that:

"In Germany in April 1965, at a Congress of Hospital Hygiene, it was suggested that blood donors should be tested for liver enzymes to prevent transfusion-transmitted hepatitis."

Of course, professor, 1965 was before the identification of Hepatitis B and before the identification of Hepatitis A. I think that's correct?

A. That's correct.

Q. You then state:

"The German Society of Blood Transfusion first considered such mandatory testing of all donors to be premature, especially in the light of losing many regular donors but yielded the following year to the growing pressure. A general ALT testing was started in Germany in 1966. Many blood banks in Italy had introduced ALT testing already in 1960."

Professor, as regards Germany, do you know whether ALT testing was introduced in every region in the late 60s or whether simply some regions used the test?

A. To my knowledge it was introduced overall in Germany, not at the same time, but gradually in all of the regions.

Q. I see. Do you know, professor, the ALT cut-off that was used?

A. No.

Q. No. If we could go to one document, please, [PEN0170869], and if we scroll down a little, please, and look at the left-hand column. This is a 2004 publication in Vox Sanguinis and we can see in the left-hand column there is, I think, an abstract by Drs Roth and others of the German Red Cross. I think the important thing here is that they are considering

the relevance of ALT testing after the HCV test is available and being used, and in short they don't consider that ALT testing is relevant in those circumstances, but we can see four lines down the authors state:

"Since 2003 the threshold is determined with the IFCC reference method for men of 134u/l and for women at 89u/l in Germany."

These are relatively high ALT cut-offs but obviously this is in the context of screening with HCV. But that doesn't give us any help, I take it, as to the ALT cut-offs being used in the 1960s in Germany?

A. No.

Q. No. Okay. Turning to Italy, briefly, professor, when you come back to paragraph 6 of your statement, please, in the final sentence you say:

"Many blood banks in Italy had introduced ALT testing already in 1960."

I take it from what you say that that isn't necessarily across the whole of Italy, that may just simply be some parts of it?

A. It's very difficult to say about the whole of Italy because the system was very dispersed and this is something that I heard from Professor Liotta, who was the Italian representative at the Council of Europe

expert committee, saying that some of our centres had already introduced this ALT testing, and this is all I know.

Q. Thank you. I think we have heard previously that there was a higher incidence of hepatitis in the donor population, or rather in the community generally in Italy, and by inference, therefore, presumably in the donor population as well. Is that correct?

A. That is correct. Yes.

Q. So there may be special factors applying to Italy. Thank you.

Then in paragraph 7 we can see what is said. In paragraph 8 you explain that:

"The German transfusion doctors remained sceptical about the efficacy of ALT screening. Professor Siegfried Seidl, the then leading German expert in the field of blood transfusion, wrote to ..."

A German publication:

"... in January 1983 and reviewed the American TTV and NIH studies. He mentioned that the ALT screening had not decreased the incidence of NANBH in the Federal Republic of Germany. He concluded that there were still too many open questions to be solved before routine donor ALT screening could be recommended. Instead, efforts should be directed towards finding a specific

marker for NANBH."

The reference for that publication is [LIT0012211]. We won't go to it because it's in German. So that's one for the German speakers.

It may be helpful, though, to look at the Vox Sanguinis series of comments in 1983 at this stage. That is [LIT0011837]. I'm not going to go through each of the comments. In short, I think, most of the contributors did not recommend the introduction of surrogate testing in their countries at this time, without further research. Is that a fair summary of the general feeling?

A. I think that was the general feeling, yes.

Q. But if we could perhaps look at the German contribution, it's at page 58, which is 1847. In the top right-hand column, this is from Dr Muller of Hannover and we can see what Dr Muller says for ourselves in the first half of his column. We come about half way down, we can see he says:

"In Germany, the main reasons for elevated ALT activity today, however, are alcohol consumption and obesity. Slightly elevated ALT activities in blood donors, therefore, are observed so frequently that blood bank services could not cover all the requirements were they to apply a strict upper normal range ALT limit of

22 iu/l.

"Lack of agent specificity and reduction of sensitivity for practical purposes are strong arguments against routine ALT screening in blood donors. This comprehension was supported by several previous studies which failed to provide conclusive evidence for a justification of routine donor ALT screening."

The references 1 and 2, I think, are to US studies in 1959 and 1971. Then Dr Muller goes on to mention the TTVS and NIH studies in America in 1981. Go over the page, please.

Dr Muller then goes on to state that:

"The proportion of transfusion-associated non-A non-B Hepatitis according to case history in 566 serologically proven non-A non-B Hepatitis cases recognised in the Hanover area between 1975 through 1980 rose steadily from 5 per cent in 1975 to 19.2 per cent in 1980 despite the fact that all donors are regularly tested for ALT".

And Dr Muller goes on:

"Since ALT testing identifies some asymptomatic carriers and a small minority of patients with anicteric acute and chronic non-A non-B Hepatitis who can transmit the agent(s), I feel that screening for ALT in blood donors should not be abandoned."

This is the point I emphasise:

"Moreover, transfusion of blood and blood products in Germany is subject to the same regulations applied to the administration of drugs, which appoint a "maximum of safety" with regard to toxicity and infectivity. Considering the costs of ALT screening on each unit of blood is therefore minimal compared with the total cost amount which may arise from one case of non-A non-B post-transfusion hepatitis running a chronic course."

I emphasise, professor, the requirement in Germany for blood and blood products to have a "maximum of safety," and that's a point I'll return to later when we look at the Council of Europe recommendations in 1987.

Could we then, please, return to your statement? Paragraph 9, please. You say:

"The TTV and NIH studies had, in 1981, shown a correlation between donor ALT and recipient NANBH, even though this finding was not confirmed in all donor populations."

When you say, professor "the finding was not confirmed in all donor populations," is that a reference to all donor populations in America or elsewhere or what?

A. I think that refers to their material that was collected from various transfusion centres in the USA, and in some

areas these correlations could not be shown, whereas in the majority of areas or those populations, it could be shown.

Q. I understand. You then tell us that:

"The American Association of Blood Banks ..."

Just to pause there, professor, can you remind us, the AABB, was that an association of independent blood banks in the US, not including the Red Cross transfusion services. Is that correct?

A. There were three major organisations in the United States, covering this field, and the American Red Cross was responsible for about, I believe, half of all the collections and then there was the American Association of Blood Banks and those were the independent blood banks and they formed this association, and the third one was the community blood centres organisation. I don't remember its name right now. But these three organisations covered the whole field.

Q. In the mid 1980s, the AABB, would that include hospital blood banks?

A. Yes, sir.

Q. And did the AABB in the mid 80s collect only from voluntary donors or did they include some paid donors or what?

A. AABB organised the yearly big conference, where these different matters were discussed, so it was clearly the leading organisation for transfusion matters in the United States. American Red Cross was participating in all these conferences but as an organisation it had not such a dominant position as AABB.

Q. Yes. I'm just wondering, professor, we have heard often references to America being different because in America blood was collected from paid donors, rather than voluntary, unpaid donors, particularly, I think, in the 70s. I'm just wondering, by the middle of the 1980s, whether the AABB members only collected blood from voluntary donors? Maybe it's a question you cannot answer.

A. Generally, they did not pay the donors. They were voluntary donors as far as whole blood was concerned, whereas the plasma donation was totally commercial and there all the donors were paid. This was a private enterprises that were performing that. It was a remarkable change from the 70s until 1980s and most of the American blood banks that were collecting whole blood really started using totally voluntary system.

Q. Thank you. I think the final point about the AABB, we have seen often a reference to the journal "Transfusion". I think that was the journal of the

AABB. Is that correct?

A. That is correct.

Q. Thank you. Picking up again in paragraph 9, please, you explain that:

"The AABB established an ad hoc committee on ALT testing and the committee concluded in 1982 that 'while we share the desire of the entire medical community to reduce the incidence of transfusion-associated hepatitis, we believe that the currently available evidence does not justify either universal testing of donor blood for ALT or the rejection of donors who have elevated levels'."

I'll give the reference for that document without going to it. It's [LIT0012217]. You go on to explain in paragraph 9 that:

"... in 1985 ... Dr Alter ... wrote 'The question of whether or not the ALT test should be routinely adopted for donor screening was widely debated and currently remains an essentially unresolved issue'. In the same article he mentions that the New York Blood Centre had initiated such testing but that they did not accumulate additional efficacy data. Dr Alter had also started ALT testing of donors at the NIH blood bank in order to obtain more information but 'there was no significant decline in hepatitis incidence after ALT testing. This

is even more striking since transfusion volume declined over this time period'."

You explain:

"The same sceptical view on routine ALT testing was presented in a review article of Transfusion, which appeared in April 1985."

I'll provide the reference for the Transfusion article without going to it. It's [LIT0012164]. I would, however, like to go to the Alter article of 1985, because I think it's interesting to compare Dr Alter's views in 1985 with what he then says in 1986.

The Alter article is [LIT0010811]. We have looked at this article before, when looking at the state of knowledge of the seriousness of NANBH previously, but if we could look at the article for a different purpose, namely Alter's views on surrogate testing at this time. If we could go, please, to page 57 of the article, which is 0821, and after a discussion of the data and evidence available in surrogate testing, Alter, about a third of the way down the page, states:

"With these analyses in mind, our options seem to be threefold:

"1. To decide that existing data are inconclusive and that in view of problems of non-specificity, diagnostic uncertainty, responsibility to the donor,

test standardisation, cost and donor loss, it is best not to adopt routine donor ALT testing at this time.

"2. To decide that although the data relating to ALT efficacy are not definitive, they are scientifically valid and overall are sufficiently compelling to warrant universal donor ALT testing at this time. Implicit is the assumption that if an interpretive error is to be made, it is best to err on the side of recipient safety and that to withhold such testing is ethically unjustified."

That sentence, professor, "Implicit is the assumption that if an interpretive error is to be made, it is best to err on the side of recipient safety," is perhaps a hint of the precautionary principle that, where evidence isn't clear, one should err on the side of seeking to cause least harm.

A. Yes.

Q. We may pick up on that a little later. Returning to Alter, he states:

"3. To decide that existing data are inconclusive but are sufficiently compelling that a definitive answer must be sought."

Et cetera. We can read for ourselves down to the bottom of the page:

"A randomised, controlled study is long overdue and

should be instituted as rapidly as possible.

"It is my opinion that option 3 is the most tenable alternative. Had this controlled study been performed three years ago when first proposed, a definitive answer would be at hand. Instead, the same uncertainties persist. A randomised, controlled trial could be completed in one and a half years, could address both the ALT and anti-core issues, and could provide a definitive and rational basis for making these complex decisions. Even at this late date, such a study should be performed lest two years from now, we find ourselves still far from the core (or the ALT) of this issue."

At that stage Alter is not arguing for the introduction of ALT screening; rather, he argues for a proper randomised, controlled study as to the efficacy of such screening.

Thank you.

Could we then, please, return to your statement, to paragraph 10? Paragraph 10 sets out a change in thinking. You say:

"In 1986 the American opinion changed. In the re-examination of the old TTV study data, the authors had found out that there was also a correlation between donor anti-HBc and recipient NANBH but ALT and anti-HBc identified different donor groups."

We can see what Dr Alter then states. You provide a quote from him and Dr Alter pointed out the fallacy of this type of predictive reasoning.

Over the page, please. In paragraph 11 you explain that:

"Later in 1986, the major American Blood Transfusion Service organisations recommended routine ALT and anti-HBc testing of all donations."

Although that was never required by the US health authorities. You go on to say:

"However, the usefulness of this testing remained controversial."

In paragraph 12 you say:

"From a European perspective, it was difficult to determine the reasons underlying the change in American thinking. At the meeting of the Council of Europe expert committee in May 1987, the consensus of opinion was that the American decision had been influenced by non-scientific reasons."

Do you remember, professor, discussion of this in May 1987?

A. I beg your pardon?

Q. Sorry. Do you remember there being discussion in May 1987 of why the Americans had decided to recommend routine surrogate testing?

A. I remember there was a vivid discussion about this ALT and anti-core testing within the committee and I'm quite sure that this decision was the main trigger of that discussion. If I recall it correct, we were thinking that it was mostly the AIDS crisis that prompted the Americans to go ahead and were compelled to do something in order to repair a little bit of that harm that had been caused by the late reaction to the AIDS infection in the United States.

So these two factors, the lessons from the HIV story and secondly, indeed, we were thinking that America was very likely going into the litigation and therefore the blood centres wanted to protect themselves by starting at least something.

Q. Yes. When you say "lessons from the AIDS crisis in America", what particular lessons do you think there were? What do you think were the main points the Americans took from the AIDS crisis, which they then applied to this question of surrogate testing?

A. Well, after 1983, I believe, then there was a discussion whether it was an infectious disease or not, and then later on it got very big press coverage and media coverage and the transfusion community was very much blamed for being slow in reaction to this potential harm, and therefore we had a feeling -- and I don't know

whether this is true or not -- but we had a feeling at the committee that this was the main reason why they had to do something also for this hepatitis question, that evidently was coming up at some point in the future or already at present then.

Q. Is it possible that in America they were in essence applying the precautionary principle perhaps in light of the AIDS experience? Is it possible they were taking the view that, "Yes, there is scientific uncertainty about the efficacy of surrogate testing but that may be a step which can improve the safety of blood; therefore we should take it"?

A. Well, I think that primarily they were of the opinion that at that time it was better to do something that was uncertain because it could be safer for the recipients' blood, and therefore decided to go ahead despite the fact that this study that Dr Alter had two years previously been advocating to be done, it was never done. But there was a new analysis of old data and therefore they got some support for this idea, that they really should go ahead and look more thoroughly at the question of the safety of transfusion as far as the recipients are concerned.

Q. We will come to look --

THE CHAIRMAN: Mr Mackenzie, I wonder if I could just follow

one aspect of what Professor Leikola said.

Professor, I understand the point that transfusionists were being subjected to a fair amount of criticism following on from the AIDS crisis, but you said that at this time there was a fear, or a thought, that there was going to be coming up at some time in the future, or was already present then, evidence that hepatitis was going to be a problem. I would like just to get a sense of that, please, from you. In 1986 in the United States, what was the understanding of the risks presented by hepatitis?

A. I think that there was good evidence that at that time already, on the basis of the TTV and NIH studies, that non-A non-B Hepatitis is indeed a risk in the United States and probably elsewhere also. Therefore, I think it was perceived as a real risk already at that time and not only in the future but I had a feeling that, because the attention was mostly directed towards HIV and AIDS, the issue of non-A non-B Hepatitis would become stronger in the near future at that time. But it was very clear that non-A non-B Hepatitis was perceived as a clear complication and a serious complication of transfusion.

THE CHAIRMAN: So the changes made in attitude in 1986 towards favouring surrogate testing, when would you

think that it was appreciated by those who initiated the change that NANB hepatitis presented a significant risk? It must have been some time before.

A. Yes, I think it came in the early 1980s, after these two studies had shown that non-A non-B Hepatitis was there and it was serious enough.

THE CHAIRMAN: So really you have sort of almost a coincidence of lines of thought, one responsive to HIV AIDS and the other predictive of a similar problem emerging with NANB hepatitis, resulting in a change of attitude towards surrogate testing. Is that the picture one should have?

A. This is true. I think that what prompted people to re-examine those data from those two big studies was the fact that now this had become a big issue and therefore after the publication of this new data, then they got some background and facts towards the idea of nevertheless introducing the screening with phase 2 tests.

THE CHAIRMAN: Of course in America, fear of litigation is always a factor that can prompt reaction in those who are in the frame, as it were, for criticism.

A. Yes.

THE CHAIRMAN: Thank you.

MR MACKENZIE: Thank you, sir.

I suppose, professor, another important factor we shouldn't forget about when considering what happened in America was that there did always seem to be a higher incidence of post-transfusion hepatitis in America, certainly when compared with, I think, the northern European countries. Is that correct?

A. Well, I think that was quite clear that the incidence of non-A non-B Hepatitis was lower in northern Europe, as compared to, let's say, big urban areas in the United States, whereas in southern Europe it was also clear that both Hepatitis C and Hepatitis B were more prevalent than in the northern countries, including, for instance, Finland and Holland, and also we considered the UK.

Q. Yes, I suppose the point I seek to make is that at its very simplest, one reason perhaps which prompted America to introduce surrogate testing may have been that it was a bigger problem there than it was in northern Europe, quite simply because of the higher incidence of post-transfusion non-A non-B Hepatitis?

A. I think both the higher incidence and also the public opinion and media coverage in the United States, I think were important factors for that. In addition, we had read the recommendation of Dr Alter two years before that the large prospective study should be really

instituted because of the differences in different populations in the original TTV study, and therefore this idea of now introducing a large enough prospective study between blood donors and blood recipients in order to see what is the real situation in those populations in Europe, was considered.

Q. We will come back to that. Returning to paragraph 12 of your statement, professor, in the second part of that paragraph you refer to the litigation-prone atmosphere in the United States. We can read that for ourselves. There are two documents I would like to take you to, which on the face of it set out American thinking on this topic at this time.

The first one, please, is [SGF0010783]. We have looked at this before at the Inquiry and we can see it's a copy of the Blood Bank Week, I think the publication of the AABB, of 21 February 1986. If we go over the page, please, we can see in the first paragraph that:

"The Blood Products Advisory Committee of the Food and Drug Administration will recommend that both ALT and anti-core testing be performed on donated blood to reduce the incidence of transmission of non-A non-B Hepatitis through transfusion."

We can see that:

"In a February 13-14 meeting, the panel received

reports and two studies showing that recipients of blood from donors with elevated ALT and anti-core had an higher incidence of NANB hepatitis."

The next sentence I emphasise:

"While questions were raised about the data, it was noted that the carrier rate of NANB is higher than previously thought, that cases are underreported and that NANB is now considered to be a much more serious disease."

So on the face of it, that sentence appears to summarise at least the public reasons for the recommendation that surrogate testing should be introduced, and I suppose to summarise that sentence again, all of the factors seem to be related to patient safety, to seeking to maximise the safety of blood. Does that seem a fair summary?

A. Yes, I think that's fair.

Q. Yes. The other document I would like to look at from this time, please, is [LIT0011675]. Again, we have looked at this before but for a different purpose, to look at the seriousness of non-A non-B Hepatitis. It's a 1986 publication by Dienstag and Alter. If we could, please, go to page 76, I think we have actually looked at this quote before. It's at page 1684.

There has been a discussion by the authors on the

non-availability of a direct test, despite, I think, over 40 candidate tests having been tried and failed, and then a discussion of surrogate testing and the negative aspects of surrogate testing in terms of low sensitivity and specificity. But could I, please, professor, pick up the article in the left-hand column. We can see the second last line from the bottom:

"Despite these negative features, however, the accumulating data that chronic NANB hepatitis leads to cirrhosis in 10 to 20 per cent of cases has served as compelling evidence for the need to rely on indirect assays as an interim measure until such time as specific NANB hepatitis assays are developed."

Pausing there, that perhaps brings us back to Dr Aach's letter of 1981, that there may be a value of surrogate testing as an interim measure until specific assays are developed and available. Then to return to the article, the authors state:

"The major components of the blood delivery complex are currently considering the adoption of either the anti-HBc test or both the ALT and the anti-HBc test. Because of the cost and significant donor loss engendered and because of the recent introduction of mandatory screening of all donor blood for antibody to HTLV-III, adoption of yet another one or two donor blood

screening tests represents a very complex and difficult decision. Nonetheless, increasing documentation of the chronic sequelae of NANB Hepatitis and the continued high incidence of this disease after transfusion have tipped the balance in favour of adopting indirect assays for NANB Hepatitis carrier detection."

So again, here the authors seem to be giving patient safety reasons for the balance having been tipped in favour of the surrogate testing, albeit there were, no doubt, all sorts of other factors in the background as well, such as fear of litigation and perhaps other factors too.

Professor, do you have any further comments on that passage I have read out?

A. I would just point out that in this type of scientific text, where this decision is either recommended or commented on, it's very difficult to say in writing some underlying development in the society in general, whereas emphasising the patient safety is sort of a very safe way of going ahead and having a good founding for this decision that has been made. I don't doubt that the patient safety and reaching a maximum safety in transfusion really was an issue but on the other hand, when you are writing these articles, it's very difficult to say that, because of political pressure or something

else, so the scientists are much -- it's much easier to say that this fact certainly was a factor there and was the leading idea.

Q. I understand. Thank you. Leaving that article to one side, please, and returning to your statement, in paragraph 13 you explain:

"The American development was keenly followed also in Europe. In the early 1980s the conclusion by the AABB ad hoc committee ..."

I think that must have been the 1982 conclusion that you referred to earlier:

"... was considered reasonable and there was no move in Europe to introduce surrogate testing. It was recognised that the incidence of NANBH varied from country to country and in different donor populations. In northern parts of Europe there were less cases of NANBH than in the south and there were also differences between urban and rural populations."

A reference to Australia. Paragraph 14:

"There was a general feeling that more information was needed of the possible correlation between screening for surrogate markers and prevention of NANBH."

A reference to the Vox Sanguinis publication in 1983, which we have looked at, and you explain that:

"All contributors took a cautious view on ALT

screening."

In paragraph 15:

"The American finding that anti-HBc correlated with NANBH was disturbing and could not be explained."

I think, professor, to this day that correlation cannot be explained. Is that correct?

A. There was no reasonable explanation for this correlation because one was Hepatitis B and it was definitely not the causative agent for non-A non-B Hepatitis.

Q. Thank you. You go on to say that:

"Correlation with ALT was much more natural since the definition of NANBH was based on elevated ALT values, and there the question was about the efficacy of the test in identifying donors at risk of transmission of hepatitis. There were soon reports appearing, notably from France, the Netherlands and the United Kingdom, showing that in the European donor populations studied, anti-HBc did not correlate with recipient NANBH. The pattern was clearly different from the American donors: incidence of NANBH much less and anti-HBc meaningless as a surrogate marker. There was some association between elevated donor ALT and recipient NANBH, but its efficacy as a possible surrogate screening test was considered weak. This view was supported by the negative findings of NANBH

incidence after ALT screening in Germany on the one hand, and in the New York Blood Centre and at the NIH on the other."

In paragraph 16 --

THE CHAIRMAN: Before you go on, I wonder could we explore just a little bit the first sentence and what lies behind it? One has a condition, Hepatitis B, with the development of anti-HB core in the person, and that is identified with the specific hepatitis condition. One then finds that NANBH is associated in some way with the incidence of anti-core Hepatitis B. As a matter of logic, one would be inclined to say that it cannot be the disease that provides the link because by definition NANBH is not Hepatitis B. What else could it be?

A. I think it's the behaviour of the donor.

THE CHAIRMAN: Right.

A. He happens to have had Hepatitis B infections some time in the past and then, because of his behaviour, he gets also Hepatitis C or maybe elevated ALT because of alcohol consumption.

THE CHAIRMAN: I think if we leave ALT aside just for the moment, because I do understand the difference there. So what in effect one is saying is that the sort of person who has anti-HBc indicators is the sort of person who is going to have NANBH. I find that very difficult.

Without further specification.

A. Yes. Well, Hepatitis C is really transmitted parenterally, even sometimes, you know, once or twice using intravenous drugs with a needle that has been used also by the community around this person may transmit Hepatitis C and therefore it may be -- you know, otherwise, a totally healthy individual that in their youth sometimes has tried these drugs.

On the other hand, it has also been shown that alcohol consumption in those patients who are positive for Hepatitis C, the prospect of developing a chronic liver disease, cirrhosis and finally carcinoma, maybe is much, much higher than in those people who are not consuming much alcohol or some other agents that may affect liver in addition to this virus, Hepatitis C.

THE CHAIRMAN: This still leaves me with the terrible logical problem that all that that would indicate would be that some people in these categories develop NANBH and can therefore transmit it but one could not generalise on that and say that all people in these categories would be in that position, and therefore if you look at the test, the universality of the test can never be supported on the particular examples that one has identified. It's a logical problem and --

A. It is a logical problem, yes.

THE CHAIRMAN: I'm not sure how one resolves it. But it may be that at the end of the day, it is a sort of emotional reaction to the situation that says we really have to do something, rather than a scientific or logical answer to the situation.

A. I would agree with that.

THE CHAIRMAN: You think that's what it was? Yes, thank you.

Thank you, Mr Mackenzie.

MR MACKENZIE: Thank you, sir.

Professor, does it not really just come down to in the American studies there was found to be a correlation between donors with anti-HBc and an increased prevalence of post-transfusion NANBH in recipients, and although one couldn't perhaps explain why that was so, nonetheless there was such a correlation so that was some evidence for screening for anti-HBc? Does it not just really come down to that?

A. One of the explanations was that maybe this non-A non-B Hepatitis is caused by a number of different viruses and some of the viruses are related to Hepatitis B virus, and therefore some of these cases could be shown by measuring the anti-Hepatitis B core antigen because the virus was not known and it was not known whether non-A non-B Hepatitis was caused by one virus or two viruses

or by a virus at all.

Q. Am I right in thinking that the starting point for the argument that anti-HBc screening may be worthwhile was the observed correlation, at least in America or parts of America, of anti-HBc in donors and increased incidence of post-transfusion NANBH in recipients? That was the starting point?

A. Yes.

Q. And whether there was logic or whether the argument was soundly based on evidence or perhaps other matters, but at least there was a starting point for what it was worth?

A. Hm-mm.

THE CHAIRMAN: The qualification, of course, rather undermines the whole exercise. If you have to say "for what it is worth", the logical basis has broken down. I really would just like to get a feel for what was thought at the time, Professor Leikola, because it's clear that there has been a great deal of revision of thought over the period between. But do you think that we have discussed it enough to get to the sense that people had at the time of the significance of these tests?

A. Well, it could be. Of course, as I said, there were some assumptions that this putative virus would

cross-react sometimes with Hepatitis B virus, and that would be prevalent on the other side of the Atlantic but would not be present in Europe, and this would be the explanation for that. Although I think that most people thought that, you know, it really doesn't make any sense and therefore these European studies that showed that there was no correlation between anti-hepatitis core and non-A non-B Hepatitis was, for me at least, a relief, to see that, you know, it wasn't logical to include hepatitis core antibody in this whole exercise, and therefore I was quite happy to see that it was confirmed in our material and also in the other European --

MR MACKENZIE: I wonder, professor, if for practical purposes that's the important point, that the reports from Europe, France, the Netherlands and the UK showed that in the European donor population studied, anti-HBc did not correlate with recipient NANBH. So even with that starting point which there was in America, there wasn't even that in Europe. So for practical purposes perhaps, I can see the force of that at the time.

PROFESSOR JAMES: Can I also just add one small thing? That is that the American studies, the TTV study and the NIH study, on which this was based, because they re-analysed the data, looking at anti-HBc, were in a pre-AIDS donor population, where there was probably less donor

selection. So it's likely that there may have been, for example, in the anti-HBc group, a higher number of people with "at risk behaviour" than in, for example, northern Europe by 1986, where there was a great deal more careful donor selection and where individuals with at-risk behaviours were being better filtered out of the donor population, of course because of what had happened over HIV/AIDS in the preceding years.

Do you think that might be another possible explanation for these different findings, that actually they were really in different groups of individuals, not just different countries but the different rigour of selection?

A. Yes, sir, I think that could be part of the explanation. When we initiated our large prospective study in Finland, one of the reasons to do that -- and that has been written also in the report -- was that now that we had started the self-exclusion of people at risk of transmitting HIV, we had to see what was the situation with the present donor population, as compared to the ones that had been taken before the HIV was emerging.

PROFESSOR JAMES: Thank you. Thank you.

MR MACKENZIE: If we could now, professor, turn to look at the European response to the American recommendation for screening, in paragraph 16 you explain that:

"After the American organisations decided to recommend the introduction of routine ALT and anti-HBc testing ..."

The European countries had to decide whether or not to follow suit. Over the page, please. You explain that:

"There was a consensus among the scientific and blood transfusion expert community that prospective studies were urgently needed before a decision could be taken."

What do you mean by "prospective studies", professor?

A. "Prospective studies". I mean a study where a number of transfusion recipients are followed for long enough to take blood samples out of those patients and then having all the samples from the donors being stored and then analysing whether any of these patients had contracted non-A non-B Hepatitis, and then compare that with the stored samples from the donors that were implicated.

Q. And what is the purpose of such a study?

A. The purpose was twofold. First of all, it was important to see how much non-A non-B Hepatitis there really was in a given patient population in a given country or region, and therefore the patient had to be followed for a long time. And we decided taking ten samples out of

each patient during a period of six months in order to see whether there was a fluctuating ALT level, and you would not find it by just taking one sample there and therefore you could determine whether in that patient population -- and that means in donor population on the other hand -- non-A non-B Hepatitis indeed exists.

And then the second purpose was to be able to then to compare the donor ALTs and recipient ALTs and later on the specific Hepatitis C test, whether these were linked together in order to show that positive mass screening of donors would indeed then protect and prevent transmission of this disease to the recipients.

Q. Thank you. So in short, the purpose of such a study was firstly to consider the incidence of post-transfusion non-A non-B Hepatitis in one's country, yes? And secondly to really evaluate surrogate testing and any specific testing which may come along?

A. Yes.

Q. Thank you. Would a study restricted to looking at surrogate markers in donors meet those objectives?

A. You mean only donors?

Q. Yes.

A. No, that wouldn't be prospective. It would show the incidence of ALT and then a possible marker within donor population but it wouldn't show whether these

individuals really had transmitted a disease to the patient.

Q. Yes. I should perhaps explain, as you may know, that it was decided in the UK around this time to not undertake a prospective study of recipients but rather to undertake a study restricted to donors, and looking at the incidence of surrogate markers in donors. Were you aware of that at the time? I think there is in fact reference to it in the minutes of the meeting of the Council of Europe committee of experts. Do you recall such a study being proposed in the UK, restricted to donors?

A. That I don't know. We decided in Finland to undertake that kind of study already before 1987 and I reported on our plans and our study design to the committee, but I don't remember what kind of reaction, other than congratulations for a good undertaking and so on -- what really was happening within the other circles and countries.

Q. We could perhaps go to look at the minutes of the Council of Europe committee of experts meeting in May 1987. It's [SNB0019445]. I say "minutes" but I see it's an extract from the report of the committee of experts on blood transfusion and immuno-haematology, the tenth meeting in Rome, 19 to 22 May 1987.

Go over the page, please. We can see in the first paragraph:

"A synthesis of replies received from members of the SP-HM to the questionnaire on non-A non-B Hepatitis was presented by Dr Gunson. These replies clearly show that this issue is in general given careful consideration by most blood transfusion services. The general impression is that the incidence of NANB Hepatitis is rather low, but varies widely between different regions. The value of 'surrogate tests', such as ALT and anti-HBc, has been studied by various groups but there is doubt about their cost/effectiveness. Professor H Weise remarked that ALT testing has been used in the Federal Republic of Germany for more than 20 years. The reduction in non-A non-B Hepatitis was estimated at about 29 per cent according to Professor Weise, while approximately 1.2 per cent donors were lost. However, controlled studies have thus far not been performed."

Pausing there, professor, on the face of it, Professor Weise, whom I assume was from Germany, appears to be reporting a positive German experience with ALT testing. Is that correct?

A. I think that the last sentence in this paragraph was reflecting some of the criticism that the other participants were giving to him because if I recall it

correct -- and I don't know; this is 22 years ago -- if it was so that when details about this 29 per cent were asked about, the answer by Professor Weise was that, "Well, it's 29 per cent. I don't know more about it." And therefore, you know, it was just a figure that he was throwing to the audience and could not explain any of the data that were behind it.

Q. I think we know that to be scientifically sound, in order to know the efficacy of surrogate testing, one would have to carry out a controlled, prospective study, and I think no such study had been carried out at that time.

Over the page, please. I should perhaps say, no full-scale, controlled, prospective study had been carried out. I think some work had been undertaken by some centres involving perhaps small-ish numbers of patients but I think not in sufficient numbers to give a statistically and scientifically sound answer to the question of the correct efficacy.

A. I think that's probably true.

Q. Thank you. Over the page at 9447, we can see your name appearing at the bottom of the page, professor:

"Dr Leikola (Finland) reviewed the literature of the last eight years concerning this topic. He concluded that many of these studies lack definitions of hepatitis

and control populations. Also there are discrepancies between epidemiological data and the results of small scale studies. He expressed his opinion that the decision to introduce surrogate testing should be based exclusively on data available or obtained from a given country or region. In Finland, a prospective study in five hospitals will be started to establish the value of such surrogate tests for the prevention of post-transfusion NANB Hepatitis".

We will come to the reports of the Finnish study soon. Over a couple of pages, please, to page 9449. At the bottom of the page we can see again the position of the various European countries at this time:

"Apart from Belgium, the Federal Republic of Germany, some Italian regions and Luxembourg, no other member countries of the Council of Europe are routinely using ALT tests and blood donations at the present time. However, a national working party in France has now recommended the introduction of both ALT and anti-HBc tests. Anti-ALT testing may also be commenced in Sweden."

What's that a reference to? Perhaps that should be either "ALT testing" or "anti-HBc testing". It may be a typographical error. Is there such a thing, professor, as anti-ALT testing?

A. I'm sorry, I didn't follow.
Q. It's simply an error perhaps.
A. Could you, please, repeat your question?
Q. Yes. We can see in the fourth line from the bottom of the page a reference to:

"Anti-ALT testing may also be commenced in Sweden."

A. That should be "ALT testing", of course.
Q. Yes, thank you. Over the page, please. I should have said, this is essentially the report of a working group comprising yourself, Professor van Aken, Dr Habibi and Dr Gunson, and at page 8, which we now have, we can see at the top:

"Two studies are proposed. In Finland a prospective study of patients undergoing open heart surgery ... in the United Kingdom there are proposals to ALT and anti-HBc test a cohort of blood donors in four centres."

We can see:

"On the basis of this information, the working group concluded that ..."

And five conclusions are set out. We can see:

"1. Surrogate testing remained a controversial issue."

And:

"2. If a stance is taken that blood should have a maximum safety, then the tests would be introduced,

but the benefits derived from this testing would not be uniform throughout every country. Also, there is no guarantee that, in a given country, there will be a significant reduction in the transmission of NANB Hepatitis."

Again we see the reference to:

"If a stance is taken that blood should have maximum safety ..."

We come back to discuss that a little at the end of your statement. In three, a reference to potential problems in blood supply. Four, a reference to problems with donors and their counselling, and five:

"The committee cannot give a general recommendation on the introduction routinely of non-specific tests for evidence of NANB infectivity of blood donors. Individual countries will have to assess the situation locally and decide on the appropriate action to take."

Professor, those five recommendations -- we know there were four individuals on the working group -- did all four of you agree these conclusions or were some members more in favour of surrogate testing than others or what?

A. Well, it's very difficult for me to recall our internal discussions within this small group, but I have the feeling that Dr Habibi, who was very much involved in

the French AIDS scandal, was the strongest proponent for introduction of surrogate tests.

Q. Thank you. That's that document. Could I then, please, return to your statement and carry on? Paragraph 17. You explain:

"It was not only a question of whether or not to introduce surrogate testing but also which tests should be used."

We can see what is said there:

"The main goal for the European countries was to find out the true incidence of transfusion-transmitted NANBH."

In paragraph 18:

"Most countries that I know elected in 1987 not to blindly follow what the Americans did but to first find out the situation in their own donor population. Thus, the attitude towards surrogate testing was not negative per se, but before making a decision in Europe, the expert community wanted to know whether the concept would really produce results."

A reference to plasma fractionators and ALT testing. In paragraph 19 we see a reference to the Chiron announcement in May 1988, that what would become known as "Hepatitis C" had been isolated. You say:

"Thereafter it was quite natural that the decisions

concerning commencement of routine surrogate testing with doubtful efficacy should be postponed until a specific test was available."

In paragraph 20 you explain the position in France and why they introduced surrogate testing. You say:

"It was not motivated by the scientific knowledge but by the political necessity. Something had to be done, whether or not it truly reduced the risk of NANBH transmission by blood. Northern countries with low NANBH incidence such as the Netherlands, Denmark, Norway, Sweden and Finland, decided not to introduce surrogate testing before more was known of the efficacy in the respective donor populations."

You refer to a number of UK articles we have looked at previously: Anderson in 1987, Dow and others in 1987 and Gillon in 1988 and you explain:

"These opinions in the prestigious medical journals were not without influence in the international community."

Returning in paragraph 21 to Finland, you explain that:

"We decided in 1979 at the Finnish Red Cross Blood Transfusion Service to undertake a prospective study to determine the prevalence of post-transfusion hepatitis in Finland."

You refer then, professor, to a publication in 1982. I think that is the only publication of all of your references we don't have. Is that publication in English or --

A. That is in English.

Q. It's in English?

A. Yes.

Q. So maybe we could perhaps get a copy of that, either from yourself or we could always use our own library resources.

A. Yes. [NB this document is now available as PEN0181141.]

Q. Thank you. You explain:

"The study was carried out in 1980-1981 ... a relatively small study involving 65 patients and 652 transfusions."

I assume, was that again a study of open heart surgery patients?

A. Yes, sir.

Q. Which would explain the high number of transfusions per patient, about ten transfusions per patient?

A. Yes, that was customary at that time in Finland, to transfuse quite a bit of blood to open heart surgery patients, and I also think that surgery has developed since those days.

Q. I see. And you explain:

"Three cases of NANBH were found."

Could I pause, professor? Just out of interest, were these cases later tested with the Ortho HCV test and, if so, were they confirmed cases of Hepatitis C?

A. Those samples were not available any more.

Q. I understand. You go on to say:

"The main conclusion was that NANBH was indeed present also in Finland but its incidence was lower than that, eg, in the United States. In one of the implicated donors there was elevation of ALT in one sample but this finding did not warrant surrogate testing."

We can then see the quote you take from the article for ourselves.

Then, moving on to paragraph 22, you explain:

"The decision in the USA in 1986 prompted a new discussion on the value of surrogate testing also in Finland."

This is perhaps Professor James' point:

"Since in Finland, as in other countries, the AIDS risk had resulted in new donor selection criteria in 1983-84 which influenced also the incidence of PTH. It was decided in 1987 to undertake a new study 'to determine the current incidence and types of post-transfusion hepatitis among open heart surgery

patients from all parts of Finland. The second objective was to obtain donor samples for future evaluation of possible preventive strategies.'"

A reference to an article by Ebeling and others in 1991, which we will come to; we will come to look at the details of that article shortly. Also then:

"Several candidate markers for surrogate testing were also investigated."

-- in another 1991 article by Ebeling, which we will come to as well. Just to finish off paragraph 23, you state:

"Preliminary evaluation of our study had indicated that there could be some correlation between elevated ALT values in the donors and PTH in the recipients, but the correlation was weak. There was no correlation between anti-HBc and PTH."

We can then see the conclusion that's set out. I suppose we have to remember that this 1991 article is written at a time or against the background that the Ortho HCV test is available. So in a way the article is comparing screening by ALT and other things with screening by the Ortho HCV test.

A. Yes.

Q. And I would, professor, like to take you to these two articles.

It may, sir, take -- in total I may be another perhaps ten or 15 minutes with Professor Leikola.

THE CHAIRMAN: I think that it's 11 o'clock and we should have a break.

MR MACKENZIE: Yes.

(11.02 pm)

(Short break)

(11.24 am)

THE CHAIRMAN: Yes, Mr Mackenzie?

MR MACKENZIE: Thank you, sir.

I would like to turn now to look at the two reports of the prospective study in Finland and really I have two purposes. Firstly to ask you a little about the difficulties in carrying out this study and, secondly, to ask you the value of this study. It's against the background that this sort of study was not carried out in the UK and it's really just to look at whether that may have been possible and if such a study had been carried out, what information may have been available.

So the first paper, please, is [PEN0171777]. This is a paper by Ebeling and others, including yourself, published in Transfusion Medicine in 1991 and I think the paper in short reports on the prevalence of post-transfusion NANBH in Finland. If we look at the summary, we can see some details of the study. We see

the summary states:

"A countrywide prospective study on open heart surgery patients was performed between 1987 and 1989 to determine the prevalence and nature of post-transfusion hepatitis in Finland. Altogether 685 coronary bypass operation patients, who received on average 12.3 units of blood products, were post operatively followed for 6 months. Ten blood samples were drawn from each patient. Hepatitis was diagnosed when the ALT values exceeded the upper normal value 2.5 times in one sample and twice in another, and non-viral causes could reasonably be excluded. Eleven hepatitis cases were recorded ..."

I think to pause there, your conclusion was that 11 out of 685 patients were considered to have post-transfusion non-A non-B Hepatitis. Is that correct?

A. Yes.

Q. And therefore the incidence of post-transfusion non-A non-B Hepatitis was considered in Finland to be 1.6 per cent. We go on to see the next column states:

"The majority had mild symptoms or were asymptomatic but two became icteric. Six patients (55 per cent) had abnormal ALT values for at least 6 months, which indicates possible chronicity."

We can see what else is said there.

Professor, can I ask you about how easy or how difficult it was to carry out this study and the cost of it and how that was met? Can you explain these matters to us a little, please?

A. Well, first of all, when we decided to perform this study, the background were the discussions at the Council of Europe and also the information coming from the United States, and we were able to perform this study mostly because our financing system at our service -- the Finnish Red Cross Blood Transfusion Service is an independent branch of the Red Cross and it charges for the products and services, the hospitals, and therefore we had the possibility of putting aside from the budget a certain amount of money for research and development, and this was considered to be very important information that we were getting out of this type of study. It was not only scientific interest but it was also interest for the development and policy of our institution.

Therefore, we hired Dr Ebeling as a young doctor, to make her thesis work on this very subject, contacted all the five university hospitals in Finland and asked about their opinion about such an approach, could we possibly follow up those patients for a prolonged period of time and take all the samples, and would they agree that

their hospital would then take these samples and store them and send them to Helsinki.

I think that it was mostly thanks to Dr Ebeling's organising skills that we were able to pull together all these surgeons and laboratories in those particular hospitals in order to carry out this study as planned, and we did not have to modify the original plan very much during the course of the study. And the final analysis of the samples, that was no problem in general, especially since during the study then Ortho came up with their new test.

It was not an inexpensive study but we had the collaboration of those university hospitals that helped us very much because they were not charging for collection of the samples and they also had the scientific interest in finding out whether blood transfusion that all the surgeons were performing every day, really was safe or not and then they could explain also to their patients that even though the amount of blood that was transfused in those days, 12 units on average -- usually it was less but in some patients they required very large amounts of blood -- they could explain to the patients that indeed there is a general feeling that blood transfusion is very safe in Finland, but then they would have data showing that indeed it is

or if it isn't, how to prevent those possible complications and consequences.

Q. Thank you. Do you know approximately how much the study cost?

A. No, I don't.

Q. We know that for the patient follow-up there had to be studies taken on a regular basis post-transfusion. Were there difficulties in getting the patients to return to hospital to take samples from them?

A. Yes, they came back to the hospital to take samples. In the beginning it was connected with their later check of their wounds and their conditions and so on, and the patients were very cooperative in general. Fortunately, the Finnish Red Cross Blood Transfusion Service enjoys a very good feeling with all its voluntary donors, and it's considered to be a very good source of services and products, and therefore I think that the patients were also quite cooperative in agreeing that they would come in in order to see what would come out of this study.

Also, I think, that Dr Ebeling was quite good in writing the information leaflets and informing those interested parties why this was considered to be important and what we expected out of that, so that the patients would understand and would come along in this undertaking.

Q. Thank you. Could we now then look at the other paper which reports on the other findings of the study, in particular the evaluation of the different tests? That is [PEN0171763]. We can see this is a publication by Ebeling. Is Ebeling male or female?

A. She is a female.

Q. Female, thank you. I take it, she is a doctor?

A. Yes.

Q. Ebeling, a publication by herself in Vox Sanguinis in 1991. I think it is worth reading out the abstract to see what is reported. We can see:

"ALT [gamma] glutamyl-transferase and Hepatitis B core antibodies were evaluated as donor markers in a prospective study of 685 open heart surgery patients. Of these three surrogate markers, only an ALT level greater than or equal to 2SD above the log mean had a significant association with recipient non-A non-B Hepatitis. Antibodies to the Hepatitis C virus were detected by enzyme immuno-assay in 7 of the 136 units transfused to the 11 NANBH patients and 29 of 3,650 not associated with hepatitis. Calculated from this subgroup of donors, the anti-HCV test would have a 15.6 positive predictive value with 0.92 per cent donor loss and thus is superior as a primary screening marker to all the three surrogate tests. The predictive value

could be substantially increased by subsequent ALT testing or by the use of a recombinant immuno-blot anti-HCV assay."

We will come on to look at the figures shortly, professor, but am I right in thinking that this study did find a correlation between elevated ALT in donors and an increased incidence of post-transfusion NANBH in recipients?

A. That is correct.

Q. And perhaps the more important point of this study, I think there was a finding that the Hepatitis C test seemed to detect post-transfusion NANBH recipients and indeed positive donors?

A. Yes.

Q. Put very badly but in short, I think this report was support for the introduction of a Hepatitis C test in Finland and that will be developed, I think, later in the day.

Could we just go through the paper and go over the page, please? We can see on the left-hand column under "Donor Samples" about half way down, that:

"Patient samples were drawn pre-operatively and 2, 4, 6, 8, 10, 12, 16, 20 and 24 weeks post-operatively."

Then over the page again, please. I'm trying to avoid those parts of the paper which relate to HCV

testing because I think we might go back to revisit that later.

On the right-hand column, if we can scroll down the page, under "Anti-HCV", there is perhaps some overlap here in our different C2 and C4 topics but it's stated:

"All 136 implicated samples from the donations to the 11 NANBH patients were tested by ELISA for anti-HCV. Seven of them were ELISA positive."

The top of the right-hand column, please.

A discussion there again of ELISA which I should perhaps refrain from going over but in the second paragraph, at the end of it:

"There was one additional factor which distinguished between the implicated and non-implicated ELISA-positive samples: 5/7 of the implicated but 0/29 of the non-implicated ELISA-positive samples had raised ALT levels."

Am I right in thinking, professor, that that is showing that there was found to be an association between elevated ALT in donors and Hepatitis C in recipients?

A. There was an association, yes, but considering all the elevated ALT cases among donors, the correlation was quite weak, but I don't remember -- and reading these figures right now, it's very difficult to explain it

more.

Q. Yes. I see. If we go down the page under "Discussion" again a question of ALT was picked up again. The paper states:

"64 per cent of the NANBH cases in the bypass patients received a donation which was anti-HCV-positive. The corresponding figure for ALT was 55 per cent, and this was the most predictive of the old surrogate markers of ALT, GGTP and anti-HBc."

I wondered again whether that was evidence of there being an association between elevated ALT in donors and Hep C in recipients? Is that a correct reading of that part of the article?

A. I beg your pardon?

Q. I'm sorry, I don't find it an easy article, professor, to understand, which is perhaps obvious from my questioning, but one point I did, I think, take from it, which I think you agreed with, was that the study showed an association between elevated ALT in donors and increased incidence of non-A non-B Hepatitis and perhaps Hepatitis C in recipients. I am simply searching for passages in the article which support that proposition of such an association. I'm wondering whether the first two sentences under "Discussion" support the proposition that there was such an association.

A. When I read these sentences, I think they support that, yes.
Q. Yes. I think the paper goes on to say that understandably the Ortho anti-HCV test was a better screening test than ALT for reasons we can understand; it's a more specific test. Could I ask you a hypothetical question, professor? Given the findings in this study, that there was an association between elevated ALT and increased incidence of non-A non-B Hepatitis and perhaps Hepatitis C in recipients, if the Ortho test had not been available at this time and if it had not been on the horizon, would that association have been sufficient in itself to persuade you that ALT testing should be introduced in Finland?
A. It's of course very difficult to answer right now, after 20 years' time, but I think that since the idea behind this study was to find out whether non-A non-B Hepatitis exists in Finland and what is its prevalence among the patients and if there is such a correlation, that makes sense, since non-A non-B was measured by ALT levels. I have the feeling that we would have introduced the ALT testing if Hepatitis C would not have been discovered.
Q. Yes.
THE CHAIRMAN: Are you going to look at the next sentence, Mr Mackenzie? Rather than just the first two? Because

it goes on to talk about the positive predictive value of ALT overall.

MR MACKENZIE: Yes.

THE CHAIRMAN: And I think the rate there is very much lower than one might infer from the first two sentences. So looking at the 4.1 per cent rate, would the answer have been the same, professor, you would have supported the introduction, ignoring the HCV on a predictive value of 4.1 per cent?

A. It's a difficult question. I still think that the answer would have been yes.

THE CHAIRMAN: And that would have been an appreciable enough incidence to make it worthwhile?

A. After this study I think that our emphasis on the transfusion safety was such that we would have introduced it.

MR MACKENZIE: And we can compare that positive predictive value perhaps with the positive predictive value for the anti-HCV test, which was found to be 15.6 per cent.

What exactly, professor, does "positive predictive value" mean?

A. Right now the question is too difficult for me to answer.

Q. Me too. I think that might be something, professor, that Ms Dunlop might explore with you later in her

examination.

I think we can put that paper to one side, thank you, professor, for now and return to finish off your statement, please. We have reached, I think, paragraph 24 and you explain that:

"After the introduction of routine screening of anti-HCV in 1990, additional surrogate screening was not seriously considered any more. Later experience has confirmed that surrogate testing after starting anti-HCV testing does not bring about any additional value."

I'll finish by asking you two specific questions. The first question was: on the basis of what was known at the time, did you consider it reasonable for the UK not to introduce surrogate testing of blood donors? In short, your answer was that you thought it was reasonable for the UK on the basis of what was known at the time, not to introduce surrogate testing of blood donors.

Can you explain perhaps reasonably briefly, professor, your reasons for holding that opinion?

A. Well, I think that what was regrettable was that no such large study was performed in the UK in order to find out what would be the value of especially ALT, both in recipients of blood and donors of blood, but I don't think that introducing a surrogate test at that point,

let's say when there was already information that the Hepatitis C would be coming, was, I think, reasonable. We did not introduce ALT testing before our study was done and I think that that reflected the general view in the mid 80s of the European transfusion community, that surrogate testing is not something that you should start without first performing such a study.

Q. In the middle of 1987 the Chiron test has not been announced, it is not on the horizon?

A. No.

Q. In the UK, in the middle of 1987, there is no prospective study of recipients. In light of that, was it reasonable in Scotland, in the middle of 1987, not to introduce surrogate testing?

A. The Hepatitis C was published in spring 1988 and I think that there were plenty of rumours around that something has been found and that would be some time in the future for use as a test. But I think on the basis of what was known by then, Finland did not introduce surrogate testing, nor would any of those countries beyond Belgium, Luxembourg, Italy and Germany, have introduced the ALT testing, except for France, that started, I think, in 1988 the ALT testing, but they had their own reasons and therefore -- I think it's understandable that the ALT testing was not introduced in Scotland in

1987.

Q. Does your position perhaps, professor, come to this, that one should ingather the evidence upon which to come to an informed decision; therefore, one should carry out a prospective study involving recipients and one can then decide what value, if any, surrogate testing may have?

A. Yes.

Q. You are nodding your head. Is that a "yes"?

A. Yes.

Q. Does your position come to this, that if you have a criticism of events in Scotland, it relates to the failure to carry out a prospective study involving recipients, rather than a criticism not to introduce surrogate testing?

A. I would say so, yes.

Q. Yes. Over the page, in your statement, professor, we really asked the same question but with the benefit of hindsight. So we asked:

"On the basis of what is known now ... should surrogate testing have been introduced in the UK and, if so, when?"

We had referred to the Crawford Paper in 1994, we looked at before, and you explain that paper:

"... found that of the donors with positive anti-HCV

test, a majority had elevated ALT values. This finding does not say much about the possible usefulness of ALT screening of all donors, since anti-HCV negative donors were not included and thus, we do not know how many donors in general would have had elevated ALT value at the time of donation. I believe still now that not introducing ALT screening as surrogate test in the UK for NANBH was correct."

I think that the point we were seeking to make, professor, by referring to the Crawford Paper was that the Crawford study did show that there was a correlation between donors with elevated ALT and recipients with Hepatitis C. I think it's one thing to say there is a correlation; it's a separate thing to be able to predict to what extent ALT screening may have reduced the incidence of Hepatitis C in donors, but it was simply given that correlation, do you think that in itself, with the benefit of hindsight, would have justified surrogate testing, at a time before the Hep C test was available?

A. I think that, if there would have been no knowledge of Hepatitis C testing at all, then I think there would have been more factors tilting towards introducing ALT testing in blood donors and that could have been then possible but this is not the only factor involving such

a decision. So it's very difficult for me to be in Scotland and trying to evaluate a decision that was made 22 years ago -- 23 years ago.

Q. I understand that, professor. We come back to local conditions and each country having to make up its own mind, taking into account all relevant factors that pertain to a particular country.

This is probably my last question, professor. It comes back to, I suppose, the philosophy with which one approaches transfusion. I can quite understand that in considering whether surrogate testing should be introduced or not, there will be a variety of factors which are relevant and which should be taken into account, but if one were to apply the precautionary principle, should one not always err on the side of the maximum safety of blood?

A. Well, I think that when you are considering such mass screening as blood donors who are healthy people, you have similar dilemmas with general vaccination programmes. You have to consider the benefits and drawbacks of a particular policy, and the attitude towards blood safety was changing during the years of 1980s and therefore something that was considered to be just a matter of fact, that blood transfusion would carry some untoward effects, was changing, and towards

the end of the 1980s that was definitely tilting towards the concept of, as you said -- if there is an error -- but erring for the safety of the recipient, because the safety of the recipient has always been of prime concern for transfusion directors and transfusion people altogether. But if you are considering all the possible untoward consequences of blood transfusion and if you want to avoid absolutely every case, then it's not reasonable to include all the possible tests within the primary screening and therefore, when considering this policy, you have to take into account a number of factors in addition to the safety of patients.

But I would agree with you that the safety of the patient is of prime concern.

Q. And perhaps looking at it another way, the safety of the patient should perhaps be the starting point in any consideration of an issue but there may be then, I suppose, other factors which one may have to take into account and address as well?

A. I would agree.

Q. Yes. Thank you, professor.

MR DI ROLLO: Mr Dawson on C2.

THE CHAIRMAN: Mr Dawson?

Questions by MR DAWSON

MR DAWSON: Thank you, sir.

Professor, I would just like to ask you a few questions about a couple of matters arising from your statement. If we could have that up, please, it's [PEN0171837].

The first area I wanted to explore with you is related to a number of comments that you make about the use of surrogate testing at a time when anti-HCV testing was either anticipated or actually available. You say in paragraph 1 in the last sentence that:

"After the anti-HCV became commercially available in early 1990, the question of introduction of surrogate marker testing became obsolete."

The area I really wanted to ask you about is really what's contained in paragraph 5, which is at the bottom of that page. You say:

"A third factor has to be taken into account. Once a test has been introduced to routine screening, it is psychologically and politically difficult to stop even if a specific test would have made it obsolete. To my knowledge, ALT testing for surrogate purposes was not started anywhere after the specific test for HCV became available."

I had a little difficulty with understanding that, professor. Are you suggesting that there may have been either psychological or political difficulties with

stopping surrogate testing if it had been introduced before anti-HCV testing came in, but after the point when the anti-HCV testing was available?

A. Yes, I think that, for instance, the American blood banks, they continued both anti-core antibody and ALT testing, even after the specific anti-Hepatitis C test was available and was in place.

The main reason is that, well, you never know that if you stopped now this screening that we have started, you never know whether it would cause some harm and we would not be able to detect everything.

What I mean here is that ALT testing as such is not a useless test but as a general screening test of all donors, I think it had become obsolete. When there was an indication that there would have been Hepatitis C case or non-A non-B Hepatitis in the patient, then I think it's very important then to test for ALT also in the donors but only in the implicated donors.

Q. What would be the purpose of that testing?

A. The testing then would be an additional test, not a screening test, but an additional test to see if the carrier of that particular Hepatitis C virus, if that is first of all confirmed that it really is Hepatitis C, whether the liver is involved, for instance, a high value of ALT would definitely indicate an active

hepatitis for that person. So from the donor's point of view, it's important to know what is his status and what is his health and secondly, that would be one of the additional diagnostic tests that are being used.

Q. Okay, thank you.

Could we just go back to the first page, please? I just wanted to ask you a couple of things about the contents of paragraph 2 and 3, where you say:

"When there is a recognised risk for disease transmission through transfusion and when the infective agent is not known, the only means of reducing the risk are selection of donors and judicious use of products. If clear risk factors are identified for the given infection, the donors with those risk factors can be asked to refrain from donation as was the case with AIDS. The policy is likely to be more effective with voluntary unpaid donors in general population than the paid donors. The second possibility is to use laboratory tests (surrogate tests) that could identify donors with risk factors."

Would it be correct to say that really the system of donor exclusion and the system of surrogate testing are two different types of the same kind of thing; they are trying to identify, either by looking at someone as a member of a recognised high risk group or by looking

at someone as having a recognised high risk on a particular test, recognising that person as someone whose blood should not be accepted into the system?

A. Yes, that is correct, that the surrogate test is used for identifying persons with risk factors. The problem is that particularly at that time, we did not know what the risk factors were for Hepatitis C. They were thought to be, you know -- with voluntary donors, you would say that it's not because of drug abuse and so on, and therefore the surrogate tests were not very good in identifying a risk group because there really wasn't a risk group or people with risk factors because Hepatitis C can be obtained from many different sources, mostly now we know that it's mostly parenteral.

Q. Right. So you make the comparison there with the situation with AIDS, and transfusion systems were able to identify groups of people and make the decision that those donors, because they are part of that group, should be excluded. Is the position with Hepatitis C that such an approach as that was not possible?

A. That's right.

Q. And therefore all you were left with was doing the laboratory type of surrogate testing in order to identify people who might be of higher risk. Is that right?

A. Yes.
Q. Right. So in paragraph 3 you go on to tell us that there are two potential consequences, about half way through the paragraph:

"It may seriously reduce the number of eligible blood donors and the donors found to be positive need to have a plausible explanation so that the test results should not raise unwarranted anxiety in the donor. A voluntary unpaid donation system underlines the obligation for the transfusion service to arrange an appropriate counselling system."

Would it have been normal practice, where someone was excluded as being a member of a group -- so the non-laboratory type of exclusion -- to offer them counselling?
A. Yes.
Q. It would?
A. That would be normal.
Q. Right. So the obligation to offer counselling to donors applies to anyone that would be excluded from the system by either method?
A. Yes.
Q. Okay, thank you. You said in answer to one of the last of Mr Mackenzie's questions that you thought that the safety of the patient to a transfusion doctor is of

prime concern. This passage here is identifying, I think, what Mr Mackenzie described as one of the other considerations, which is obviously the welfare of the donor. Do you think that it would be fair to say that in your experience there would be an inclination on the part of transfusion doctors to consider the welfare of the donor to be the prime concern, rather than the safety of the patient? Or is that not your experience?

A. No, I wouldn't say so. I think that the concern for the safety of the patient or the recipient is of prime concern, but in this counselling system and identifying those risk groups and so on, you have to remember that with laboratory tests the donor has already given a unit of blood and then he is contacted afterwards, and saying that, your unit of blood is no good. Whereas for AIDS that was meant for donors that they would refrain from donation, and therefore it would be much simpler to say that, "No, we are not taking your blood because of so and so and so".

So there is a philosophical difference between these sort of risk factors that could be identified either by identifying the risk group or the laboratory test.

Q. But is it not the case that in both groups what has happened is that you have identified a non-specific marker --

A. Yes.
Q. -- which tells you that the person is of a higher risk of having a disease and therefore you have excluded their blood, so that the situation is quite similar, is it not, for both cases?
A. In a way, but from the donor's side it makes a difference if he has already been accepted as a donor and gives blood and then later on is contacted saying, "No, your blood is at risk of transmitting a disease", instead of trying to explain that before the donation, it is sort of from the psychological point of view -- it's easier when you can explain that before the donation.
Q. Okay, thank you. Could I just ask for your CV to be put up, please? It's [WIT0030004]. Could we just scroll down a little bit further? Thank you very much.

We have gone on a number of occasions to articles which come from the publication Vox Sanguinis. I just wanted to ask you. You say there under "Positions of Trust Scientific", that you were involved in the foundation of the Vox Sanguinis journal, and you were a member of the board between 1992 and 1994 and president from 1994 to 2003. Do I take it from this that you were not a member of the academic editorial board in 1987?

A. So, I was not a member of the editorial board. The foundation was the owner of that journal and its main functions were to appoint first of all the editor-in-chief and secondly to take care of the finances of the journal. But it had no role in the scientific content of that particular journal; it was really up to the editor-in-chief and the editors that he had appointed and then confirmed by the foundation.

Q. I see. The reason why I'm asking is that Professor Cash in his evidence yesterday told us about discussions about surrogate testing that took place at a meeting of the academic editorial board of Vox Sanguinis in either January or February 1987, and suggested that you might have been at that. Would I be correct in saying that you were not at that because you were not a member of the board?

A. I was not.

Q. Thank you. I just want to ask you some questions about the evidence you have given already about weight that can be placed, in the context of surrogate testing, on studies and approaches being taken in other countries.

Could I ask you just to have a look, going back to the statement, please, at paragraph 15, which is page 3 of [PEN0171837]. You will recall this passage, which Mr Mackenzie took you through in some detail. This is

with the American development in the background and you are saying that:

"There were soon reports appearing, notably from France, the Netherlands and the United Kingdom, showing that in the European donor populations studied anti-HBc did not correlate with recipient NANBH. The pattern was clearly different from the American donors: incidence of NANBH much less and anti-HBc meaningless as surrogate marker."

So against the background of, I think, an evolving position in the United States, would I be correct in interpreting that as meaning that you were relying upon data that was emerging from other countries in Europe to tell that the position in European countries, or at least northern European countries, was different from that in America?

A. Yes, we were relying on that and then also the information from the large TTV and NIH studies. They were coming from the late 70s and early 80s and therefore this more recent information, especially, I would say in the Netherlands and the UK, were much more influential, I would say, for our decision-making.

Q. Were these studies upon which you were relying of a similar scale to those which had been conducted in America?

A. Not quite, but they were large enough to draw meaningful conclusions.

Q. Right. If we flip over the page, one can see what the recommendation was at this stage at the top of page 4; where you point out that:

"There was consensus among the scientific and blood transfusion expert community that prospective studies were urgently needed before a decision could be taken."

I'm just trying to explore the extent to which there appears to be a slight inconsistency there. You are relying upon the data that is available but suggesting in that sentence, as I read it, that perhaps that data is unreliable and a bigger prospective study is needed. Could you just explain that for me?

A. The idea of a prospective study is really to find out first of all what is the incidence of non-A non-B Hepatitis in patients who are receiving blood products, and then from the donors, when they have stored samples, try to find out any laboratory correlation between those patients who have been established to have non-A non-B Hepatitis and the corresponding donors.

This has to be prospective in order to be non-biased and to have material that is absolutely objective, and therefore this need for these prospective studies is very much the same as was indicated by Dr Alter two

years earlier, or three years earlier, that a large prospective study would be needed in order to get objective data that would support the decision-making process.

Q. If you were in a situation where you simply, for whatever reason, could not instigate a local prospective estimate of that nature, for example if there was simply no funding for that available, then to what extent could you at that time draw upon conclusions that had been reached and data that had been collated in other countries, to make a decision reliably about whether surrogate testing should be introduced?

A. To some extent, yes, if they would have a fairly similar population and similar donor structure, then I think that the only way of trying to find data behind the policy decisions would be to try to learn from those studies, taking into account that the conditions may vary but still there is something to be taken.

Q. Right. Okay. I mean, obviously at this time, in particular in your role on the Council of Europe committee of experts, presumably you were discussing this, amongst other issues, with your international colleagues in some detail.

A. We were very much discussing that, yes.

Q. Am I right in thinking that at this time Finland was not

part of the European Community?
A. No, this was not a European Community. This was the Council of Europe.
Q. Right, yes. No, no, I'm asking specifically about the European Community?
A. No, Finland was not.
Q. I'm just wondering whether or not individuals in other countries responsible for transfusion felt that the European Community Directive, which was issued in 1985, relating to consumer protection meant that they were in a slightly different position from you from a legal perspective as regards surrogate testing. Was that something you were aware of?
A. To my understanding, in the European Community health matters were not really discussed very much, at least in the field of blood transfusion, and started only in the very late 80s or early 90s. And finally when a Directive on -- I think it was 1995 it came out. So the consumer protection within the European Community, that is something that I cannot comment on.
Q. Okay, thank you. Could I go back to page 2, please, of your statement, just one last area I wanted to cover with you that we have not touched on. You give us a very interesting analysis on this page of the position in various different countries around the world. One

I wanted to ask you about was paragraph 7, where you say:

"The example was not followed in other countries. Japan started ALT testing of donors in 1975, but this was part of the biochemical testing service package offered to Japanese donors in order to enhance the recruitment process."

I just wonder whether you could explain why it was perceived in Japan that offering ALT testing as part of this package would enhance the recruitment process.

A. That was meant to -- they had a large pattern of different biochemical tests there and ALT was one of those tests and it was not taken out as a special service to the donors, but the whole pattern of biochemical tests were done for each donor by an automatic machine.

The idea was to have a sort of health check for the donors and therefore, you know, it was supposed that they would come in because they would get this as a prize for their blood donation, and it would be good for the donors to know more about their blood and whether they are sick or not.

Another matter was that this particular collection of biochemical tests really didn't indicate whether they would be healthy or not but at least they would get some

information about their blood and therefore ALT was one part of the big package.

Q. Would you say that that kind of attitude from a public health perspective, to trying to give individual citizens information about the state of their health, is a responsible one?

A. No, I don't think it's a responsible one at all, since it's tempting those donors who are not feeling well and who may be thinking that, "There is something wrong with me," and what we have been trying to emphasise is that the donor has to be perfectly healthy when he is coming and there shouldn't be any way of trying to convince him or to explain to him that, "Since you have now given blood, you are healthy".

This was particularly important in the early days of AIDS transmission, when we were trying to exclude those risk groups and trying to avoid all those donors who would be coming in in order to be tested. And therefore the whole attitude and approach of offering these health services that were outside the safety of blood or safety of donor, I wouldn't agree with.

Q. Okay. Thank you very much, professor.

Thank you, sir.

MR ANDERSON: I have no questions on this topic, thank you, sir.

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: I have no questions.

MR MACKENZIE: Thank you, sir. I have no further questions.

Ms Dunlop will now conduct the C4 examination.

THE CHAIRMAN: Are we ready for the change of gear?

MS DUNLOP: Yes, thank you, sir.

Questions by MS DUNLOP

MS DUNLOP: Professor, we would like to ask you now about the assay and the introductions of anti-HCV screening, and plainly we are interested in looking at the position in Scotland.

You have provided for us two statements on this question and the first of them is [PEN0171957]. So we would like to look at that, if we could.

You tell us in the second paragraph that you were approached by Ortho in the spring of 1989 and asked to arrange for a study on the new test, together with Sweden and Denmark. I suppose I was interested in that. There must have been a pattern of collaboration between the Nordic countries, what, in matters of blood transfusion or more widely in medical research?

A. At least in blood transfusion there was definitely quite a lot of contacts and some of the contacts were within the Council of Europe expert group that I have been referring to and secondly, we had also some so-called

Nordic meetings, where the Nordic countries, Scandinavian countries and Finland were participating and then these different matters were quite a bit discussed there.

But the difference between, let's say, Sweden and Denmark and Finland on the other hand, was that the organisation of transfusion system was totally different. Sweden had hospital blood banks that were independent and within the hospital authority and this was true also for Denmark, whereas in Finland, there was a Finnish Red Cross that took a countrywide organisation for this transfusion service.

But in professional matters we had quite a bit of contact.

Q. From what you have just said about Sweden and Denmark, would it be correct for us to understand that the blood supplies were more local rather than having a countrywide system?

A. Yes, that was quite local, yes.

Q. Right. We see that the work was divided up, so Denmark was doing one aspect of the study, Sweden another and in Finland you were looking at the material that you had from Dr Ebeling's research, and we know already from the questions earlier this morning that that is the post-transfusion hepatitis study in open heart surgery

patients. You received test kits at the beginning of June 1989. You refer back to Dr Ebeling's study in paragraph 3. Although we have looked at it already this morning, I would like to have another look, if we can, please. That's [PEN0171777].

One of the things that's striking about this, professor, is the apparently low overall incidence of non-A non-B Hepatitis in Finland. So you are one of the lowest incidence groups or one of the lowest incidence countries globally. Is that correct?

A. I think that's correct, yes.

Q. I had a look at the map which Professor Howard Thomas showed us, on which there is a colour coding to show the prevalence in individual countries, and Finland, in common with the United Kingdom, is shown as being under 1 per cent.

A. Yes.

Q. Looking at some more information in this, I noted the description of the background, and indeed that point about prevalence worldwide is made, if we look at the first part of the text on the left-hand side. So if we could perhaps scroll down a little bit.

The authors observe that:

"The incidence of non-A non-B Hepatitis tends to be higher in southern Europe and the USA and lower in mid

and northern Europe."

These authors, Reesinck and Van der Poel are Dutch authors, I think?

A. They are Dutch, from Amsterdam.

Q. Yes. And then some reference to the characteristics of the disease.

Then some explanation of the purpose at the bottom of the page, determining the current incidence and types of post-transfusion hepatitis among open heart surgery patients from all parts of Finland, and then the second objective being to obtain donor samples for future evaluation of possible preventive strategies. There is then an explanation of methods.

Can we move on to the next page, please?

Obviously, when the study began, it was necessary to agree a definition of post-transfusion hepatitis and that was essentially a clinical definition, as I understand it, and you explain here how hepatitis was defined and it was linked --

A. We wanted to avoid all possible bias in this type of study and therefore the investigator herself and our group was totally outside of the process of making a diagnosis. But those were the clinical hepatologists and other people who then determined whether a person had non-A non-B Hepatitis or not.

Q. I see. And it was linked to measurements of ALT?
A. Yes.
Q. Yes. And indeed we see also some further factors that were considered and that's on the right-hand side, and I suppose there must have been the possibility of some patients being discounted because it was thought that their hepatitis could be explained by another factor or that their liver symptoms could be explained by another factor?
A. Their biochemical hepatitis, yes.
Q. Yes. Then on to the next page, please. There is more information about what happened. So we can see that figure 37:

"Coronary bypass patients developed ALT elevation during the six post-operative months."

And obviously some investigation of whether Hepatitis B was involved was carried out and then some possible hepatitis cases identified and some ruled out. Then we can see the 11 non-A non-B Hepatitis patients referred to on the right-hand side and some description of their disease, their symptoms, how many were icteric and so on.

Then some explanation of the follow-up and then finally the discussion section, if we go on to the next page. Some interesting statistics about different

findings regarding incidence and then the reference to the 1.6 per cent incidence, which is the 11 out of 685. You have already said that at that time quite high numbers of blood products were given to individuals and that's borne out by the mean number of transfusions being 12.3 units per patient.

And then you go on to talk about many contributing factors -- I think this is to the low incidence -- and some discussion about follow-up and how long follow-up might need to be. And then at the bottom of the right-hand side you say:

"Although a rare phenomenon in our country, NANBH is still the most common infectious complication of blood transfusion and deserves further preventive measures, especially because of the often protracted course of the disease. The newly developed test to detect antibodies to the Hepatitis C virus ..."

And that's a reference to an article we have examined already:

"... offers major advantages in this respect."

So it seems fair to say that even in Finland where the prevalence of non-A non-B Hepatitis was relatively low, you had a positive response to the news that the test had been developed?

A. Definitely, yes.

Q. Yes. And you tell us, if we could go back to the statement, that obviously when you had the kits, it was of great interest to use the kits on the 11 patients who had been identified. And actually I think the information which you record in your statement, that six out of the 11 patients were positive with the new test, comes from a memorandum which you wrote on 10 October 1989 and to which you make reference in paragraph 5. So I wanted to have a look at that too, please. [PEN0171828].

We would have struggled with the Finnish, professor, and you have fortunately provided a translation for us. And this takes the story a little further. You explain what has happened in America, in other words the achievements of Chiron. I also notice that you remarked on the omission of Norway from the Nordic study, which no doubt others noticed as well. Then you go on to talk about the situation in Finland.

A. If I may, I think that the reason was that Ortho was considering Finland to be too small to carry out a study itself. They wanted to cover the whole Nordic area with maybe 25 million people. That would be much more convenient for the manufacturer to have data from all over. But then it turned out that Norway was probably not interested in the approach of Ortho. They had also

individual hospital blood banks. And Denmark and Sweden were interested, and therefore I contacted then my colleagues in Sweden and Denmark but that didn't then lead to any common approach in this respect, just because of the diverse organisations in those countries.

Q. Right. So in the end there wasn't some kind of Scandinavian solidarity principle that required you all to introduce testing at the same time or anything like that?

A. Totally forgotten.

Q. Right. Looking at the situation in Finland then, you refer to Dr Ebeling's work and then the reference to the identification of 11 patients, and then we see that six patients seroconverted within two to ten weeks when studied with the anti-HCV test, and these cases were considered post-transfusion C Hepatitis. Of the six, five were connected with an HCV-positive donor.

Then on the other hand, of the remaining five patients who had been anti-HCV negative, two had an anti-HCV positive donor. That seems to a layperson slightly odd.

A. I think it only shows that the initial test was not particularly sensitive and those may have been positive with the later test.

Q. Right. Because what you have is five patients who

clinically were thought to have non-A non-B Hepatitis, who have then tested negatively using the Ortho ELISA, but they can also be connected to an anti-HCV-positive donor. It does sound as though something may have gone slightly wrong there.

A. I think that at this stage the test was not particularly sensitive and a level of Hepatitis C antibody was sort of fluctuating, and sometimes it was below the cut-off level even though it would have been slightly positive but below the cut-off level, and therefore they were considered negative.

Q. Right. And you then mention also examination of 137 people with haemophilia in Finland, a large population of approximately 200 patients needing treatment. We will look at the article which deals specifically with that.

Then we have the overall percentage, which you had ascertained at about 0.73. You say:

"Possibly slightly higher than in the rest of Scandinavia, which number is somewhat surprising considering the clinical background."

Then your conclusions. We note, because we have heard this point made a number of times, that you were concerned by the lack of a confirmatory test, but you said:

"The repeatability of the screening test is good. The FDA may register the test still before the end of this year and the American blood services will start using it as soon as possible. Testing may start next year also in Europe, wherever it is technically possible."

You record that:

"Investigations so far had shown that the virus existed in Finland and caused post-transfusion hepatitis but all the cases were not necessarily found."

Then there is a reference to the serious end of the Hepatitis C cases, those which become chronic, and you comment:

"Since a specific test now exists that may reduce the blood inventory by as little as less than 1 per cent, a general screening test has to be introduced in our country to safeguard the transfusion safety."

A very clear view, Professor Leikola, from October 1989.

In the next paragraph you refer to the possibility of starting screening during the first quarter of next year. That would be 1990. You have explained to me before we began today that only one laboratory was involved. Is that correct?

A. That's correct.
Q. Yes, could you explain that for us, please?
A. In the whole organisation, mostly because of historical background, the Finnish Red Cross Blood Transfusion Service has only one laboratory, in Helsinki, and all the samples are sent in from different places in Finland.

We rely very much on mobile teams going out and when they are coming in, all the samples come to the same laboratory and therefore both automation and introduction of new tests would have been depending only on the laboratory facilities and then on particular decision-makers, and would have been much simpler and was much simpler than having various different centres with their own laboratories.
Q. Yes. Although one imagines that samples in some cases must have to travel quite long distances?
A. That's right.
Q. But arrangements are in place for that to happen?
A. It was quite complicated logistics behind sending them by aeroplane and train and whatever but it worked.
Q. Right. Another interesting point to note from the third paragraph is the possibility, which is envisaged, of what we would call a "staggered start"; in other words, you say testing cannot be started right away to cover

the whole country but the populations with higher prevalence may be screened first. You say that:

"A similar approach was used with anti-HIV screening, which seems to have begun in Helsinki. We may use such a system also this time and widen the testing to cover the whole country within a few months."

Was that ever seen as controversial in Finland, that screening might be introduced in a staggered fashion across the country?

A. No, I think it was generally understood that such a large screening test is very difficult to start. You know, if you want to have a timely start, to start with all possible samples at the same time, but to start first from a limited number of samples in order to see the feasibility of testing in general and then widen it to the whole country -- we followed this pattern with HIV and then also with the Hepatitis C, and since this is a very centralised organisation, I don't think that any dissident voices at least came to my ears.

Q. Right. There is then finally some mention of cost, and no doubt with some resignation you noted that the manufacturer effectively had a monopoly at that time?

A. Yes.

Q. And we can all understand the implications of that. And you have some, I suppose, fairly rough calculations.

Can we just look to the end of the memo, just to see where these go. Additional costs in the region. You have added, helpfully for us now, about 1 million euros. Then on to the final page we can see the other adverse consequence, the discarded blood, and then obviously also costs associated with information to donors, delay in testing the units, et cetera:

"Despite the costs and other difficulties, anti-HCV screening has to be started at the FRC blood service as soon as it is technically possible."

Back to the statement, please, if we may. That memorandum, you say, presumably intended for internal discussions and for the National Board of Health. Where did the National Board of Health fit in?

A. Since this was the only transfusion organisation in Finland, we had agreed -- I don't think there was a decree for that but at least we had agreed with the National Board of Health, which was under the Ministry of Health really, taking care of the practical matters in healthcare. We had agreed that we would provide annually our budget and price list for our products to the authorities at the National Board of Health, with the explanation why this price has been increased or whatever has happened, and then we had some comparison with other countries; how much they were charging for

these products.

This became statutory later on, but this was more or less voluntary at the time, since it was quite easy to explain to the hospital administrators that now the increased fees for our services and products had been approved by the National Board of Health, and these are the reasons behind that. So they were not always very happy about that but at least I think they were satisfied.

I think it was very important to have a sort of strong background for our financial decisions. And I think it's very important to say that the transfusion service really was an independent unit of the Finnish Red Cross. So the Finnish Red Cross had the final approval of our budget but the factual approval of that was done by the health authorities.

Q. Right. So when you wrote this memorandum, which would go to the National Board of Health, did you have to obtain permission from the National Board of Health to introduce screening or were you sending the memorandum simply to inform them?

A. We didn't have to have permission to introduce it but we had to have permission to increase the price for blood, and therefore I sent the memorandum and then we convened with the director general and one of the officials to

discuss that and to see whether it was reasonable to increase it by a fairly substantial percentage, because of the screening costs.

Q. I see. The other article which concerns patients with haemophilia, you referred to earlier and I thought, just to keep ourselves informed, we should have a look at the actual article rather than the reference to the statistics. It's [PEN0171773]. This is interesting for us too. If we look at the abstract, which narrates that 137 Finnish patients with haemophilia were looked at to detect signs of chronic viral hepatitis and its possible aetiological associations. Then, when the patients were tested with the new kits, the prevalence of Hepatitis C seropositivity was 50 per cent.

I think perhaps, professor, there are no surprises in the article, given the information that we have learned about the pattern of Hepatitis C in patients with haemophilia. Just to look at some of the facts that are highlighted, firstly on the left-hand side, if we could scroll down a little bit. Finland is one of the few countries that have been self-sufficient in the production of clotting factors.

It also mentions the fact that until 1984, small pool, two or eight donors, lyophilised cryoprecipitate was exclusively used to treat Haemophilia A,

von Willebrand's disease and Factor XIII deficiency. And then on the right-hand side, a little bit of explanation about how patients with haemophilia were cared for.

Then January 1988, all 230 patients with a coagulation disorder using clotting factor concentrates were asked for a blood sample. You obtained material from 137. They were the study group. Then narrative of the performance of ELISA testing.

On to the next page for the results. We can see there on the left-hand side:

"Anti-HCV":

"68 patients (50 per cent) were anti-HCV positive, most of the samples showing strong reactivity."

Then October, the final passage, where we can see some of the other factors in patients who were positive. So on page 3, if we look on the left-hand side, "Viral markers, ALT and severity of haemophilia":

"Patients with severe haemophilia had Hepatitis C antibodies significantly more often than those with milder forms."

Again, in the next paragraph, about half way down:

"Anti-HCV positivity was significantly more common in AHF-20 ..."

That is the large-pool concentrate:

"... than cryoprecipitate users."

Then the discussion on the right-hand side:

"The prevalence of anti-HCV was highest (74 per cent) among those with persistently raised ALT values. Patients with severe Haemophilia A or B had significantly higher frequencies of both anti-HCV and HBV markers than those with milder forms ... the small-pool cryoprecipitate was associated with a significantly lower anti-HCV prevalence than ..."

The large pool concentrates. Then you note two paragraphs down:

"The 50 per cent prevalence ... was lower than in results recently reported for Australian, Spanish, French, British, American, German and Italian haemophiliacs ..."

You say:

"HCV antibodies sometimes seem to disappear and the above percentages may underestimate the number of patients with a previous HCV contact."

Then actually by this time you were able to say that the new RIBA had also been used with this group of people and the results have been shown to be very specific:

"This means that false positive results were only a minor source of error among these patients."

We can see the information tabulated at the bottom of the page. Just on to the final page, please, for the conclusion. You said:

"We conclude that the significant association of raised ALT and anti-HCV points to the possibility of the HCV agent being a major cause of chronic hepatitis among haemophilia patients. Even so, the absence of the HCV antibodies in 26 per cent of the patients with persistently abnormal ALT leaves open the possibilities of heterogeneity in antibody response to various HCV epitopes and also the existence of still more blood-borne non-A non-B Hepatitis virus."

Might this in fact have also involved different genotypes rather than different viruses?

A. It could very well be, yes. This, of course, we didn't know at that time.

Q. Yes. I should, I think, professor, just draw your attention to the fact that even though there hadn't been an analogous, large-scale prospective study in Scotland in the late 1980s, there was an attempt made once the Ortho kits arrived to do a study using the kits.

Sorry, this isn't on the list but could we have a quick look at [SNB00061596]?

We did look at this last week, professor. This is a report from October 1989 -- it's 5 October 1989 in

fact -- of research work that was carried out in Glasgow with samples from different parts of Scotland.

Indeed, if we look at the fourth page, 1599, we can see really what looks to be quite a comprehensive list of objectives, including number 1, determining the prevalence of anti-HCV in the Scottish blood donor population; looking at surrogate markers; looking at sera from patients with alleged post-transfusion non-A non-B Hepatitis, along with the implicated donations; looking at higher risk groups. Then, six, looking at the prevalence of the marker in select patient groups, such as haemophiliacs and multitransfused individuals.

Then perhaps more practical aspects as well. Looking at how to use the kit, how suitable it was, looking at batch to batch variation, even.

We have looked at the results which were obtained from looking at the non-A non-B Hepatitis samples. Can we look at page 1609, please?

We can see there that actually they had 15 NANB PTH patients to look at, and obviously you might want to know what the criteria were for defining something as a case of non-A non-B Hepatitis and so on, we understand that, but with the new kits they only found a third of them, five of them, to be positive.

That's perhaps a slightly disappointing result, is

it?

A. Yes, I would say so.

Q. Yes. What do you think might be some of the reasons for it?

A. As you said, I didn't know what were the criteria for non-A non-B Hepatitis. Secondly, those patients, as was said earlier, the antibody may disappear in time, over a prolonged period of time, from the blood, but otherwise this was not quite what we had seen. On the other hand, if you would have added two or thee patients, then that would be very well fitting to our whole pattern. So it was not very far but of course the material was not very big.

Q. Yes. I suppose too, the opposite point can be made about the antibody, that it is, I think, a late appearing antibody, the one that was being screened for at this point. So the samples may have been too early.

A. Yes.

Q. I think you were also noting that the samples dating from as far back as 1987 which --

A. You must remember that we took ten samples altogether, sequential samples from the patient in order to find at least one positive.

Q. Yes. Excuse me a moment, professor.

Yes, is there also an issue about samples which have

been frozen? Do they sometimes yield unreliable results?

A. I don't think that the freezing would interfere with test results.

Q. Right.

A. I'm not sure but this is what I think I remember.

Q. Right. The other aspect of this part of the study is reported on the following page, if we could look at that. That looking at sera from donors in 28 cases of non-A non-B Hepatitis, actually only revealed six donors being anti-HCV repeatedly reactive.

So according to that measurement, only 21 per cent of cases had a donor identifiable as being anti-HCV reactive. Again, not a particularly encouraging result perhaps but certainly an improvement on a situation where no screening is taking place.

A. Hm-mm.

Q. Yes. Unsurprisingly similar results to your results were obtained with patients with haemophilia.

So there was some effort being made in Scotland, and indeed there was a study in England as well in 1989, looking at these new kits and what sort of results were obtained with them.

Can we go back then to the statement, please? At paragraph 7 you tell us that you heard from Ortho,

either in late November or early December, that the FDA had given an export permit to the new test. We have seen that Professor Cash was similarly informed at the end of November 1989. You had a meeting on 11 December 1989 with the director general and the medical officer responsible for blood transfusion related matters at the National Board of Health. You make the point you have already made about the need for their approval of your increased charges, and that was obviously a fairly straightforward matter, was it?

A. I beg your pardon?

Q. Was the obtaining of approval from the National Board of Health quite straightforward?

A. It was very straightforward and it was made by the director general at that meeting, so it was not sort of put to any committee or anything else. He said, "Just go ahead".

Q. Well, I was actually going to ask you, Professor Leikola, if it was all achieved at one meeting, and I think that possibly reflects a battle weariness at having looked at a tract of time in which different committees met for a total of 19 meetings, almost all of them to discuss this issue among other things.

THE CHAIRMAN: Timing, Ms Dunlop?

MS DUNLOP: Yes, that would be a good point to stop, sir.

(1.04 pm)

(The short adjournment)

(2.00 pm)

THE CHAIRMAN: Yes, Ms Dunlop.

MS DUNLOP: Thank you, sir.

Professor Leikola, I just wanted to ask you generally about the information which started to come through in 1989 about the Ortho test or even about its predecessor, Chiron's own RIA test.

There were reports from other countries -- we looked at some publications from the summer of 1989 from Germany and the Netherlands and Spain. So different European countries were looking at the new tests. What was the attitude in Finland to material from other countries like that? Did you think, oh, well, it doesn't come from our population, so it's not really relevant?

A. I think as far as northern Europe was concerned, especially Netherlands and the UK, I think that these data were quite relevant to us also. They were supporting our view that this is really something that should be started and we have finally found specific, not an ideal test but finally a test for Hepatitis C. And we were very much following what was going on in

other places, especially at the meeting in Rome, where the different experiences from various countries were collected and then discussed together.

Q. Right. So, for example, information about how many patients with non-A non-B Hepatitis clinically tested positive with the new kit in the Netherlands. That would have been interesting to you?

A. Yes.

Q. Yes. And somewhere like Spain, less interesting or still something you would want to read about?

A. Of some interest but it was very clear that the prevalence of hepatitis both in Spain and Italy was higher than in northern countries and therefore the main emphasis was on the northern countries.

Q. Right. We were in your statement, [PEN0171957] and we are now on 1958. Could we have that in front of us, please?

You tell us at the top of the second page that routine testing commenced in the beginning of February 1990 and was extended to all blood donations in Finland as of 1 April.

So did it indeed begin in the Helsinki area?

A. That's right, that's correct.

Q. And then you say that you explained to your clinical colleagues why you had taken the step and you wrote an

article in the journal of the Finnish Medical Association, which, sir, we don't have and it's in Finnish.

Paragraphs 9 and 10, Professor Leikola, are still in Finnish. You explained to us that you wrote in your book a comment about what you describe, I suppose, as a general philosophy as far as testing is concerned, that if a new test seems to be inevitable, it pays off to start it as soon as possible and then with flags waving.

The book is "A History of the Finnish Red Cross Blood Transfusion Service and its Predecessors". Is that correct?

A. That's correct.

Q. Right. Published in 2004.

Do you cover this issue specifically in your book?

A. Not specifically but it had almost 350 pages so this period of time was, of course, very important for the transfusion service.

Q. Right. At paragraph 11 you say that you published the preliminary results of Dr Ebeling in The Lancet, 21 April 1990 and I think we should look at that, if we could, please. That's [LIT0010270]. It's a letter and we see it beginning on the right-hand side, towards the bottom.

You refer to an earlier publication from Dr Van der Poel and colleagues. So that would be a Dutch piece, I imagine. And that had reported that:

"Screening of low risk populations, such as blood donors, for antibodies to Hepatitis C ... by the available ... ELISA may yield false positive results."

You go on to record the consequence, that it's difficult for blood transfusion services to decide on policies for discarding suspect blood units and for donor counselling. And on the next page you explain that you have had the opportunity to use the Chiron RIBA. So this being April 1990, you had already had a look, I assume -- I think you say this actually in your report -- at a research kit. It would be a research version of the RIBA kit that you were using. Is that correct?

A. Yes.

Q. And you had used that to detect HCV antibody. The test was distributed by Ortho. Yes, it says here, "For research use only". Both antigens have been coated in distinct bands on nitrocellulose strips.

Then you describe what had been done, that you had applied the ELISA and the RIBA to a frozen panel of donor and patient samples from your prospective study. So obviously you had looked at the same 11 patients, of

whom we have been speaking, and seven of the 11 patients had received a product from an anti-HCV ELISA positive donor.

I think it's perhaps most easily seen if we look at the table. These are the first seven donors, numbers one to seven, implicated in cases of post-transfusion hepatitis, and of those, six show two positive bands in the RIBA. Is that correct?

A. That is correct.

Q. Yes. You say:

"All six donor samples that were reactive for antigen bands 511 and C100 ..."

And this is the third paragraph in fact:

"... were associated with hepatitis in the recipient."

So that reference to all six samples is the reference to everybody in implicated donors one to seven, apart from number six. Is that correct?

A. Yes.

Q. Right. And then for those donors there is also a record of whether the recipient was found to have seroconverted when tested using the ELISA. There are five yes's and two no's and then the RIBA results from the recipients are also tabulated.

So on the basis of this research, you were

suggesting that the RIBA may offer help in differentiating infective from non-infective blood donors, that reactivity for both antigens and 511 especially, was associated with infectivity.

I think this is actually the research that you referred to earlier, when Mr Mackenzie was questioning you, and it was also written up subsequently in a longer article?

A. Correct.

Q. Yes. So that comment that you had made in your memorandum, about the lack of a confirmatory test, was beginning to be addressed, it appeared, by the appearance of the RIBA. Is that right?

A. Yes.

Q. If we could go back to your report, please, you point to the fact that this was in The Lancet, so was obviously available to readers in the United Kingdom.

You also refer to another publication, which we will look at, and this is an article from 1993, so more of a retrospective review really, called "Viral Risks of Blood Transfusion" in a publication called "Reviews in Microbiology". That's [PEN0171723]. We can see from the summary that this is really a review of, as it's entitled, the risks of blood transfusion, particularly viruses. So mentioning also HIV and Hepatitis B.

As far as Hepatitis C is concerned, if we scroll down the page a little, we can see a general discussion of hepatitis and then on to the next page, Hepatitis B is covered and then Hepatitis C on the right-hand side. There is mention of the Chiron breakthrough and at the end of that first paragraph, under Hepatitis C, we see their method, their application of recombinant gene technology:

"Led to identification and isolation of one clone, which was used to produce a protein called C100-3. It turned out later to be part of a non-structural protein of the Hepatitis C virus."

Professor, I have seen references to antibody testing which tests for non-structural antibodies, as being less desirable than structural antibodies. Is that a correct understanding?

A. Or a structural antigen.

Q. Sorry, structural antigen.

A. Antibodies against that. I'm not able to comment on that.

Q. Have you seen reference to that, that if you can have a test for a structural antigen, it's better?

A. In general if there is a structural antigen, then I think that the virologists think that the virus itself is involved, whereas if there is a non-structural

antigen, then it could be like a Hepatitis C surface antigen, which is just an antigen and not the virus itself.

Q. I see. I'm sure that's good enough for us, professor. I'm sure we don't need to go any further than that.

Then there is a little bit of the history since the Chiron breakthrough, given in your article, particularly that paragraph beginning:

"The production and use ..."

And by this point, this being 1993 the same antigen is being used by several manufacturers:

"The first generation assay looked very promising for diagnosis and prevention of NANBH. In patients with NANBH, the test gave positive results in a high percentage."

You refer to the American study of 16 well defined PTH cases, where the antibody was found in 14 of the respective donors. I think we should just check the reference. Could we go to the references, please, which must be on the last page?

I think that's the very early report in 1989 but we will just check reference 10. That's Harvey Alter and others in the New England Journal of Medicine. I think I have seen that as a well characterised group of samples that they were able to use?

A. That is right.

Q. And if we go back to page 2, please, you do say that:

"In subsequent studies from Europe, the percentage was lower ... There was no true confirmatory tests since everything was dependent on only one recombinant antigen. Partially to circumvent this drawback, a recombinant immunoblot assay was developed using two different sources of the protein."

We have had some difficulty, I think, in getting a good working understanding of the features of a true confirmatory test. Is it fair to say that the term "confirmatory test" is sometimes used a bit imprecisely?

A. Yes, I think that a true confirmatory test should be based on the principle that it is different from the original antibody/antigen reaction, in order to show from another point of view that it really is a true reaction between the virus and the antibody. We have these days for many viruses, the PCR test that detects the virus itself, and therefore that can be considered as a good confirmatory test because it's based on a different principle. Here we are dealing with only one protein that was isolated from a bacterium, that presumably was a part of the virus and the difficulty was that this protein, to confirm that it really belonged to the virus, would have needed a test that

would have detected some other part of the virus or the virus itself.

Q. I see. So --

A. So we called it usually the "supplementary test", instead of "confirmatory".

Q. So using that language, the first RIBA, strictly speaking, was it a supplementary test, rather than a confirmatory test?

A. This is how we considered it, yes.

Q. Yes.

A. But it could be used to confirm the results. This is a little bit ambiguous but it really was a supplementary test that helped us to convince ourselves that this was a true positive.

Q. I see. And can we look then to the following page, please? You refer to the Finnish prospective study and to the results we have looked at, which were reported in The Lancet; and of course, by this time, by 1993, you are able to talk about second generation testing, and you say that:

"The sensitivity and specificity of the test have been improved by adding two more antigens to the assay, the non-structural protein, C33c and the structural core protein C22."

So in your Finnish material -- this is the 11

patients again, I take it -- the number of seropositive patients increased from six to nine when assayed with 4-RIBA and the same outcome in Dutch patients. In a similar Dutch study the number of seropositives increased from six to nine when the second generation ELISA was applied. And then some information about other manufacturers using other approaches to establish confirmatory tests and then you are saying that:

"Anti-HCV is a relatively late indicator of the infection. Antibodies appear on average 10-12 weeks after inoculation with infected blood but it may take 6-12 months before the tests become positive. Direct tests measuring the virus would obviously be preferable but the presumably low titres of the virus make immunological detection difficult or impossible."

Then some quite technical material about PCR and even then you comment -- and this is reading from the second paragraph on the right-hand side -- that:

"The sensitivity of the confirmatory tests is not yet optimal, and it can be estimated that the true prevalence of anti-HCV antibodies in northern European populations is approximately 0.05-0.1 per cent ..."

Which would fit with the findings of the results here the first few months after screening was introduced:

"It increases up to 1 per cent or more in geographical areas where hepatitis viruses are more common."

Then some comment on the clinical significance of Hepatitis C infection, that:

"Longitudinal studies had shown that about half or more of NANB PTH cases become chronic and 10 to 20 per cent of these eventually develop cirrhosis."

And that the association between post-transfusion hepatitis of the NANB type and hepatic carcinoma was especially marked in Japan.

Then the rest of the article is concerned with other viral risks. So we can put that to one side.

Can we go back to the statement, please, and move to the specific questions? We asked whether it was reasonable for the United Kingdom to wait until September 1991 before screening donors for Hepatitis C, and you said:

"It was interesting to read the preliminary report and the chronology of the UK studies ..."

Perhaps not just studies into surrogate testing but studies more widely:

"... into ... testing for NANBH from autumn 1989 until September ..."

We can see from the evidence that we have already

covered that it does appear that Ortho approached a number of different countries around the same time, that the material was discussed in Rome. We know that our Dr Mitchell was in Rome, and then you go on to reflect that there seemed to have been two camps in the discussions: the academic scientists and the practical transfusionists.

And from the scientific point of view there were many reservations: lack of confirmatory test, which was the most serious one; lack of understanding the virus itself; deficient specificity in identifying the putative virus and an assumption that the situation in the UK may differ from the US, where most of the information was gathered.

The second last difficulty, the deficient specificity in identifying the putative virus, is that really the problem of false positives?

A. Well, I think that the fact that the virus itself was still hidden and the virologists didn't know what kind of virus that would be, there was just a lone protein floating somewhere, I think especially for basic virologists that was a very disturbing factor that we were not talking about the virus but just a single protein that was indicating the presence of the virus or, as a matter of fact, an antibody to this particular

protein.

Q. Right. In the next paragraph you contrast what I suppose is the attitude of the practical transfusionist. Is that right?

A. Yes.

Q. Yes. One of the difficulties which certainly we have seen referred to is the difficulty of coping with false positives?

A. Hm-mm.

Q. You can introduce a new test which will generate a large number of people who are testing positive but who do not in fact have the virus, but I find it difficult to imagine that if the test was good enough in identifying and preventing some cases of disease, that the problem of false positives would ever stop you introducing the test. Is that not just a price you are going to have to pay with a new test?

A. Well, in our opinion it was very clear that as long as the number of positives -- that's including false positives -- in the primary screening is low enough so we can handle figures that are less than 1 per cent, and explain to the donors what is the situation, that this may be true or may be not true, and in our opinion at the time it would not prevent introducing such a test.

Q. How much of a factor in the Finnish decision was it that

a confirmatory test, in crude terms, another test, was coming?

A. We didn't know really that it was coming. There was many rumours saying that many new manufacturers are coming into the picture and so on but when the decision was made in November 1989, then we didn't know about the confirmatory tests. So our decision was based really on the first studies with the first generation screening test.

Q. Right. What were you intending to do with all the positive donations?

A. I don't remember that in detail but we contacted all these people and we explained to them the situation, where we were, and asked them to come again and to give a new sample in order to see whether they would be repeatedly positive after a certain period of time and then follow that up and offer the possibilities for consulting our doctors. This is what I recall. I don't remember the details.

Q. Right. Did you introduce the first generation RIBA pretty quickly after it became available?

A. Yes, we did.

Q. Right. Just moving on then into that paragraph about the practical transfusionists, you have seen Dr Perry's note and perhaps we can just look at it again. Can we

go to [SNF00117710]? That's Dr Perry's letter to Professor Cash on 2 May 1990 and that's after the VSB meeting on 24 April, and if we look over the page, we can see his notes and it's actually on the final page. So we need to go one more page, please.

This is the passage you have highlighted, professor. It's really the last of the bullets under "General Comments". It's not perhaps very clear whose particular comment that was or whether that relates to the note at the end, but you have highlighted this note at the end, that Dr Gunson and Dr Perry -- and this is at the very end, the conclusion -- felt there was sufficient data to justify testing now. But they were in the minority.

It's interesting also that reference was made to testing already being in place in France, Belgium, Luxembourg, Finland and Australia. So this is the practical transfusionists at work really, is it, in your description of the two camps?

A. Yes.

Q. And then can we go back to the statement, please, to this question of the FDA? You say that:

"An important argument was that the FDA had not approved the test even if it had given the export permit."

That was obviously something that featured in

a number of different discussions in the United Kingdom and I just wondered what the attitude had been in Finland to the fact that the FDA had not formally approved the test for use in the United States. Did you take that into account?

A. No, I don't think it was a very important factor for us. We had decided to go ahead anyway as soon as possible, based on our own observations and based on the observations that we had on this particular test. So as soon as the FDA had given the export permit for the test, then we decided to go ahead anyway and not to wait until formal licensing of FDA for the US blood banks.

Q. So you weren't deterred by the possibility that the FDA might refuse to license the test for use in the United States and that would put you in an awkward position?

A. No, we were not, no.

Q. Right. Why not? Can you expand that answer for us? Why do you think that didn't have any impact in Finland?

A. I think that the FDA, when it was dealing with the United States blood banks, had to consider very different aspects of their system in the US and to see that, you know, the different laboratories were fit to use the test in the correct way and other aspects; whereas we, having just one laboratory and having seen

that this test in our opinion works, did not expect any refusal of FDA of using this kind of test.

If that would have come forward, of course, we would have looked at the matter and seen, based on our experiences, whether we would follow suit or not, or whether this negative decision from the FDA would have been based on particular conditions in the United States.

Q. Yes. I suppose we might say you would have crossed that bridge if you had come to it. So if that had happened, that there had been a subsequent refusal by the FDA, you would have wanted to know what the basis of that refusal had been and you would try to decide what relevance, if any, that had on the testing you had already commenced in Finland?

A. That's right. I could have imagined that, for instance, they would have found something incorrect in manufacturing this test and inconsistency of getting different batches of the test and then we would have been worried about it and have come back to the quality control of the test, but otherwise if that would have been based on practical considerations concerning the routine introduction in the United States, then that wouldn't preclude our continuation.

Q. Thank you. And you go on to say you obviously were

aware of the positive signs from the new first generation RIBA tests and then that it seems to you on the basis of this development -- I think that means the RIBA, does it? -- in regarding the practice in other countries, the UK ought to have decided earlier to start screening of blood donors. You say:

"It would have interfered with the planned and ongoing studies on the incidence of transfusion-transmitted NANBH but eventually one of the studies was too small for meaningful conclusions in any case."

A. Yes, you have to remember that we had to test 15,000 blood donors that were connected with the patients, and that gave only 11 cases and six of them were positive. So that only showed that in a low prevalence country, as we considered the UK to be, it would have needed a fairly large study.

Q. Yes. And then our second question was:

"On the basis of what is known now, ought screening for Hepatitis C to have been introduced earlier in the UK?"

You begin your answer by identifying, you think, three factors which contributed to the long interval in the United Kingdom, and these are:

"... the lack of a proper prospective study,

pressure from the scientifically-oriented members of ACVSB and ACTTD to get more precise information on the usefulness of the test, and the reluctance of some blood centres to introduce a new screening of questionable value, involving discarding appreciable amounts of blood products, counselling of donors, et cetera."

You point, I think, to what you would not really accept as a reasonable basis not to introduce a test; that is the notion that better tests are coming. You think the answer to that is to say, "Fine, we will start screening now and introduce the better tests when they arrive"?

A. That was my point, yes.

Q. And if you had done that or if a country had done that, introduced screening even when better tests were on the horizon, would time have been lost in changing from the first type of test to the new and better test?

A. No, I don't think so.

Q. I mean, practically speaking, is there quite a lot involved in introducing a second generation test to a laboratory which is carrying out first generation testing?

A. If that is basically similar tests, so it doesn't involve totally new machinery and so on, I don't think that it's too cumbersome to do comparative tests with

the currently ongoing test and the new test, and to see whether the sensitivity and specificity are really better than before. It's not too complicated.

Q. Right. And even if you decide that the new test is better, the practicalities of introducing the new test --

A. That would take time. First of all how the manufacturer would be able to deliver all these test kits and then secondly, what kind of agreements you would have with a previous one and changing everything. So it would need some time.

Q. But is the idea that newer kits are coming enough to stop you from starting with currently available kits?

A. Usually, if the new test is really better than the old test, then, of course, the change should be made as soon as possible.

Q. Right. And whether you wanted to not start using the old tests because the new test was imminent would really depend on how close the manufacturer was to releasing the second type of test?

A. That is true, and if the new test would be only marginally better, then I mean you would have some time for this overlap period. The same is true if new a manufacturer would offer that for a cheaper price.

Q. All right.

A. Then you would have some time in between to introduce the new one.

Q. You say that you think a decision to introduce anti-HCV screening could have been made in June or July 1990. From reading the preliminary report, you got the impression that:

"... there was no clear mechanism for making a definitive decision concerning the whole UK. The time needed for practical arrangements in the blood centres could have been a maximum of four to five months, so the screening could have been in place in late 1990, possibly in October/November 1990."

That would be assuming a linear progression so that the decision to start is made and then preparations commence for the introduction. You would be able to save some time if you had commenced your preparations ahead of the final decision, would you not?

A. Yes, that was based on our straightforward approach, that, you know, once you make a decision, then you just go ahead and start implementing it, taking all the practicalities and so on but, you know, in our conditions and our organisation, that was much easier.

Q. Right. Can we look at the meeting from July 1990, please? That's the ACVSB meeting of 2 July 1990, [SNF0011705]. This is a meeting which was brought

forward. It was originally supposed to take place on 24 July 1990 but it was brought forward to 2 July, as far as we can tell, because of developments since the previous meeting in April, particularly the availability of the RIBA and the grant of a licensing approval by the FDA.

If we look to the particular passage in the minutes of this meeting, in which the decision is recorded, and can we go on to paragraph 8, please, which is on 1707? Perhaps we should look too, at paragraph 6. There was the reference to testing now being carried out in America and other countries. The meeting's main purpose was to reconsider the principle of Hepatitis C screening. Then paragraph 8:

"The committee concluded they should recommend to ministers that Hepatitis C testing should be introduced in the UK, but that first a pilot study using the Ortho and Abbott tests was necessary to decide which was the better test for the regional transfusion centres."

You think there was another way of doing it, Professor Leikola?

A. I don't know.

Q. Well, did testing have to be deferred until the end of the comparison?

A. Well, to me the reasoning in that is not totally valid.

Doing the comparison is quite fine and I understand that they want to make this comparison, but just to delay the introduction of the testing because of this comparison, I don't think it was fair. It could have been introduced, of course, already in May, after the FDA decision, and latest in July decide that now we go ahead and start screening, but meanwhile you could compare these two tests and see if there is substantial difference between those tests.

You have to remember that both tests were based on the same protein and the same patent from Chiron, so it was not to be expected that there would be a major difference between these two tests, and this had been stated also by Professor Zuckerman already; I think it was in the February meeting or April meeting of the committee.

Q. Can we then move to your second statement, because we did come back to you and push you a little bit harder on some of the key meetings at which decisions were or weren't made. That's [PEN0171961].

I am afraid we are going slightly back in time here because we are looking again at the meeting on 6 November 1989, which certainly was one point at which a decision in principle could have been taken, but you note that the committee -- and this is VSB, reading from

paragraph 4 of your statement:

"The committee supported the general introduction of the Ortho anti-HCV test if the FDA approved it and a pilot study showed it to be feasible and non-problematic."

Perhaps we can just have a look at the minutes of that meeting, [SNB0019563]. I think, Professor Leikola, what this meeting stops short of being is a decision that testing should be introduced as soon as the FDA has approved the kit for use in America, or as soon as a confirmatory test is available. There isn't anything quite as clearcut as that in this meeting?

A. I was a little surprised to see that there is no clearcut decision. There was a sort of recommendation that this would be very nice to have this test, but you have to remember that at that time the FDA had not licensed it for export.

Q. Yes.

A. And therefore everything was on the preliminary and research level and therefore I think it's sort of natural that the committee was in general, as far as I read the minutes, in a positive mood towards a future screening by this test but decided then to wait and see the developments and make a definitive decision later on.

Q. Yes. If we look at paragraph 28, which is really the key paragraph as far as the decision is concerned, we do see that positive note that you have identified:

"The test represented a major step forward, but ... the committee need to know a great deal more about it, and acknowledge the need for a confirmatory test."

We have had some discussion, Professor Leikola, about saying that the UK wouldn't introduce screening in advance of an FDA decision not being quite the same as saying, "We will introduce it as soon as the FDA has decided," and that may have been a difficulty, that it's really not very clear whether the approval by the FDA is or is not to be an automatic trigger. Would you agree with that?

A. No, it's not very clear in these minutes, no.

Q. Yes. Can we go back then to Professor Leikola's statement. So your opinion, that that decision at the meeting of 6 November 1989 was reasonable, that's really on the understanding that the test was going to be introduced?

A. Yes.

Q. Once the FDA had approved the kit and once there was a confirmatory test?

A. Once these three conditions were fulfilled, then I think -- at least in my understanding -- once the

committee would have information on these three points, then the decision would be positive if there wouldn't be any major problems.

Q. Right. So if the decision had been clear that there would be these automatic triggers, you would agree with it or you would regard it as reasonable?

A. I would agree with that.

Q. Right. And then you comment on the January 1990 meeting, and I think we will have a look at that as well actually. Can we look at [SNB0019657], please?

This is the meeting of the same committee on 17 January 1990 and there is a discussion on page 9659 and we see it there. Professor Zuckerman spoke to a paper which had been circulated. It's actually a letter from him in which he makes the comment that you refer to about not really being able to justify a delay much beyond approval by the FDA. So that's in the letter, which is described here as "Paper ACVSB5/4".

In the following paragraph, I think we are agreed that that sentence about:

"The figure of 5,000 members of the donor population who could be excluded from donating but 50 per cent could be false negatives ..."

It says. That should probably be "false positives", would you agree. That would make more sense, I think:

"People are being excluded from donating."

It's probably the case --

A. I think both false negatives and false positives since it was known that this test would not detect all implicated donors.

Q. Right. So with the first generation kits, there were appreciated to be problems with false positives and false negatives. I think we understand that that was true.

Then there is quite a lengthy discussion and on the next page we find Dr Mortimer, as a public health physician, being apparently quite keen to introduce the test. This is 24 and then 26, Dr Gunson. You knew Dr Gunson, didn't you, professor?

A. I beg your pardon?

Q. You knew Dr Gunson?

A. Yes.

Q. Yes.

A. Yes.

Q. Very much a practical transfusionist?

A. Very much a practical transfusionist, yes.

Q. Yes. So it doesn't surprise you to see him apparently pressing for the introduction of screening?

A. Well, I remember very well Dr Gunson from our committee, the Council of Europe committee, and I think that he

always represented a very reasonable opinion on different practical policy matters, and when we were discussing the introduction of Hepatitis C testing, I think that he, in private discussions anyway, was a great proponent for the introduction of this testing.

However, I think that he did not have, to my knowledge, a very sound scientific background with academic degrees and academic positions and so he took the practical, rational approach to these problems, whereas the so-called academics -- I'm an academic myself also. The academics took a much more research-like, scientific view on these matters. But I had a great respect for Dr Gunson, for his common sense and practical mind.

Q. Thank you. There is quite a bit in these minutes about people thinking it was unlikely that the FDA were going to license the Ortho test. If we look at paragraph 20 actually at the top of this page, Professor Zuckerman:

"... felt it was unlikely the FDA would license the Ortho test in the absence of a confirmatory test. Dr Rotblat added that it was also her understanding that the FDA was also unlikely to approve the test at this stage."

Do you remember any rumours at this stage that it was unlikely that the FDA were going to license the

test?

A. No.

Q. Would you ever expect them to withhold approval because there wasn't a confirmatory test?

A. Not really, no.

Q. It seems to be two different things; yes? The approval of the ELISA and then approval of an RIBA or some other form of additional test. It would be two different processes, one would imagine?

A. That's right.

Q. Perhaps I'm missing something. Dr Gunson's comments are in paragraph 26 and then we have already looked at the -- sorry, the "Summing Up" is the chairman's summing up at 29 and 30:

"Routine testing not to be introduced in advance of the FDA decision."

So if anything, a decision as to what's not going to happen, rather than a decision as to what is going to happen.

And then paragraph 30 obviously has a bit of a forward plan.

This meeting also made reference to the fact that there were symposia about to be held in February, both Ortho having a symposium and Abbott having a symposium, and there was also a conference that was going to be

attended by Professor Zuckerman in Houston, the International Hepatitis Meeting in Houston.

Can we go back to Professor Leikola's statement, please? And you have quoted a bit about Professor Zuckerman's contribution in your paragraph 6 and the decision in paragraph 7, and you say:

"There was no clear recommendation at this meeting that testing should be introduced as soon as the FDA had given a green light to the US blood banks."

One of the documents which came to the attention of different groups in the United Kingdom shortly after this was a document from the United States. As far as Scotland is concerned, a copy of it seems to have been brought back from the Abbott symposium by Dr Mitchell.

If we have a look at that, that's [SNB0019825]. If we look at the very end of it, professor, we can see who's responsible for it. This is dated 8 February 1990, and these guidelines come from the American Association of Blood Banks, the American Red Cross and the Council of Community Blood Centres. Then if we could return to the first page, please.

This seems to be an exercise in pre-planning for the introduction of screening in the United States. Have you seen these before? Have you seen these guidelines?

A. These guidelines? Yes, I saw them yesterday.

Q. Right. I suppose one thing which occurs to me is that if there was a kind of expectation that the FDA were not about to license the test, it would be surprising if these organisations were going so far as to publish guidelines for what was to happen, so this is perhaps a clue that there was an expectation that testing was going to be starting in America quite soon.

A. I think that these people had some preliminary knowledge about the RIBA test, that was probably in the coming and therefore they decided, obviously according to this memorandum, to make all the preparations, expecting the FDA to approve this test as soon as there was a supplementary test or something that could be added to the primary screening test.

Q. Right. So the approval by the FDA was in some way connected to the need for a supplementary test?

A. I believe it was in some way, yes.

Q. Right. We can see there is reference to the need to facilitate rapid introduction of the anti HCV test. So it certainly looks to be quite a focused document, setting out steps that need to be taken so that no time is lost.

A. Hm-mm.

Q. In making practical arrangements. Quite a lot of references to haste:

"Blood centres should implement anti-HCV testing, including testing of complete inventory as rapidly as possible."

And so on. The other interesting paper from around this time is the set of abstracts from the Ortho symposium. If we go back first, please, to Professor Leikola's statement. You take the narrative on, professor. You talk about the US blood bank organisations recommending to their members that the implementation of the anti-HCV screening should be introduced as soon as possible after the FDA had licensed it. I think that's the set of guidelines we looked at really, that evidence?

A. Yes.

Q. Then there is your letter in The Lancet and we have looked at that, and then paragraph 9, the FDA licensing the Ortho test. Then the next meeting of the ACVSB in April 1990, at which, as you say, reservations seemed to have grown. And in paragraph 11, you commented that:

"The change of attitude of the ACVSB between January and late April 1990 was remarkable."

So that comment of yours made us wonder what could be the explanation for the change between January and April 1990, and one candidate, I think, is the Ortho symposium. Can we have the papers of that again,

please? That's [SNF0011628]. Professor, we gave you these to read in hard copy overnight.

A. Yes.

Q. And you have, I think, had a chance to have a look at them?

A. Yes.

Q. Did you get an overall impression from the abstracts from this conference, and if so, what was it?

A. Of course, these different abstracts, they consist of a variety of quite different approaches towards this question, but judging from these abstracts, it would be difficult for me to interpret them so that this test would be no good and therefore, you know, any possible delay in the introduction would be justified on the basis of those abstracts.

It's very natural that in that kind of symposium, the investigators, they are not marketing people for this commercial manufacturer, but they want to have a critical approach to these tests and I think it's natural that they emphasise the fact that they have found, you know, that it's not a perfect test and so on. So much are not detected and so many are false positives also. But to draw this conclusion that it should not be introduced at that time, I think I, at least, couldn't make out of these abstracts.

Q. Right. That comment that we see, which is on the front sheet of the set of abstracts, that the test is not sensitive or specific enough, that also found its way into the minutes of the ACVSB meeting of 24 April 1990. The overall impression was that the test was not sensitive or specific enough for reliable testing. You would have disagreed in April 1990, would you?

A. It's very much a question of the definition of the word "enough". What is enough and what is not enough? We thought that it was good enough to be introduced, while admitting that there were a number of weaknesses with this kind of test.

Q. Yes. Just thinking still about that symposium in London, which was obviously quite a gathering of leading figures, we know that Dr Boulton also attended. He was the deputy director of the transfusion service in Edinburgh and Southeast Scotland. And he prepared a report. Can we have a look at that? That's [SNB0141645].

THE CHAIRMAN: Ms Dunlop, do you want to stop at some time soon?

MS DUNLOP: Yes, I can stop now.

THE CHAIRMAN: Rather than getting into a new document.

MS DUNLOP: Yes.

(3.11 pm)

(Short break)

(3.25 pm)

THE CHAIRMAN: Ms Dunlop.

MS DUNLOP: Thank you, sir.

Professor Leikola, we were still talking about the Ortho symposium in London in February 1990 and I was saying that Dr Boulton, the deputy director from Edinburgh, from the Blood Transfusion Service, was one of those who attended.

Can we look at his report, which is [SNB0141645]? As would be expected, he mentions some of the contributors, whose abstracts are included in the bundle we just looked at. So the contribution from Professor Thomas really talking about the nature of the illness, and then Dr Barbara. Predictive value in low prevalence populations is low.

With some trepidation actually at this point, let's just digress. Can we keep that document open, please. Positive predictive value, which has been mentioned already today. Could we just go back to [PEN0171763], please?

Can we go to page 3 of this article. It's Dr Ebeling's article from Vox Sanguinis in 1991. Mr Mackenzie saved for me the possibility of going into the issue of what "positive predictive value" means and

I simply wanted to suggest to you that there is actually a working definition given in the article. Under that heading "Discussion" after the use of the term "positive predictive value", there is a passage in brackets:

"The percentage of NANBH cases among all recipients of marker positive blood."

Professor, please correct me if I am wrong. I took that to mean that if you took 100 units of blood which had tested positive on a test, and gave it to 100 people, either 15 of them or 4 of them would get non-A non-B Hepatitis. That's what I understand from that explanation there.

So if you had your 100 units of blood which had tested positive, using the anti-HCV ELISA, and you gave them to 100 patients, 15 patients would get Hepatitis C; whereas using ALT as your test, if you took 100 units which had tested positive on a test using raised ALT as a marker, and if you administered those 100, only four patients would get Hepatitis C. That is the understanding that I took from that explanation. Is that accurate?

A. When I read these lines, I think you are correct.

Q. I hope so. I hope that's right, yes. Thank you.

Sorry, just to go back.

THE CHAIRMAN: It becomes predictive because if that's the

result you have found, you can then use that as a basis for estimating what would happen thereafter?

A. That's right.

MS DUNLOP: That really was a digression. Can we go back to Dr Boulton's report, please. It was just a prompt because he used the words "predictive value". Thank you.

We were looking at Dr Barbara's words. Then on the second page there is the end of Dr Barbara's contribution, as seen by Dr Boulton.

An interesting reference there to the Harvey Alter study:

"Indicated 80 per cent correlation by strict definitions. In Holland Reesinck showed a lower value (50 per cent) using field criteria."

I'm not sure I completely understand that but it looks quite good.

PROFESSOR JAMES: I can explain that if you want. The strict definition is the ones that, you know, were the very, very carefully selected patients in the NIH group, whereas presumably the Dutch ones were done by the similar kind of way that you had defined and colleagues in the UK had defined non-A non-B, without sort of "pedigreeing" it to quite the same extent.

MS DUNLOP: I see. By definition more likely to include

some false positives?

PROFESSOR JAMES: Yes, if anything.

MS DUNLOP: Yes, right.

Then a resume of Dr Lee's contribution, not entirely favourable comments. Although I should say, no reflection on Dr Lee. On to the next page of Dr Boulton's report, thank you, just to look at the ones he has summarised. On to page 3. Dr Philip Mortimer:

"All studies so far having small numbers."

And the next page as well, please. Comments on a presentation relating to HCV and the drug addict, and then HCV, some tropical studies. Then on the final page there are references to hospital -- well, actually it's not hospital but liver cancer connection between HCV and liver cancer from Dr Johnson. What is also interesting is Dr Boulton's covering letter, with which he sent this report. That's [SNB0141644].

Dr Boulton obviously felt he should send his report of the Ortho symposium to Professor Cash, and he says that:

"In spite of obvious difficulties with the current Ortho ELISA, I have developed a very strong feeling that the screening of donors for HCV antibodies should be introduced at the earliest possible opportunity. This is not because of the 'science' but because there

appears to be little doubt that people have contracted HCV as a result of transfusions which they would not have received had those transfusions been screened for HCV antibody."

That's quite easy logic to follow, Professor Leikola, isn't it?

A. Yes.

Q. Yes. So he has been at the same symposium but seems to have come away with a different view about the need to introduce the tests in the United Kingdom.

A. Correct. I think this is very much the same view as Drs Perry and Gunson had in their earlier statement.

Q. Yes. And indeed he makes reference in his letter to the possibility of legal action as well.

Right. Let's complete your second report, professor. Could we go back to it, please, at page 1962?

We were looking at what might possibly have contributed to the change of attitude between the January and April 1990 meetings of ACVSB and you have given us a little precis in paragraph 11 of the apparent mood of the meeting in April, firstly the reference to better tests on the horizon and then:

"The US may start screening out of fear of litigation, the French and the Australians have their

own reasons and some small European countries may follow suit, but the UK should not rush in before a reliable confirmatory test was available and the specificity and the sensitivity of the screening test were improved. A large prospective study was needed for the evaluation of whether or not screening would be suitable for the UK conditions."

I suppose like the sort of study that you had?

A. Yes.

Q. Yes. And no doubt with your tongue a little bit in your cheek, you are noting that you would be included in the "some small European countries" who had taken a different course. Would that be right?

A. Yes, I didn't want to spell it out.

Q. No, I think we got the point.

And then you move back to the July meeting and observe that:

"Contrary, perhaps, to the impression that might be created from the very meeting having been advanced by three weeks, there was still no rush."

And we are returning again to this idea of taking a sort of decision in principle but saying that first there needs to be a comparison between the Ortho kit and the Abbott kit. And you make the point, which we have discussed already, that that comparison could equally

have been undertaken with screening up and running?

A. Simultaneously, yes.

Q. Can we move on to the last page then, please?

The July 1990 minutes record an estimate -- I think it's four months roughly -- that it would take to do the comparative study but in fact that proved to be an underestimate, and you say:

"In essence, the outcome of the 2 July meeting meant at least half a year's delay in the introduction of the screening. As it turned out, the timespan was more than two times longer."

Your understanding is that:

"Only few preparations had been made concerning the practicalities of the large-scale routine testing."

Then in your final paragraph you attempt a summary, which is a difficult thing to do because I think there are a number of different factors at play. But you identify firstly enthusiasm and a welcoming of the new test in 1989, perhaps particularly. A view that there should be some approval by the FDA before the test could be introduced in the United Kingdom and indeed, as a matter of practicality, there would have to have been an export permit. But perhaps crucially, professor, I think we have seen there was never a clear decision taken that approval by the FDA would in itself trigger

the process of introduction of screening in the United Kingdom.

A. No, that is true. Those conditions were aligned already in November and when they were all fulfilled, there still was no clear decision as to go ahead.

Q. And the same could really be said of the confirmatory test?

A. Yes.

Q. That it wasn't set out that as soon as a confirmatory test of some sort, or a further test was in place, that it would be time to begin the introduction of screening. That caused enough delay for the arrival of new information. You say:

"Preliminary information of new developments."

Then what you describe as a "wait and see" attitude becoming stronger:

"It would be foolish to rush into the only available inadequate test when new possibilities were around the corner."

You think you can see also questions about the seriousness of the transfusion-transmitted Hepatitis C that seemed to be quite often very mild or totally asymptomatic, and that may be part of the background to all of this. Then:

"By July 1990, it had become clear the UK could not

postpone this matter forever, since the examples of other countries, public health aspects, media coverage, lessons of the HIV epidemic and other non-scientific factors were so pressing that some decision had to be taken even if reluctantly."

So I suppose if we think of a decision being taken perhaps in January or in April at one of those meetings, that testing should be introduced once a confirmatory test, in its broadest sense, was available and once the FDA had approved the test, and if some initial plans for implementation had begun and some practical steps had been taken, it would have been possible to save quite a bit of time, it seems to me. Would you agree with that?

A. I would agree with that, yes.

Q. Yes. In fact a year or more.

A. Yes.

Q. Yes. Thank you very much, Professor Leikola.

THE CHAIRMAN: Mr Di Rollo?

MR DI ROLLO: Sir, I'm grateful to my learned friend for her comprehensive treatment of this and I have no questions.

THE CHAIRMAN: Mr Anderson?

Questions by MR ANDERSON

MR ANDERSON: I'm obliged.

Can I just ask about one matter, professor. We know

that during 1990 various countries throughout the world introduced first generation screening. Can you help us with what second generation tests were introduced in, say, European countries? Do you have any information about that that you can help us with?

A. I don't think I can help you very much in this matter. I don't remember.

Q. Thank you very much.

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: I have no questions, thank you.

MS DUNLOP: We have no further business for today, thank you, sir.

THE CHAIRMAN: Professor Leikola, thank you very much.

A. Thank you.

THE CHAIRMAN: Ladies and gentlemen, the proposal is that, because of the volume of business, we should start tomorrow morning at 9.15. That is no problem to me provided I am able to turn up at all, but we will see how we can get on.

(3.42 pm)

(The Inquiry adjourned until 9.15 am the following day)

I N D E X