Tuesday, 22 November 2011

(9.30 am)

DR BRIAN DOW (continued)

Questions by MR MACKENZIE

MR MACKENZIE: Good morning. We have Dr Dow with us today, sir, who will firstly help us with topic C2, surrogate testing. After that, Ms Dunlop will examine Dr Dow on topic C4, the question of screening for anti-HCV. So Dr Dow good morning.

A. Good morning.

Q. Starting with topic C2, surrogate testing, we don't have to go back to your CV but, just to remind us, we know that between 1974 and 1991 you were a scientific officer with the West of Scotland Blood Transfusion Service and between 1995 and 1999, you were acting director at the SNBTS Microbiology Reference Unit. Between 1999 to 2010 you were head of the SNBTS microbiology reference unit and you were consultant clinical microbiologist. Is that correct?

A. Yes, that's fairly correct, yes. You missed out a five year period but ...

Q. I'm sorry?

A. I thought you missed out a five year period between 1991 and 1995.

Q. I think you are right, I did. What were you doing

between 1991 and 1995?

A. I was a principal scientist in the Microbiology Reference Unit.

Q. Thank you. You are quite right. You have provided a statement, which we will bring up on the screen, please. It's [PEN0171925]. We asked you a number of standard questions that we asked the other witnesses. The first question concerned whether a large-scale prospective study, of the type proposed by Dr McClelland in 1981, along the lines of the American TTV and NIH studies and including the follow-up of recipients -- should such a study have been carried out in the UK in the early 1980s or at some point thereafter with the aims we set out? You responded:

"I am not aware of any funding application in the UK to perform a prospective study on the lines of the US TTV ... and NIH ... studies."

I think that's probably right, Dr Dow. We are aware of Dr McClelland's proposals --

A. I wasn't aware of Dr McClelland's proposals at the time. Obviously I am now, after reading the preliminary report.

Q. I understand that. But, in terms of the evidence we have heard, we are aware of Dr McClelland's proposals to the MRC group in 1981 and then to the transfusion

services' group in 1983 for prospective study, but I don't think we have heard any evidence of any funding application actually having been made.

A. I wouldn't be in the situation to actually know of any funding applications anyway. I didn't sit on any committee to actually review these things. I just was not aware of it.

Q. I understand. But you then do go on to say:

"The complexities of these studies should be realised."

You explain that both of the American studies were based in total on 8,923 blood donations and much fewer, 1,796, patients:

"The NIH study obtained samples from patients pre-transfusion and 3 months, 6 months and 9 months post-transfusion. The TTV study was more thorough, obtaining samples from patients pre-transfusion ... and then post-transfusion 2, 4, 6, 8, 10, 12, 15, 18, 21, 24 and 40 weeks post-transfusion."

A. Yes.

Q. Approximately 10 per cent of patients were considered to have potential non-A non-B Hepatitis on the evidence of an elevated ALT. In the NIH study, over 110 IU and in the TTV study, over 90 IU. Both levels being in excess of twice the upper limit of normal. We can see what is

then set out in your answer and we have seen these figures from the papers. Also your point that:

"2.9 per cent of control hospitalised patients in the TTV study developed NANB hepatitis although they had not received any blood or blood products."

A. That's correct, yes.

Q. Then at the bottom of the page you say:

"It had also been pointed out by Hornbrook et al (1982 New England Journal of Medicine) that the true incidence of NANB PTH as reported to volunteer blood collection agencies in the United States was around 0.1 to 0.2 cases per thousand units issued (compared to 10 to 28 cases per thousand units in the NIH and TTV studies. This was a hundredfold less than that found in the NIH and TTV studies."

We should go to this paper because we haven't looked at it before. It's [PEN0171950], please. We don't have to go into the paper in detail. We can see the heading for ourselves and the subheading, "Economic considerations."

I think, in summary, the paper is looking at an economic cost/benefit analysis of surrogate testing based on certain assumptions. If we go to the bottom left-hand of the paper, we can see where the various authors come from. We can see the division of

intramural research. What's intramural research?

A. I have not a clue, to be honest.

THE CHAIRMAN: It means inside the walls; domestic in some sense.

A. It is used in university circles.

Q. Yes.

MR MACKENZIE: We can also see, a few lines down, "Department of economics and preventative medicine, I think we can understand that.

A. I think Roger Dodd was one of the main co-authors of the paper and he was a well-respected transfusion scientist in the United States, that knew a lot about microbiology as well. He came from England.

Q. Thank you. If we go to the abstract, in the final paragraph of the abstract we can see the author's conclusion. They state:

"Our results suggest that, if prospective studies demonstrate that exclusion of blood with elevated immunotransferase elevations decreases non-A non-B Hepatitis in recipients, the net economic impact may be positive. However, because of major uncertainties about the medical consequences of non-A non-B Hepatitis, the benefit estimates are so broad that they preclude a definitive policy decision."

I don't say any more about the substance or merits

of the paper. I would, please, like to go to page 1953, which is page 1318 of the paper. If we look at the left-hand column, please, second paragraph, we see the paragraph commencing:

"Other factors suggest that the actual severity of non-A non-B Hepatitis may tend to lie at the low end of the range of estimates. For example, the actual incidence of post-transfusion hepatitis reported to voluntary blood collection agencies is in the order of 0.1 to 0.2 cases per thousand units issued."

A reference to Dodd, RY: unpublished data. I think that's the reference which you refer to at the bottom of page 1 of your statement, doctor. What's perhaps slightly puzzling, I think, is that the NIH study, I think, used only volunteer blood and found a much higher instance of post-transfusion hepatitis and I think similarly we saw the TTVS study involved four centres, three of which used only voluntary blood and one, the Los Angeles centre, the fourth, I think used most voluntary blood but there was a two-year period, perhaps 1974 to 1976, where they used also paid donors. So, on the face of it, perhaps, it seems slightly surprising that there is this large difference in incidence of post-transfusion hepatitis in the different studies.

A. I mean my point I was trying it make was that Roger Dodd's data there, represents the number of actual cases that have been reported to the transfusion --

Q. I understand.

A. Whereas the NIH and TTV studies are all based on ALT studies on patients --

Q. I understand.

A. -- defining the non-A non-B Hepatitis just by a simple raised ALT.

Q. So the Dodd study is looking at reported cases, where, of course, the NIH and TTVS study involves prospective follow-up of recipients, testing ALT levels so many weeks and months after transfusion?

A. My point I am making is Roger Dodd's observation is quite similar to our observation of non-A non-B Hepatitis in the reported cases that we got in the period 1977 to 1985. I think we had something like 23, whereas if we had done NIH and TTV studies, we may well have had 100 times that in patients.

THE CHAIRMAN: Dr Dow, when you talk about the reported cases, the reports of what, please?

A. Reports of individuals, patients, who have developed hepatitis after a blood transfusion.

THE CHAIRMAN: Hepatitis meaning what?

A. It may be defined as an ALT, but normally it would be

a jaundice, a severe hepatitis.

THE CHAIRMAN: It is quite important to know, because if the reports are of jaundice or other clinical signs within a reasonably short time of transfusion, that clearly has one significance which distinguishes it from something solely based on ALT or AST measurements. So I think if you would help me, please, by keeping that distinction to the forefront. That applies to your study as well as --

A. It's a pretty woolly one, because it encompasses what a clinician actually feels at the time. It could be a severe hepatitis, a person may not be jaundiced. It really depends on the clinician himself that is reporting the particular case.

THE CHAIRMAN: Do you know what the lowest common denominator might have been?

A. No.

THE CHAIRMAN: I ask you because I am aware, from reading these early documents, that really the trend away from treating hepatitis in the sense of a clinically observable condition towards more complex definitions really is quite slow and patchy(?).

MR MACKENZIE: Looking at matters now, doctor, it may be that the TTV and NIH studies may have overestimated the prevalence of post-transfusion Hepatitis C because we

know that elevated ALT can be caused by other things apart from Hepatitis C. Is that correct?

A. That's quite correct, yes.

Q. But, on the other hand, the work -- the reference in Hornbrook to reported cases of post-transfusion hepatitis and reported will probably mean jaundiced cases, that's likely to be an underestimated --

A. The fair proportion would be jaundiced, yes, the rest would have severe hepatitis.

Q. We will come on to look at your study in the West of Scotland, to see how many of the reported cases were jaundiced. Thank you. That's the Hornbrook paper. We can put that to one side, please. Return to your statement, if we may, please, at the top of page 2. At the top of page 2 we see you say:

"A large scale prospective study, using the scales within the American studies to assess the prevalence of post-transfusion non-A non-B Hepatitis in the UK with the above aims would have had a prohibitive cost element, mostly due to the work involved in recalling patients to obtain follow-up samples. Substantial funding would have been necessary."

Et cetera. You say:

"Even if such an application had been made, I would have expected it to have been declined, based mainly on

the cost element and other factors described below and even if a large-scale prospective study had been carried out in the UK, I doubt whether anything novel would have surfaced."

I think Dr McClelland's ultimate position was that such a large-scale prospective study could have been carried out in the UK, but it would have been a large and difficult undertaking, which would have required support at the highest level, ie government and the corresponding funds. Do you have any comment on that?

A. I agree, it would be close to 1 million pounds anyway for a simple study and, obviously, the more complex it got, it would involve increasing in cost at that time. I think -- to be honest, I think there was a better use for that money at the time in the health service.

Q. You say 1 million pounds. Firstly how do you derive that estimate broadly and secondly, do you mean it would cost 1 million at the time or 1 million now?

A. I think it would be about 1 million pounds then. Really a lot of this cost would be in getting the patients back and, obviously, the medical power that would be required -- the manpower required to actually take the necessary samples off these people. Obviously, it would all mount up to be a considerable cost.

Q. Thank you. Moving on to question 2, please, we asked:

"If such a study had been carried out, to what extent is it likely to have met the objectives set out in 1 above? To what extent would such a study have provided more information upon which to base a decision on whether surrogate testing should be introduced?"

You replied:

"Assuming that any proposed study would have been carried out roughly following the protocols of the NIH or TTV studies."

You address the four aims we have set out as follows. (a). We can see what you say there for ourselves. But half way through your answer you say:

"Most cardiac surgery follow ups tended to be around 6 months following surgery, whilst the incubation period of non-A non-B Hepatitis appeared to be around seven weeks. Therefore, there was a strong responsibility that where the NANB hepatitis may have been mild, then a 6-month follow-up would have been unlikely to indicate hepatitis. A study similar to the NIH study (with limited sampling) would have possibly missed some milder cases ..."

A. I was trying to point out there the NIH study was based on three-month sampling.

Q. Yes.

A. On the face of it, if you had actually have forgotten

about a three-month sample and just gone to a six month sample, you could well have missed an acute case of non-A non-B. Obviously a chronic case you would have recognised it because, even at six months, the ALT would still be raised.

Q. What do you mean in the last sentence of your answer (a), where you say:

"Looking back now at the findings of Hornbrook ... that the TTV and NIH studies gave 100 times the number of NANB PTH cases compared to the actual cases being reported to volunteer blood collection agencies meant that simple arithmetic should have resulted in a rough prediction of NANB PTH."

A. I'm really just taking Hornbrook's evidence, that Roger Dodd provided within Hornbrook's paper saying that the reported cases were about 100th of what was found within the NIH and TTV studies. Therefore, just multiplying up a hundred-fold the number of NANB reported cases you had, as potentially the number that were actually occurring.

Q. I see. Thank you.

THE CHAIRMAN: That's an interesting sort of approach to it. Did anyone apply an approach of that kind at the time?

A. No.

THE CHAIRMAN: I can see the reasons. If the ratio was

roughly right, then it would apply generally, would it?
A. Very difficult, because the American situation could be that -- it depends who was doing the ALTs. The ALT levels are not international. They may have international units -- per litre -- as a means of actually defining what they are, but they are definitely not international, as far as you can't actually say one level is the same in another area. So there are huge problems to try to actually compare studies from different countries or even within countries.
MR MACKENZIE: Another way of seeking to use the data concerning the number of reported cases may be this, that -- we will come quite soon to look at a passage in Mollison, where he reports that about one fifth of cases of post-transfusion hepatitis are icteric. If that's the case, then why not simply multiply by five the number of reported cases to give you a very approximate incidence?
A. Yes, I mean, it's up to -- you have to define -- if you are going to accept, you know, what you are actually seeing and then you have to try and prove it. Rightly so; had a study been done to actually show this, that would then probably have confirmed it. But, obviously, that study was never done.
Q. Yes. We will perhaps come back to this a little in due

course. Then answer (b), you quite correctly point out:

"There was only one surrogate marker used in the 1981 studies, ALT. Use of this marker in a prospective study in the UK would have been fraught with potential ethical problems."

You set out various questions there and then you say:

"The inclusion of anti-HBc as a further surrogate marker could perhaps have been useful but, from memory, it was a few years later that anti-HBc was also included in the TTV study."

I think that's right as well. Then you set out various comments about again anti-HBc, not of course being a specific marker for HCV. Then answer (c):

"The investigation of the natural progression and seriousness of the disease would not be a short-term outcome of any study."

We can quite understand that. You go on to explain about the HCV national register held in the UK. It has followed up patients identified through the HCV look back process and even 20 to 30 years post infection only a small proportion have had evidence of ongoing liver problems. To pause now, to observe Dr Dow that we know now that cirrhosis may take 20 or 30 years to develop in a patient. So any prospective study of post-transfusion

hepatitis would have to run for decades to really, I think, obtain any reliable evidence about the natural progression of the disease.

A. Correct.

Q. Answer (d) concerned:

"Would a large-scale prospective study have been helpful in producing a library of known infective sera with which to evaluate any future assays when they became available?"

In answer (d) you say that:

"The production of a library of 'assumed known' infected sera would have proven to be a very difficult test."

Et cetera. You explain that, in the west of Scotland:

"BTS had an established system of investigating the comparatively few reported cases of possible PTH ..."

We can see what's set out there and you say that:

"Stored sera from implicated donations involved in reported PTH cases were examined for evidence of HPV infection and ALT levels, see PhD study..."

Which we will come to. And:

"Such sera were actually included in panels used to evaluate the Ortho HCV first generation test when it came available in 1989."

Then yes 3, we asked:

"Did the conclusions of Dr Dow and Follett place sufficient emphasis on the likely prevalence and seriousness of post-transfusion NANBH?"

I will come on at the end of your statement, doctor, to look at certain panels in your evidence, but in your written answer you replied:

"The work that I carried out, supervised by Dr Follett, was intended to identify cases of NANB hepatitis in the west of Scotland."

Am I right in thinking, doctor, that the two main purposes of your work were firstly to seek to determine the incidence of post-transfusion NANBH in the west of Scotland and, secondly, to seek to develop a serological marker for the disease?

A. I think it was a bit wider than that. We were really looking at non-A non-B Hepatitis in any patient population. Obviously, my angle was the post-transfusion side of it and that's why I was involved in that study. But obviously it was wider than just transfusion-associated non-A non-B and that's why we looked at drug abusers and other agents within this study.

Q. Thank you. You say that:

"The conclusions we made were based on the evidence

available at the time. There was no attempt to evaluate the seriousness of the disease which would have required clinical evaluations by gastroenterologists."

I quite understand that, that you didn't seek to follow up the clinical course of the disease in any patients.

A. Some of the patients obviously would come back through the system, especially so if they had been recognised as being negative before, for the likes of Hepatitis B or Hepatitis A, and if they were still jaundiced or still had really severe ALT levels, they would come back through the system.

Q. But there was no systematic attempt, as part of your study, to follow up the course of the disease in patients?

A. Only haemophiliacs and renal dialysis patients. I have tried to monitor as much as possible by doing the equivalent of ALTs on them.

Q. I understand that. We will come back to look that. You say that:

"Within the study, ALT levels were determined for 24,629 samples in several patient groups or blood donors."

Then the different patient groups are set out. We can see the main findings of your study and we see the

conclusion was that:

"NANB hepatitis was usually subclinical and occurred in 25 per cent of haemophiliacs at some point within the investigation ..."

The conclusion was that NANB hepatitis was usually subclinical. That was already known in 1985, wasn't it?

A. No. Really non-A non-B Hepatitis was a definition of -- originally put as somebody with severe hepatitis that had been obviously reported as non-A non-B post-transfusion hepatitis, similar to Hepatitis B et cetera. They tended to be very severe, the ones that were reported up to that point. The subclinical ones were ones that came out in the TTV and NIH studies.

Q. I should perhaps ask, what do you mean by subclinical?

A. Subclinical means the patients never actually need to seek medical attention. That's what I would declare to be subclinical.

Q. So cases not --

A. It has not been recognised that the person has anything wrong with them.

Q. I think certainly the American studies from quite an early stage, perhaps the late 1970s/early 1980s, I think all reported that most cases of non-A non-B Hepatitis were subclinical and that the elevated, fluctuating ALT levels of patients, in particular recipients of

transfusion, wouldn't be picked up unless they were prospectively followed. But I suppose are you saying that that was what the American studies showed; you wanted to investigate the problem in the west of Scotland?

A. Yes, we were looking at the -- if there was a problem in the West of Scotland, that's really what we were looking to see, to identify if there was non-A non-B Hepatitis as such.

Q. The other point in the sentence; you say that:

"The conclusion was that NANB hepatitis ... occurred in 25 per cent of haemophiliacs at some point within the investigation ..."

I can see -- and we will come to your thesis -- you are reporting there what you found in the patients you studied.

A. Yes.

Q. Isn't the bigger picture, at this time, that it was by this time, by 1985, known that really all previously untreated haemophilia patients who received concentrate, whether NHS-produced or from commercial companies, developed non-A non-B Hepatitis?

A. Well, it was known that -- we even did a paper in 1980 or 1981, which actually showed four haemophiliacs through a period of time and within, I think we actually

had a chap within that paper anyway that showed that someone had two or three bouts of hepatitis.

Q. Yes. We will perhaps come back to see exactly what was studied and concluded in your thesis shortly. You said:

"This led to the belief that perhaps Scottish blood donations were less infective than blood products."

What do you mean by that sentence?

A. The meaning behind that is that blood components from single blood donations were less infective than blood concentrates as such and Factor VIII.

Q. Again, wouldn't that have been known in 1985 that it was a matter of simple arithmetic?

A. It was not really known at that particular time.

Q. It may have been a hypothesis?

A. A hypothesis, yes.

Q. You wanted to test it and see if it was correct?

A. Just like Factor VIII -- the heat treatment of Factor VIII, it wasn't known that actually -- the treatment would actually kill off Hepatitis C or even HIV before that, until such time as Hep C came along and was actually identified.

Q. I see.

A. That was some considerable number of years afterwards.

Q. I see. Carrying on --

THE CHAIRMAN: I'm still not sure that I fully understand

what the sentence means. When you refer to, "Blood products", are these blood products produced from Scottish donations?

A. They could be from Scottish blood donations or they could be commercial as well.

THE CHAIRMAN: Then --

A. There is two meanings to that and you can take both because what I'm saying is that the components from single unit blood donations, the likes of red cells, platelets, or fresh-frozen plasma, on the whole, are less infective than concentrates made from pools of plasma from, say, 2,000 blood donations, whether they be Scottish or American.

THE CHAIRMAN: I suppose something may turn on what one means by infective and I can see that a component will affect a fewer number of -- a smaller number of people than a blood product but is that all this means or does it mean something else?

A. No, what I was trying to get across was that if you had 100 blood donations, single components -- let's say you had 100 platelets, that the likelihood of you coming down with non-A non-B Hepatitis was less than you getting one dose of Factor VIII.

THE CHAIRMAN: Yes?

MR MACKENZIE: Thank you. Continuing with your written

answer, please, Dr Dow, you explain three lines from the bottom of page 3 that:

"Both HAV and HBV patients tended to have clinical symptoms, such as jaundice. Non-A non-B Hepatitis patients were classified mainly by lack of HBsAg and a negative test to IgM anti-HAV. Within this study it was noted that some individuals classified in such a manner were actually infected with HBV.

"Indeed it was estimated that 5 per cent of acute HBV infections would have been misdiagnosed as non-A non-B Hepatitis and this would continue even today (in laboratories only performing HBsAg and Ig, anti-HAV) as being misdiagnosed. With regard to the number of NANB PTH cases that were reported to the west BTS, many of these were reported because of the active involvement in following up patients (within the PhD study) with raised ALT levels to determine if they had been recently transfused. Even using this active involvement a total of only 23 cases of NANB PTH (including 3 haemophilia patients using commercial factor VIII) were reported to the west BTS in the years 1977-1985."

We will come on to look at that in your PhD study, but what do you mean by, "Even using this active involvement?"

A. We did actually go back to some of the clinicians to ask

if the patient had actually had any blood in the past. Obviously, if they had blood in the past, we would get the details and they would be added to the number of cases reported to us.

Q. Then we then see you say:

"Within the PhD study the blood donations (collected between 1980 and 1985) with grossly elevated ALT levels ..."

Can you remember what, "Grossly elevated ALT level", meant?

A. That was two and a half times above the level of normal.

Q. We might see what that translates to in your thesis when we come to it. You say:

"These donations were frozen down."

Does that mean defrosted?

A. The plasma gets frozen very quickly after someone donates blood. So it's like a great big lollipop in a plastic bag and they are just being kept frozen.

Q. What does frozen down mean?

A. Kept frozen at minus 20°C.

Q. So they were frozen down, ie frozen. Presumably they must have been -- or were they defrosted before they were tested?

A. No, the way a unit of blood was taken at that time was that the plasma was actually frozen very quickly because

it preserved Factor VIII. So, normally speaking, if the donation was going to be suitable for use, it would go through to the Protein Fractionation Centre and they would thaw out the lollipops of plasma and they would make Factor VIII from it. What I was doing was, I was capturing the donation before it went to the protein fractionation centre and putting it into microbiological quarantine.

Q. I'm just wondering -- it probably doesn't matter, but you have got me curious now. The donations were collected between 1980 and 1985?

A. Yes.

Q. At some point later, perhaps the end of the 1980s, 1989, I don't know, they were tested with the first, second and third generation HCV tests. So the donations were collected --

A. They would actually -- we could go in and -- there would be an occasion where we would probably thaw out the donation to take a further sample from it, but on the whole the donation has been kept frozen.

Q. Yes. Do you test the frozen sample?

A. We take a sample out and test it and then refreeze the sample.

Q. So you take the sample out for testing?

A. Hm-mm.

Q. Do you have to let the bit you have taken out defrost before you can test --

A. Obviously, yes.

Q. Right. Okay, thank you.

A. Sorry.

Q. I think I understand.

THE CHAIRMAN: I think it's just the mechanics, Dr Dow. Were these particular samples that did not go on to PFC for processing or were you taking some of the material and sending the balance on?

A. No, the entire donation was kept.

THE CHAIRMAN: That, therefore, was kept within your control, as it were?

A. Well, it was still under my control up to October last year when I retired.

THE CHAIRMAN: Yes, I don't expect you to have it now.

A. It's still at Gartnavel.

THE CHAIRMAN: Can you add this bit of information? To get a sample for testing, did you defrost the lot or did you scrape a bit off.

A. Obviously we thawed some material at one point and used that material to do the test because we only need a small amount to do testing. A 200 ml plasma donation -- we will only need something like, in some instances only 20 microlitres to be able to do a test.

MR MACKENZIE: Thank you. Completing what you say in that paragraph, page of your statement, doctor, you go on to say -- talking about the blood donations you collected as part of your study with grossly elevated ALT levels, I think they were helpful essentially for evaluating the test, once they became available for Hep C. You say:

"The vast majority of these samples with grossly elevated ALT levels were later shown to be HCV-positive."

A. That's correct, yes.

Q. We see what else you say there. There is reference to a report in Vox Sanguinis in 1994. I think we looked at that under topic C1, the reference is [PEN0140072]. You go on to say this demonstrates that the PhD study was actually on the correct line with the isolation of several donations (with grossly elevated ALT levels) that were shown a decade later to be HCV-positive."

Does it follow from that that the SNBTS directors were also along the correct line in arguing for surrogate testing to try and prevent cases of post-transfusion non-A non-B?

A. Well, that's debatable.

Q. There are perhaps wider questions to take into account when considering whether surrogate testing should be introduced?

A. What I was trying to make the point of there was the grossly elevated ALTs -- if you actually screened donations and took out those that were grossly elevated, you would obviously take out quite a number of Hep C positives but unfortunately, these grossly elevated ALT ones that I had within the study, the vast majority were obviously from prisons.

Q. Just to continue that a little; I suppose if surrogate testing had been introduced in Scotland, one could have set the bar fairly high: that only grossly elevated ALT donations would be screened out. But I suppose the question then becomes: was it known at the time that those with grossly elevated ALT levels were most likely to have non-A non-B Hepatitis?

A. No, they weren't and that was the whole point, that in hindsight obviously it would have been a great thing to have actually done surrogate testing, but really, at the time, there was very little evidence to actually show that it would be a cost benefit.

Q. In the final sentence you say:

"As most cases of NANB hepatitis appear now to be subclinical, how could these cases have been identified when there were no specific assays?"

Just for the avoidance of doubt, what do you mean by that last sentence?

A. Without having specific assays to demonstrate that somebody is truly infected with non-A non-B Hepatitis, you can't actually go and diagnose somebody as having non-A non-B Hepatitis really.

Q. It really comes back to the problem --

A. It's all by exclusion, you know.

Q. The problem of using a surrogate marker for a disease one can't specifically diagnose?

A. Hm-mm.

Q. Thank you. Question 4. We asked about SHHD medical officers and you say you can't comment on that, other than that Dr Forrester had sight of your completed PhD thesis. Question 5 we asked:

"If surrogate testing of blood donors ... had been introduced in Scotland ..."

Various questions and you answer:

"The introduction of such testing would not have been simple, careful consideration would have been had to be made regarding donor counselling."

We can see all you set out there. Over the page, please, I should perhaps say that you say:

"When anti-HBc can be present in around 80 to 90 per cent of Chinese and black populations and also in a high proportion of Arabic populations."

We have heard that ALT levels can vary depending

upon one's sex, male or female, depending upon one's age as well. I suppose these would be further factors to have to take into account when interpreting the results of anti-HBc screening, that apparently the prevalence of anti-HBc can vary according to different ethnic groups?

A. Correct, yes.

Q. Then, top of page 5 you say:

"Furthermore a number of non-specific factors, such as Rheumatoid Factor produce false weak positive results in most of the anti-HBc tests available ... with reference to the posed questions."

(a). We can see for ourselves what you say. Then (b) you say:

"The maintenance of the blood supply would have been difficult."

I will explore that a little more with Professor Cash when he returns. (c) you say:

"I have always regarded the period September to December 1991 as the definitive period to determine the actual HCV prevalence in the Scottish donor population as this period would have generally not included any repeat donations from the same donor."

As I understand it, Dr Dow, looking at that four month period -- September to December 1991 -- the prevalence of HCV in donors was 0.9 per cent?

A. 0.09 per cent.
Q. I'm sorry, you are absolutely right, it's 0.09 per cent. Whereas, extending that to the six-month period the prevalence is 0.088 per cent.
A. Yes.
Q. So I don't think there is actually a huge difference between the two figures?
A. It's the denominator. You have really got to remember that, within that period, several donors would actually come back and donate again. So your denominator number would -- was not strictly correct to do it.
Q. Yes, but in terms of if one were to ask: what was the true incidence of Hepatitis C among donors following --
A. You would normally use a September to December period.
Q. Which gives a figure of 0.09 per cent?
A. Yes.
Q. But if one were to look at the incidence in the first six months, the figures --
A. It wouldn't vary that much, but obviously I'm quite surprised it was so close, to be honest. I would have expected there to be a slightly greater proportion in the first three/four months.
Q. Because they are then being screened --
A. Because you are weeding out the positives and thereafter that you have got regular donors coming back that are

going to dilute the number out.

Q. I don't think it's a matter that need detain us, given the figures are fairly close but you also say --

THE CHAIRMAN: That may be Dr Dow's point, that the figures are close when, given that the returns are counting twice perhaps, you might have expected a bigger discrepancy.

A. Yes, on average we got, I think it was, around about 1 point -- the number of donations over the number of donors would actually come out to give you a ratio of roughly 1.8 per year. It varies from year to year, I don't know what it was away back in 1991.

THE CHAIRMAN: I think one would be slow to adjust the figures, though, on that basis. It may be it's just casual, the relationship between the numerator and denominator.

A. There are a lot of factors that can happen when you start doing a screening test. Obviously the publicity can bring a lot of people as test seekers, which we don't want but, it does happen.

THE CHAIRMAN: I think maybe the only inference we can draw is that the number was very small.

A. Yes.

MR MACKENZIE: Yes. I suppose the other point to bear in mind, perhaps, is that double counting works both ways,

in that, yes, if one looks at a six-month period, there may be some positive donors who have returned but equally, there will be many, many, many more negative donors who have returned as well.

A. Correct, yes.

Q. We can see, third line from the bottom of answer (c):

"The attached figure shows the HCV prevalence varied according to region, with Glasgow, Dundee and Inverness regions having relatively high prevalences compared to Aberdeen, Edinburgh (and also Belfast, not shown)."

Just in case the colouring doesn't come over particularly well, as we look at the columns in the table in figure one in your statement, I think Dr Dow, just going through them from left to right, the columns represent Aberdeen, Dundee, Edinburgh, Glasgow and Inverness. Is that correct?

A. I think that's correct, yes.

Q. I'm not going to begin to speculate as to the different reasons as to why there may be different prevalence in different regions. Over the page, please.

Top of page 6, the last page on the statement. We see the reference to the figure of 0.09 per cent, four lines down. We have discussed:

"We were aware that 25 per cent of all HCV confirmed positives were anti-HBc reactive (indicating past

infection with HBV). With hindsight, assuming from Crawford et al in 1994 ... that 59 per cent of HCV positives had ALT levels above the upper limit of normal, then it is likely that 69 to 70 per cent of the HCV-positive donors would have theoretically been deferred, had both ALT and anti-HBc tests been used. This would have been associated with a loss of 3.5 to 4 per cent of the normal healthy donor population."

I don't know if you have read the evidence of Dr Gillon?

A. I have, yes.

Q. Also Dr McClelland and I think they would both be more cautious about simply taking the Crawford figure 59 per cent. Has that given you pause for thought --

A. No, you have put the thing within your question as using that figure of 59 per cent. I have just taken that figure of 59 per cent. I have not taken any caution. You have presented the data. I have used the data to get the conclusion that you have asked for.

Q. Well, I think to be fair, the question was not quite as narrow as that. The question was:

"If surrogate testing of blood donors had been introduced in Scotland, to what extent are cases of post-transfusion Hepatitis C likely to have been prevented?"

Then we say:

"Having regard for example, to the finding in Crawford ..."

So we have drawn Crawford to your attention but we certainly don't wish to use that to prescribe your answer.

A. I have used that to describe the answer and only that to describe the answer because obviously that's its way it was put to me.

Q. Well, let me put it in a wider way: what do you think would have been -- if surrogate testing of blood donors had been introduced in Scotland, to what extent do you think cases of post-transfusion Hepatitis C likely to have been prevented?

A. It's very difficult. But, using Crawford's data -- which I'm part of that paper as well -- I would agree with what we found at the time. We have to go with what we found at the time and that's the nearest we will probable get, but I would have to say it might be a slight overestimate.

Q. With the benefit of hindsight do you think that surrogate testing is likely to materially reduce the incidence of post-transfusion Hepatitis C?

A. I would probably have expected it to maybe halve it.

Q. I understand.

A. But, going with the evidence that we had, I would have to go with the 70 per cent, based on us knowing that a quarter of our Hep C positives will have anti-core and based on the 59 per cent from the Crawford paper.

Q. Okay. Then the final paragraph at page 6. You say:

"The fact remains that very few actual cases of HCVPTH were being reported to the regional centres. The use of ALT and anti-HBc (using the data as suggested) would, with hindsight, have likely reduced the number of reported indicates by 70 per cent."

Don't just use the data as suggested, use any data you think most appropriate. If that is the question, would you still say that the use of surrogate testing, would with hindsight, have likely reduced the number of reported cases by 70 per cent?

A. Well, I would have probably said -- I would have been quite happy with 50 per cent actually there.

Q. I understand.

A. Obviously with what's provided, 70 per cent -- we are talking about down to either 11.5 or 7 and it's not that much different really.

Q. Thank you.

THE CHAIRMAN: Could I ask about the expression "reported cases"? What does that mean.

A. That is the cases that are reported to the transfusion

centres as potential -- post-transfusion hepatitis.

THE CHAIRMAN: So that would be cases that gave rise to a similar trigger for reporting --

A. Yes, that is right. A clinician would feel that there has been transfusion involved at some point in the not too distant past that could have caused this particular hepatitis.

MR MACKENZIE: Thank you. We can see what else you say in your written answer, Dr Dow and you say:

"It should be emphasised that there have been no proven transfusion-transmitted HCV cases associated with Scottish anti-HCV-tested blood."

A. I feel that's quite an important thing for the Inquiry to actually remember; that there have not been any transfusion-transmitted Hep C cases associated with Scottish anti-HCV tested blood, since September 1991.

Q. That's why I read it out.

A. Had you changed the thing about and had we gone with first generation testing a bit earlier, there would have been cases reported --

Q. I think --

A. -- because the first generation test did not pick up all Hep Cs.

Q. That may be an issue that's looked at further perhaps later on today, but I'm not going to go into that. You

do say that:

"Since the advent of HCV PCR tests in 1999, there have been no proven transfusion-transmitted HCV cases in the UK. Current UK risk estimates are that around 1 in 40 million to 1 in 80 million donations would result in HCV transmission, ie one HCV transmission in 20 to 40 years."

That's your statement, thank you, doctor. I would now like to take to you one or two other documents, firstly, please [PEN0171734]. This is an extract we have looked at before. If you have been reading the transcripts, you have probably read it as well on our web page. It's from a textbook by Professor Mollison, "Blood transfusion in clinical medicine", the seventh edition published in January 1983. If we can go over the page, please, page 73 of the textbook -- I should pause and ask, doctor: did you have access to this textbook back in 1985?

A. There are several edition of Mollison, but I don't know what edition was on the book shelves in the BTS library. I wouldn't have referred to it for non-A non-B Hepatitis because Mollison was completely out of date for most of it.

Q. I see. Am I right in thinking this was the main or perhaps the only UK textbook on blood transfusion at the

time?

A. Yes, but again, as I said, I would probably have used it for other purposes than transfusion microbiology.

Q. Okay. Let's see what it does say about non-A non-B Hepatitis at page 773. About half way down the paragraph we can see the passage commencing:

"As a rule, non-A non-B Hepatitis is symptomatically mild. Patients seldom need to be admitted to hospital. Nevertheless, up to 60 per cent of cases have abnormal ALT levels for more than one year; if a liver biopsy is taken, most of the cases show histological evidence of a significant chronic liver disease and approximately 10 per cent show features of cirrhosis."

A reference to a paper by Alter in 1980:

"A striking feature in non-A non-B Hepatitis is the tendency for serum hepatic enzyme levels to fluctuate markedly over a relatively short time."

Now, what is set out in that passage; is that something that would have been known to you in 1985?

A. We knew of some cases that actually did fluctuate like that, not ones I personally remember too well, but there had been reported at various scientific meetings.

Q. If one was familiar with the literature from America, then I think what is set out by Mollison is essentially sets out -- correctly summarises knowledge of NANBH,

I think mainly coming from the American literature. Is that correct?

A. Probably the vast majority was coming from America, yes.

Q. Yes, and were you aware of the American literature at the time?

A. Some of it, yes, not all of it because there were thousands of articles on non-A non-B Hepatitis at the time.

Q. Rather than look at a thousand articles, this seems to an outsider an obvious place to start looking.

A. Harvey Alter was a -- obviously he has been mentioned here and Harvey Alter was obviously one of the persons involved in the NIH study and obviously was well-known to most of us.

Q. He was an authority on the question of post-transfusion hepatitis?

A. He was authority, yes.

Q. Yes. Then look over the page, please, page 774, 1736 of our court book reference. Under, "Frequency of post-transfusion hepatitis", we see the passage:

"Anicteric cases of PTH are commoner than icteric cases. For example, in a study reported from the USA in which 2204 patients were followed, and in which PTH was diagnosed in 241 patients, the disease was icteric in less than one fifth of the cases. It follows that

repeated sampling of recipients is necessary if all cases are to be detected and that only prospective studies are likely to give a true indication of the frequency of PTH."

Did you know what is set out in that project in 1985?

A. Probably not.

Q. Why not?

A. I probably hadn't read Mollison at that point. As I said before, I read Mollison for other purposes at the time. It wasn't my way of finding out about non-A non-B Hepatitis.

Q. Yes. I suppose the starting point is perhaps an awareness that anicteric cases of PTH --

A. I would agree with all that's said there. I would be aware of all these things.

Q. Yes. If one has that awareness, that anicteric cases of PTH are commoner than icteric cases, I think it then follows as a matter of logic that repeated sampling of recipients is necessary if all cases are to be detected.

A. That's what we tried to do within the PhD with the haemophiliac population and the renal dialysis patients.

Q. That's an indication that you were aware of the need for repeated sampling of recipients in order to give a "true" indication of the frequency of PTH?

A. Yes.

Q. Thank you. I would like now, doctor, please, to come to your thesis. I should say in passing that I won't go to a document, your final report, you produced in July 1984. It's [SGH0028040] because we covered that when you gave evidence on C1 on 18 March of this year at page 151 in the transcript onwards.

So I won't go back to that report. Rather, I will go to your thesis, which we haven't looked at before. It's [LIT0013300]. I would like to take to you various passages in it, but the central question I'll ask you at the end is this -- I should perhaps say by way of preamble that, in going through these passages, I don't intend to criticise your thesis; I quite understand that it was a work properly undertaken using your best endeavours at the time.

I have a different purpose in looking at it; rather, the central question I will ask at the end is whether the general medical reader, ie someone with a medical degree but no particular experience or expertise in blood transfusion or hepatitis, whether they are liable to get a misleading impression of, firstly, the likely prevalence of post-transfusion non-A non-B Hepatitis in Scotland and secondly the potential seriousness of the disease on reading your thesis?

A. Hm-mm.
Q. I hope you understand that's not a criticism of the thesis --
A. The thesis was supposed to be written so a layperson could read it and maybe understand.
Q. Okay. Let's, with that in mind, go through parts of it, please. Could I start, please, at page 3302? We can see the title of your thesis, "Non-A non-B Hepatitis in West Scotland", by yourself and it's dated October 1985. Could we then, please, go to page 14, which is 3315:

We can see in the second paragraph under the summary:

"In this thesis, the occurrence of NANB hepatitis has been noted in the West of Scotland population, particularly amongst drug abusers."

So that's really pointing out, Dr Dow that I shouldn't look at this thesis as just being work on post-transfusion hepatitis?
A. As you explained, it was wider than that. It was supposed to be the whole West of Scotland population, but obviously it's mainly patients.
Q. It goes on to say:

"Transfusion-associated NANB hepatitis is a very rare occurrence with an average of only three reported cases annually."

To pause there, I suppose what one would need to know in order to form a view on the true prevalence of non-A non-B post-transfusion is that most cases are anicteric.

A. Obviously, yes.

Q. Yes. You go on to say:

"In these cases, the incubation period of this presently transmitted form of NANB agent was found to be on average seven weeks. A study of haemophiliacs and renal unit patients has shown that there are occasional episodes of hepatitis (usually mild) in such patients."

We will go on to see what study in the haemophiliac population was carried out shortly.

The next page I would like to go on to is page 24, which is 3325. The last paragraph of the page:

"These -- I should say this is now in chapter 2, which is entitled "historical review of NANBH" and the last paragraph on page 24 says:

"These two US studies have given a moderately high estimation of NANB PTH. In actual fact, Hornbrook et al in 1982 ..."

That's the paper we looked at:

"... have indicated that the 'true incidence' NAB PTH, as reported to volunteer blood collection agencies, is around 0.1 to 0.2 cases per thousand units ... thus

when ALT follow-up studies are not performed on transfusion recipients, around one in every 100 hepatitis cases is actually being reported.

"Put in another way, 99 of every 100 hepatitis cases are never brought to the attention of the transfusion centres or are not considered to be hepatitis by practitioners or are not even thought to be serious enough by the patients themselves to warrant medical attention.

"Furthermore, 2.9 per cent of a controlled hospitalised population in the TTV study developed NANB hepatitis, although they had not received any blood or blood products. This suggest that the ALT criteria used for diagnosis may be too low. Nevertheless, these two important studies have proven that, in the USA, a mild form of hepatitis after transfusion is not uncommon, especially if the transfused blood has an abnormal ALT level. No comparable study has been carried out ..."

The reference, doctor, to a mild form of hepatitis, what was that a reference to, can you remember?

A. Obviously, we felt that was -- that the vast majority of these people in the NIH and TTV studies were -- didn't have a severe form of hepatitis. It was just mainly based on a blip in the ALT.

Q. Can you remember whether, in October 1985, you are

likely to have been aware of the evidence, I think mainly from American studies, that a small number of patients with NANBH, who had had liver biopsies had signs of cirrhosis?

A. The trouble with some of these things was that you didn't know what the control population was, as regards biopsies. Obviously, gastroenterologists were interested in a big way, but I certainly was not convinced that there was a sufficient number of people coming through to actually prove that it was definitely to do with non-A non-B Hepatitis, the situation with the cirrhosis, et cetera.

Q. Yes and we have seen, I think, reference to the number of biopsies being in a very small number of patients, but against that, nonetheless, there was some evidence that at least some patients with NANBH had evidence of cirrhosis following liver biopsy. We saw the reference in Mollison, for example, in 1983. My question really was whether, in October 1985, you were aware of that evidence and essentially discounted it, or whether you weren't aware of it at all?

A. I was aware of it but kind of discounted it as far as -- really I was looking to actually identify people with non-A non-B Hepatitis. I wasn't doing any follow-up of these people at all.

Q. It goes back to the purposes of your study. I can quite see, because you weren't following up the clinical course of the disease in patients, why you wouldn't perhaps say too much in your thesis about the likely seriousness of the disease. But equally, one perhaps may have expected to see some discussion of the likely seriousness of the disease, if nothing else by way of background or scene setting?

A. It's a very difficult one to do, because there was a lot of conflicting evidence around: some people said it was very severe and other people said it wasn't. I was unconvinced and I felt that to go down the route of actually discussing that in my PhD was more or less going up a blind alley, as far as I was concerned. It wasn't going to help me with my PhD, it was going to cause more and more problems.

Q. I understand that, just to pause there, we have heard evidence about how there was a growing awareness or acceptance of the potential seriousness of NANBH throughout the 1980s. Was there a point in the 1980s, where you personally thought, well, this is perhaps a more serious disease than we had originally thought?

A. I don't think I actually thought it until the 1990s. I actually came along when Hepatitis C had actually been discovered and we had real tests that actually diagnosed

non-A non-B Hepatitis as being Hepatitis C. That's when I obviously became a bit more aware that gastroenterologists could actually treat these people and obviously prevent, hopefully cirrhosis at some point in the future.

Q. Just before I leave this question of the potential seriousness of the disease, I don't think the word "cirrhosis" appears at all in your thesis. I may have missed it did you I don't think it does.

A. I think it was carefully left out, I think.

Q. I see, thank you.

THE CHAIRMAN: Before leaving this section, Dr Dow, you mentioned that there was no control population to refer to when considering the American data. How would one have constructed a control population for this purpose?

A. For liver biopsies I wouldn't like to be one of the control when one in 1,000 could obviously die through that procedure.

THE CHAIRMAN: You see, that's what I had in mind, that it really perhaps isn't a situation in which the technique of using a control population would have had very much point.

A. No, but my point being that I don't know how many normal healthy individuals being liver biopsied, with how many the pathologists would find something wrong; with them

or their liver.

THE CHAIRMAN: Yes.

MR MACKENZIE: Now, the next page, if I may, doctor, is page 33, which is our page 3336. This is still in chapter 2, "Historical review of NANBH". Under, "Animal model system", the last paragraph on the page, please we see it states:

"Despite NANB hepatitis being relatively mild and often symptomless in humans compared to the other hepatitis viruses, there is a disturbing propensity for it to become chronic, especially in those infected via the parenteral route. On the other hand, sporadic NANB cases tend to resolve naturally."

So at least there is reference there to a disturbing propensity for non-A non-B Hepatitis in humans becoming chronic and by "chronic" I assume you mean chronically elevated, albeit fluctuating ALT levels?

A. Yes, that's correct.

Q. The next page, please, is page 44, which is 3349. Again we are still this chapter 2, "Historical review of NANBH". Under this study you say:

"This project was basically designed to search for a NANB hepatitis serological marker."

So does that take us back to what I think I suggested were the two main purposes of the study:

firstly to look at the prevalence of NANBH in the West of Scotland generally?

A. Really, to actually identify non-A non-B Hepatitis was one of the main purposes of the study.

Q. To actually identify --

A. The post-transfusion non-A non-B was part of that obviously.

Q. When you say to actually identify NANBH, is that actually to identify the virus?

A. That was an aim at one point, I don't think it ever succeeded, obviously.

Q. That would have been nice.

A. That would have been nice but, to be honest, I think we would probably have identified donations with it.

Q. Okay. Then at page 45, the next page, please, we can see several questions were raised at the start of this project. I won't read them out but we can see for ourselves what's set out.

I would like now, please, to go to page 98, which is 3436. We are now in chapter 4, which is entitled, "Non-A non-B in blood donors" and the conclusion of this chapter, we see half way down:

"Conclusion. Whether routine donor ALT or SGPT screening should be introduced in the West of Scotland is still debatable. The cost of such screening would be

extremely high and the benefit appears to be minimal, especially when only a few cases of NANB PTH are reported each year."

Et cetera:

"Although the study on West of Scotland blood donors did identify donors with elevated SGPT levels with evidence of recent viral illnesses, there is no evidence to prove that these units would have been detrimental to any recipient."

What does the second part of that sentence mean:

"There is no evidence to prove that these units would have been detrimental to any recipient"?

A. To satisfy Koch's postulates, you would have had to have allowed these units to be transfused to someone and then follow that person and find the disease in that person: it would be a bit unethical to do that, isn't it?

Q. So what's that saying, that donors with elevated levels, their donations were transfused?

A. Had these donations been transfused, there was no evidence to prove that these units had been detrimental to the recipients.

Q. So these units weren't transfused?

A. What units are you actually talking about? I know there was some units that I did not pick up and capture. I know that. There was about, I think, seven or eight

units that were unable to be obtained at the time we did the study. We didn't, obviously, follow them up fully but we waited for cases to happen and they never happened.

Q. Right. But -- can I take it that there wasn't any follow-up of the recipients of these units?

A. No, we didn't go personally and follow up where the units went to or anything like that.

Q. Okay.

THE CHAIRMAN: You see, if I were to read this as you invite me to read it, as some sort of layman, without specialist knowledge, the expression, "There is no evidence to prove that these units would have been detrimental" might not mean, "We didn't look to see whether there could have been evidence --"

A. Correct, yes. You can only do so much in a working day.

THE CHAIRMAN: I'm aware that one can only do so much in PhD thesis, Dr Dow --

A. Yes.

THE CHAIRMAN: -- but perhaps it might have been more accurate to say that it would not have been possible to determine whether these might have transmitted, since biopsy and other examination would have been unethical following transmission of a risky product, or something along that line?

A. At that time I didn't know it was that risky, we were only taking the further evidence from NIH and TTV studies. That was the problem.

THE CHAIRMAN: Anyway, we shouldn't take this expression too far?

A. I wouldn't go into great depth. I'm not going to change the PhD now.

THE CHAIRMAN: It's probably a bit late --

A. A bit late.

MR MACKENZIE: Thank you. Over the page, please, page 99 and 3437, in the second paragraph we see:

"SGPT/ALT testing has such a high false positive rate and also a high false negative rate, such testing should not be introduced routinely. On the other hand SGPT/ALT testing should be essential in the investigation of any suspected PTH case."

Why should ALT testing be essential in the investigation of any suspected PTH case?

A. At that time that was -- our only way of trying to identify non-A non-B Hepatitis, was actually using the surrogate test actually to investigate the cases. Anti-core would have been included in that anyway.

Q. Thank you. On, please, to page 105, which is 3443, this is now chapter 5, "Transfusion-associated hepatitis". We see under "results" we see:

"BTS notified cases. A total of only 23 cases of PTH non-A non-B have been notified to BTS Law since 1977, table 5.1 ..."

Which we will come to in a moment:

"...One case each in the years 1977 to 1979, three in 1980, five in 1981, three in 1982 and 1983, two in 1984 and four to date in 1985. All cases have clear evidence of clinical and/or biochemical hepatitis and are not merely slight biochemical changes elevated to the status of NANB hepatitis because the patient was transfused at an appropriate time in the past."

All cases have clear evidence of clinical and/or biochemical hepatitis; what's meant by clear evidence?

A. They are either jaundiced or the ALT was sufficiently high that the clinician themselves declared that the person had severe hepatitis.

Q. Yes. If we can, please, then go over the page, we will see table 1. I think these are the 23 cases of post-transfusion non-A non-B notified since 1977 in the West of Scotland. I'm not going to go through it in detail, but we can see a symptoms column, where jaundice appears on a number of occasions. I think 16 of the 23 reported cases were jaundiced. Where hepatitis appears in the column as symptoms, does that mean the patient didn't have jaundice?

A. Yes, I would have said that jaundice was not evident. It would be anicteric as such.
Q. Because if the patient had jaundice, it is likely the clinician would have reported that fact?
A. Correct, yes. We can see there are quite a number there with ALT levels, and I think the lowest ALT level is about 310.
Q. Of course, yes, the ALT, of course, refers to ALT levels, thank you, yes, we can see that it's very helpful. They are all very high, aren't they?
A. As I said in one of my statements that for Hepatitis A and Hepatitis B, they expect thousands. So non-A non-B Hepatitis was comparatively mild compared to Hepatitis A or Hepatitis B.
Q. Even for -- the highest levels are still comparatively lower than the others?
A. The ALT levels I have quoted there are relatively low.
Q. Compared to?
A. Compared to Hep A or Hep B.
Q. I understand. Could we then, please, move on to page 107, which is 3447, we can see that the work carried out under, "Implicated donors of BTS notified cases:

"(a) elevated SGPT levels:

"All archived samples from implicated donors for the

10 cases, from late 1982 to date, were available (apart from those involving Factor VIII or IX concentrates) and none showed raised SGPT levels. Where archive samples were not available, there was no evidence in subsequent donations of any donor with chronic SGPT elevations ..."

We can see what else is said. Then (b):

"HBV markers: Where all archive samples were available from implicated donations in a NANB PTH case. All samples were tested for any evidence of prior HBV exposure. Three cases, in particular, were shown to be associated with donations with HBV markers."

I suppose these findings would perhaps cast some doubt perhaps about the likely effectiveness of ALT as a surrogate screening for NANBH is that the point, in short?

A. I am afraid that's what I used as my evidence that would influence others.

Q. Yes. Over the page please, at page 108 we see:

"NANB in haemophiliacs."

We see the study you carried out into haemophilia patients in the West. You say:

"A total of 457 specimens from 208 haemophiliacs were tested in the period 1982-1984. Table 5.5 shows the results of SGPT tests performed. 72 samples from 49 individuals had levels in excess of 92 SFU/ml. Of these

49 patients, 34 had only one sample with an elevated SGPT level ... 10 individuals had two samples with elevated SGPT values, 4 with three samples and one individual had six elevated SGPT samples over the two-year period."

So it seems to be that the study in haemophilia patients was carried out over a two-year period. Can you remember, doctor, how frequent the testing was?

A. It was just as and when we had a sample from a haemophiliac.

Q. So as and when the haemophilia patient turned up at a clinic perhaps?

A. Yes.

Q. Okay. The next page please, is page 112, which is 3461. Again we are still in chapter 5, "Transfusion-associated hepatitis". Under "discussion" in the second paragraph we see:

"In contrast to the USA, only 23 cases have occurred in this region in the past 8 years ... "

When you say "occurred" does that mean reported?

A. Reported, yes.

Q. "... a period when over 800,000 units of blood have been transfused. It might be assumed that these 23 cases are only the tip of an iceberg and that many similar cases have not come to our attention. Indeed six ... of the

NANB PTH cases were notified only as a result of this study.

"However, within the study on haemophiliacs and RDU patients, the few who became jaundiced were actually reported to the BTS. As it would appear that in these higher risk groups the majority of NANB PTH cases are reported, clinical NANB PTH may not be a serious problem within this region."

Pausing there, it's stated:

"It would appear that, in these higher risk groups, the majority of NANB PTH cases are reported perhaps comes back to the question of the follow-up of patients and how regular ALT testing is, as to how confident one can be in the results."

A. If they weren't a member of the high risk groups like haemophiliacs or renal dialysis unit patients, they wouldn't be checked at all for ALT, unless the person became obviously really ill and attended their doctor, and only if their doctor then requested an ALT.

Q. I suppose, as well, with haemophilia patients, it may be that some or many or most of these haemophilia patients had NANBH previously. I suppose we don't then know --

A. Yes, looking back now, yes, we now know that.

Q. A difficult picture perhaps?

THE CHAIRMAN: Mr Mackenzie, are you coming to a suitable

stopping point?
MR MACKENZIE: Sir, let me see. I have another six pages of the thesis and then Dr Dow's special report. I don't intend taking more than a minute on. So I could probably finish in by five past 11 and that would be me completely finished Dr Dow. I'm not sure if that would be possible or not.
THE CHAIRMAN:
Thank you.
MR MACKENZIE: You do then carry on to say that:
"Alternatively, there may be a large iceberg of very mild subclinical cases which are never presented to GPs or clinicians and hence are never reported."
It did strike me, doctor that, from looking at least at Mollison in the 1983 edition, that perhaps all that needed to be said was that only about one fifth of post-transfusion NANBH cases are icteric?
A. I don't know where the fifth came from.
Q. It came from American studies which I think were reporting --
A. We were trying to look at non-A non-B Hepatitis in the West of Scotland, not the United States of America.
Q. So you are seeking to look at the matter afresh --
A. Yes.
Q. -- in the West of Scotland?

A. Correct.
Q. Yes. So one would really perhaps need to have that wider knowledge of the literature if one were perhaps to -- one perhaps should read your thesis along with that wider literature, perhaps, to get a more informed view of the knowledge of non-A non-B Hepatitis?
A. I would have said that would be required, yes.
Q. I understand that. The next page, please, is page 117. This is again still in chapter 5, "Transfusion-associated hepatitis". We can see the final paragraph, what's said there. In the final sentence you say:

"Again, as with the donors with HBV antibodies, both --"

I should just read the paragraph before that, the sentence before that:

"Of the Scottish cases presented, only two may have been prevented had this policy of ALT screening been in force here."

Then it goes on:

"Again, as with the donors with HBC antibodies, both donors have donated since with raised SGPT levels and their blood has apparently not caused any adverse reactions in the patients transfused."

How did you know that?

A. The way this was done was that I had -- I kept an eye on the individuals who were involved in any of these cases. So all the donors that were involved in these cases, I had a list of their donor registration numbers.

I would go into the West of Scotland computer database and actually challenge that as to had these individuals donated; what was their most recent donation? Having obtained their most recent donation, I then went and got an archive out from the archive, the stored archive and then tested it for ALT. But obviously, by that time, the donation would have been used anyway.

Q. Yes, but am I right in thinking there was no follow-up of the recipients?

A. The recipients would not have been followed up at that time, no. Talking about -- obviously there are over 100 donations involved in these 23 cases. So to actually declare that every single donor involved in these cases was actually infective would obviously have been wrong because they weren't all infective. Some of these cases were involving maybe 20-odd donations.

Q. I suppose when, at the bottom of page 117 you say that:

"Their blood has apparently not caused any adverse reactions in the patients transfused".

The general reader may imply from that that there

has been some follow-up of the particular patients?

A. No, there was no follow-up of the patients, no.

Q. Thank you. Over the page, please, just to finish this part off at page 118, and we can read for ourselves what you say there. I think in short your position is that the:

"Present UK policies of accepting donors with raised SGPT levels ... and those with HBV antibodies would appear to be correct."

Then go on to page 149, please. I'm not going to dwell on the final few paragraphs, I think we have got the flavour of the thesis. But page 149 we can see what's said about NANB PTH in the West of Scotland and we can read all of that for ourselves. Then, over the page at page 150, please, we can see the paragraph commencing:

"Overall NANB PTH cases are ..."

We can continue reading down until seven lines from the bottom. We see a statement:

"Nowadays there are around 3 NANB PTH cases per annum ..."

I take it that again a reference to reported case per annum?

A. Yes, correct.

Q. ... from possibly 18 non-A non-B infectious blood

donations, ie 18/100,000 or 0.18 units per thousand transfused."

The other thing which occurred to me on this Dr Dow, was that firstly I think this is the figure at 0.18 units per thousand transfused. We see in a memo from Dr Forrester in the SHHD, another occasion when he talks of a 0.018 per cent incidence. But the other matter which occurred to me was that that incidence of 0.018 per cent, the 0.18 units per thousand, is about one fifth of the what was discovered to be the true incidence, ie roughly 0.09 per cent, when HCV screening started. This did bring me back to Mollison in 1983, suggesting that about one fifth of icteric or reported cases of the disease are actually -- I'm sorry, only about one fifth of cases of non-A non-B post-transfusion are reported.

A. Yes, this has obviously been taken from extrapolating from Hepatitis B, this fifth. As I say here -- because obviously we had been doing Hepatitis B surface antigen screening from 1970 but, before that actually happened, there was some, like, ten cases of Hep B post-transfusion hepatitis per annum. We realised there were about six Hep B positive donations in that time, that's where that fifth comes from. It's from the West of Scotland's own experience of Hepatitis B and we are

extrapolating Hepatitis B into non-A non-B sphere, the one fifth.

Q. Yes, the figure of one fifth that I used, though comes --

A. From Mollison. I don't know where Mollison got that figure from.

Q. From, I think, quite a lot of American literature but it was just an observation.

A. Yes.

Q. Just to complete the thesis -- I won't read anything out but if we can go to page 152 we can see "Characteristics of NANB agents". We can read that for ourselves and then over the page, the last page, page 153, we can see what is set out there as well.

Now, Dr Dow, that's the end of your thesis. The final document I will refer to but not go to is -- you did also for completeness provide a special report, for the regional transfusion directors in May 1986 on the question of surrogate tests for non-A non-B Hepatitis, the reference being [SNF0011109].

I think in short, based on your research work, your opinion was that surrogate testing should not be introduced. Is that correct?

A. That's basically -- I came to that conclusion, yes.

Q. We know that, in 1987, the SNBTS director,s in any

event, decided to recommend that such testing be introduced?

A. It was really a discussion document that was required.

Q. Thank you, Dr Dow, I have no further questions.

A. Thank you.

THE CHAIRMAN: We are going it adjourn at that point. Is there an arrangement about follow-on?

MR MACKENZIE: There is not sir.

THE CHAIRMAN: Would you like to consider that?

MR MACKENZIE: Yes.

(11.10 am)

(Short break)

(11.32 am)

MR MACKENZIE: There was one final question I should have put to Dr Dow. It was the question I indicated at the beginning, namely whether the general medical reader of your thesis was likely to get a misleading impression, firstly of the likely prevalence of post-transfusion non-A non-B Hepatitis in Scotland and secondly, the potential seriousness of the disease. Have you any comment on that suggestion?

A. The comment being that I probably would agree that they could get a misleading impression that non-A non-B Hepatitis was obviously milder, in my PhD, than what it actually is and that -- what was the other part there?

Q. A misleading impression of firstly the likely prevalence of post-transfusion non-A non-B.
A. Obviously, the prevalence at the time was unknown. The prevalence that was found within the PhD was based on reported cases. But reading through it, you would actually see that I said several times that it was the tip of the iceberg.
Q. Perhaps another way of putting it is this, that if one, in the middle of the 1980s, wished to get a more informed view of post-transfusion NANBH, then one shouldn't only read your thesis, one should undertake some wider reading as well?
A. I would have said that that would be required if they were going to make an informed judgment based on the non-A non-B Hepatitis, not just based on my PhD but you would actually have to look at some other literature as well.
Q. Thank you very much.
THE CHAIRMAN: One possible view of a wider range of evidence than yours is that your thesis was given very counsellor weight by those responsible for formulating policy in Scotland. Would that have been a surprise to you?
A. It was a surprise. While I (inaudible) it actually going through to Dr Forrester, I was actually very

surprised that it had gone to that sort of level. I didn't realise it was being obviously looked at by such a person. So I was obviously quite surprised about that.

THE CHAIRMAN: Without devaluing your work in any way, you would have expected your PhD thesis to be the beginning of your study of a subject, rather than the culmination of it in a sense?

A. It was the beginning of my study.

THE CHAIRMAN: Yes. You would be surprised to be held to the views that you entertained at that time, ten years later.

A. Yes, I didn't think I would be here 25 years on either. But to be fair, though, it was probably the only study done on Scottish patients et cetera, and it probably did give a grass roots level of what was actually happening. It may have given the wrong impression but it was what we actually saw at the time and it was mild in comparison to Hepatitis A and Hepatitis B which really are very severe diseases in their acute form.

THE CHAIRMAN: I'm not trying to put it down in any way, Dr Dow but just to have a realistic view of what the stage is likely to be in the development of a researcher's thought process and investigations at the end of his PhD thesis. I would be surprised if that

were it, considering how many post-docs I'm aware of in another institution who follow on.

Mr Di Rollo?

MR DI ROLLO: It is Mr Dawson.

THE CHAIRMAN: Mr Dawson.

Questions by MR DAWSON

MR DAWSON: Thank you, sir. Dr Dow, I have a few questions for you on the C2 topic. Could we have up first of all your CV which is document [PEN0130421] and I'm looking in particular at page number PEN0130432.

It's 0432, please.

This is obviously a list of committees that you attended. I was particularly interested in the second one there, where you point out that you deputised for Dr Mitchell at the November 1986 meeting of the UK working party on transfusion-associated hepatitis, held at the DHSS. That's a meeting that we have had occasion to ask some questions on and look into in this section. Do you remember anything about what happened at that meeting, Dr Dow?

A. Yes, I was asked to go by Dr Mitchell, to attend it because he couldn't attend it for some reason. All I can remember was it was held in London, just along from Euston Station in a great big tall tower block. Dr Gunson was at it, I remember that and a few other

people who I did know at the time; Professor Tedder, I think was there. I thought I had the minutes of this meeting. I have been looking for the minutes of this meeting but I don't know where they are.

Q. Presumably you had been asked to deputise for Dr Mitchell because of your interest and experience in the area of surrogate testing?

A. It was really because I think there was going to be some discussion regarding ALT testing at that meeting.

Q. Indeed. Could I just --

A. I think there was discussion at it, but I was more or less told that I couldn't offer anything because I want in a situation to be able to offer anything anyway.

Q. You didn't play an active role in the discussions?

A. I was really there as a passive observer, but I was asked a few questions. I'm pretty sure there was a representation from the Scottish Home and Health Department there. I'm not sure if that was Dr Forrester or not.

Q. I'm just take to you a document to see if it perhaps refreshes your memory. The document is page 3 of [PEN0171542]. This is a memo that was written by Dr Forrester and circulated amongst various people within SHHD. You will see at the top there, it's entitled, "UK Working Party on Transfusion-associated Hepatitis". You will see from

the first few lines there that it's talking about, I think the meeting that you attended. Is that right?

A. It must have been that one, if that was the case.

Q. Can I just skip over to the second page, please, 1555. This is, obviously, Dr Forrester's note, as you can see there, from 1 December, of what happened at the meeting. In paragraph 5 he said:

"There was some discussion of the cost of screening all donations (perhaps £8 million). I asked the chairman whether he would advise screening if it were free of cost. He said no.

"The position explicitly reached at the meeting is to recommend research of no great significance or scientific interest because the prospect of research would serve to counter pressure from, for example, haemophiliacs and Haemophilia Directors to embark on an indirect and largely ineffective form of screening, which would also lose a certain amount of perfectly harmless blood.

"Figures were produced at the meeting for the total number of non-A non-B Hepatitis cases encountered annually among haemophiliacs A and B and patients with von Willebrand's disease. The average UK total per year is 35 over the past six years and 1985 saw a sharp decline to 11 in all. A proportion of these cases among

haemophiliacs and similar patients are asymptomatic."

Did you remember at all there being any discussion about the pros and cons of surrogate testing at the meeting?

A. There probably was. I prefer to look at the minute of that meeting, if that's available.

Q. That's the difficulty. I don't think we have access to the minutes, so we are just trying to reconstruct it. That's the reason why I'm asking you these questions Dr Dow.

A. I must have been given the minutes at some point, because I attended the meeting. I would have expected to see the minute.

Q. Do you remember, for example, the reference there to the position being explicitly reached at the meeting; to recommend research of no great significance or scientific interest because of what appeared to be wider political considerations. Do you remember that --

A. Not really, no.

Q. -- decision being reached?

A. To be honest I have read this because I asked for this when the documents came out in the court book. I asked for this particular document, thinking that this may well have been the meeting I had been down to in the Department of Health. I didn't think it was this one

after seeing this because you thought that doesn't ring a bell -- any of it.

Q. Is your position you don't remember what was discussed or is your position you don't think that was the conclusion of the meeting?

A. To be honest I don't what was discussed and I would prefer the minute.

Q. I understand. Does it seem to you, just looking at it now, that the position being outlined there -- which was apparently explicitly reached at the meeting -- to recommend research of no great significance or scientific interest is a slightly unusual conclusion to be reached by, effectively, men of science?

A. This is just completely, you know, when I read that, I thought that wasn't the meeting I was at.

Q. So in answer to my question, it does seem to you quite unusual that such a decision would be reached at a meeting like that?

A. I don't think they put it down in black and white like that, if it was.

Q. Shall I just ask you now, looking at the reference in the first paragraph there to what appears to be a discussion between Dr Forrester and the chairman who, as you will recall, was Dr Gunson and it says there that --

A. I don't know if Dr Gunson was the chairman. That's what I don't know. I just know he was there.
Q. Do you take it from me that Dr Gunson was the chairman?
A. Okay.
Q. It says there, "I asked the chairman if he would advise screening if it were free of cost, he said no."

It doesn't look like that's something you necessarily would have been privy to, but what's your reaction to that suggestion about surrogate testing?
A. Surprise.
Q. Okay. Thank you very much. Could I just move on to a slightly different area, more connected with the questions that you have been answering this morning. Could I ask you to have a look at document number [LIT0010346]. I'm sure that you recognise this, Dr Dow. This is a Lancet letter, dated 13 June 1987 as we can see in the top right hand corner.

It's a letter from yourself, Dr Mitchell and Dr Follett entitled, "Non-A non-B Hepatitis surrogate testing of blood donations". Presumably this is one that you are familiar with, since you are the author?
A. I'm the author, yes.
Q. You refer in this document to a previous letter, of 18 April, from Dr Anderson. I think broadly your position was that your research had generally agreed

with what Dr Anderson was saying. Is that right?

A. I think so, yes.

Q. You refer to the US studies and some of the conclusion that we have been looking at this morning from your own research. You conclude in the final paragraph that:

"It would it be prudent to do a UK study to assess the real incidence of acute post-transfusion non-A non-B Hepatitis and to assess the proportion of those chronically affected before considering following the American surrogate testing policy."

You were asked earlier about the extent to which you felt that general conclusions about surrogate testing could be drawn from your research. But do I take it, from the position being adopted in this letter, that your view at this time was that you required a bigger study to be able to draw such general conclusions?

A. I think what we were asking for was a bigger study to actually see if there were actual cases that we were obviously not seeing as such.

Q. Right. But in order to be able to -- it's headed up, "Surrogate testing".

A. Correct, yes.

Q. Obviously you are suggesting there that this would be something that would be required before that step should be taken?

A. Surrogate testing had obviously just started in America at that time. Obviously we were under pressure in the UK to follow suit.

Q. Okay. Could we have a look at [LIT0010328], please? This is another Lancet article from the following month. It's the July 4 1987. You will see in the bottom right-hand corner the letter is entitled, "Testing blood donors for non-A non-B Hepatitis: irrational perhaps but inescapable."

If we skip over the page in the top right-hand corner, who the authors of this letter were. These were Dr McClelland, Cash, Urbaniak et cetera, et cetera.

A. It's all SNBTS directors.

Q. Yes, indeed. I think it would be fair to say that this letter was written in the aftermath of the recommendation that surrogate testing be introduced that you were asked about earlier?

A. Yes.

Q. You said earlier that the advice that you had given to the SNBTS directors in your special report was ignored by them. Could I just take you to the opening paragraph of this letter, which is on the previous page, please? In the opening paragraph these doctors point out:

"In three letters in the Lancet Dr Anderson, Dr Gillon, Dr Dow and their colleagues point out

weaknesses in the arguments which have been used to support the introduction of blood donor screening to reduce transfusion-transmitted non-A non-B Hepatitis, using ALT and Hepatitis B core antibody as surrogate markers.

"All thee letters suggest that the UK transfusion services should not start donor screening until prospective controlled studies have been done in the UK to find out how many cases of post-transfusion hepatitis would be prevented. No large study to answer this critical question has yet been presented and we agree that the size of the benefit to be gained from surrogate testing cannot be accurately established without such a study. However, the time for this study has already passed. Starting now will give us an answer in 3-4 years -- and that is probably 3 to 4 years too late."

Then there is a list of the various factors relied upon here. Would it be fair to say that these doctors, the SNBTS directors, had not ignored your position but considered it and taken a different view?

A. Yes.

Q. Okay. I wanted to ask you in particular about Dr Mitchell's position because Dr Mitchell was a signatory to your letter and also to this one. Were

you aware of the circumstances in which that apparently slightly unusual situation came about?

A. That was up to Dr Mitchell and I think he has already described that to you.

Q. Was it something that he had discussed with you at that time?

A. No, was up to him.

Q. Did you discuss it with him at the time?

A. No, I did not discuss it with him.

Q. Thank you. Could I just ask you a couple of questions about a couple of matters which are in your report, please? The report is [PEN0171925]. I'm looking at the second page of the report, which is 1926, please. This was obviously a passage that we went through earlier. I wanted to ask you about the passage at the top there. This was in response to the question about the larger prospective study, which I think you said you weren't aware of at the time, but obviously you have become aware of during the course of your consideration of materials for the Inquiry.

I just wanted to ask you if you could expand upon the final two sentences. First of all you say:

"Even if such an application had been made, I would have expected it to have been declined based mainly on the cost element and other factors described below."

I just wonder if you could expand a bit on why it was that you thought it would have been declined and whether that related just to the time period when the application was made or it was your view throughout the 1980s, that that would be --

A. No, I was talking about the early 1980s there because the question was based on the early 1980s.

Q. Yes.

A. Obviously, as I described earlier, to have actually more or less redone the NIH or TTV study would have cost in the region of probably £1 million to have just done it for Scotland. It would have required a lot of collaboration from clinical colleagues, and obviously a lot of medics, to actually follow up the patients. So really the cost element was going to be very, very huge. When the health service obviously could provide a lot of good healthcare for that sort of money.

Q. Do I take this that your view is, no matter how good a case one put for the potential benefits of such --

A. You have got to step back and look at what the costs are and see what you can do with the money. If I was on a committee looking at that -- I wasn't on any committee, but if I had been on one of these committees I would have declined it.

Q. So you think cost would have been the deciding factor?

A. Yes.
Q. Thank you.
So I just wanted to ask you a similar question about the final sentence:
"Even if a large-scale prospective study had been carried out in the UK, I doubt whether anything novel would have surfaced."
Does that relate, again, to the early 1980s or does that relate to a study having been done at any time during the 1980s?
A. Early 1980s.
Q. Early 1980s. Is it your position that that is the likely outcome -- that would have been the likely outcome of a study done at any time during the 1980s, or did your view move on?
A. I would have said it was probably the same throughout the 1908s.
Q. I'm trying to reconcile that with the position you adopted in The Lancet letter, which was that a study should be carried out?
A. That was mainly to actually identify the number of actual cases.
Q. Right.
A. That's what we would have been after at that point.
Q. I see. What your contemplating here is something

different from that; is that right?

A. I'm looking at it in hindsight at this point.

Q. So your recommendation in 1986 was that a prospective study should be done, but your position now is you do not necessarily think that that study would have showed anything novel?

A. I don't think so, no.

Q. Okay, thank you very much. Could I just ask you about one other area which you cover in your report? This is on page 5 of [PEN0171925]. This is in response to the question number 5 that was posed to you by the Inquiry and I just wanted to ask you in particular about the passage in -- under letter A. You say there:

"As ALT testing was (and still is) based on excluding the upper 3 per cent of individuals deemed to be above the upper level of normal then 3 per cent of blood donations would have been excluded. The question would have arisen as to whether these donors would have been permanently excluded for a minor elevation."

I just wanted to try and understand that a bit more fully. Is what you are saying there that there would have been an issue as to whether or not someone who showed positive on one ALT test would have been permanently excluded as a donor or temporarily excluded as a donor?

A. That would have had to have been discussed and worked out -- obviously taken on ALT testing, what threshold would have actually gone and actually counselled the donor. If we went and used the cut-off at that upper limit of normal, obviously 3 per cent above that would have been deemed to be unusable. We might not have gone back to the donor and actually told them that and just allowed them to donate again.

Q. It might be slightly clearer if I take you to a passage in the PhD thesis, which seems to be on to this topic. It's [LIT0013300] at 3466, please.

I think you raise a similar issue at the top there of page 98. You say:

"This also raises the issue of whether donors with raised ALT levels be permanently deferred or not. From the studies on West of Scotland donors, no deferrals were made and donors were not informed of the result. Only three donors with subsequent donations continued to have elevated SGPT levels, suggesting that raised levels are normally transient but a few, particularly drug abusers, appear to be chronic (table 4.5)."

Further down you draw a conclusion which is:

"This data would provide a strong argument against permanent donor deferral, as practised by the GNYBP."

A. That's Greater New York Blood Programme.

Q. "Except in those with apparent chronic elevations."

What I'm interested in exploring is whether -- what your view would have been about whether someone who had a positive ALT test should be permanently excluded as a donor, or would it only be a temporary exclusion?

A. I wouldn't call it a positive ALT, what we are talking about is an elevated ALT or a grossly elevated ALT. My view would have been that a grossly elevated ALT -- I would have obviously tried to identify what the reason was.

Q. Right.

A. That person needed clinical help but I wasn't in that situation -- to be able to follow up the donors at that point.

Q. Okay. This certainly seems to be an important issue that one would have had to consider?

A. We would have discussed that, had we taken on ALT testing.

Q. Absolutely. The last question I want to ask you is: are you aware of whether there was any discussion about how this issue would be dealt with if surrogate testing were introduced within SNBTS?

A. I wasn't aware because I wasn't medical. I'm a scientist. I'm there to do the tests et cetera.

Q. It does seem, though, that you might well have been

someone who could have been involved in that and given a useful view.

A. I was not a medic. It would really have been medics would have to treat these people and they would have had to have the manpower to do it.

Q. They didn't consult with you about this issue. Is that right?

A. We didn't discuss this issue.

Q. You are not aware of there being any decision taken within SNBTS on this issue?

A. There could well have been decisions made, but I wouldn't be party to them.

Q. Right. So you are not aware of any such decision having been taken?

A. That would have been done at the medical level.

MR DAWSON: Thank you very much indeed, Dr Dow, thank you sir.

THE CHAIRMAN: Mr Anderson?

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

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: I have no questions, thank you.

THE CHAIRMAN: Is there any follow-up?

MR MACKENZIE: I have no further questions for Dr Dow. Ms Dunlop will now conduct the examination of C4.

THE CHAIRMAN: I did appreciate Dr Dow wasn't being let out.

Ms Dunlop?

Questions by MS DUNLOP

MS DUNLOP: Thank you, sir. Hello again Dr Dow. As this is a new topic, it may assist if I make some introductory remarks about my approach to it.

THE CHAIRMAN: Certainly.

MS DUNLOP: The backdrop to the consideration of this topic is obviously the debate about surrogate testing, which Mr Mackenzie has just been exploring. I hope that that will provide quite a neat context for our examination of the period 1989 to 1991. We have, of course, already considered a screening-related topic, and that was our topic B4 about the screening of donated blood for HIV, which we looked at in September.

I'm hoping that some of the science that was explained to us at that time will be material on which we can draw when we hear terms like "ELISA" or "RIA".

Just to remind ourselves of what we discovered when we look the at HIV screening in September, that tests for the virus were available in the first half of 1985, that evaluation of the tests was undertaken and that screening was introduced in October 1985.

The analogous timeframe for topic C4 is really set out in the wording of the topic itself, so topic C4 concerns:

"The interval between the availability of tests for the Hepatitis C virus in 1989 and the introduction of screening of donated blood for the virus in the United Kingdom in September 1991".

In evidence relevant to topic C4 there are perhaps two principal streams, which I would characterise, no doubt somewhat roughly, as the science and the decision-making. The science plainly concerns the nature of the tests that were available, their performance and the studies which were made of that.

The decision-making covers principally meetings of two committees: the ACVSB, The Advisory Committee on the Virological Safety of Blood, and the ACTTD, The Advisory Committee on Transfusion-transmitted Diseases. Still within the context of the decision-making, plainly it's relevant to try to explore what it was that was regarded as necessary or what were the necessary steps that apparently had to be in place before testing could be begun.

Most of the factual material underlying this topic is contained in the preliminary report between pages 272 and 320. It's, I think a story with a beginning, a middle and an end, but I'm not planning at the moment to try to sketch out where those stop and start.

Perhaps the only other relevant point to mention, at

this stage, is that as far as the end or the last part of the story is concerned, we have extended the narrative in the preliminary report to refer to some additional material which we didn't have when the preliminary report was published.

So, with those introductory remarks, I should turn now to ask Dr Dow to have a look at the statement which he has provided on topic C4 and that is [PEN0171915]. Dr Dow, a similar sort of approach was followed here, in that a standard schedule of questions was prepared and you, among other people, received that set of questions and you were asked really just to answer the ones you could and you have done that and this is the result.

I thought it would be useful to begin with some material on the discovery of the virus. Can we look then, please, in that connection at [PEN0160290]? I should say, sir, that there are two documents from May 1988. There is a Chiron news release and there is an article from Nature, which we are going to look at in a moment. In the preliminary report it's possibly not entirely clear which is which, but this is the Chiron news release, which is dated 10 May 1988. We can see for ourselves what was said.

First of all, it's an immediate release -- I think it's explained that, because the disclosure had been

made on 9 May at a conference, it was thought proper not to delay wider publicity of the discovery so this news release was issued the following day.

We can see a couple of contacts at Chiron, Ginger Rosenberg and Larry Kurtz and then the headline:

"Chiron clones non-A non-B Hepatitis virus which may allow screening for previously undetectable disease."

Just to read it perhaps for ourselves, mention of the fact that the virus was long sought. Perhaps interesting to not that they say:

"It's a long sought blood borne hepatitis non-A non-B virus" rather than "the long sought". So no doubt correctly they weren't claiming that they had explained 100 per cent of the unexplained cases.

A. Yes.

Q. They also say that they had developed a prototype immuno-assay that may lead to a screening test, again perhaps slightly tentative: it may lead to a screening test and then they explain how the research has been carried out. It has been a joint venture and that the immuno-diagnostic products which result, are going to be marketed by Ortho diagnostic systems, which is a subsidiary of Johnson and Johnson, a big American pharmaceutical company, Johnson and Johnson?

A. Very big, yes.

Q. Then a bit of timing is given, that this research has been going on for more than 15 years. Work on a vaccine can begin. No vaccine yet, Dr Dow?
A. Definitely not, no.
Q. Over on to the next page, if we could, please.
A. I think to be fair, Chiron, up to that point, had been like a charity in a way. What they did up until that point. From that point they became a big conglomerate that very cleverly more or less patented the Hepatitis C virus and raked in a lot of money from it.
Q. Right. If we look at the second page, just a little bit of explanation about the background on other major types of hepatitis, different from Hepatitis A and Hepatitis B. Then a bit about the symptoms, including the statement at the end of the second paragraph that:

"In the chronic form, infected patients at high frequency developed chronic liver disease including cirrhosis."

What's actually meant by "high frequency".
A. A high number of them. Again this is marketing jargon. Really this is a marketing thing from Chiron. To be honest, it's not scientifically sound.
Q. Let's just leave it at that then. Then some figures for the United States, including a suggestion that some 50 per cent of those infected developed chronic

hepatitis and 20 per cent of those, or 30,000 people each year, eventually developed cirrhosis of the liver. Then screening for Hepatitis B. Then a mention of surrogate testing:

"In 1987, blood banks began screening to eliminate a portion of non-A non-B infected blood using two tests that substitute for actual identification of the virus. The first test screens for Hepatitis B anti-core antibodies to identify people at higher risk.

The second, called ALT, indicates liver damage. This surrogate testing has reduced the incidence of post-transfusion hepatitis non-A non-B by 40 to 60 per cent."

Then a quote from the president/chief executive officer at Chiron. Another mention of vaccine and then on to the next page, please. Slightly harder information about another aspect of the discovery, Chiron estimates that the hepatitis non-A non-B market in the US is approximately $85 million annually."

Then mention of the likelihood that blood banks will be able to apply a relatively simply assay procedure using a plate coated with the virus protein. That would be a solid phase in the jargon, would it?

A. Yes, any -- the plate would be the solid phase, yes.

Q. Yes.

"Plate coated with the virus proteins are screened for blood infected with hepatitis non-A non-B virus. Antibodies from the infected blood bind to the plate, which is then rinsed. If the antibodies are present a second coating of indicator antibodies will signal a colour."

Then a bit of more detailed explanation of the science. Then at the bottom of the page:

"Houghton, the project leader presented the research result at a scientific seminar on May 9 at the University of California, San Francisco. The process of disclosure involved screening millions of clones to find a single viral clone."

Dr Dow, both you and Professor Thomas have at least attempted to explain to us already the science behind the cloning, as it were. Obviously, we went into that with quite a bit of detail with Professor Thomas and, in case anyone wants to refresh their memory, that evidence is in the transcript for 11 October.

Can we go on to the next page, please? Don't worry, I'm not going to ask you to give another explanation of it. I think we will quit while we are ahead, if we are.

And so on. Then we note and recognise the paragraph at the bottom of that page, that:

"Currently, cases of blood-borne hepatitis non-A

non-B are diagnosed by exclusion."

I take it you remember the announcement?

A. I have never seen this before, to be honest.

I obviously saw the thing in Nature.

Q. Okay. Let's look at that. That's [SGH0028036]. Really the same information, but published in Nature on 19 May 1988.

A. Yes, more a sort of newspaper at that point, Nature, this particular article anyway. It's mainly done by a journalist and it's written in the same format as what you saw with the Chiron news release.

Q. Do you think this was your first awareness of the discovery?

A. It probably wasn't the first time I was aware that Chiron had allegedly, you know, discovered it. I had to wait until the first generation test came, about a year later before I could actually prove to myself that they had actually done it.

Q. Right. So any relief or enthusiasm you might have felt at this news would be provisional because you would be waiting to see the detail?

A. At this point we were heavily into HIV screening. We were more concerned with that than we were non-A non-B, which had been put on the back burner.

Q. Right. Sir, I think the missing word, which is about

eight lines down is "partially":

"Chiron had announced --

A. Responsible for a large proportion of cases.

Q. I think where it says:

"Chiron had announced that its researchers had isolated and partially characterised the virus responsible for ... The commercial prize is the sale of blood screening diagnostic tests in the near term and of vaccines in the future."

Much of the information in this article has plainly been drawn from the news release.

A. Yes, that's right.

Q. Yes. Interesting in the third column, the right-hand column, that the journalist has plumped for the figure right in the middle of the range of the reduction that surrogate testing was said to have effected in the United States. In the news release it was said to have reduced non-A non-B Hepatitis by 40 to 60 per cent. The journalist, no doubt legitimately, has said it has reduced it by a half.

A. Hm-mm.

Q. And so on. Can we go back to Dr Dow's statement now, please, and look at your schedule of questions. Paragraph 1 is not so much a question as the imparting of some information. We said that we now had the

correspondence which is referred to in paragraph 9.93 of the preliminary report. It would be useful, I think, to look at that correspondence, showing, as it does, a certain swiftness in attempting to find out more about the discovery.

Can we look firstly at [SNB0083584], please? Here we have Professor Cash writing on 5 July 1988 to -- I assume that is Ginger Rosenberg, as mentioned on the news release, Ginger Rosenberg in California.

He is asking for some kits for evaluation purposes. He is also writing to Ortho. Can we look at [SNB0083585]? Just possibly correspondence sent out just as Professor Cash goes away, holiday or conference or something, because we can see these letters were dictated and signed in his absence. But he has also fired off a letter to Dr Alan Follett at Ortho in High Wickham, seeking confirmation that Ortho will be marketing the recently announced development of Chiron, a kit to detect NANB antibody.

Dr Alan Follett, is he a relation of Dr Eddie Follett?

A. No, no relation at all.

Q. I thought we would clarify that.

Dr Cash is also looking for a time schedule. Can we go next, please, to [SNB0083586]? Here is Alan Follett

responding, and he is confirming that:

"Ortho do have an agreement with Chiron to develop and market the product but I do not know precisely when this product will be available."

The next sentence has been underlined:

"The best, of course, I have been able to obtain is that the product may be available towards the end of 1989."

So quite a gap actually between --

A. These things do take a time.

Q. Yes.

A. The thing is that, obviously, when Ortho isolated their clone, they developed a radio immuno-assay in house.

Q. Chiron?

A. Chiron did, and they did a lot of work on that radioimmunoassay and they reported that, obviously, in various papers in 1989 but they never marketed that radioimmunoassay. They've obviously developed it into an enzyme-linked immuno-assay that Ortho marketed initially, and then Abbott came along behind them and got a licence using the same agents, producing the same thing, but it took a long time. 12 months to actually develop an assay is quite a long time but, to be honest, it's standard nowadays; it takes that sort of time nowadays. In fact it probably takes longer nowadays to

actually develop something into a useable assay that can be launched commercially.

Q. You have mentioned the publicity in 1989 and that's indeed what we are going to look at next. Can we look firstly, please, at [LIT0010629]? This is from the journal "Science".

A. Yes, this is probably the first real report that is worthwhile looking at, scientifically.

Q. Yes. 21 April 1989. It's an article entitled, "Isolation of a cDNA clone derived from a blood-borne non-A non-B viral hepatitis genome."

Do you remember reading this at the time?

A. Yes.

Q. We can see in particular the name of Michael Houghton there?

A. He was the chief -- Lacy Overby was on it as well. We had had a good relationship with Lacy Overby when he worked with Abbott Diagnostics. He moved to Chiron when Chiron was this charity-type organisation, that were involved in doing a lot of things for the common good of man at that point.

Q. Right. It turned out to be a good move then?

A. For him it was a good move, yes.

Q. Yes. This is a fairly technical article. In fact there is no fairly about it, it's a very technical article,

explaining the process which had led to the discovery of a cDNA clone. The first clone, as we know from previous evidence, was labelled, "511".

A. That's right, yes.

Q. Yes. I think we will go on to look in a bit more detail, though still superficially, at some of the genetics of that.

The following article in Science is to do with the Chiron assay and we can look at that too. It's [PEN0172764], that edition of Science at their page 362, an even longer list of contributors, including Harvey alter?

A. Most of the contributors there are people who are widely acknowledged to experts on hepatitis in the United States of America.

Q. Right.

A. We can see Miriam Alter there, as well as Harvey Alter, Bob Purcell, Dienstag, CE Stevens, Bonino, a whole lot of people there.

Q. Colombo's name we have seen before as well.

A. Colombo, I think, from Italy, Lacy Overby again, and Dan Bradley and Mike Houghton finishing off. Like a rugby team.

Q. There probably are about 15. I haven't counted.

Perhaps worth just noting in passing some of the

comments in this article. In fact, before we do, we will just look at the end because it shows us that this is hard work, the use of these kind of assays.

Can we look at the last page, please? Here we are. Can we blow that up? Thank you. It's obviously an attempt pictorially to represent some of the difficulties working in this area. That's you toiling away at your bench, is it?

A. It probably was, yes. I recognise the teeshirt.

Q. Can we go back to the first page, please? If we look in the middle column, we can see the first full paragraph there, which begins with the word "three". So:

"Three overlapping clones were isolated by means of the cDNA in HCV clone 5-1-1 ..."

So I suppose in lay language what they did was from that very first clone they were able to move a little bit further alone the genome?

A. That's right, yes.

Q. Is that reasonable?

A. Hm-mm.

Q. Right. So finding a slightly longer strip, if you like, of the genome?

A. That's right.

Q. And it says:

"The clones have one common open reading frame,

extending throughout them that encodes part of a viral antigen associated with NANBH."

Perhaps we can take most of this as read, but note from the paragraph that goes on up to the top of the third column that:

"A polypeptide, C100-3, containing 363 viral immunoassays was synthesised at high levels in recombinant yeast."

Then:

"C100-3 was used to coat the wells of microtitre plates so that circulating HCV antibodies in blood samples could be captured and measured. Detection of bound antibody was achieved with a radioactive second antibody."

So this is the RIA?

A. It was in-house, in Chiron only.

Q. But using the same concept as an ELISA; it's just that the signalling is different?

A. They substituted the second antibody with an enzyme-labelled antibody.

Q. Yes, so, rather than a radioactive signal, one gets a colour change?

A. Once you add substrate, you will then get a colour change, yes.

Q. I think in fact the horseradish peroxidase was involved

here, as well as in early HIV ELISAs. Is that right?

A. Yes, that's right, it's more or less identical to HIV development of the ELISA there. Radioimmunoassay was really a no no, especially for the UK, to go on to use radioimmunoassay as a new test. They were actively encouraged to go to an ELISA.

Obviously, radioactivity -- if you know a little bit about Dalgety Bay, it's not really the best thing for people to be exposed to.

Q. Obviously, in the laboratory they had been able to look at what they describe as a panel of well pedigreed and well characterised samples.

A. Yes, well, Harvey Alter had a panel of samples that he distributed to people who claimed they had specific non-A non-B serological tests, and obviously some of that panel would be used as well as Dan Bradley, who was a co-author there; he would have used material that he had to infect chimpanzees.

So they were well characterised samples that were used by the Chiron crowd to actually show that they were detecting something.

Q. And we can see that this assay appears to have performed well --

A. Yes.

Q. -- in that, of seven NANBH serum samples, all but one

gave very high signals in the assay, as compared to the results obtained with sera from two controlled patients with alcoholic hepatitis or primary biliary cirrhosis and five non-infectious, normal blood donors.

Perhaps also interesting to note is that the only proven infectious sample that was negative in the assay was obtained from an individual in the acute phase of post-transfusion NANBH.

A. Certainly, we followed up some of the drug abusers in 1990 with this first generation test and very few of them actually were detected at the acute stage of non-A non-B.

Q. Right. This is jumping forwards slightly but this is, relatively speaking, quite a late appearing antibody. Is that right?

A. C100, obviously, appears within genotype 1 mainly, C100, because it was obviously based on genotype 1, the C100 that they were using at that time. I wouldn't say it's too late but normally you get C33 appearing a bit earlier than C100, yes.

Q. So a better way of putting it perhaps is that later tests, particularly second generation tests, were able to include tests for earlier appearing antibodies?

A. That's right, yes.

Q. Is that right? And, of course, if you can do that, you

are shrinking the window period?

A. That's correct, yes.

Q. So in April 1989 more detail is published, both of the methodology underlying the discovery of the clone and also of the early radioimmunoassay which has been developed.

Could we go back to the statement, please? Around about this time, particularly around the turn of the year 1988 to 1989, the two different committees to which I referred earlier, ACTTD and ACVSB, were established. I'm not going to go into this with you, Dr Dow, because I think it is probably more appropriate to look at some of these aspects of the decision-making with other witnesses.

A. Correct, yes.

Q. Particularly, sir, I'm going to ask Dr McClelland about this because he has gone into this aspect of matters in more detail.

Indeed you said yourself, in response to our third paragraph asking about how the membership of each body was determined, that:

"Dr Mitchell and Perry should be able to answer better than I."

A. That's, I think, because they were on both committees.

Q. Dr Mitchell was on both committees.

A. That's right.

Q. And Dr Perry was on ACVSB.

A. Correct, yes.

Q. Perhaps we can just note at the moment, though we will certainly be coming back to this, that the Scottish members of ACTTD were Professor Cash, Dr Mitchell and Dr Follett, and then with ACVSB, again Dr Mitchell, Dr Perry from PFC, and Dr McIntyre attended as an observer on behalf of SHHD.

We then narrated in our paragraph 4 that ACTTD was first off the blocks, meeting on 24 February 1989.

Can we then look on to the following page, please? I'm sorry, I should have said that paragraph is wrong in saying 21 February; it was 24 February. So I should record that correction.

Paragraph 5. Each group had a meeting in May 1989. In fact it was, for each committee, the second meeting: the second meeting of ACTTD on 19 May, the second meeting of ACVSB on 22 May.

As far as the story of assays is concerned, we can take that on a little bit by looking at the minutes of the transfusion-transmitted diseases committee [MIS0010009]. We can see there that that's the minutes of the meeting held on Friday 19 May 1989. Dr Barbara, Professor Cash, Dr Follett, Dr Mitchell, Dr Mortimer and

Dr Wagstaff and then apologies from Dr Contreras and Dr Gunson. Then can we move through this, please, on to the next page? Sorry, further on, until we find the non-A non-B Hepatitis section. There we are.

At the bottom of the third page we can see that Dr Barbara gave an oral report. He told the committee that:

"At present ordinary donor samples from the tri-centre trial of ALT testing were being tested, before proceeding with selected groups."

So some samples that were already available and had been used in a study of ALT testing were being subjected to the new assay. If we look on to the next page, please:

"To date, the test is running consistently with the manufacturer's expectations. At present, 400 samples per day were being processed and this was a considerable drain on resources."

Then we see:

"Anti-HCV testing of donations from Scotland.

"Professor Cash reported that the SNBTS would be interested in taking part in evaluative trials of the Ortho Pharmaceutical Company's Chiron test and said he would be grateful if Dr Gunson would contact him about this matter. In particular the West of Scotland centre

has a bank of frozen donor samples already tested for ALT, from which further samples are available of IV immunoglobulin, known to have produced raised ALT levels in recipients."

So Professor Cash is obviously keen that Scotland is to take part in some of the evaluative work as well?

A. Yes, he was very proactive as a national director. He was obviously on the ball and tried to keep us at the coalface with the best of tests.

Q. Yes. Can we look then back at the statement, please? The only comment you made about this meeting, Dr Dow, was that, as we can see from the minutes, it appeared that the English blood service had already started evaluating the Ortho first generation ELISA, and we can look at some information about that, if we see [SNB0019545], please.

This is dated 23 June 1989. We can see that it is in fact labelled, "Preliminary Report Number 2", on the HCV assay. We are told that the results for the individual centres are shown in tables 1, 2 and 3. Just to clarify, the three centres involved are North London, NLBTC, and Manchester, and Bristol?

A. Yes.

Q. I think that was thought, Dr Dow, to give a reasonable demographic spread. Is that right?

A. There was coverage of the three zones of the English service: one London zone, a south-west zone and a northern zone.
Q. Right.
A. So that covered the UK, according to them.
Q. So I suppose we would be Manchester for these purposes, would we? Who can say?
We can look at the data. There were 22 initial reactive samples out of 3,282 tested and 14 repeat reactive, and that's just when you repeat the test too?
A. That's right, it's just a straight repeat of the test, usually in duplicate. So you would have three results from any sample that has had an initial reactive resulted and, based on being two out of the three, you would call it a positive or a repeat reactive. If there is only one initial reactive followed by two negatives in the repeat testing, you just call it an initial reactive.
Q. Yes, I'm glad you said that, Dr Dow, because that's how I was remembering it from September, that there was a best of three concept.
A. Yes.
Q. So an initial reactive test is repeated. If it's then negative, you don't know which one is actually correct, so you would do a third one?

A. Correct, yes.
Q. And then the tables are on the succeeding pages. If we look on to the next page, please, this is North London. We can see their results.
A. I have done ALT tests on them down the right-hand side, which is -- so there was a couple -- maybe three out of the 12 repeat reactives have ALTs slightly higher.
Q. Just at first site, it's not hugely impressive as some sort of assessment of the correlation with raised ALT. The ALT results are not very dramatic, are they?
A. It's not impressive when you see handwritten reports in, obviously, a minute.
Q. I suppose maybe somebody was thinking time was of the essence, but it's easily readable that there were 18 -- we can see on the top right, there were 18 initially reactive and then the repeat reactive column, the two Rs, that totals 12. Then on to the next page, please, we can get Bristol and Manchester.
A. A problem with all this, though, is that we didn't know if any of these were true positives or not because there was no confirmation.
Q. Yes, indeed. So Manchester, one initially anti-HCV reactive, not positive on repeat?
A. Yes.
Q. Then Bristol, three initially anti-HCV reactive and two

of those were repeat reactives.

So that's how we get the total of 14 repeat reactives out of 22 initially reactive. A much more full report on the exercise in England was prepared later and it makes sense to have a look at that. That's [PEN0160075]. This is in fact from April 1990. The first 20-pages relate to ALT, pages 21 to 33 in this relate to anti-HB core, pages 34 to 45 relate to a clinical study of those with raised ALT and then we should look at page 46, our page 46.

This is actually described as volume 4 and it's a report on the evaluation of the ortho HCV ELISA test system. The introduction doesn't contain anything surprising.

A. No.

Q. Narrative with which I think we are certainly more familiar than we used to be. Worth noting the comment at the end of the first paragraph that:

"Since the introduction of self-exclusion policies for donors at high risk of HIV infection ... the blood donor profile has dramatically changed contributing to a reduction in the incidence of post-transfusion NANBH."

Then we can see in the next paragraph some of the background to this particular study, a national multi-centre study initiated in September 1988:

"Three regional blood transfusion centres ... participated in the study. In addition this project aimed to clinically evaluate the donors with positive surrogate markers. The detailed results of these studies are the subject of volumes I, II and III of this report."

Then mention of Chiron and the discovery. Then on to the next page, please. Much larger figures obviously. Material and methods. So all three centres having recruited a number in the 3,000s of donors.

Then we can see that a total of 9,683 samples had been tested with the ELISA. Then I think that's the point we were just making, Dr Dow, about the best of three:

"All initially reactive sera were re-tested in duplicate."

Is that right?

A. Yes, it was a standard practice throughout the UK, probably from the time of HIV testing I think.

Q. "Testing of sera for anti-HCV was completed by early October 1989."

Then the results. The results in relation to ALT and anti-HBc and then in relation to anti-HCV. Initial screen reactivity rates.

A. They are really quite higher. If we started screening

nowadays, with a new test, to get levels of 1 per cent means you are going to have to run about trying to take 1 per cent of your blood supply and quarantine that while you do repeat tests on them. It would cause major headaches.

Q. Right. Of course, testing generally has improved?

A. Yes, thankfully.

Q. Right.

A. If we started a new test now, these sort of levels would cause horrific problems.

Q. Right. Interesting to see that the initial screen reactivity for North London was about double that of Bristol.

A. Yes, but Manchester is still high as well.

Q. Yes.

A. I think they say this that they did all the testing in North London. Is that right? I'm not very sure. No, they did it various places, they must have done.

Q. Yes.

A. You then wonder about the reason why Bristol was low, were they using a different washing system or whatever? I certainly would have been concerned, if I were an English transfusionist, what the reason behind that was.

Q. Right. Certainly, from a lot of material relating to this, it seems to have been anticipated that North

London would have a high rate?

A. Yes, you would expect London to be high for most things.

Q. I think because of their particular donor profile --

THE CHAIRMAN: Could you just look up to the data a little bit, there is something that has been worrying me just a little. We see that it said there that:

"If hepatitis testing consent was obtained from 3,036 from North London, 3,014 from Bristol and 3,691 from Manchester."

If we go to the next paragraph it's 3,010 from North London, 3,032 from Bristol.

A. Yes.

THE CHAIRMAN: It is looks as if there has been a transposition of numbers. I'm just wondering, you know, how far has that been taken.

A. I would imagine that the 3,014 is wrong, it should have been maybe perhaps slightly higher. Some of these donations would have been -- would be failed donations, so they wouldn't have been tested.

THE CHAIRMAN: Yes, but the problem is getting 3,032 results.

A. It should have been 3,104, probably, in Bristol, I should imagine. I would put my bets on that anyway.

THE CHAIRMAN: Sorry, Ms Dunlop, I just cannot make the numbers work.

MS DUNLOP: Yes, I can see that, sir. I suppose the alternative explanation is that somehow 18 people's samples were tested in Bristol, for which consent had not been obtained.

A. I don't think that's the case.

THE CHAIRMAN: The only worry is that, when one comes to expressing percentages, it's quite important to know that the data is accurately related to the centres in question.

MS DUNLOP: Yes. We can look further at that, sir and see if we can get to the bottom of these different figures.

THE CHAIRMAN: Because it might have been expected that the 4.54 per cent would apply to North London on the projections that it would give a relatively high ratio. I don't want to go too far. It may not be fundamental to us but --

MS DUNLOP: Right.

THE CHAIRMAN: -- see what you can find out.

MS DUNLOP: Yes. Can we go only the next page, please? The repeat reactive rates are given as 0.83 for North London, 0.36 for Bristol and 0.68 for Manchester, giving 0.62 overall.

A. That's quite high as well.

Q. Then some measurements are given of different cohorts. So people who tested positive for anti-HBc, how did they

do when analysed for HCV seropositivity and then similarly, the same sort of exercise with ALT. The raised ALT group were looked at in their own right to see what their HCV sero prevalence was there.

It looks as though, Dr Dow, one can say from this that, if you were found to have raised ALT, you were more likely to be HCV seropositive, but the correlation in the other direction is more impressive, that if you were HCV seropositive, you were much more likely to have raised ALT.

A. Yes, I would agree with that.

Q. Right.

A. I mean, we can see there that the number of raised ALTs in Bristol is only 0.7 per cent with HCV which is very low and about four or five times that in North London, 3.2 per cent. This is the problem with using an ALT test. If we had been using ALT in the mid 1980s, you can see the number that were going to be repeat reactive in a test which -- maybe only a tenth of them are true positives.

Q. Yes. We should look at the tables. I think can we -- I should have said in relation to anti-HBc, there is a good correlation, I think particularly in North London, between that and HCV seropositivity. Can we just have a look at the tables, please? If we go on to

the next page?

A. Yes, that's just showing you overall results.

Q. Yes, and then the next one. That's the cohort of donors with raised ALT and then the next table, please. That's combined anti-HCV positivity and raised ALT.

On to the next page, please. Really a pretty comprehensive exercise of matching or pairing of all sorts of different groups to see whether anything that was statistically significant would emerge. Can we move on, please, to the next page?

A. The raised ALT in those with HCV-positive is a lot lower than we would expect in table 4, I'm sorry, the previous table.

Q. Yes, can we go back to page, please?

A. If you look there, there is only five raised ALTs amongst the 61 Hep C -- so-called Hep C reactives. But again this is where you must caution. This is data that were unconfirmed positives. These are only screened reactives, repeat reactives. They are not confirmed and, of these 61, I would love to know how many were actually truly confirmed. I would expect only about six. And whether these five ALT or all the six or whether they were -- that would be the -- what you really need now to actually look at.

Q. Can we go on to -- we were looking at table 5, the next

page, please. That's combined anti-HCV and anti-HBc.

A. Again, looking at these results, it adds weight to why we didn't do surrogate testing, I would have said.

Q. Hm-mm. The discussion. Can we look at the next page, please:

"Geographical variation in the prevalence of HCV seropositivity."

Then that point I was trying to make about ALT and HCV, that it depends on the direction of travel. If you look at the group with ALT and ask if you find HCV seropositivity, that's one exercise. But then if you look at HCV seropositivity and ask you find raised ALT, that's the other.

Can we look towards the foot of this page, please.

THE CHAIRMAN: Sorry, before we go, do you agree that there is a correlation?

A. There is a correlation. If we look at the Crawford study.

THE CHAIRMAN: Yes, but on these data?

A. In this there is a very poor correlation.

THE CHAIRMAN: There is a correlation, but it's not much of a correlation?

MS DUNLOP: Yes. I think perhaps the only interesting point is that the correlation works better in one direction than in the other which I think -- is.

THE CHAIRMAN: Which is not a surprise.
MS DUNLOP: What we have been told, yes.
THE CHAIRMAN: Yes.
MS DUNLOP: Yes, it's not -- as we say, it's not a very impressive correlation. No.
THE CHAIRMAN: Sorry, you were going down to the bottom.
MS DUNLOP: Yes, I was just going to go down the page.
He -- the authors say:
"One essential criticism of the assay system is the lack of a weak positive control."
Perhaps you could plain that to us, Dr Dow?
A. Most assays would prefer to have an external control, external to the actual kit itself, that's totally independent of the kit that we would run ourselves and we would prefer that something that is fairly weak. So if the assay wasn't working, it would get a negative result and thereby, if you got a negative result, you would actually avoid all the results and start again.
So, really, it's nice to have something that is a weak positive control. You would run it in a routine manner and if, obviously, it wasn't detected, you would then nullify the results and start again, to make sure you had good sensitivity.
Q. So, just in layman's terms, you really -- if you have a weak positive control, you are really putting the test

to the test because you are confronting it with something that's quite hard to pick up because it's only weakly positive?

A. Yes, correct.

Q. If it fails that test, then you lose confidence in its value as an assay?

A. That's right. This obviously came out of HIV testing, because HIV testing, when we started, took some time before we got real confirmed positives. So in order to give ourselves confidence in what we were doing, from a day to day point of view, we demanded a very weak control. So we put a weaker control in every single test we did, to ensure that we were obtaining good sensitivity and we did the same obviously with Hepatitis C.

It became more or less a norm that we did this for any assay that we brought in. We wanted a weak control that we could use on a day-to-day basis. Quite often, we had to synthesise these things ourselves by diluting samples or whatever down to a particular level. With Hepatitis C, in particular with this test, if you diluted one in ten you quite often got a negative result because the test wasn't really that good. With HIV you could dilute maybe 1 in 10,000 and get a good result.

Q. Right. The authors also say that the shelf life of the

kit wasn't great, in being only three months?

A. That's right.

Q. That's quite short?

A. That's quite common when a test is actually introduced that it's introduced with a fairly short shelf life, mainly because you need to get ongoing studies to actually be able to learn from these. Quite often now ELISAs will come with maybe 18-month expiry, rather than three months. But when you introduce a kit, normally it would only be a three-month expiry.

Q. I see. But the authors do say that the test system was acceptably user-friendly?

A. Yes, and saying that about the shelf life as well -- radioimmunoassay, had it been a radioimmunoassay it would have been a shelf life of two weeks.

Q. Right. It says:

"Although from the results obtained so far it appears that the ortho HCV ELISA has an acceptable specificity and sensitivity, these issues cannot be definitively addressed as part of this evaluation, as there were no samples with well established links with NANBH tested in this study."

A. I would have questioned the specificity because 1 per cent is quite horrific.

Q. So you think there were a lot of false positives in

there?

A. Of course there were, yes.

Q. Yes.

A. At that time that was the first time we had anything to actually look at, for the likes of non-A non-B and therefore it was obviously accepted at the time.

Q. I should reiterate that of course I'm jumping ahead because, as it were, I am approaching the matter thematically, having looked at the preliminary report on the English study, it seemed sensible to look at the end report. We have jumped into April 1990. Can we move on to the next page, please? There we have the overall results given as a total. The repeat reactives are coming in at 0.62 per cent and then again some more tables. Perhaps we could just quickly look through these before we break.

"HCV seropositivity in donors with raised ALT." Very similar to tables that we have looked at already.

One feature of this study, Dr Dow, seems to have been that either one of raised ALT or anti-HB core seems to have produced a better correlation with HCV seropositivity than the combination of the two?

A. Really they were a very poor correlation. That's what I felt, compared to what we had expected. The problem being it's just repeat reactivity and an ELISA that you

need to have the confirmed results to actually be able to make any correlation here. Really it was quite poor; disappointing in fact.

MS DUNLOP: Well, of course, in Scotland an exercise of similar type was carried out in 1989 and we need to look at that too. But, sir, perhaps it would be better if we did that after lunch?

THE CHAIRMAN: Are these all the tables that we are to look at?

MS DUNLOP: Yes, the tables, I think, are quite repetitive. Maybe just so that we can seek what's there, can we just quickly look at them. That's table 2. That's donors with raised ALT. Table 3. Combined anti-HCV positivity and raised ALT. Table 4. That's looking back the way again from anti-HCV-positive donors to see if they had raised ALT. Table 5. That's the combined anti-HCV and anti-HBc. Table 6, the next page.

A. It would look as if there is only one anti-core positive, HCV-positive out of the whole 9,000. We don't know if that was confirmed Hep C positive.

THE CHAIRMAN: The impression that one has is of a very low level of correlation really coming through.

MS DUNLOP: Yes.

THE CHAIRMAN: What worries one is, when you read the general conclusions against that background and see

support for this exercise, without explanation, there may be an explanation, of course, but let's have a break.

MS DUNLOP: Yes.

(1.02 pm)

(The short adjournment)

(2.00 pm)

THE CHAIRMAN: Yes, Ms Dunlop?

MS DUNLOP: Thank you, sir. I think just before lunch, I confused myself and possibly a number of other people as well in looking at the final report of the English study. Just for the record, our page 46 to 49 is the narrative in this report, so that's our pages rather than the pages at the foot of the document, and then page 50 onwards are the tables.

The tables become, I suppose, increasingly esoteric with all sorts of characteristics of different donors being measured and checked for compatibility with anti-HCV seropositivity and so on. I don't think it's necessary to look again at the tables, but we have the general idea of what's in the narrative and what's in the tables. With that in mind, perhaps we can return to Dr Dow's statement, which is [PEN0171915].

We diverted at paragraph 5 to look at the English assessment. Paragraph 6 takes us back to Scotland:

"Professor Cash duly proceeded with his intention to arrange testing of the Ortho assay."

We will look at that but just not quite yet. We had posed the question as to whether this exercise was the Scottish equivalent of the English exercise and you have said, Dr Dow, that the Scottish exercise had more objectives. In fact there were a total of nine different objectives and we will see that when we come to look at it in more detail, whereas, as you say, the English assessment, dated 23 June 1989, only reported on the incidence of anti-HCV reactivity at three different English centres.

That's, of course, the preliminary report. We have looked at the final report and we can see that certainly the numbers were far higher by the time they came to write up the final report and various different features were paired together to look at the different effects.

Question 7 was about the relationship between the assessment process in Scotland and an exercise which is described in the preliminary report, which is the assessment of samples of special interest. We were trying to work out whether these were two different exercises but you think that the assessment of samples of special interest was subsumed in the general Scottish exercise?

A. I think it was, yes.
Q. Right. Then paragraph 8. We asked about the ACVSB meeting on 3 July 1989 and about the sense of timescale within which the committee was working. That is not something that you are able to tell us because you weren't there; it is not a committee on which you sat. But you did explain that there is this difference -- and I think we went on to ask you about this later on -- difference between a dev kit and the HCV 101 kit. Is this standard that a manufacturer will release a dev kit for laboratories to examine?
A. Not really, no. This was one of the first times we had seen a developmental kit being used to do an evaluation. It had happened in the past where we occasionally looked at connects for companies and they would obviously be developmental kits that we looked at, to do a sort of mini evaluation for a company. But this was more or less us doing something different, where we had actually requested a kit to evaluate it on our own behalf, rather than the company's behalf.
Q. I see. So it's really -- the company in a way is doing you a favour, if that's not putting it too strongly, but they are letting you see -- to have advance notice of what the kit is going to be like?
A. Yes, sometimes companies will approach the likes of the

transfusion service to actually try out a particular test and the company, obviously, are interested to see how it would behave in the field, which they can't do themselves because they don't have ready access to fresh samples.

In that situation, we could actually be looking at developmental kits rather than production batches and it's really to show whether the kit is suitable for mass production and mass distribution, whereas obviously a production batch, once it's a production batch, that's it, they can't change anything.

Q. So the difference between them really is that, with the dev kit, the manufacturer can still make changes depending on any feedback?

A. I think that was done in some of the instances. They could well have tweaked the cut-off to be slightly different, things like that.

Q. I see. There is then some information sought about the decision-making process. Again you say you can't really comment on that. Paragraph 11 deals with the desirability of a common UK front, if one can call it that, insofar as the introduction of screening was concerned, and we are into the summer of 1989. At this point, because it fits chronologically, I want to ask you about some more information that appeared in the

medical literature, concerning the Ortho test. In fact it's both the Ortho test and the Chiron RIA. It was published in The Lancet of 5 August 1989, something of a bumper issue, as far as HCV testing was concerned. The reference for the first document is [LIT0013848].

A. Yes, this was really an editorial. I don't know how actually wrote this, but obviously -- they had obviously seen the two or three other papers within the same journal and were able to actually do a little editorial on the whole thing.

Q. Yes.

A. The important thing about the papers behind it is that again all the testing was done within Chiron premises. Samples had obviously been sent to Chiron and they had actually done the tests using their radioimmunoassay. So it wasn't the ELISA that everyone else was going to be using in Europe, it was the radioimmunoassay that they were using.

Q. I think that is true of the Spanish and the Dutch research, but perhaps not of the German material. But can we just have a look at the editorial first to orientate ourselves. We can see that the question posed is:

"Will the real Hepatitis C stand up?"

I suppose there is a pun in that.

A. I think Harvey Alter maybe might have written it actually.

Q. Yes. I'm sure just because something is in The Lancet doesn't mean it's not occasionally humorous. There is background given to the latest announcement and then, in the right-hand side again, the reference to the work of Michael Houghton and his colleagues at the Chiron Corporation in California, a little bit of history about how it was done.

About half way down in the right-hand column, mention of the discovery of the clone 511 and then the isolation of a larger clone, the overlapping clone. Then work to show that the assay was reasonably sensitive. Then, on to the following page, material we have looked at already, a reference to seven serum samples and six of them giving clearly positive results on the assay.

This is the Chiron radioimmunoassay that's being discussed here.

A. That's right.

Q. Then they go on to comment -- or the editor goes on to comment that:

"In this issue, there are published four series of results with the new test system. The Spanish and Dutch workers used the prototype radioimmunoassay, originally

developed by the Chiron researchers, whereas the two German groups used the second generation enzyme-linked immunosorbent assay marketed by Ortho. The antigen is the seam for both assays."

The reference to "second generation" there is potentially confusing.

A. It certainly is.

Q. I wonder, do you think they mean second generation only insofar as if one counts the Chiron RIA as the first test?

A. Yes, but I would claim that that second should probably -- looking back at it now, it's totally misleading. It's really just the test that Ortho marketed eventually throughout the world.

Q. Yes. By conventional nomenclature, as we will go on to see, that is really the first generation ELISA?

A. Yes.

Q. Yes. The editor says that:

"In general, the results support the sensitivity and specificity of the test system. And underlying both the urgency of making the test system available for blood donor screening and the importance of depositing the sequence of the viral genome in the GenBank database where it would be available to the wider scientific community."

Where was the GenBank database?

A. I think that was in America, but I know by that time Chiron had done the full patent of the virus and anybody doing any work had the Chiron lawyers chasing them.

Q. Right. It's pointed out that there are many questions yet to be settled. But a view is expressed nonetheless that:

" ... this new test system represents a clinically important advance in the detection of one of the causal agents of NANB hepatitis, which has the characteristics of either a toga virus or a flavivirus. It would be logical to confer the title of 'Hepatitis C' on the newcomer."

With that introduction, can we look, please, then at the research from Spain, which is [LIT0013834].

A. This is the one from Esteban?

Q. Yes. Based, it would seem, in Barcelona?

A. That's rights, yes.

Q. We can see also that Michael Houghton and two of his colleagues from Chiron are shown as contributors to the paper. From the summary, it looks as though they were mainly endeavouring to research prevalence. Is that right?

A. Yes, yes.

Q. They were looking, I suppose, where they thought the

virus might be found; they were looking at patients at high risk of infection?

A. Table 1, on the following page, actually gives you a summary of the groups of people that they looked at. It's quite a good summary.

Q. Okay. If we look at the next page, we can see they were looking at --

A. I think this is the wrong paper because that's the Dutch one you are looking at, rather than the Spanish.

Q. Sorry, are we in [LIT0013834]?

A. You have jumped a page. 3835. That's it at the top.

Q. Yes, here we are. Right. We have the right table and this shows you -- as you say, this shows the groups of people they looked at.

A. These that were quite impressive at the time because obviously, to get 85 per cent of post-transfusion non-A non-B Hepatitis reactive in a test, the test is obviously pretty good. Intravenous drug users, 70 per cent, that's kind of what you would expect. Haemophiliacs, 64 per cent, again you would maybe expect a bit higher, but it's still pretty good. The rest of the patients, relatively few. Then, going into the group, two people -- two people obviously with liver problems and it's not as high as you would probably expect.

Q. Just noting in passing and I'm sure this is, I hope, at least this is correctly described as a casual event but in your own paper, the Scottish paper, which we are going to look at, the finding of anti-HCV positivity in patients with haemophilia was 63 per cent. So very, very similar.

A. Very similar, yes.

Q. Yes. These groups of people plainly being selected because they were suspected of having a higher likelihood of having a virus than other groups of people.

A. As you can see on the right-hand side there, that was the radioimmunoassay they actually used. So this was stuff based in Chiron itself.

Q. Yes, indeed, yes. It's the Chiron RIA that they are using. There is a discussion of the results on the right-hand side of that page:

"Group 1, post-transfusion hepatitis and chronic NANBH patients. Unequivocal seroconversion was documented in 42 patients, 78 per cent. Four additional patients, low level antibodies were present, thus 85 per cent of our post-transfusion NANBH cases became anti-HCV-positive."

A. That's obviously a lot more than what we got.

Q. Yes. Well, again, I'm continuing to trail the paper at

which we haven't yet looked, but yours is about 33 per cent.

A. Yes.

Q. Yes. Then haemophiliacs, 64 per cent, they say. Interestingly, that overall percentage is arrived at by looking at two different groups, 85 treated patients, of whom 60 were anti-HCV-positive, 12 you had never been treated, only two had anti-HCV antibodies. Then intravenous drug abusers, haemodialysis patients, homosexual men and heterosexual contacts of intravenous drug abusers.

This is on the next page, if we can look at the next page. So, just to finish looking at the discussion of the results of the different groups: group 2, as you say, Dr Dow, was people with liver problems, liver disease, and then group 3, the healthy pregnant women and random blood donors.

The authors go on to say that their results showed that HCV accounts for most cases of post-transfusion hepatitis in Spain, although seroconversion may occur, during the acute phase of the infection, in about a third of cases. In more than half of our patients, anti-HCV antibodies were first detected four to six months after transfusion and, in some, the antibody response was considerably later."

A. Again we saw a similar thing in some the drug abusers found in Glasgow; that they had a bout of non-A non-B Hepatitis, which was negative in this first generation test. But when they later developed Hep B 2 months or 4 months later they were Hep C positive at that point.

Q. Right. So that is what the authors are calling here a delayed response?

A. That's right.

Q. They say:

"This delayed response could explain why anti-HCV was not detected in all our post-transfusion cases."

They say they:

"... might have underestimated seroconversion."

They go on to comment that it was also possible that transient seroconversion might have been missed. It seems to be based on information from Harvey Alter.

A. I have seen occasional instances of that, where people lose their antibody very quickly. Generally speaking, these people are cured.

Q. I see. Then:

"The frequency, high frequency of anti-HCV antibodies among haemophiliacs and drug abusers was not unexpected."

Do you remember this issue of the Lancet, Dr Dow? Is this something you would have looked at, at the time?

A. I would have looked at it at the time, yes.
Q. Yes. Do you remember finding this sort of material of interest?
A. Of course it was of interest, yes.
Q. Sorry?
A. Obviously it was of great interest at the time. I was surprised at their hit right for the non-A non-B hepatitis cases because ours was considerably less than that in the paper we did.
THE CHAIRMAN: Could I ask, at this point, whether the fact that this was done in-house by Chiron, using their RIA could have been a factor.
A. That's one of the reasons that I kind of dismissed this, that it wasn't the same assay completely as what we were using. It was a radioimmunoassay used in-house so it would have been a lot fresher than what we were using, because our kits were probably made probably two months earlier and had been lying in store quite some time before we got our hands on them.
THE CHAIRMAN: That wouldn't necessarily make it less reliable in absolute terms.
A. It could mean a 50 per cent drop in sensitivity.
THE CHAIRMAN: In your case?
A. In our case, when you are using an ELISA that has been stored.

MS DUNLOP: Right.
THE CHAIRMAN: So it may just be that, if they are doing it in-house -- would the fact that it was an RIA make a difference?
A. Not really, no.
THE CHAIRMAN: So it's the fact that they are doing it in-house with fresh material would mean that you would expect them to get a higher frequency than you.
A. That was just an assumption, that's all.
THE CHAIRMAN: Sorry, Ms Dunlop.
MS DUNLOP: Thank you, sir. The Dutch material is also, I think, of some interest, albeit it a slightly different exercise. If we look at [LIT0013834], we can see the Dutch results and theirs was a prospective study of patients undergoing open heart surgery.
A. Again it's Van der Poel and Lelie and a big crowd of Dutch people who are well-known in the transfusion world. But again they sent samples to Chiron who used their radioimmunoassay.
Q. Yes.
A. But it was good work at the time.
Q. We can see from the summary what they found. They had 393 patients receiving a lot of blood product transfusions, 5,315 blood product transfusions. Post-transfusion hepatitis of the non-A non-B type

developed in nine patients and they looked at those nine patients and nine control patients:

"Sera were tested ... with a radioimmunoassay ..."

A. At that time open heart surgery used quite a lot of blood. It doesn't do now.

Q. Yes. The results in the group of nine post-transfusion hepatitis patients:

"Four of nine seroconverted and none of the group of nine controls. Seven of the transfusions given to those patients, but none of those given to control patients, were anti-HCV-positive. In seven of nine serum sets from PTH NANB index cases, plus implicated donors, either the donor or a recipient was anti-HCV-positive."

Interestingly they found a strong correlation between raised ALT and the presence of anti-HCV antibodies.

Is this interesting work as well?

A. Yes, again I would have looked at it at the time because Van der Poel especially, we had good links with him. He features a lot in a lot of Hep C papers thereafter.

Q. Yes, I've noticed the name cropping up. Can we go on and look at the discussion of the results, please, which is on the next page? There is a table, a couple of tables, as well, actually. They say that:

"In a Dutch blood donor population, the new anti-HCV

RIA ... specifically identifies blood products associated with NANB hepatitis in patients who have received transfusions. In recipients, seroconversion ... was found only in patients with PTH-NANB. Sensitivity ... for detecting probable NANB infected blood products was 67 per cent in our study population. 44 per cent of recipients with PTH-NANB seroconversion within six months ... but extended follow-up might have shown a higher conversion rate ..."

Various discussions follow, or various observations follow on different sets of statistics and then the conclusion at the end, if we go right down:

"Despite its limited sensitivity, the high specificity of this first generation anti-HCV assay should permit greatly improved donor screening procedures for the prevention of PTH-NANB."

So Dr Dow, this work coming out in the summer of 1989, you will have been aware of at the time?

A. Yes.

Q. What, if anything, were you taking from it?

A. I was taking -- obviously the Dutch study was a lot closer to our own, as far as the conclusions that they came to. The big problem between the whole lot was that we didn't have any proper confirmation. We had a lot of initial reactives, repeat reactives but what could we do

with them? What would we tell people? Were they infected or were they not infected? It is coming out within these other two papers as well. The other thing is it's a radioimmunoassay that they are reporting on. Where is the ELISA that we are using? How are people getting on with that?

Q. Right.

A. I like the table 3 with the ALT. It's obviously quite good, the different standard deviations they put on top of their mean log and worked out how many they would actually be testing with Hep C; how many they had actually got.

Q. Can you expand on that for us a little bit?

A. Within that -- they only did 150 ALTs by the looks of it and out of that they had seven Hep C positives, which is quite high. But when they looked at the seven, all seven were actually with ALTs greater than 2.25, greater than two standard deviations above the mean log, which is roughly speaking similar to what we were doing ourselves, but none of them were above three standard deviations above the mean log, so they are all very minor elevations of ALT.

Q. Right. But generally a more satisfying result than the result we saw in the English paper?

A. Yes, yes. Again the problem is there that, of the seven

that were Hep C reactive, we don't know how many were really confirmed.

Q. Yes.

A. It leaves a lot of questions actually. Nice to know now but unfortunately I don't know if they followed this up or not.

Q. This issue also contained correspondence from Germany and that did relate to the Ortho assay. Can we look, please, at [LIT0013856]? There are, in fact, two letters from Germany and this first one comes from Hamburg, Frankfurt, Hanover, Lower Saxony. Those authors are narrating that they had set up a multi-centre study in four German blood banks looking for anti-HCV antibody in donors and they were using the Ortho ELISA.

A. Again the big problem with all of this was their conclusion, the final sentence in their letter anyway, which is what I homed in on at the time, was that there is no confirmative test for acutely active ELISAs; the results hadn't yet been developed and they don't know the true frequency of Hep C.

Q. Right. There is also quite an important point made in this last paragraph about the nature of a confirmatory test, isn't there?

A. Yes again when Ortho did eventually come out with

a RIBA, which was only a two band RIBA, one band had 511 and the other band was C100. When we ran confirmations ourselves on it, it didn't really help us at all because it was just the same material as what was on the ELISA. So all it showed was that you got the same sort of reaction. Again, you didn't know whether it was true or false and, based on that, we couldn't go back and inform people they had been infected or they were okay.

Q. Can you explain --

THE CHAIRMAN: When you say the same material, this is on the ELISA, that's the solid phase stage?

A. Yes, the solid phase was different. That was all -- the solid phase for the ELISA was a microtitre polystyrene plate. For the immuno-blot it was actually a nitrocellulose strip where they actually just painted on recombinant material on to the strip.

THE CHAIRMAN: But the recombinant material was the same.

A. Yes, the recombinant material was identical.

MS DUNLOP: Does it come back to what we were talking about this morning, Dr Dow about the overlapping clones. If 511 is the first clone, if we picture that as being, if you like a short strip.

A. The 511 is just a small amount of protein and the C100 actually compassed that, along with a little chunk of NS3 as well.

Q. So it's not a different antigen?
A. It's the same.
Q. It's just that it's a slightly longer strip?
A. That's right.
Q. And, contained entirely within it, is the strip which relates to 511?
A. Correct, so if you had a reaction to 511 you would have a reaction to C100 and in the RIBA you would get two bands becoming reactive as well.
Q. Is it important to bear in mind the difference between a supplementary test and a confirmatory test?
A. It's hard to actually differentiate between what's supplemental and what's confirmation. It just depends on people's opinions actually. The RIBA-1 strip we would called probably a supplemental, because it wasn't telling you much more than what you knew already.

You had a reaction against C100, that's all you're shown, whereas the RIBA-2 we would have said was a true confirmatory test. It actually had other bands on it for core and also NS3 as well as NS4. So the RIBA-2, that had four bands, was a true confirmatory test. It actually confirmed the presence of antibody.
Q. Just as a sort of working understanding, Dr Dow, would it be right to say that, if you are looking for the same antigen but using a different method or a different set

of reagents, that would be a supplementary test?
A. Again it depends on -- it depends on what you are actually looking at. But it's very hard to define this.
Q. Let's think about a confirmatory test then.
A confirmatory test, is that something that looks for a completely independent part of the genome?
A. Sometimes it is that case. Sometimes it's using this -- a similar test but with a different technology. It could be ELISA with one and a blot with another. It could be an ELISA on one system and a radioimmunoassay in other system, using completely different reagents. Or it could be two different ELISAs, one using one format, which -- maybe an indirect ELISA, versus a competitive ELISA.
We need for the likes of -- for Hepatitis B core, which we touched on this morning. Most of the assays were competitive. If you used another competitive assay you would still get the same weak positive reaction. You had to go to an indirect assay and then you would find out that you had a false reaction.
Q. As in many areas of human existence there are people who use the language strictly and those who use it loosely, I take it?
A. Yes.
Q. The point that's being made in the last paragraph of

this letter is that, if you are using the language strictly, as perhaps might be expected in this area of activity, something which is looking for the same thing, even using a different method, is not a confirmatory test. So it's not scientifically correctly described as a confirmatory test.

A. If you use these identical reagents to do it, it won't be a confirmation. That's why you have to define what you are actually looking at.

Q. I'm trying to define what you are looking for.

A. The thing is that Innogenetics in Belgium, I think it was, they actually had an independent Hep C line immuno-assay that came along a couple of years later, that we did have access to. That was totally independent of the Chiron system, so it provided really good confirmation for us.

Q. Right. For the moment -- and we will come back to this to look at what counts as a confirmatory test -- but for the moment we need to be alert to the fact that there is a difference between a supplementary test and a confirmatory test --

A. A subtle difference, yes.

Q. -- and of the two, a confirmatory test, properly so-called, is better?

A. Yes.

Q. I think that will do for the moment, sir. But the language -- the term "confirmatory test" is sometimes used, I think, with a lack of precision.

THE CHAIRMAN: I have a slight concern at the moment that I don't pick up the nuances altogether. If one had a thing that had some single, unique characteristic, that it possessed exclusively and there were two different ways of identifying that characteristic, would that be confirmatory or supplementary proof of the character of the object?

A. Probably -- I mean, the thing about hepatitis --

MS DUNLOP: I think it would be supplementary.

A. -- we often say that PCR was a good confirmatory test. It was good, but it doesn't actually confirm antibody. What PCR does is confirms the virus there. That's totally different from antibody. If we are looking for antibody we have to confirm that antibody. We know that people may be PCR negative, yet the antibody will be real.

THE CHAIRMAN: The other situation is one in which one knows that the unique characteristics of the thing possess more than one different state or whatever and you apply either the same test or a similar test and pick up both. Is that confirmatory or supplementary?

A. Again, it depends how you define it. It has to be

properly defined.

THE CHAIRMAN: I don't need an answer yet, Ms Dunlop but just in due course can we pin it down, if there is a precise application.

MS DUNLOP: I think it may depend how strict you are, sir.

THE CHAIRMAN: Well, it may depend whether it's a Tuesday or a Friday, Ms Dunlop.

A. To put it another way, there are people in the world who will actually use one ELISA for HIV and to confirm that HIV ELISA result, they will just run another ELISA, not knowing that that other ELISA has the same reagents that were used, even though it's from a different company, it's got the same reagents as the other company. Based on the two results they will report it as a positive result.

Q. If they don't know any better, they might say to people that they have done a confirmatory test?

A. Correct. Whereas we, with blood donors, we have to be extremely careful when we go back to them and say they have actually infective with something. That's why we insist on a proper confirmatory test.

Q. Right. As I say, we will probably come back to this but we shouldn't leave The Lancet without looking at the second German letter in conclusion. The first German letter is obviously reporting what they have found using

the Ortho ELISA. So, categorising the donors in different ways, they have found certain numbers which were repeatedly reactive and that's broken down also demographically.

A. Yes, again the other important thing to take out of that particular study was that it is considerably less -- the repeat reactives are considerably less than the English one.

Q. Yes. Apart perhaps from central Germany, which is coming in at 0.79 per cent, although even there the actual number is low, at 8.

The second letter, which is entitled, "Antibodies to Hepatitis C virus", is -- if we look at the next page, we can see it's coming from Munich and Berlin. The nature of this exercise -- can we go back then, please to the previous page? -- is that --

A. I think this is more to do with patients rather than donors.

Q. Yes. So this is perhaps more analogous to the Spanish work?

A. Yes.

Q. Yes.

A. Again Roggendorf and Deinhardt were famous people.

Q. Looking -- this is the second paragraph:

"Patients with acute and chronic NANBH and

three groups at risk of parenterally transmitted forms of viral hepatitis, that is patients with haemophilia or on haemodialysis or drug addicts."

Again they use the Ortho ELISA and if we look on to the next page, please:

"4 of 20 sera drawn during the acute stage of post-transfusion hepatitis and 44 of 56 sera of patients with chronic post-transfusion hepatitis were positive for anti-HCV. 72 per cent ... of patients with chronic sporadic NANBH of unidentified cause were also positive for anti-HCV."

Then, perhaps quite a predictable result in the patients with haemophilia, and then drug addicts, maybe a slightly lower figure than some of the other research?

A. Again they were akin to what we got ourselves really at the time.

Q. Right. Their conclusion, which we can see in the middle of the final paragraph, is that:

"HCV is probably responsible for a similar proportion of all cases in Europe and worldwide. Seroconversion seems to occur late after onset of disease since acute post-transfusion patients have a lower prevalence of anti-HCV than chronic cases and seroconversion occurred at 3-4 months post exposure in 3 patients with haemophilia. The low prevalence of

anti-HCV in haemodialysis patients in our study may reflect a selected population."

When research like this was reported from other European countries, what was your attitude to it? Did you think, well, that's Spain or the Netherlands or Germany, it's not really relevant to us? Or was it more subtle than that?

A. I felt that was more relevant than looking at American data.

Q. Right. Can we go back to your statement, please? That's [PEN0171915] and we are now at 1917. We are still in the summer of 1989 and looking at what was happening around that time. There was a meeting in London on 23 August 1989 between Dr Mitchell, Dr Follett, Dr Gunson, Dr Contreras, Dr Barbara and representatives of Ortho. You weren't there, Dr Dow but I did just want to look quickly at Dr Mitchell's report of the meeting. Certainly we have Dr Mitchell coming and we can ask him too, but there is interesting information in it.

Can we look, please, at [SNF0011449]? This is, I think, quite a long letter, reporting in some detail on this meeting. The first page is interesting because it tells us about the relationship between Ortho and Abbott?

A. Yes, Abbott at that moment were unable to launch any kit, so they were a good bit behind Ortho.

Q. We can see why when we read this letter --

A. Yes.

Q. -- that there has been some quite careful negotiating on the part of Johnson and Johnson. Dr Mitchell says that:

"Johnson and Johnson had ensured Abbott would not develop any form of test similar to that of Ortho and it was arranged that Abbott would be at least one year behind in the availability of any such test."

Then certainly it says at the end of this paragraph:

"Abbott cannot start clinical trials until at least July 1990."

Can we move on through the letter, please. There is a press release from Wall Street. One assumes thought to have financial implications, rather than medical implications, if it was given in Wall Street. Can we go down -- I think that's the bottom of page 1 and then on to -- yes, on to page 2 and Mr Davis of Ortho wanting some answers to a number of questions: Has any decision been made? He has been told by those present that no decision has been made. How would it be made? Well, the decision, said those present, would be subject to the advice of the National Advisory Committee on the Virological Safety of Blood.

It has been made clear that no decision was possible before 17 October 1989. That's the meeting following the Rome symposium. Then Mr Davis is looking for a time and events schedule and it has been explained to him that:

"If such a decision were to be made, the UK would move in unity. There would be a simultaneous announcement, as happened with HIV antibody testing."

A number of other matters which would require attention were highlighted. Counselling of donors, staffing, and other matters. Ortho offering to run training seminars.

Then on to page 3, please. Dr Mitchell is talking about what he had said about the position of the Scottish transfusion directors: not likely that they would want to have any kits until a decision had been made:

"Ortho had been keen to know the total number of kits that might be needed, but I did not commit Scotland to any such arrangements except note that the national procurement directorate would be a useful source of funding in the short term to give some hands on experience of mass screening of blood donors."

Mr Davis seems to have offered some possible deals, so some discussion about pricing.

A. It was a very expensive test compared to HIV or Hepatitis B. The Hepatitis B at that time was roughly about 25 to 50p, HIV somewhere between 50p and a £1 and all of a sudden we were getting a Hep C test that, in some instances, was £2 or £3. Obviously the 1990 price at £1.60 was a good offer at the time.

Q. We can see if we read about ten or 12 lines into paragraph 3:

"It was emphasised that Ortho needed to have a confirmatory test and they indicated that this would be available in time for the Rome meeting."

Slightly over-optimistic it turned out, whatever we mean by confirmatory test. Can we then look on to page 4? "Training needs." Then paragraph 5, we can see that both Dr Barbara and Dr Mitchell had presented figures from the studies in, respectively, England and Scotland.

A. I think that would be only fair because the company probably provided our kits free of charge.

Q. Hm-mm. The company no doubt would be very interested --

A. They would be, yes.

Q. -- to hear how the kits were performing and what sort of results were being obtained:

"Again emphasise the importance of having a confirmatory test and it's likely that in Rome a test

using the Western Blotting technique will be discussed, albeit the genetic basis for this will be the original isolation procedures described by Michael Houghton."

We can see that there is a feeling that matters in the United Kingdom are moving towards the making of a decision. Can we look on to the next page, please? Dr Mitchell is saying that it was made clear that this group of people couldn't pre-empt the decision of the advisory committee. That's, I think, in context the Advisory Committee on the Virological Safety of Blood. They were not representing that committee and they were not representing the departments of health.

Dr Mitchell is at pains to stress that he has -- he and his colleagues have not made any decision or created the impression that a decision has been made in advance of the recommendations of the ACVSB.

We asked about the concept of a turnkey system and I think you have answered that actually later, Dr Dow, but can you explain: what is that term meant to mean?

A. I don't know if I did answer that.

Q. We did ask. Can we go back to the statement, please?

A. Was the turnkey referred to in paragraph 4?

Q. Yes.

A. I don't know the answer to that.

Q. What is a turnkey system?

A. I don't know what he is referring to there. I take it it's just something that you switch on, switch off.

Q. One of the other witnesses has said it's really just something that's ready to roll, as it were. It's something that's ready to be implemented.

Can we move on to the next page of the statement, please? The next paragraph is not really a matter for you, Dr Dow, it's about internal SHHD documentation and then question 14 does address, again, the question of a confirmatory test. The letter discussed in paragraph 9.140 is something I wanted to look at. It's a letter dated 26 August 1989 and it is [LIT0013858].

I think there are actually two letters here. There is the letter from Dr Contreras and Dr Barbara and then there is the one that I was really focusing on, which is from SNBTS, from Dr Cash, Dr McClelland and two other directors, and Dr Follett from Ruchill.

The Contreras and Barbara letter is sounding some notes of caution, I think it would be fair to say, would it?

A. Yes, it would.

Q. So they are really highlighting the problem that may be destined to occur with the number of people who may have to be contact and counselled?

A. That's right. Very high, 0.5 to 1 per cent.

Q. Yes, and they are also pointing out that the test takes a long time to conduct.

A. Yes, when the second generation test came in, they used the shorter incubation period, we in Scotland decided we would go with the longer one.

Q. Right. Then can we look at the Cash letter, please? This is saying that the:

"Apparent absence of a confirmatory test will cause serious problems for blood transfusion services, which are likely to bear the brunt of sensitive donor counselling."

"The existing difficulty: using the same antigen is scientifically less than satisfactory, but it is better than nothing."

So I'm not sure, sire sir, that this helps because this is using the language of confirmation in what strictly speaking, I suspect, ought to be the notion of a supplementary test. But anyway, perhaps Professor Cash can explain to us how he sees the difference between the two types of test.

THE CHAIRMAN: I think, even at the moment, I would be anxious not to conclude that just doing the same thing again is confirmatory.

MS DUNLOP: Yes.

THE CHAIRMAN: But it might be. I suppose if you can hit

the bull more than once, it tends to confirm that your eye is in for whatever weapon you are using. But --

A. When you do a pulmonary screen and you get a reaction and you get a repeat reactive from that, that's obviously the first phase gone. Anything after that is supplemental really. Whether it be a true confirmation or not, obviously it is just a play of words, supplemental and confirmation.

MS DUNLOP: Just to finish looking at this letter.

THE CHAIRMAN: Suggesting that everything that is supplementary is supplementary, but only some supplementary things are confirmatory.

A. Are truly confirmatory, yes.

MS DUNLOP: I feel a Venn diagram coming on. That's always a dangerous moment.

A. One of the things that we do is a secondary screen needs a third screen and the third screen quite often is the full confirmation. For example if we do a repeat reactive now with our present machines, we will send that one for confirmation. We will not go to a blot at that point because a blot costs about £50 to do. So we will do a second ELISA, using different reagents. If it's reactive in that we will then confirm properly by using a Western Blot or whatever. So, anything after the first initial repeat reactive is supplemental to

that, but the true confirmation might be the Western Blot at the very end. It could be a test-related screen. Or a fourth line, even.

THE CHAIRMAN: I'm keeping quiet at the moment.

A. It's quite complicated.

MS DUNLOP: Yes. Let's just complete looking at this letter, because whatever else the letter is saying, it is saying we need a second test, so can we just go to the end of it, please? This is making the same point about the need for Ortho and/or Chiron to deposit the sequence in the GenBank database. Professor Cash is wondering whether European governments could push for action in this area.

Let's go back to the statement, please. We were at page 4 of [PEN0171915]. We are going to ask Dr Mitchell about the Rome symposium. You weren't there, I don't think.

A. I wasn't there, no.

Q. You weren't there, no. Let's look only the next page, please. This is the Scottish study. We do need to look at that. [SNB0061596]. This is the work that was carried out in Scotland in 1989. This particular version of it is the report dated 5 October 1989. There is a final version, which was dated 13 December and is very, very similar, Dr Dow. There are only some small additions made to it. So I don't propose to go through

both.

A. Okay.

Q. If we can look at the October 1989 version and go in, please, one page, we remember that this is the work really instigated by Professor Cash, wanting to have evaluations carried out in Scotland. Very similar introduction to other material we have looked at. Narration of the obtaining of kits:

"It was agreed that the West of Scotland would carry out the evaluation."

There we see you named:

"Testing commenced on 2 August, using the manufacturer's protocol."

If we move on two pages, please, we can see the nine objectives. It's really quite an ambitious study, Dr Dow.

A. It was, yes, but we had quite lot of material left from my PhD which obviously helped it, and there is also an ALT study done in 1988 and the SNBTS and there was material left from that which given allowed some sort of similar examination to what was done down in England.

Q. Right. We can see for ourselves, if we just look at the nine aims, looking at prevalence amongst the blood donor population, looking at surrogate markers, the efficiency of the test, and examining sera from patients with

alleged post-transfusion non-A non-B Hepatitis and looking at the implicated donations, looking at donors in higher risk groups, looking at the correlation, if any, with those who had a jaundice episode, looking at selected patient groups such as haemophiliacs, trying to work out how long the antibody lasts, Directive 7, looking at blood products and looking at batch to batch variations between kits.

On to the next page, please, we can see random blood donations. 2,745 random blood donations were examined and these came from Aberdeen, Dundee and Glasgow. Perhaps it's easiest if we just look at the table, which is on the next page. There are your --

A. In the table we had 0.47 per cent. That was comparable to what the Germans were getting and considerably less than what the English were getting.

Q. The English figure, I think the correct comparison would be with an English figure of 0.62 per cent, which is their overall repeat reactive rate. Does that sound right?

A. Some areas -- North London was up nearly 1 per cent which obviously I was quite surprised about that, especially when Hep C was developmentally confirmed. We seemed to have a higher prevalence than -- of the real virus --

Q. Well, yes?
A. -- compared to England. So I don't know what they were doing wrong down there.
Q. Right.
A. I believe at that time Aberdeen was slightly lower, but again this is unconfirmed samples that we are looking at in the random population.
Q. Yes.
THE CHAIRMAN: Are we going into the detail of it?
MS DUNLOP: I want to look at some bits of it, sir.
THE CHAIRMAN: We will break.
MS DUNLOP: Yes, this would be fine. Okay.
(3.09 pm)
(Short break)
(3.23 pm)
THE CHAIRMAN: Yes, Ms Dunlop?
MS DUNLOP: Thank you, sir. We were looking at the Scottish study from 1989. That's the paper which is [SNB00061596], and we were at -- going on to 1603. Can we go to that?
This is looking at anti-HCV tests on different groups of donors with evidence of abnormal liver function tests. Plasmapheresis donors, random blood donors, and looking at ALT and anti-HBc. Then an interesting comment on the following page. Sorry,

Dr Dow, we should have noted, at the bottom of that page, a better correlation really between raised ALT and anti-HBc positivity, at least in Glasgow.

A. Yes.

Q. Then, the next page does have an interesting paragraph at the end. This is work carried out on a group of samples, which you had used in your research between 1980 and 1985. Is that right?

A. These were the bags of plasma that were kept stored frozen, which we referred to this morning.

Q. Yes, and you say here that most of the 36 donors -- this is obviously at some point identified in the early 1980s -- most of the 36 donors were prison donors. So obviously the factual background to that particular finding had changed by the point at which this research is being carried out?

A. That's right.

Q. Then you have the tables: table 3, table 4. Then I wanted to go on to 1609, if we could, please. This is the actual research in relation to anti-HCV positivity in cases of non-A non-B post-transfusion hepatitis. 15 patients were tested and 33 per cent were shown to be positive.

A. Yes.

Q. By cases of non-A non-B post-transfusion hepatitis, is

it meant people who had been acutely ill?

A. These are the reported cases that had always been seeking medical attention. Most of them, I think, were hospitalised.

Q. Right. So is it possible that the limited positivity in this group of people was due to their being tested quite early in their illness?

A. Yes, that's one of the features, obviously, of this first generation test that others saw well, that at the early stage of the acute non-A non-B Hepatitis that the test doesn't actually kick in.

Q. Yes.

A. Also because the genotype --

Q. I'm sorry because?

A. The genotypes of the Scottish population would have probably had an influence on it as well.

Q. Yes. Can we look down through that. The characteristics are given of the five post-transfusion hepatitis patients who tested positive with the Ortho ELISA. Then on to the next page. We can see that further work was done on associated donors.

A. Yes.

Q. So you looked at donors who were associated with 28 cases of non-A non-B Hepatitis and only six donors were identified as being anti-HCV repeatedly reactive. So

only 21 per cent of the cases -- that is six, as a percentage of 28 -- had a donor identifiable as being anti-HCV reactive.

A. Yes.

Q. You say -- you make the point that I have just tried to make and you also say:

"It's theoretically possible that individuals positive for anti-HCV could lose this antibody over a period of time."

Testing indexed donations may not reveal those who have still to develop anti-HCV."

A. Again, we didn't know about genotypes at that point either.

Q. No, indeed.

A. Again, there is -- none of these confirmed.

Q. There is a table which sets out those results on page 1612. So we can see it at a glance. We can see the five out of 15 in the patients and six out of 28 cases in the donors. Then -- I'm not going to take up time by looking at the next group of tables. These mirror the different objectives that were set out in the list of nine that we looked at before the break.

A. Certainly table 6 actually, to us, was disappointing compared to what we had found in America and Spain et cetera. They had a lot higher hit rates than what we

had.

Q. Yes. Then can we look at 1625, please? That's where your conclusions are set out. You do articulate that disappointment, I think, Dr Dow.

A. Yes.

Q. It says:

"Unfortunately, the Ortho test would only have prevented 21 per cent of the NANB PTH cases, a somewhat lower figure than reported elsewhere. Perhaps this is due to our cases of NANB PTH being due to another agent or agents."

I suppose that's an early suspicion of what became the understanding of the different genotypes?

A. Yes.

Q. Yes. You do say at the bottom of the page in the final paragraph that:

"From the limited evaluation carried out, the Ortho HCV ELISA test has been shown to have an acceptable specificity."

But you flag up a diminution in sensitivity between the production kit, as compared to the development kit. Obviously that necessities checking of the kits before they are put into use; is that right?

A. To be honest, Ortho weren't the first company to actually have the same sort of situation where

a developmental kit was more sensitive than the launched kit.

Q. Right. Then a comment which echos those made elsewhere, that the test itself was user friendly, although there may be a need for automated sampling. I suppose, however, there will still have been the issue about how long it took?

A. We didn't really particularly care about the three hour procedure. We were able to work that within our working day --

Q. Right.

A. -- although the English made a big issue about it. They were determined they had to have something that could be done within less than two hours.

Q. Right. I suppose the point, which I'm not sure that you make in this paper but I have seen elsewhere, is that if you are waiting three hours to know whether a donor may be going to transmit Hepatitis C, then that's three hours in which you can't release the other blood products, you know, you can't release the platelets and so on?

A. Yes, but the platelets were tested, generally speaking, only on a Friday and a Monday afternoon. We would get a session back mid-morning. So it would arrive at the session at about 1 o'clock, back at the centre and we

would be able to test them by about five o'clock and release the platelets that evening.

Q. Right. Can we go back to the statement, please, at 1919? You clarified something which had puzzled us slightly that, although Edinburgh, the Southeast Scotland region, wasn't referred to in the description of the exercise, that the exercise did actually include some materials from Edinburgh as well. We wondered if this was an exercise that we had failed to identify but apparently not; it's in there too.

Then question 17. Perhaps we should just note that this is also related to confirmatory testing. The first generation RIBA, you tell us which was a test that was being proposed as a confirmatory test, it was also based on proteins both products of the same area of the genome. That is the same as the ELISA, that these are products of the non-structural region. I think very strictly speaking, a little bit overlaps into the NS3 region as well. Is that right?

A. Yes, a small fragment does, yes.

Q. Yes. So this was seen as a defect of the first generation RIBA, as a possible confirmatory test, that the same cross-reacting antibodies would produce false positive reactives in both ELISA and RIBA systems.

Can we move on then to the next page, please? You

have actually given us a picture of HIV Western Blot strips.

A. Very early ones.

Q. Right.

A. Again, the picture there is just to show that there are no brainers. You can see that all five are confirmed HIV positive.

Q. Dr Dow, I'm going to share with you my working understanding of a blot test and you can correct me if this is wrong. But as I understand it, the feature of a blot test is that the material you are testing separates out along a -- can you just hang on a minute -- separates out along a piece of paper or similar and then when the reaction occurs, because it is known what constituent part of the material goes to what place on the paper, you can see where the reaction is?

A. Yes.

Q. So you can rule out a reaction, if it's occurring in the wrong place?

A. Correct, yes.

Q. Would that do as a working understanding?

A. That's a working understanding. The thing about Western Blot is the original sample electrophoresed along -- it could be a great big square of paper and that square of paper is then done into strips, as you

see in the diagram there. These strips are then used to test your sample. So you don't do any electrophoresis yourself. You buy -- your strips already come with electrophoresed fragments along it.

The RIBA is completely different. The RIBA is where the recombinant protein is actually just painted on as a little wee band in a particular area. That's all. It's like a Chiron(?) Western Blot. You paint on the band where you want it to be along that nitrocellular strip and generally speaking they do it at equal spaces along the strip, whereas a Western Blot, you will find bands, as in the picture there, all over the place, to correspond to the different molecular weights of the proteins.

Q. But the general feature of any blot test is that separation of material?

A. Yes, whether it be a RIBA or a Western Blot.

Q. Right and that is an advantage over an ELISA because in an ELISA --

A. You do not know what's reacting.

Q. Thank you. So that the blot enables you to be more precise in your understanding of what it is that's causing the reaction?

A. In some instances, the likes of HIV, you can look at the blot and you can actually see the development of

antibodies through time. With Hep C you can see things similarly but we don't really have that good an example. We only have four different bands with Hep-C and they are all a recombinant material. With HIV you can certainly see the seroconversion happening.

Q. We were puzzled by an editorial by Dr Barbara in December 1989, which seemed to suggest that Ortho were developing Western Blot. But I think this may just be wrong, that Ortho were working --

A. On a RIBA.

Q. -- on a RIBA, yes. Can we just look at those two letters that are mentioned there? These are letters that have turned up since we published the preliminary report. [SNB00061560].

A. I think that's just to show FDA acceptance.

Q. Yes, that's showing that in November 1989 an export permit for the Ortho ELISA was approved by the United States FDA and that's coming from Peter Savage, product development manager. Can we look at 1561 as well, please?

A. This was obviously to do with the RIBA.

Q. This is to do with the RIBA, yes.

So, again just to locate this in time, this is November 27 1989 as well.

A. Yes.

Q. Saying that:

"Ortho have just completed production of a small number of prototype confirmatory tests in their immuno-blot format."

So, the next stage in their plan is to do some field testing and get feedback. Then they are hoping to introduce the test in the first quarter of 1990.

A. We did try it and we didn't find it very useful.

Q. Yes. Excuse me a moment, please, sir. (Pause).

I think there was -- it's also worth pointing out, although I don't think we need to go to it, that there was a piece in the BMJ in October 1989 by Professor Zuckerman, just recording his view of how the land lay.

I think because time is short, I'll just give the reference to it and we will not go to it. It's in the BMJ, 7 October 1989, [PEN0170022]. I mean, he is plainly an important figure in this story, Dr Dow, and he is recording some of the research which has been done so far, including research from Spain, which we have looked at, and sounding some notes of caution, unsurprisingly he is bothered by the absence of a confirmatory test. Saying that there may be more than one type, so he is also alert, unsurprisingly he is alert to the fact that there may be different types

which are not being picked up by this first generation test.

A. Yes.

Q. That's taking us towards the end of 1989. Can we go back to the statement, please, back to 1920. Paragraph 20 refers to the final report of your work in December 1989 and that's mentioned in the preliminary report. I think it's not necessary that we go there because, as I said earlier, it doesn't really include much additional information at all.

A. Correct.

Q. There is a little bit of extra information about material from Edinburgh --

A. Yes.

Q. -- but the thrust of it is really the same as the report we looked at from October.

Then the discussion of dev kit again. Then can we look at a report written by Dr Gunson and discussed in January 1990? This is a report of a study that was undertaken towards the end of 1989, another study, just to give a little bit of background. The fourth meeting of the ACVSB, which was on 6 November 1989, had decided that a pilot study of the Ortho test should take place at Brentwood, which is northeast Thames, Sheffield and Birmingham, to show the feasibility of adding the test

to routine practice.

This seems to be more an assessment of practicability, but just so that we don't miss a study because there are a lot of different studies in this area, we can have a look quick at the report on that? [SNF0011491]. At 1505. I think that's page 15, is it? It would be page 15 of our document.

A. I think we did eventually get some samples from the repeat reactives from these studies at Ruchill to do confirmations of them some time later when we had RIBA-2.

Q. How did they stand up?

A. I can't remember now --

Q. Given that --

A. -- it was a long time ago.

Q. -- the main thrust of this was practicability?

A. I think, again, it's about roughly 10 per cent that were confirmed. That seems to be true with most of the things we did.

Q. We can see the aim of this study from the first paragraph that:

"The objectives of the trial were to assess the performance of the tests in the daily work routine of the regional transfusion centre and to try to estimate the costs of carrying out the test on a routine basis."

We can see the findings there in terms of repeat reactivity. Then the comments by the participants:

"All commented that the test was straightforward and easy to perform."

So whatever the problems may or may not have been with the first generation ELISA, it doesn't appear that difficulty in performing it was one of them. Everybody seems to be saying the test is reasonably easy to carry out:

A. The important thing there is that Sheffield and Birmingham were both getting very low repeat reactive results, a lot lower than what we were getting and that's probably more akin with what we'd expect of England, whereas northeast Thames, being part of Essex area, London area, was a bit higher.

Q. Right. Then can we go over the page, please, just so that we have seen this study. That difference is commented on, Dr Dow, the point you have just made, threefold difference in positivity rate between Trent and northeast Thames, with the West Midlands occupying an intermediate position, maybe a clustering within a given region. So it was difficult to estimate the costs involved with respect to loss of products, counselling and further testing of donors nationwide since there will be significant regional variation.

Then there is a plea for automated sample handling.

A. Yes.

Q. Can we go back to Dr Dow's statement, please, at 1920? Look at paragraph 21. We asked about this need, which we see repeated in a lot of minutes of the meetings at this time, for the Ortho test kit to be approved by the Food and Drugs Administration for use in screening in the United States. You don't really comment on that, other than to point out that the FDA were notoriously strict controllers of the quality of test kit systems so it would have been, I suppose, very reassuring to know that a kit was FDA approved. Is that right?

A. Yes, indeed more recently it takes sometimes up to three years to actually rubber stamp new kits.

Q. Right. Then on to the next page. Most of this material is not really as you say, for you. 26, we look at this in more detail tomorrow and Thursday, but you comment that the RIBA test, which was around by the middle of 1990, was still just RIBA-1 and that was not entirely satisfactory for the reasons you have already explained in relation to the particular antigen involved.

Then, next page, we can see Professor Zuckerman at least using the terms in a precise manner, saying at the ACVSB meeting in April, 1990 that the RIBA test wasn't good enough to use routinely as a confirmatory test.

Then, just staying with the theme of the various different tests and studies that were conducted, if we look at 29, we can see that July 1990, there was still felt to be need for another study and this one was a comparative study of the Ortho and Abbott tests.

If we think back, of course, as a result of a contract between Ortho and Abbott, Abbott had been held back, as it were but their test did come through -- their first generation test did come through in 1990. So once it had arrived, it was the view of some people that some kind of study of how it performed in relation to the Ortho test was necessary.

A. We needed to do a comparison between the two.

Q. You were involved, I think, in that?

A. We were involved with that, as was the Glasgow centre itself. I was involved more in doing confirmation from that and we were also involved with other English centres that were doing the same study.

Q. Right. We can see a report of that particular study if we go to [PEN0160028]. This is Dr Gunson's report. It's shown, in fact, as being dated in February 1991 but it was a test that was begun, or a study that was begun in 1990 and conducted, I think, largely in the second half of 1990. If we can look at the next page, we can see an introductory narrative. This was a study to

compare Abbott and Ortho. The centres participating are Glasgow northern and North London.

A. That would be Manchester.

Q. Manchester, yes, and North London and it was a phase 1 and phase 2 trial. There was a hiccup, we see from 1.4, that the initial test kits supplied by Ortho failed what I suppose one could describe as a quality control test. Would that be --

A. Each plate, had to pass various parameters before it would be declared valid. Obviously what was happening there was they couldn't get valid results.

Q. Right. And then there was also an IT issue, I think?

A. That's right, yes.

Q. 1.5, 1.6 and then 1.7:

"All three centres reported that the tests were easy to perform and that the manufacturer's instructions were user-friendly."

Then on to the next page Northern Regional Transfusion Centre bemoaning the lack of a suitable computer package. Then summary of results: so Ortho were producing more initial screen positives than Abbott but the repeatable positive rate was similar with both tests at Newcastle and North London. It looks as though it wasn't Manchester, but Newcastle?

A. Newcastle, sorry, yes.

Q. So, for Manchester read Newcastle. It's a good thing Professor James isn't here actually. Newcastle and North London regional transfusion centres. The repeatable positive rate for Abbott tests at Glasgow was higher than that for Ortho.

A. The important thing to remember here is that Abbott test was based a polystyrene bead, rather than a microtitre plate. But it was the same reagents, all sourced from Chiron, so we were using the C100, similar to what Ortho had.

Q. Were you, in the West of Scotland, more familiar with Abbott products than Ortho?

A. I think at that time I was up at the virus lab. So the West of Scotland BTS itself was more familiar with bead technology, whereas I was in the reference labs, so I did deal with both beads and microtitre work.

Q. Interesting to see what happened with the repeat positives. We note from 3.2 that the two test kits identified two populations of donor samples which overlapped. I suppose one would be particularly interested in the ones that tested above on both.

A. That's quite correct, those are the ones we would home in on.

Q. Yes. If we look at the next page, in section 4 we are told that a total of 69 samples were referred to each of

the three specialist laboratories and, at each specialist laboratory, six of the repeatably positive samples were PCR-positive and then 4.3 seems to be important; that all six PCR-positive samples were reactive using both Abbott and Ortho tests.

A. That's right, yes. That's what we would hope for.

Q. Indeed, yes. So, using the kit made by the other manufacturer seems to add some value?

A. It adds some value, yes, but again you would have to look at the tables themselves to see the number that actually did overlap.

Q. Yes. Well, I think in that regard, what we need to look at is page 0033. The previous table gives you initial positive and repeat reactive but then if you look at this table on 0033.

A. That was the problem we had, that quite a number were obviously reactive in both. 26 were reactive in both, yet we only had six PCR-positive. One of the tables here will actually show the number confirmed positive by RIBA. From that we would say that Abbott had the more specific test because Abbott positive only ones were less than Ortho positive only ones.

Q. Yes. Right. I don't think there are any further tables in this Dr Dow, I think all that's left is a graph.

A. That says table 2 there. I don't know where Table 1

would be.

Q. Table 1 is on the page before. It just tells you about initial positives and repeat positives. Can we look at the table before, please?

A. No, it doesn't really say.

Q. No.

A. I'm surprised it didn't have the number confirmed by RIBA because it says that RIBA-2 was actually done on all the 69.

Q. Yes. Can we move on through this, please and can we look at the next page? Sorry, the page after table 2. If we look at table -- yes, there we are.

A. That shows repeat reactive in all tests. That just shows you the difference between Ortho and Abbott in the different centres. Anything after that?

Q. I think the next page is another graph.

A. Figure 3 analysis of repeat reactives. That's just divvying up the ones that were up with the different assays. Are there any pages after that?

Q. No. Actually that is the last page of that document. I think there may be more pages that we have possibly indexed separately. Yes. Can we try page 7 of [PEN0160028] and see if that's in its own right, please?

A. You have to remember that this was a very complicated study that had a whole lot of other data.

Q. Hm-mm. Sorry, that is all that we have in relation to this paper. Maybe what we need to do is have a look and see if we can find what you think should be another table. You would expect there to be another table.

A. It mentions RIBA-2 there, so I would expect the results on it.

Q. Yes. Although the text doesn't actually refer to any other tables. So it may be that the results of the RIBA-2 were not recorded in tabular form. Right.

A. We certainly can take from all that that there are only six PCR positives, probably only seven or eight that were confirmed antibody positive, out of 69 repeat reactives, of which 26 were up in both Ortho and Abbott. And that Abbott had slightly better specificity than the Ortho test.

Q. Can we go back to the statement, please? I think one of the things that puzzled us about this particular study -- and we will look at this in more detail tomorrow with Dr Perry -- but this is a study that was initiated after the ACVSB meeting on 2 July 1990. One of the things that puzzled us was whether it actually served any benefit in the end because the recommendation that came out of it was that any one centre could choose either test.

A. But again it was important to know how the Abbott test

would perform compared to the Ortho. So it was a very important study because they did nearly 10,000 donors -- donations, anyway, with both tests, both Ortho and Abbott at the same time, and it did show that there was some overlap between the tests. It also showed that there was a number of Ortho ones and a number of Abbott ones that obviously were false positive.

Q. I suppose, though, Dr Dow, if testing had simply been introduced, some centres would have chosen Ortho and some centres would have chosen Abbott?

A. That's correct, yes.

Q. And everyone could have got together and worked out which one worked better?

A. That eventually did happen anyway with the second generation tests anyway, that some used Ortho, some used Abbott. Again, the important thing was there was confirmatory results with this study which there hadn't been with any previous study.

Q. But you do get the same information about the comparative --

A. Although it seems to be missing from what you have got there.

Q. Right. But you do get the same information about the comparative performance of two different kits if you start using them?

A. Correct, but this is three different centres using them, which again gives you a fairly independent corroboration.

Q. Right. Okay. And then questions 30 and 31 I don't think are really for you. We are scratching our heads about the interval between November 1990 and the introduction of testing in September 1991. The only point you make in response, Dr Dow, which is at the top of that page, is that the -- sorry, I think at the top of the next page -- announcement that second generation kits were coming from both manufacturers meant that the second generation kits had to be evaluated.

I suppose the same sort of point can be made there, can it, that, just because second generation kits are in the pipeline, it doesn't mean you can't start testing; you could test for a short time with first generation kits and then replace them when the second generation kits come along?

A. It would have been quite a hard thing to do. Already, to actually move to actually start Hep C testing, to go to first generation testing, would have meant that any staff you had would have been fully employed to do that. To then start doing evaluation of a second generation test on top of that just wouldn't have been possible and we would have been in the situation of probably waiting

for somewhere else in the world to actually evaluate the second generation assays.

So we could have been using the first generation tests, albeit a lot earlier than what we would have done had we the second generation, but I would have said there would have been a big delay before moving on to the second generation test.

Q. We have then asked some more questions, more focused on the decision-making process, and you do tell us at the bottom of this page that the West of Scotland actually started routine donor HCV testing towards the end of May 1991, and that was because you were part of that evaluation of the second generation tests?

A. Correct, yes. We had done the evaluation and then we realised that we could obviously move on and do to it routinely. So 50 per cent of the blood in Scotland was obviously screened in the Glasgow centre anyway at that point. So they went full-time as of May 1991. It was later on in May.

Q. Okay. Then on to the last page, please. We asked you in the final question to reflect on the whole process and you say you were actively involved in the evaluations of the first and second generation HCV test systems and various means of confirmation, and you mention first generation RIBA and the eventual gold

standard, second generation RIBA.

A. Yes, there were other assays we used prior to that as well, using your (inaudible) for validity testing and Abbott neutralisation confirmatory tests, that they had for their assay, and they are all pretty useless compared to RIBA-2.

Q. Okay. You accept that first generation HCV testing would have been introduced earlier than in September 1991 but you wonder whether that would have delayed the introduction of second generation HCV testing, and I think that's the point you have just made, and you also draw a distinction between the first and second generation tests insofar as they relate to different genotypes?

A. That's right. Obviously, the first generation test detected genotype 1 very well and detected about a third of genotypes 2 and 3 and, of course, that meant that in our Scottish population we would lose 30 per cent of our Hep C positives if we only used first generation testing.

Q. Right. So just so that we understand the picture -- and I think we did cover this when you were here in March -- the first generation test really was not very good at picking up genotypes 2 and 3. It would have picked up some of them?

A. Some of them, but not all.
Q. But not all. So the introduction of screening using first generation kits would have picked up, what, the majority of genotype 1 cases in Scotland?
A. It would probably have picked up most of the genotype 1 and overall it would have picked up about 70 per cent of what we would have later found with the second generation Hep C assays.
Q. Right. Is that based on the research that you did or is that your own estimate?
A. No, that's based on the studies that we published in Transfusion in 1993.
Q. Right.
A. Based on the first 100 Hep C confirmed positives we found with the second generation test.
Q. Right. So the point you are making is that the first generation testing, a number of cases which were picked up with second generation testing would have been missed?
A. Yes.
Q. And that the use of first generation testing might have caused delay in the introduction of second generation testing?
A. I certainly think it would have delayed considerably.
Q. Right. And the final point you make is that you repeat

that benefit which those in the West of Scotland were able to enjoy slightly earlier than some of the rest of transfusion recipients in Britain but, because Glasgow was one of the centres taking part in evaluation of the second generation kits, all their blood was tested really from the end of May 1991 anyway?

A. That's right.

Q. Right. Fine. Thank you very much, Dr Dow.

A. Okay, thank you.

THE CHAIRMAN: Now, Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: Sir, there are just two points I want to ask Dr Dow. I realise it's late in the day and I don't want to take up too much time. It's just relating to the final matters that we have been talking about. Can you just explain why it is you say that there would have been a delay in introducing the second generation tests if there had been an earlier introduction of the first generation test?

A. It would be a staff manpower problem. Whatever slack you had would have been taken up by going full-scale with the test. So you wouldn't have time to actually do any evaluations of another test over the top of what you are currently doing.

Q. Is it your job to allocate staff and to be involved in

the manpower?

A. It's not my job to do that but I know that's what would have happened.

Q. Why do you know that would have happened?

A. Because there was no slack left in the SNBTS to be able to do extra work if you had actually used all your staff to do the first generation Hep C antibody testing.

Q. Could evaluation not have taken place in a limited group, in other words --

A. What I would have said is probably somebody else would have had to have done it, some other centre down south, and we would have had to wait on them doing it and obviously there would be a big delay.

Q. How long a delay would you say?

A. It would be months anyway.

Q. How many months?

A. You would have to look at how the other people who use first generation tests, how long they took to move on to second generation tests. I don't have that data in front of me at the moment. You would have to go and find that to answer your question. I would be interested in the answer.

Q. Right. All right.

The other question I want to ask you is you do say in your statement:

"I would accept that first generation HCV testing could have been introduced earlier than September 1991."

When could it have been introduced? In other words, you accept that it could have been introduced earlier than September 1991, so when could it have been introduced, in your view?

A. That depended on a few things. Obviously, we needed a good confirmatory test. I think it was there by the time you saw that last Gunson report, which was dated in February 1991, I think it was. So I think at that time we were more or less ready to go at that point. Obviously, 1 April would have been a doable point of moving on to first generation test. It could have been done earlier. Who knows?

Q. All right. Thank you, sir.

THE CHAIRMAN: Mr Anderson?

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

THE CHAIRMAN: Mr Johnston?

MR JOHNSTON: I have no questions, sir.

MS DUNLOP: I have no further questions, sir.

I should say, before we rise, that, because there seems to be an awful lot of studies, Mr Mackenzie prepared a table of the different studies, which people may find of assistance in their preparation. I just highlight it in case anybody hasn't come across it.

It's [PEN0172192]. If we could have a quick look at that, please -- could we just quickly see it on the screen?

Just to say that that reference in the fourth box to 1991 is 1990, just to correct that. ACVSB on 17/1/91, that was actually 1990. That's the only thing and --

THE CHAIRMAN: Sorry, I have not got it yet. Oh, the very last line?

MS DUNLOP: Yes, and similarly the reference to 10 January is 1990 as well. But it does summarise all the tests that we think were carried out, or all the studies that we think were carried out.

Mr Mackenzie has looked at box 1 and then today we have looked at box 2, box 3, box 4 and -- well, really the boxes going right to the end of that heading:

"Further evaluation of first generation tests".

THE CHAIRMAN: Which I have not yet seen.

MS DUNLOP: We have really discussed the different tests today. We haven't looked at the meetings at which they were thought to be necessary but we have looked at the different studies. I should say "studies", not "tests" because that's confusing, but the studies comparing the different tests.

THE CHAIRMAN: Has Mr Mackenzie found anywhere where the PCR tests that Dr Dow referred to are written up? Is it

possible that just some pages of that report are messing?

MS DUNLOP: We will check that, sir.

THE CHAIRMAN: Check it.

MS DUNLOP: We will, yes.

THE CHAIRMAN: Right. Is that us for today?

MS DUNLOP: That's us for today.

THE CHAIRMAN: Thank you very much, Dr Dow.

A. Thank you.

(4.13 pm)

(The Inquiry adjourned until 9.30 am the following day)

I N D E X