Wednesday, 12 October 2011

(9.30 am)

PROFESSOR HOWARD THOMAS (continued)

Questions by MS DUNLOP (continued)

THE CHAIRMAN: Good morning.

MS DUNLOP: Good morning, sir. Thank you for allowing me a little extra time. I'm sorry for having gone off to print something out at the last minute.

Good morning, Professor Thomas. Can we return to your report, which is [PEN0171071], please? We were at 1080. So could we go back to that, please?

We were about to begin the section entitled "Clinical Features of Liver Diseases Caused by HCV". You have listed for us, professor, a number of features common in acute hepatitis, and just to run through these influenzal-type symptoms with malaise, myalgia -- muscle pain?

A. Muscle pain.

Q. Arthralgia, joint pain?

A. Yes.

Q. Anorexia and nausea. There may be a mild pyrexia. That's a raised temperature? And an ache in the upper abdomen, and then you go on to explain other symptoms which may ensue.

You say:

"Jaundice is rare in Hepatitis C infection. The jaundice usually lasts one to four weeks and heralds improvement in most cases. The feeling of --"

A. The rareness of jaundice is quite important because that was always used in surveillance of post-transfusion hepatitis as the indicator of it having occurred, and only a small population of the cases using that screening method actually are picked up. But the better way is to do prospective ALT testing after blood transfusion. It obviously picks up the majority of the cases.

Q. Right. So looking for jaundice as your hallmark would not be a very sensitive screen?

A. Exactly.

THE CHAIRMAN: Was always, Professor? How long ago should we be thinking of as the period when that was used?

A. I think Colindale, the public health laboratory, up until, to my knowledge, the present time, they have always used jaundice incidence as the measure really, and it has been a point of contention really because the Americans have always done the biochemical screening and this difference, of course, is the reason why the incidence after transfusion of UK blood is apparently much lower. I think indeed it is lower but it's confounded by the different screening tests used.

THE CHAIRMAN: I'm aware that in some of the early literature jaundice is very much highlighted as the diagnostic feature, but that has actually continued at Colindale until recently?

A. Yes, and they are really interested in comparative changes year on year really, where, if they are using the same screening method, I think it's -- you know, I can see the logic for doing that. They don't come up with absolute figures on incidence, which could only be determined either by serological testing, in other words, looking for antibody seroconversion or prospective ALT screening, looking for liver damage.

THE CHAIRMAN: Yes. I think I can see that consistence in the application of a single test does tell one something.

A. Yes, it can.

THE CHAIRMAN: If there are changes in pattern, but I think, Ms Dunlop, that the early papers that we had looked at before quite clearly focus on jaundice and I had something of an impression, let's say, that that had ceased to be the test being applied, but that would be wrong.

A. So far as I know, that's wrong. Of course, there is a massive difference in costs, sir, if you are doing biochemical screening as opposed to doing jaundice

reporting.

MS DUNLOP: I think it might be helpful, professor, if you could recap for us why jaundice is rare in acute Hepatitis C.

A. By "rare" I think maybe a fifth of cases or something of that order, less than a fifth, have jaundice.

Essentially jaundice occurs when the liver cell mass is reduced, so that bilirubin can no longer be excreted. Bilirubin is a breakdown product of the red blood cells of the body. The bilirubin that derives from that broken-down haemoglobin is excreted through the liver and because of a reduced liver cell mass and also the fact that the liver cells swell and therefore the bilirubin can't pass into the bile duct so readily, what we call biliary obstruction cholestasis, those two reasons, reduced liver plasma and reduced ease of flow of bilirubin into the bile ducts, both of those cause the rise in bilirubin in the blood and the eyes then go yellow. Usually it means that the bilirubin has gone above 40 millimoles per litre. Normally it's up to 17.

Q. Why does that tend not to happen in Hepatitis C?

A. Because the insult to the liver is less severe than, for instance in Hepatitis A or B, when a larger proportion of the liver cells are infected and destroyed by the immune system as the infection is cleared.

Q. Right. So is there a paradox here -- I'm looking at that sentence that you have:

"The jaundice usually lasts one to four weeks and heralds improvement in most cases."

So jaundice is a good sign from the long-term perspective but it probably means the patient is more acutely ill?

A. Exactly.

Q. Yes. And you have pointed to the fact, which you mentioned yesterday, that fulminant hepatitis is rare in Hepatitis C, much more so than in Hepatitis B, I think is right?

A. Yes.

Q. You then move on to discuss chronic infection and the ways in which that may present. I think in a nutshell chronic infection may not declare itself until quite a lot of damage has been done. Is that right?

A. Yes.

Q. You say, on the following page:

"The infection may not come to medical attention until late-stage disease is reached and the patient presents with signs of chronic liver disease or a complication of cirrhosis, such as variceal haemorrhage, ascites or the development of hepatocellular carcinoma."

Then you go on to say:

"An unknown number of individuals may be infected, asymptomatic and destined never to develop complications."

I suppose that group by the very nature of its features must be very difficult to define and identify?

A. Yes, it's complicated also by the fact that these cases may have related to experimenting with drugs, for instance, in the late teens or early 20s, which people are not keen to admit to and, of course, they put that to the back of their minds. They don't have any symptoms, they don't probably know about Hepatitis C. So that group of individuals is probably significant but of unknown size, really.

Q. Yes. You then point out that:

"There is growing recognition that in some cases Hepatitis C causes chronic ill-health with decreased quality of life, depression and general malaise, regardless of the degree of liver damage."

And this is back to brain fog, I think, is it, but not exclusively brain fog?

A. That's correct. In fact, in your annex 4, relating to the Skipton fund, you quote a paper by Wright et al, which involved quantitative data using SF36, which are measures of mental and physical wellbeing. Dr Wright

was a member of my own group and during a clinical trial did these studies, and that shows that they have a general reduced mental and physical wellbeing, of a comparable level to what you might see in diabetes or an illness such as that.

It's also worth noting that when we start to treat patients with interferon, their quality of life goes demonstrably down initially because of the side effects of interferon.

Q. I'm not convinced, professor, that I got the name of the author of the paper?

A. Wright, M Wright.

Q. Thank you.

A. It's on page 54 of the document that you gave me just prior to the meeting.

Q. We are going to come to that, so perhaps when we look at it, we can highlight the specific reference.

I wondered from your statement about this effect being regardless of the degree of liver damage, whether it is possible for somebody to have these, I suppose, neurological and psychological difficulties, really with minimal effect on their liver?

A. Yes, I mean, yesterday we discussed the issue of these mental symptoms being possibly due to one of three things. One is, of course, severe liver disease, where,

because of liver failure and an accumulation of nitrogen compounds derived from the gut, they develop what we call hepatic encephalopathy. That's a correlate really of severe liver disease.

The second possibility is, of course, that they are mentally blunted if you like, because of current or past use of drugs, I mean recreational drugs. And the third, which you can only determine by exclusion of the first two, is this thing that is termed by the Americans "brain fog", and represents infection of the central nervous system.

Q. Yes. So that in the third category, could that actually be more severe in an individual patient than what is going on in their liver?

A. Usually not. The type 3 I'm talking about, due to infection of the brain, those are really very subtle changes, changes in ability to concentrate, an increased prevalence of depressive problems. And you can't really detect those if the patient also has liver failure, the type 1 thing I described, which is the hepatic encephalopathy, where all of these symptoms of diminished cognitive function and depressive problems are much more severe than you would see with the infection of the brain.

Q. Right.

A. Just to relate it to HIV, where there is also infection of the central nervous system, this progresses to dementia; that is not seen with Hepatitis C, it's a much more subtle and milder form of infection.

THE CHAIRMAN: In Hepatitis C, is the brain fog independent of damage to the liver?

A. Yes, it is.

THE CHAIRMAN: In the sense that one can have one without the other?

A. Exactly.

THE CHAIRMAN: So Ms Dunlop's question, at a more basic level perhaps, is yes, you can have symptoms that are real in the brain when there is nothing observable in the liver?

A. Yes, correct.

MS DUNLOP: Yes. You go on to tell us that the most reliable way of monitoring the severity of liver disease is to obtain histology by liver biopsy, and we have discussed that and you have alluded to the fact that your own personal experience includes that of fatality in people with haemophilia undergoing liver biopsy. I think that's correct, isn't it?

A. Yes.

Q. You say:

"The degree of necroinflammation (grade) and

fibrosis (stage) are the key to interpretation and consequent clinical decision-making regarding treatment."

I just wanted to return to the concept of severity of disease, and we have talked about severity of an acute attack and there seems to be some possibility that that could correlate with a high titre. So if what has caused the acute attack of Hepatitis C is a very high dose, as it were, of viral infection, then the severity of the symptoms you have outlined in your paper may be worse in the acute infection. Is that correct?

A. Yes, I think the -- there are two factors contributing to the severity of the infection. As you pointed out, the first is the size of the inoculum and as a result of the size of the inoculum, the rate of spread through the liver and therefore the number of infected liver cells, and then the second factor is how quickly your immune system kicks in. Don't forget, the virus is not directly cytopathic. It does not directly damage the liver. It's the attempts of the patient's immune system to get rid of the virus-infected cells that causes the problem. So if that immune response is very rapid, then you get rapid clearance of the infected liver cells.

Q. But at a cost?

A. At a cost and faster than they can be replaced by liver

regeneration. And the rate at which cells are killed is related to the quality of the immune response and women's immune systems are better than men's.

Q. That's generally true, is it?

A. That's generally true.

Q. Right. A piece of good news.

When we look at the notion of severity in chronic disease, I wonder if I'm right in thinking that the measure of that is really rapidity of progression? Is that how one understands the notion of severity in chronic Hepatitis C?

A. Yes, I think that's, in a nutshell, true.

Q. Right. We understand from you that groups of people who may experience more rapid progression are the co-infected patients, so patients who also have HCV, and also patients who are immune-suppressed for other reasons, drug reasons or -- I don't mean drug use, I mean pharmaceutical preparations which they are taking, which may cause immuno-suppression.

But aside from those factors, is it possible to correlate other factors with rapidity of progression, for example high initial inoculum, or does that just disappear as a causative factor when you start looking at chronic infection?

A. I can't give chapter and verse but the impression I get

from the literature is that what you have said is true. So, for instance, if you are transfused a whole unit of infected blood, which, of course, entails receiving a large amount of virus, then a greater proportion of patients are likely to be jaundiced, whereas if you are infected as the result of a small amount of blood on a shared needle in the context of intravenous drug use, then that is more likely to produce an asymptomatic infection without jaundice.

As I say, I can't just, off-the-cuff, give you chapter and verse on that but I think if you look at the frequency of jaundice reported in the post-transfusion studies of Harvey Alter and colleagues, you will find that he may be reporting jaundice in maybe 15 or 20 per cent, whereas if you look at the number of intravenous drug users who can recount an episode of jaundice, it will be much smaller.

Q. So is it right then to think of the rapidity of progression as possibly being connected to some factors but unlikely to be connected to whether the initial dose of virus was very high or very low?

A. I think -- whether the dose of virus is very high or very low will be a factor.

Q. In the rapidity of progression of the person who is chronically infected?

A. I say that because of the two examples you cited, where, as a result of co-infection with HIV or in a transplant setting, immuno-suppression, there is a higher level of viraemia and a more rapid progression. Whether the one is causatively related to the other, we don't know, but the two are present and does beg the question of whether part of the rapid progression in these two situations is related to the high level of viraemia.

Q. I suppose what I was wondering was whether in those situations the high level of viraemia is maintained; it is maintained by the ongoing presence of HIV or by the fact that the patient is continuing to take particular drugs which are causing immuno-suppression. With the high initial dose scenario, that's a one-off?

A. Yes, I see what you say.

Q. A long time ago they received a high titre of virus but I wondered if that made it much less likely to feature as a factor in how rapidly their disease will progress in the chronic sense?

A. I think that may be true because ultimately, although you may in one case have a very high initial inoculum, it may eventually set at a more moderate level. If, for instance, the rate of production of the virus, what we have discussed, around 10 to the 12 particles per day, and the rate of clearance of those particles, the

ultimate level will be dependent on those two variables, and the size of the initial inoculum becomes less important, as you say, as time progresses in that setting.

Q. I think, professor, just to stay with this topic, the next section in your report is about treatment. You have mentioned the recent review and I think it would be convenient to look at that just now, even though that's the very last paragraph of your report. You have headed the last paragraph "Bassendine Review of Natural History of HCV Infection."

I think because we asked you?

A. You asked me to read that and comment.

Q. Yes, and tell us if there was anything in it with which you disagreed, and I think the answer to that was "no", but for completeness, if we could perhaps look at that. It's going to come up on the screen. We don't have it in court book but it's available on the Internet and that's where we have inspected it. The particular part of this report which outlines the medicine, if you like, is annex 4 and that's page 45. So could we go to that, please?

I don't want to ask you anything in the introduction. We can see that in the second section the authors firstly discuss the clinical course of acute

infection and I just wanted to look at what is on the second page here, so page 46. We can see various statistics are given but what interested me was the end of the second paragraph, the statement:

"The proportion of patients who develop chronic HCV infection may be determined by many factors. These include age at time of infection, gender, ethnicity, presence of symptoms during the acute infection, genotype, immuno-suppression and HIV."

It was that reference to genotype that interested me and I wanted to put that to you.

A. I think, if you look at the literature in the round, there is a consensus on certain factors which do influence outcome, and some others come up but aren't sustained -- by confirmation, if you like -- in other studies.

The reason some of the things are not confirmed is that they are not direct determinants; they are correlates of something that is a direct determinant. The things that come through are -- male gender in all of the studies indicates a more severe outcome in the chronic infection. Ethnicity, it does have a role, in that the -- I have forgotten the appropriate terms actually, but the Spanish Americans and the Black Americans have a much lower response rate to treatment

than the white Americans, and of course, whether you respond to treatment is an indirect determinant of what the disease ultimately results in.

That's now known to be related to the frequency in which the IL28 genetic polymorphism -- the frequency of which this is found in these various ethnic groups. So we now have an insight into the mechanism of why the response rate to interferons, which will in fact determine whether you do well after infection, because most people are offered treatment, or whether you do not, that that polymorphism is a different frequency in different ethnic groups.

The presence of symptoms during the acute episode, we have already discussed that.

Genotype. I don't know of any consistent data on genotype 1 being more severe than the other genotypes and part of the reason for that, I suspect, is that you can never be sure about the duration of infection. So whilst in the United States much genotype 1 infection occurred after blood transfusion, where they knew the onset and therefore they could control for the duration of the infection, in genotype 3, the infection occurs mainly in the Asian population and there, in large group studies, it's apparent that they are infected in early life, and by that I mean infancy, and that turns out,

when you look in later life, to be more severe than genotype 1, but it's probably related to the fact that you are looking 40 years after the onset, whereas blood transfusions usually are, you know, in the 20s or 30s, after acute illnesses and you look 20 years later rather than 40 years later.

Q. Yes.

A. So I think genotype is confounded by being unable to determine the duration of infection.

Immuno-suppression and HIV infection we have already discussed. They are well documented as being associated with more severe disease and of course, in the haemophilia population, that has clearly been evident, in that those with the co-infection have in the main had a higher mortality than those who have just had Hepatitis C.

Q. You anticipated, Professor Thomas, the point I was going to put to you, which is that that mention of genotype is slightly fleshed out on the next page, because they do refer to genotype 1. So you have answered that question about how valid that observation might be.

It does seem as though the exercise of measuring the effect of any one factor is bedevilled by lots of confounding variables.

A. Yes, and their interrelationship, really.

Q. Yes.

Something occurs to me -- I'm going backwards here -- but this difference we were discussing at perhaps rather a speculative level, between somebody whose high titre of virus particles is maintained by the fact that they have HIV or are immune-suppressed and somebody whose initial inoculum might be high titre, I suppose one could further refine that to say that for patients with haemophilia, the level of virus might have been constantly topped up by their treatment?

A. Yes, that's conceivable, yes. And I suppose that would be supported by the observation that, unlike people with Hepatitis C, after a single unit of blood, the haemophilia patients often have several genotypes present.

Q. Yes.

A. Which would support that concept.

Q. Yes. I suppose, again, it's very difficult to measure the rapidity of progression in a group such as a group of haemophilia patients, because of the difficulty you mention of knowing when the first infective dose was administered?

A. Yes, and that has bedevilled the field since the beginning.

There is a French group who have really tried to

categorise patients into fast, intermediate and slow progressors, and I was involved in a study with a group in Lyon, which was an international European group, to try and do similar things, and all the time you came back to the issue that you were never sure, in the majority of the cases, about the duration of infection. So that was always the unknown variable.

So what you ended up having to do was to say: well, we are going to look at cases where there are second and third biopsies, where we know, let's say, when biopsy one was done, that they had, let's say, stage 2 fibrosis and then when biopsy two was done five years later, they would, let's say, have stage 3 or 4, and then a third biopsy done another five or ten years down the line and they might have stage 5 fibrosis. So there you could relate the increased stages to the other variable, which was time between the biopsies, in other words duration of continuing disease.

Q. Yes.

A. So when we did that, then we got better data and you could look then at the range of rates of progression, and one thing I have used when discussing with my patients how rapidly their disease is progressing -- I usually said to them, "Well, it progresses one fibrosis stage every four or five years," and that data

is from the sort of situation I was describing a few minutes ago.

Q. Right. Thank you.

THE CHAIRMAN: At the moment I'm finding it difficult to see how one can generalise on that data.

A. Yes.

THE CHAIRMAN: When the total period is unknown, since one doesn't know the starting point. There are stages along the way but no overall period as a reference point.

A. Well, you can't, as you say, go back to time zero, because you don't know when time zero was, but if I'm talking to a patient who has just had their third biopsy and that's showing stage 5, I would go back in the case notes and try it find the second and the first biopsies and then look at the intervals, and I would then be able to say to them, "Last week when we did your biopsy, you had stage five disease" -- or let's, for the sake of argument, say they had stage 3 on their third biopsy, because what we are going to try to do is make sure they get treatment before they get to cirrhosis.

So on the third biopsy they have stage 3 disease. I find a biopsy done five years earlier, which showed stage 2 disease. So I would discuss with them, "It looks as if your fibrosis is progressing one stage every five years; you are now at stage 3, I want to move

heaven and earth to stop you getting to stage 6 but I think you have got another ten to 15 years before you get to that stage, because it's another three stages and you are progressing at five years, one stage every five years."

So in that context, I can't project it back to how quickly they got from the earlier stages but I do know that at the last biopsy, they are progressing at one fibrosis stage every five years.

THE CHAIRMAN: I understand that, I think. I think that I can see from the clinician's point of view what's wanted is a measure of the future period over which there is freedom to decide whether or not to start treatment.

A. Yes, that's what we are trying --

THE CHAIRMAN: That's what you are trying to do. So you are trying to fix the point at which, for the particular patient, it's right to go from simply observing into treatment with the drugs, that have their side effects and all the rest of it.

A. Yes.

THE CHAIRMAN: But in a sense that seems to me to be totally independent of the overall duration. It depends on the measurement of progression over the period for which you have data.

A. Yes.
THE CHAIRMAN: And that alone allows you to make the projection, and it's independent of total duration --
A. Yes, and in fact, where we had more complete data, in other words, we had these sequential biopsies and we knew the time of infection, it became apparent that the gradient, in other words, the rate of change of the fibrosis, was changing.
THE CHAIRMAN: Yes, there is no straight line.
A. Exactly. That's exactly --
THE CHAIRMAN: It's a complex graph that will vary from case to case.
A. But more frequently increasing with older age.
THE CHAIRMAN: Yes.
MS DUNLOP: Yes, I think we will come on to look at age, not least because you have discussed it in your report, and I want to look at that section but I see it's mentioned there "Older Age at Infection". That's on page 47, where there is the mention of genotype 1. There is another list of risk factors. Can we just see that? Yes, there it is at the end of the first paragraph.

I suppose for children infected -- and you have spoken about the vertical transmission that occurs particularly in certain areas of the world -- the sheer difficulty there will simply be the long life for which

they are going to have to live with Hepatitis C.

A. Yes.

Q. But their youth doesn't in and of itself have any independent mitigating effect, does it?

THE CHAIRMAN: Age has an aggravating effect, I think.

MS DUNLOP: It's just with HIV we have been told that age at infection may be relevant, so for those who were infected in childhood, HIV does appear to be progressing less rapidly.

A. The reason I'm pausing is that it is never, in the data that's in the literature, possible to 100 per cent sure dissect away duration of infection from the age at which infection occurred.

Q. Yes.

A. You know, it is said -- and indeed it's true -- that if you look at people between 50 and 60 years of age, what I was alluding to earlier, the gradient of passing through the various fibrosis stages increases, and that's part of the reason for saying that if you are infected after age 50, you have a more rapid progression. You don't have the slower gradient of progression of those earlier years.

But, of course, it's never clear that they have been infected after 50 years -- well, it may not be -- and therefore you always have the confounder of how long

they have been infected in the back of your mind.

Q. Yes, and for the person infected at birth, does their gradient steepen if they are alive and they reach 50? Does their gradient steepen?

A. Yes, I'm not sure that we have got it for people infected at birth. It probably is people infected in their 20s to 30s. 95 per cent of the people have, in the UK, been infected as a result of intravenous drug use, and that's usually in their 20s to 30s. So there is most danger in that area.

I don't know of a cohort where we know they have been infected at birth and they have been sequentially followed. What we do know is when we studied the Bangladeshi population in east London, when we looked at them in their 50s with the knowledge that in cross-sectional studies in Bangladesh, the peak of the time of infection is in the infancy period. So putting that together with the observations made when they are 50, where most of them have cirrhosis, we concluded that, you know, because of duration of infection, they progress more rapidly.

But, I mean, just to confuse you even more, they have genotype 3 and they get fat in the liver and that is something that also is correlated with more rapidly progressing fibrosis and --

Q. The whole area is bedevilled by the difficulty in isolating any one factor and measuring its impact?
A. Yes.
Q. Yes.
A. And that's why you do multivariant analysis.
THE CHAIRMAN: Can I ask you a question which is perhaps very naive and totally misdirected?

If one assumes two individuals, males between 40 and 60, and all other factors, other than the date of infection, are the same, whatever those factors are, would the gradient differ depending on when the initial infection was or would one have, between 40 and 60, correlation between the progression in the diseases? Maybe you just cannot do this.

A. I have the impression there from the work that we did with the group in Lyon, Trepo and colleagues, that there is an inflection point. In other words, the gradient of the curve does change. You cited 40 and 60. I couldn't be precise about that.
THE CHAIRMAN: I was merely giving a 20-year period.
A. We got data which suggested in people who had had several biopsies, that I was alluding to earlier, the gradient did change. The rate of moving between different stages increased the older the individual was.
THE CHAIRMAN: And that was general, was it, independent of

when infection started? Or don't you know?

A. We did multivariant analysis and there appeared to be an independent variable.

THE CHAIRMAN: That I find fascinating. That does suggest that simply by growing older, one reaches a point at which there is going to be a change in the gradient and an acceleration of the deterioration in the condition.

A. I think that's what we believe at the moment. And if you are looking for an explanation for that, it is actually counter-intuitive because we have discussed earlier that the damage is caused by your immune system recognising the cells and destroying them. What we do know is as you get older, your immune system weakens. That's why I say it's counter-intuitive.

PROFESSOR JAMES: Could I just add very briefly, it's my special subject as Howard knows, aging and the liver.

The analogy is with a baby who cuts its thumb and an older person who cuts their thumb. The baby cuts its thumb. Actually, by the age of ten, you can't see where the cut was. The 60-year old person cuts their thumb. The place where they cut it, in a comparable way, the scar is there for the rest of their life. And actually the aging process itself causes the liver, along with the thumb, to respond less well to injury, and fibrosis tissue, which is what's going on in the liver, to

probably accumulate, and regeneration in a good way, of the liver, is less good in a 70-year old person than in a ten-year old person.

So in a sense this inflection that Howard has mentioned is that a person gets to a certain age -- and different people different ages -- and then gradually they are just able to deal with this continuing injury from the virus that's going on all the time in their liver in a less good way.

A. Yes.

PROFESSOR JAMES: And, if you happen to pick the virus up when you are 65 through a blood transfusion, then you are sort of starting from a bad place.

Would you think that would be a fair summary, Howard?

A. Yes, I mean, both with Hepatitis B and Hepatitis C, if you get an acute hepatitis in your later years, let's say 60, then there is a syndrome called "failure to regenerate". You remember I said earlier that you have a wave of destruction of liver cells, which is essential for part of the recovery process because the cells contain the virus, you have to destroy them to get rid of them, you are then producing antibody to stop the virus moving into the neighbouring cells, but in addition, the neighbouring cells have to regenerate to

replace the ones that have been killed.

So there are four components, if I could summarise it. There is the number of infected cells; there is how quickly they are being destroyed, which is dependent on the cellular immune response; there is the production of antibody, which is going to be important to stop the virus released from the destroyed cells to infect the cells next door; and the last thing is you are down on the number of liver cells that you have, because of the ones that have been destroyed, so you are dependent on the liver regenerating. So if any of those components result in a situation of a reduction in liver cell mass, then you will ultimately enter liver failure.

Is that okay?

MS DUNLOP: Yes.

THE CHAIRMAN: Yes. I don't find it difficult to understand that these factors may all be contributing --

A. I was only just meaning have I explained it adequately. I wasn't meaning a complete story.

THE CHAIRMAN: I think we know not to expect a complete story, after Professor Alexander told us how delighted his students were to learn that he was 58, when their studies were showing that that was the point beyond which there really was no advantage in doing anything to reverse processes that had already started. Those of us

who are really beyond 58 can't take much comfort from it.

A. I agree.

MS DUNLOP: Just before we leave genotypes, I think we have covered this yesterday, but to be sure that we understand: for many people with haemophilia they will have had more than one genotype circulating, and you have explained to us that you can have successful treatment against what at a particular point is the dominant genotype in an individual, only to find that they relapse because another genotype has, as it were, popped up and taken the place of the treated genotype.

So I think we can understand that sequential series of events, but at any given point, would the factor that there were several genotypes in an individual make their rate of progression more rapid, or is that simply not known?

A. I don't think it's known. You could deduce that if the sum of the two resulted -- in other words, the two genotypes replicating -- resulted in a higher total level of viraemia, then you may get more rapid spread to the liver and more liver damage. You could argue in that way. But I don't know of any data to suggest that, if you have, let's say, genotype 3 and genotype 1, for the sake of argument, you get more rapidly progressive

disease.

Q. Yes. It does intuitively feel as though it might be more of a problem for the immune system to have two distinct battles on its hands.

A. Yes, you could -- I think that would be the case and, of course, we discussed yesterday this antigenic overload or immune exhaustion where, if the virus is continually presenting the immune system with variations of its antigenic structure, then the immune system has to continually produce new clones of cells, recognising those new antigenic epitopes, and that eventually exhausts the system.

Q. Yes.

A. And in a virus like Hepatitis C, irrespective of whether you have two genotypes, even if you just have one genotype -- you remember that I mentioned that there are multiple quasispecies, multiple virus particles which are all differing in genetic sequence and therefore in antigenic structure. So the immune system doesn't really know -- you know, it's looking at a rapidly changing field of things that it needs to respond to.

Q. Yes. I think we also covered yesterday what might happen in somebody who had Hepatitis B and Hepatitis C, and you spoke about the interference, so that the Hepatitis B might, as it were, be waiting in the wings.

A. Yes, we had one case where the individual had only had one inoculum and therefore it wasn't a case of the later-appearing Hepatitis B having been introduced at a second stage because of another infusion. There was only one infusion and I think, if I remember the paper correctly, six to nine months later only then did the Hepatitis B appear, whereas normally you would expect it to be detectable at three months, the standard incubation period.

Q. Yes. Just one other factor, I think, Professor Thomas, which again is mentioned in this report, and it's in the next list. There seemed to be several different lists actually of factors but if we go down page 47, there is a list here, which we have covered, apart from what occurs at the top of page 48, which is smoking. What can you tell us about that?

A. It depends what you are smoking. The French came up with some data to suggest that if you are smoking cannabis, that is pro-fibrogenic; in other words that stimulates fibrosis.

I don't know any data about just tobacco smoking as opposed to cannabis smoking. And there is a mechanism now whereby cannabis causes it, because on some of the cells that are responsible for laying down fibrous tissue there are receptors, cannabinoid receptors, the

receptors to which the cannabis molecule bites. So we know the cells that are stimulated to produce more fibrosis tissue have the right receptors, and that always encourages one to think that if you know the mechanism, that the observation is true. It may not be always so but it does encourage you to that end.

Q. I think actually, just really because I didn't want to leave a loose end, we were discussing something after the conclusion of yesterday's hearing and we felt we would like some more explanation of the mechanism of the rise in viral titre after a fatty meal.

We understand about the LDL receptors on the surface of the virus, as it were, being associated both with uptake of fat and also with the portal of entry for the virus, but how actually does it work that the fatty meal promotes a rise in viral titre?

A. You know, it's the usual dynamic really, in that the fat's coming in and if the virus particles are being incorporated into those fat globules, then as they pass by the liver, they are then taken out, by virtue, not of the LDL receptor recognising the envelope proteins but recognising the fact that the virus is now covered in fat globules, which are indistinguishable from those that have come in in the diet.

So if you like, the virus has piggy-backed in on the

fat and then, of course, you have got more virus coming in so then you get the facilitated replication and production of virus. Don't forget, if you are putting out 10 to the 12 virus particles per day, small changes in virus replication will fairly rapidly alter levels of viraemia, which is essentially what we are measuring.

Q. So to go back to the lock, the key and the door, the door is open more widely, as it were?

A. Yes, or you have got a -- yes, I don't want to go into more detail with the analogy. It will do, yes.

PROFESSOR JAMES: It's the exit which is open. Really it's a traffic problem. More fats kind of going into the cell and coming out of the cell, and that allows more of the virus. Remember the diagram from Professor Thomas yesterday.

MS DUNLOP: So the exit is open more widely as well?

A. Yes. Just to go back to this smoking of tobacco, of course, again that's probably confounded by the fact that people who smoke often take more alcohol. The two are correlated. So you have to do, you know, co-variant analysis, looking for whether each of these is an independent variable or really whether it's merely related to something else which is causing the change. It's the old chestnut about, you know -- I have forgotten what it was now but, you know, people who

watch television are more likely to get bronchogenic carcinoma or something like that. It's an indirect correlate. Not a good example, probably.

THE CHAIRMAN: No, it's like Professor Cairncross, who was professor of economics at Glasgow just before I went there in 1956, used to give an example which was passed on, that after the war the birth rate in the general Clyde area increased in precise correlation to the importation of bananas.

A. I thought you were going to say that it was correlated with the number of televisions that there were in the household.

THE CHAIRMAN: I think at that stage it would be an inverse correlation because people who couldn't afford a television set ...

MS DUNLOP: Professor Thomas, I think these are the only parts of this annex that I wanted to put to you but is there anything else that we should particularly note? I think the author you mentioned earlier, Wright, is referred to in this paper. Is that correct?

A. Yes, yes.

Q. That table is on page 50 to 51.

A. Yes, Wright et al, 2006.

Q. Yes.

A. I'm a co-author of that paper. So that's why I know the

detail of it.

Q. I see. And there are some details of the sorts of factors you have mentioned. The brain factors, for shorthand, in this paper as well.

There was also detail in the section dealing with antiviral therapy about quality of life.

Can we just perhaps move on to 54? We can see the scale, something rating quality of life. And a lot of this, I think, is perhaps common sense, that we understand the treatment to be very demanding and obviously people are feeling very unwell with treatment. That must have an effect on their quality of life. We can see that statement at the top of 54:

"Symptoms such as depression, myalgia, lethargy, influenza-type symptoms and biochemical and haematological abnormalities are common on treatment."

A. You have noticed that many of those symptoms are the same that are seen in acute hepatitis and that's because in acute hepatitis they are caused by your body producing interferon.

Q. Right, yes.

A. And when we use interferon therapeutically in larger amounts than you would otherwise produce, it's not surprising that you would get the same symptoms.

Q. Then we have extra-hepatic manifestations.

About half way down 56, there is a reference to impaired cognitive function, which I think is exactly the material you have been narrating to us. So we understand from your report that you don't have any significant difference of view with the conclusions of this paper. Is that right?

A. That's correct, yes.

Q. Yes.

A. One particular thing I was asked really is whether I thought the response to the perceived inadequacies of the Skipton ex gratia payments had been addressed.

Q. I think all we were concerned to focus on, Professor Thomas, was whether the medicine in this was accurate.

A. Yes, that's -- yes.

Q. Yes. It was appendix 4 that we wanted you to look at and tell us if there was anything in the description of the disease, or the symptoms or the treatment, with which you took issue, and my understanding of the position is that there isn't.

A. No.

Q. Is that right?

A. Yes. Correct.

Q. Thank you.

Can we return to your report, please, and look at

the section on page 11, which deals with treatment? Will you excuse me a moment? (Pause)

Thank you.

Treatment of Hepatitis C infection. I think before I ask you about this, I wanted to put to you something that somebody who has Hepatitis C might think when they hear about the virus being identified towards the end of the 1980s. Would it not have been expected that around that time a concerted effort would be made to test people who were thought likely to have Hepatitis C and to offer something to them, treatment or advice or information?

A. Yes, and in fact that was the focus of the Hepatitis C strategy and action plan, which I was the chairman of. The intention being -- and one of the few targets in that was that year on year the number of cases of Hepatitis C should increase towards identification of all those that were infected.

That becomes difficult because of what I mentioned earlier, that 95 per cent of those infected are either current or previous intravenous drug users, and that group of individuals are not easy to reach for testing.

Q. I'm sorry, could you date that action plan for us, please?

A. Sorry?

Q. Could you date the action plan? I'm just looking at your CV, wondering if it's there.
A. Yes, it should be there. Chairman of the Hepatitis C steering group, I think it was.
Q. Yes, the steering group on Hepatitis C national strategy, 2000 to present. You were the chairman of it.
A. Yes, there was a significant delay between producing the action plan and the information that we provided really, probably close on two years or something like that. So I would need to check which dates are which, really.
Q. But people didn't sit down in 1990 or 1991 and say, "Now that we have a means of identifying people with Hepatitis C, how will we respond to this group of people?"
A. Well, there was a look-back exercise launched, which was to identify those that had received infected blood and, of course, that was a recommendation of the committee, that we should try to find those individuals, and there are data in the microbiological safety of blood documents in which that's discussed, as to how that look-back exercise is going, and the feeling that that needed to be looked at regularly, so that one of the problems in doing this was that the case notes in British hospitals -- as opposed to just English -- are often mislaid.

Q. Yes.
A. And the only way of finding an individual is often to locate his case notes. So I think Dr Robinson, who was asked to head-up this on behalf of the National Transfusion Service, had to look at, you know, ways of getting the names through the system, finding the case notes and then for those individuals to be counselled about testing and then to actually receive treatment.
Q. Yes. But there --
A. So that group that was flagged up should be the first group or one of the early groups to be looked at.
Q. Yes. You would have, of course, people who had acquired Hepatitis C from a blood transfusion, who were not picked up by look-back because the donor never returned, for example.
A. Yes.
Q. The people with haemophilia who had Hepatitis C.
A. The haemophilia centres were also looking at this but one thing that came out of the look-back exercise in relation to transfusion of whole blood and blood products was that -- I have forgotten the precise figure but, you know, maybe as many as half or more than half had, of course, died because people received blood transfusions often for major surgery in the context of cancer care. So it was surprising how many individuals

had actually died, you know, by virtue of their primary condition, not because of the liver disease related to Hepatitis C.

Q. Yes, we have had some evidence about that.

A. Yes.

Q. I suppose if we perhaps put it another way: if there had been a systematic identification of all of those who had Hepatitis C, once testing became available, and accepting that that would have been an extremely challenging exercise, the logistics of that are not easy to conceptualise. But suppose it had been done around about 1990, what could have been offered to that group of people?

A. I think in 1990 we were just at the early stages of having interferon. Our study of the use of lymphoblastoid interferon, which was an interferon produced from a cell line, was the first European study, a randomised control study. And that used thrice-weekly lymphoblastoid interferon, and we were looking at response rates there of 12 or 15 per cent. And by "response rates" I mean sustained viral response, what we now know to be, essentially, a cure; long-term clearance of the virus with resolution of the liver disease.

So in 1990 -- the reason I'm pausing is that, of

course, there is -- the stage of the randomised controlled trials being done, there usually is then a confirmatory study because in medicine often the first studies don't give you the total picture. That, of course, results in a licence and then NICE would actually have to agree that this should be generally available.

Q. I see.

A. I don't know how long you would expect -- from the reporting of the trial, which we reported in the BMJ in 1989 -- how quickly you would expect that to feed through. But one thing that was apparent to me as a clinical investigator and a physician taking care of patients outwith the clinical trial, was that many patients weren't technically impressed with a year of lymphoblastoid interferon treatment and the prospect of being cured in 12 or 15 per cent of cases, which is where, what I was discussing earlier, it became important to tell patients where they were in the course of the disease. Because you will recall, it's important to treat them before they get to the cirrhotic stage. So the first position was: let's treat those patients who are nearest to cirrhosis, moderate or severe stages, to get those through the system first off.

Many patients, of course, with the milder stages of

fibrosis would ask the question: "Well, how quickly will it progress and what's the prospect of better treatment giving response rates above 12 or 15 per cent in the timeframe that I, as a patient, would have before I got to stage 5/6, the cirrhotic stage?"

Q. And was the staging of fibrosis in place around 1990? That's not a more recent innovation. That's something that's longstanding, is it?

A. Yes, I mean, Ishak and Nadel(?) had this out a long time prior to that.

Q. Right. So what about lifestyle advice? Around about 1990 could people have been told about the synergistic effect of alcohol, for example?

A. Well, the real scientific proof for the synergism of alcohol really came as a result of studies, I think, by Ralf Bartenschlager, where he had what was called a "Replicon" system. They were essentially cells which were supporting a model virus replication, a model of Hepatitis C. And he was looking at a variety of things that altered the effectiveness of replication, and if my memory serves me correctly, it was out of that sort of work that the synergistic effect of alcohol came.

THE CHAIRMAN: When was that?

A. Right ...

THE CHAIRMAN: Roughly.

MS DUNLOP: We can look into that.
THE CHAIRMAN: Well, of course. It's just to get a feel at the moment.
A. I guess that would be in around about 2004/2005, that sort of timeframe probably.
MS DUNLOP: Right, yes, and we do have also in our preliminary report, just to go back to your previous report, it was November 1994 when a licence was granted for alpha interferon to be used in the treatment of chronic Hepatitis C.
A. Yes.
Q. So that's an interesting point as well, exactly in accordance with what you were saying about the stages that have to be gone through.
A. Yes, and I think at the same time as we were working with lymphoblastoid interferon, which was produced by Burroughs Wellcome, the Americans really didn't like lymphoblastoid interferon. It was really a biological product where there may have been seven or eight different interferon subtypes in lymphoblastoid interferon. Essentially what they did was add a virus to a lymphoblastoid cell line and purify the interferons that were produced. And as I say, it may be seven or eight different subtypes of interferon were present in that, and from batch to batch that varied.

So the American regulatory authorities didn't like this. And they knew in the background that Weissmann and colleagues had cloned the genes for interferon alpha, the alpha 2 gene, and the recombinant interferon would be coming through the pipeline. And they liked that because it was, you know, a nice clean purified recombinant protein. Even to this day, I think nature didn't provide seven or eight interferons just for no reason, and I think there is some indication that lymphoblastoid interferon is better than just recombinant alpha 2. That's a digression but ...

Q. I should have said that the particular paragraph is 9.297 in our preliminary report. And lest I forget to say this too, we may be able to include the link to the annex 4 in the Skipton Fund paper, so that if anybody wants to read that, they can get a link from our transcript. People are nodding. That seems to be possible.

Just to look then at what you do say about treatment, Professor Thomas, if interferon --

THE CHAIRMAN: Do you want to start on that now? It's five to 11.

MS DUNLOP: I'm in other people's hands. We can try and --

THE CHAIRMAN: My primary interest, as usual, is the stenographer who does get tired. I think we should have

a break.

(10.57 am)

(Short break)

(11.21 am)

THE CHAIRMAN: Yes, thank you for the break.

MS DUNLOP: Thank you.

Professor, your report, [PEN0171071]. We were on 1081. We have talked about acute infection, and obviously the success rates have improved hugely since the early 1990s.

Then chronic infection. You do talk about the risk of developing hepatocellular carcinoma and we established yesterday that cirrhosis is a necessary pre-condition for that with Hepatitis C. Are there many successful treatments against hepatocellular carcinoma? Are there established chemotherapy options, radiotherapy options and so on?

A. The preferred option is liver transplantation but that requires that the tumour is less than a certain size and that the number of tumours is small, two or three.

Q. Right.

A. I mean, there are forms of chemotherapy but they are used only for the cases that are not suitable to be treated by liver transplantation, and radiotherapy is not used to any significant extent.

Q. Right. Does HCC tend to occur with several different tumours, rather than one manifesting itself.
A. Sorry, different types --
Q. I just wondered if, when HCC is detected, there are often several tumours, or is it the norm that there would only be one tumour?
A. Yes, often these tumours arise, in the context of cirrhosis, by one regenerative nodule giving rise to a cancer. You will recall we were discussing earlier that as well as infective liver cells being destroyed by the immune system, they are continually regenerating, and if that regenerative component gets out of control, often because of mutations, then that regenerative nodule will give rise to a tumour.

Usually, initially, that is a single focus, just one nodule, but you may get a second and a third area also undergoing the same change. But in most cases it's a small, single nodule and it's picked up by ultrasound scanning when it's between a half and one centimetre in diameter, that sort of size, and then those patients go rapidly for consideration of liver transplantation, and that gives an excellent result.
Q. It's not practicable to operate to remove the tumour?
A. In some cases, yes, that is offered as an alternative, and it's being considered more and more because, of

course, there is a limited number of organs for transplantation and as the number of HCC has increased, then we push more patients towards having a resection.

It's not ideal because, of course, you haven't then dealt with the background cirrhosis and other nodules may undergo malignant transformation in the way that the first nodule has done. There is a third modality of treatment, which is what we call thermal or chemical oblation, in which under imaging control you inject either alcohol or other materials to kill the tumour nodule, or you put in a radio frequency signal which heats it up, or a laser fibre which heats it up, and those approaches are also being increasingly used.

Q. Thank you.

A. That can be done almost as a day case.

Q. I see. Can we move on the next page, please? Much of this we have already discussed, professor. For example, you mention determinants of the presence and quantity of virus in the blood stream, and we know that these levels tend to be higher in immune-suppressed people such as those infected with HIV. But you say the level of viraemia does not appear to determine the rate of progression to liver cirrhosis in the non-immune-suppressed, although we have had some discussion about that this morning?

A. Yes, I think it's a moot point, really.

Q. It's a moot point.

The levels of transaminases also fluctuate over time but you say that the presence of normal transaminases is not necessarily a reassuring sign because it doesn't exclude significant liver fibrosis. Then we come on to look again at the rates of progression and we can see here major risk factors, and you have given us a table showing the possible impact of different factors.

A. In the illustration marked "figure 5", the range is given to give you a feel for what would be the difference between somebody with, you know, a full house, if you like, of the poor risk factors, as opposed to absence of these risk factors, when the lower figure would pertain.

Q. Yes.

A. So, you know, if you are male and you are infected -- it should be after 50 years of age, by the way, not 55 in the little red insert. If you are male and infected, an older age group, and you are taking significant amounts of alcohol, then you might go down the one, five, 15, 20-year progression route; in other words, the left-hand of the two figures. Whereas if you were female, infected in earlier life, not taking any alcohol, then you might go through the 15, 25, 35 series of figures

really. They are just guides.
Q. I'm sorry, the correction you made is in the little red box?
A. Yes.
Q. It says "55" and it should say 50?
A. Yes.
Q. Right. We see there mention of obesity. How does that impact?
A. Yes, it's becoming increasingly the case that three things are operating adversely in many patients. One is Hepatitis C itself. Second is, as we have mentioned, alcohol, and whether there is obesity, which is associated with deposition of fat in the liver. So what's becoming clear with all of these so-called insults to the liver is that the accumulation of fat, which ultimately may burst the liver cells, is bad news in terms of creating a risk of fibrosis.
Q. Right.
A. And those three things that I have mentioned, alcohol and obesity and certain genotypes of Hepatitis C, all cause an accumulation of fat in the liver. And the genotype that is most involved in the accumulation of fat is genotype 3.
Q. Yes. You give us underneath the diagram what I suppose are really the bookends. So at the severe end of the

spectrum you have the quarter who are predicted to progress from infection to cirrhosis in under 20 years and then at the less severe end you have the third who aren't going to progress to cirrhosis for at least 50 years, and everyone else in between.

A. And the slow progression group, as well exemplified by the Irish women who were infected with rhesus immunoglobulin where, at various intervals of follow-up, the incidence of cirrhosis has been extremely low. That's obviously because they are female. They have heeded the don't drink side of things and in the main they have been infected, obviously, during their child bearing years. So they have been infected at a young age.

Q. The likelihood of your female patients adhering to the advice not to drink is greater, is it?

A. I don't know that it's greater. I just happen to know that in that group -- there aren't any pregnant males in that group, of course.

Q. Yes. It's perhaps wise to be circumspect on these matters. You explain -- and again I think we can follow the logic of this because you have mentioned it several times -- that the decision regarding which patients to treat depends predominantly on histology.

Then you go on to tell us on the next page what

current gold standard treatment involves.

A. "Gold standard" here means the current NICE recommended, and in Scotland it would be the SIGN recommended approach to treatment.

Q. And indeed, some improvement, I think, is anticipated in the length of time for which people may have to take these medications -- indeed, I think it's already here, and this is the third paragraph -- that if the RNA is undetectable by the fourth week of therapy, then the patient presumably receives the welcome news that treatment duration can be shortened. But the other side of the coin is that if RNA is still positive at the 12th week of therapy, treatment is usually stopped because the chance of a sustained viral response is insignificant.

The protease inhibitors, which are presumably very close to being used for patients, you say, will increase the response rate in genotype 1 patients to around 80 per cent?

A. Yes, I think 70 to 80 per cent. That's the clinical trial data. And I think they are going before NICE in March -- in the next six months up to March, that sort of timeframe.

Q. Right. I think I have understood from you that these are quite expensive drugs. Is that right?

A. Yes, I guess we don't really know what will be charged at the moment, but I think the -- the reasoning that I have heard -- because the doctors have said to the companies, "Why are you proposing charging this amount of money?" And of course, they have calculated it on the basis of how much it costs to provide a cure, an SVR. So if you are doubling the sustained viral response rate in genotype 1, you are moving it from 40 to 80 per cent for instance, then the market would withstand, if you are expressing it -- as the new health service reform might ask us to do -- as a cost per cure -- and this would be not only in Hepatitis C but perhaps in other conditions as well. The cost per cure would be the same if you charged twice as much, if you are getting twice the number of cures.

So there seems to be that sort of logic in the system somewhere but, of course, there are two drugs, telaprevir and boceprevir, and there are many more coming through the pipeline, which presumably will create competition and force prices down.

Q. Yes.

A. These are used, by the way, along with pegylated interferon and ribavirin.

Q. Right. So the side effects won't necessarily change?

A. I think the side effects will be more severe with the

protease inhibitors because when similar compounds, but not identical compounds, are used in HIV, then they have caused liver toxicity. You know, accumulation of fat in the liver, for instance, has been seen with some of the HIV-active protease inhibitors. So how that will work through with Hepatitis C is not 100 per cent clear.

Telaprevir has been causing quite severe rashes. But the final costing is going to be dependent on this last thing that I mentioned, which is a predictive polymorphism of IL28, which is a lambda interferon. There is a polymorphism, which is strongly associated with response to treatment. So it might allow you to pick out those people who are going to respond to pegylated interferon and ribavirin from those which won't, and that latter group might then, instead of going through a trial of the pegylated interferon and ribavirin, they might start initially into those two drugs with the protease inhibitor.

And that will influence the health economics. And then there will be the issue of early-stopping rules of the type that we mentioned in interferon and ribavirin because if you can, at an early stage, identify those that are going to be successfully cured, then again that will increase the cost-effectiveness. So there are several groups now looking at, in preparation for NICE,

what the management algorithm might look like, and I presume that ultimately that may influence what the costs would be.

Q. Yes.

A. And the unknown, of course, is the competitive issue as well.

Q. Yes. Are telaprevir and boceprevir made by different manufacturers?

A. Yes, telaprovir is made by Vertex and boceprovir is made by Schering-Plough, but they have just been bought by Merck Sharp and Dohme.

Q. As you say, in Scotland we use SIGN and no doubt similar sorts of guidance is being looked at for Scottish patients?

A. Sure. One of the figures that was cited was that it might cost up to £18,000 for a combined course of pegylated interferon, ribavirin and one of these protease inhibitors. And, you know, I think, if my memory serves me correctly, a full year's course of interferon and ribavirin probably costs about £10,000, that sort of level. So they are looking at doubling it in anticipation of the doubling the response rate, so that the cost per cure is slightly improved on what it is now. So when you do the cost-effectiveness analysis, it will come out as a significant improvement.

Q. Right.
A. Which is one thing that NICE and presumably SIGN will be looking at.
Q. Yes. And you look to the future, Professor Thomas, and you say that the current situation, I infer, is not static, that there are attempts to develop further drugs with which to treat Hepatitis C.
A. I read somewhere that there is no condition with more drugs in the pipeline than Hepatitis C.
Q. Right.
A. I was in the position of having to do a review of that recently, and by 2015 I think there will be about 30 new drugs waiting in the wings. And that will, of course, influence what happens in terms of pricing, I guess.
Q. Right.

Well, Professor Thomas, there has been a lot of unhappy information over the past day and a half and perhaps that slightly more optimistic note is a good note on which to end. So thank you very much for giving us all this information about Hepatitis C.

THE CHAIRMAN: Mr Di Rollo?

Questions by MR DI ROLLO

MR DI ROLLO: Professor Thomas, I just want to pick up on one or two points in relation to what has been said today and yesterday.

Just now and also yesterday you used the word "cure". Yesterday, I think, in the context of different genotypes and treatment with interferon and ribavirin, and whether or not the outcomes would be different depending on the genotype. I don't know if you remember that passage in your evidence?

A. Yes, I do, yes.

Q. One thing I would like to ask you about is the use of the word "cure". Would it not be more accurate to talk about effective treatment, rather than cure in this context? Are you ever really cured, is what I'm trying to get at?

A. In short, I think you are, so long as you are treated before you have cirrhosis. And, I mean, the phrase that's used is "sustained viral response"; in other words, undetectable HCV RNA six months after the end of treatment. If any reappearance of RNA is going to occur, it will occur in the first few months after the end of treatment.

You are right to question this because, of course, we were conservative about translating an SVR, a sustained viral response, into the word "cure" for many years, until we had decent long-term follow-up, and long-term follow-up has shown that viral relapse is a very infrequent occurrence.

The other aspect of cure, of course, is not just a virological cure but we were also wanting to imply that if you treat before cirrhosis has developed, then the existing scarring there, or fibrosis, if you do get an SVR, regresses slowly, so that the scarring is reabsorbed, as Professor Oliver James was saying in relation to a lesion of the thumb or the liver.

And that is an evolving field, by the way, because it hasn't been possible to, in the haemophilia population, do frequent liver biopsies for the obvious reason. But we have got non-invasive techniques now, so-called vibro-elastography, where, with an ultrasound wave, you flick the liver and measure how much the liver wobbles, which tells you how stiff it is, just like a jelly being flicked, if you like. And the stiffness of the liver is related to the scarring in it and that should reduce in somebody with an SVR, and indeed it does.

But it may be several years before it actually goes back to normal and we don't have a big enough cohort of patients really to make that comment.

Q. Is it correct to say then that there may be situations where there will still be a lingering damage to the liver?

A. I think the really important group, of course, is the

patient who comes for treatment once they have got cirrhosis, because even though we cure the viral infection there, cirrhosis really doesn't disappear and, as you heard during the course of the discussion, the cirrhosis puts you at risk of liver cell cancer.

So there are patients who have undergone a sustained viral response. They are cured virologically speaking, who already had cirrhosis prior to treatment, and in that group some of them have gone on to develop primary liver cell cancers. So in this group you are quite right, we shouldn't be talking about a cure of their overall condition because they are still at risk of this severe complication. But for all the others, short of cirrhosis, who have a sustained viral response, then ultimately their liver should go back to normal. And that word "should" is in there intentionally because we have only got a few years observing that at the moment, and it may take longer than that period to go back to stage zero, which is normal in terms of scarring of the liver.

Q. Does cirrhosis occur in situations where the condition doesn't become chronic? I think at one point in your evidence yesterday -- I may have misunderstood what you were saying, but is it possible to have a situation where you simply have an acute episode but still, at

a later stage, suffer from cancer, liver cancer, as a result of that acute episode at a later stage? Is that possible?

A. No, no. I think the march of events is acute infection, failing to resolve, giving chronic infection and then cirrhosis, and then the risk of liver cancer. You can't miss out any of those stages, if I could phrase it in that way.

Q. I think there was a point at which I did misunderstand that.

A. I'm sorry if I have given the wrong impression.

There are cases where somebody will have reported an acute hepatitis and then many years later have developed a -- it has become apparent they have got a cirrhosis and then a liver cancer, and that we have interpreted as being an asymptomatic cirrhosis where they have had a superimposed acute viral hepatitis which could, of course, be A, B or C -- superimposed on top of cirrhosis.

Not everybody, for instance, will declare how much alcohol they are taking. We used to be very cynical about that as doctors, we are less cynical about this now. Patients are much more forthright about what they are taking.

Q. There is a sentence in your report which may be

misleading or may be misunderstood. It's at page 11. Could we just have that up on the screen?

A. I have that, yes.

Q. It's under the "Chronic Infection" headline. I'll just read out the whole section:

"The main aim is to prevent development of cirrhosis and death from liver failure and liver cancer. It is worth noting that it is only those that have progressed to cirrhosis who are at risk of HCC. Even those who have cleared the virus, either spontaneously or on treatment but already have cirrhosis, are at risk of developing HCC."

We should understand from that, from when you are telling me, that, unless you have developed cirrhosis, you are not at risk of developing HCC. Is that right?

A. That's right, and I think the area of confusion may be -- because you are thinking of spontaneous clearance after acute infection.

Q. Yes.

A. That a small number of patients each and every year will clear the virus and this could occur at one or five or ten years after the onset. So that's probably why that's a bit confusing.

Q. Thank you for that.

One of the things that I wanted to ask you about is

the question of the statistics relating to the percentage of people that spontaneously clear the virus and then there is another percentage that go on to develop the condition. And relating in particular to haemophiliacs, who had repeated doses of concentrates over a period of time, if someone has been infected with the virus and then cleared it spontaneously and then has a concentrate again later on, presumably the percentage chance of not clearing it -- that person is back into the pot again in terms of what the chances are for that individual.

In other words, is it that the more times you have concentrates, the more times eventually you are not going to clear spontaneously and you are going to develop a chronic condition. Is that reasonable?

A. Well, I think that probably is reasonable. I think it's going to be a deduction for me to say that it's reasonable because I don't think there is good data on that. You know --

Q. What I was going to suggest was that in some board games you have to throw a double six to start, and you keep throwing a double six until you start the game or get your turn to go. Presumably, the more times you take concentrates, one would have thought, intuitively, the more likely it is eventually you are going to get

a chronic condition as opposed to situation where you are going to spontaneously clear every time.

A. I see where you are coming from. The only factors that I know of that differentiate between those that clear the virus and those that don't are the HLA class 2 proteins. And Mark Furze(?) and I published in the Lancet ten years ago that there are certain HLA types which have a strong possibility of leading to clearance of the virus and other HLA types which don't allow clearance, and that, of course, won't change. Your HLA type is genetically determined, and those HLA proteins present parts of the virus to the immune system and say, "Look, this is a virus. I'm a cell. This virus is in me, kill me." And you know, if your HLA proteins present the virus fragments well, then the outcome will be clearance.

Now, that comes through in the data, is probably the bottom line, and it comes through statistically significantly so, and it has been confirmed in three or four other studies subsequently, and that HLA phenotype won't change. If, when you are throwing your double sixes, everything is the same. I know in random situations you are going to not throw double sixes but it isn't random here. Your environment has stayed constant, your HLA proteins have stayed constant.

Q. I mean, have any detailed specific studies been done in relation to haemophiliacs or are the studies more general than that?
A. The studies that we did were mainly in intravenous drug users, not in the haemophilia population. I think the principle would still apply but it could be that haemophiliacs have a lower proportion of the good HLA genes or a higher proportion. It could go either way. I don't know the data and I don't think it has been looked at.
Q. Obviously your studies, as you have now told us, didn't concern haemophiliacs. Do you know if studies have been done by others in relation to haemophiliacs in relation to this particular point?
A. I don't know of any information.
Q. Right. As far as treatment is concerned, and having more than one genotype, is it correct to say then that if you have more than one genotype of the virus, then treatment may be more complicated and less likely to succeed? Is that reasonable? Are those three things reasonable? More complicated, more difficult and less likely to succeed.
A. You would think that that would be the case and particularly if you have a mixture of genotype 1 and 3, for instance, you would expect the genotype 1 to require

a year of treatment. Your genotype 3, all else being equal, would only require six months. What happens when the two are there together, I don't think we know. There is only relatively small numbers of patients treated.

I think the other thing that has been a problem in treating the haemophilia population is that the interferons have been given subcutaneously and of course, we are worried about forming haematomas by having to inject three times a week. The pegylated interferons, of course, we only inject now weekly. So that problem is starting to diminish. And initially, when we had to give the injections more frequently, we gave them intravenously to make sure we didn't cause haematomas.

When we were only looking at 12 to 15 per cent response rates, when you are explaining the risk/benefit to the patient, the need for repeated intravenous injections was something that would be considered -- in genotype 1 it would have to continue for a year. That would be discouraging to the patient, I would think.

Q. When was it appreciated that there could be more than one genotype of the virus? When did that realisation become apparent?

A. It would be in the first two or so years after its

discovery in 1989.

Q. Right.

A. I would guess around about sort of 1991/1992, that sort of time.

Q. Have you heard the term "occult hepatitis"?

A. Yes.

Q. Can you explain what that is, what it means; what is meant by "occult hepatitis"?

A. Occult hepatitis is when really you are arguing that the virus is present in the liver or in a cell but not in the circulating blood. It has been raised in relation to sustained viral responses. You know, could it be that you cleared the virus from the blood but not from the liver? And I think in the first few months after -- you know, when you are coming up to the end of treatment, there may be situations where you can't detect it in the blood but it is still present in the liver.

It has also been described with Hepatitis B, where it has been more complicated actually, because whether the virus is detectable in the blood is partly dependent on antigenic assays, Hepatitis B surface antigen assays. One case that we dealt with in southern Italy, where the patient was DNA positive but HBsAg negative, turned out to have a mutation at position 145 in the envelope gene

of the virus, in the surface antigen gene, which destroyed its antigenicity. So that virus was occult, if you like, but still there. And there are situations where it has been argued that the virus, Hepatitis B, may be present in the liver but not in the peripheral blood, other than that situation I have just described.

Why do you ask particularly?

Q. Some of those who I represent have raised the matter and are interested in the question of what it is.

THE CHAIRMAN: Could I know what the nature of the interest is, Mr Di Rollo? Is it something I'm going to have to consider and report on because if it is, at the moment I have an answer that there is something called "occult hepatitis" but I don't really know what its relevance is.

It's quite important, Mr Di Rollo. I hope we are reaching the end point of oral evidence in the Inquiry and I'm anxious to get an answer, as we go, rather than to have to extract answers from Professor James later.

MR DI ROLLO: I think it's in the context of those that feel that they are suffering symptoms but there is a negative PCR test, and it's in that --

THE CHAIRMAN: That does begin to give context but I think that you really have to develop that with the professor, that there is a group of people within the total

haemophilia population who are reporting symptoms but who, on test, prove negative.

There could be a vast number of reasons for that, I suppose: the sensitivity of the tests and all sorts of others. But I think you have to explore it, Mr Di Rollo, really.

MR DI ROLLO: I was going to explore it in the context of extra-hepatic manifestations but it's plain from the report, the review that we were referred to by counsel to the Inquiry, at page 55 of that, that according to this chronic HCV infection may have an impact on patients beyond liver damage.

These extra-hepatic manifestations can involve multiple organ systems, including renal, dermatological, haematological and rheumatological systems. In the course of your evidence you have mentioned specifically, I think, issues in relation to brain fog and the like, that there are patients, I think, that do report symptoms where there is apparently a negative PCR test and they have other kinds of symptoms. So it's in that context that I'm raising this issue of occult hepatitis.

THE CHAIRMAN: I'm still a bit worried, Mr Di Rollo. I had understood the extra-hepatic manifestations here largely to relate to circumstances in which there were hepatic manifestations but also other manifestations. But at

the moment are you figuring a situation in which there are extra-hepatic manifestations of the kinds described in this report, but no hepatic manifestations.

MR DI ROLLO: That's is what I'm asking about occult hepatitis. That is what I'm asking about.

THE CHAIRMAN: I think you have to ask the professor whether that sort of situation exists, where the symptoms are real as distinct from imaginary or whatever.

A. I would say, first of all, that these extra-hepatic manifestations -- and you mentioned specifically renal, dermatological and, you know, the non-Hodgkin's lymphoma, all of those, I think without exception, really, have continuing viraemia detectable by HCV RN PCR test systems.

In the context of brain fog, the majority of the virus is being produced in the liver and these patients have viraemia. Where there has become an issue in some respects is that -- we were discussing Koch's Postulates, which are that, you know, if a group of symptoms are associated with an infection, when that infection is cured you would expect them to go away. If that doesn't happen, can you argue that there is occult Hepatitis C? And one of the problems that, for instance, has been -- when we have done physical and mental wellbeing scores, these so-called SF36 scores,

which were cited under a reference of Dr Wright -- perhaps we could pull that up actually.

MR DI ROLLO: I'm sure we can.

THE CHAIRMAN: I'm sure someone will have the reference for it by now.

A. Sorry, I can find it actually.

THE CHAIRMAN: Maybe we should all see it rather than just you have it available.

A. I could tell you the page reference. It's page 51 in this document that's on the screen at the moment.

This is the table at the top. You can see that people who have a reduced quality of life score initially get worse when they are on treatment. So in mild disease it goes from 0.77 to 0.65. 1 is normal by the way. SVR after mild disease, in other words, after we have got rid of the virus, goes back to 0.82 but it doesn't go back to 1. People have said, "Does this mean that there is any residual virus left?" But, of course, how somebody feels is a very complex situation really. They are still worrying about, you know, what all this means. They might not have had all their questions answered adequately, and I don't think you can take any residual, compromised quality of life scores as indicative that there is occult HCV; particularly in the context of the 95 per cent of patients who have, either

currently or in the past, used recreational drugs, because their quality of life score would be dependent on whether they have an addictive propensity, you know, whether they need addictive drugs still.

So in short, I think the evidence both in the extra-hepatic manifestations which are well established -- like cryoglobulinemia, like renal disease -- those patients have viraemia, it isn't an occult infection, and those that, after a demonstrable sustained viral response, where more than six months after the end of treatment they are undetectable by the most sensitive HCV RNA tests, if those people have residual cognitive abnormalities, it is often related to non-viral related problems.

Of course, there are other issues about compensation, et cetera, which are also there in the background, which the neurologist will always tell you make it difficult to evaluate residual symptoms after an acute illness really. These are often subconscious. They are not a deliberate intention to promote continuation of symptoms. You know, they are still worried and they do have symptoms that are not related to viraemia.

THE CHAIRMAN: Professor, I wonder if I could try and tease out an example from the table.

If one had a haemophilia patient, whose HRQoL is measured before manifestation of Hepatitis C appears, would that person have a score of 1 or would it be likely already to be compromised by living with haemophilia?

A. I suspect -- these studies have been done in non-haemophilia.

THE CHAIRMAN: Yes, indeed.

A. I suspect that it would be compromised, yes.

THE CHAIRMAN: That's the first point that I'm interested in because if that is the case, then restoration to the status quo ante would not be to a score of 1. But if we then look within that, a person who has had moderate disease, to take that example, and has suffered from it and then has treatment, would that person not, even after being told he or she -- in this case he -- was successfully treated, be concerned enough about the history to score under par, as it were?

A. Yes, this starts to come out when you -- if you blind -- in other words, if you look at the scores after treatment, before the patient knows the outcome, then there are studies that have been done in the USA which suggest that part of the improvement is related to the fact that the patient knows that his SVR is negative. If he doesn't know that, then there is a group where it

does return to the pre-treatment level, but there is also a group where it doesn't.

THE CHAIRMAN: That, I have to say, at the moment doesn't surprise me because it seems to me that just the nature of the human response to having been ill is a continuing concern whether there is some sort of residual deficit, as it were, and if that were the case, then it would make it very difficult perhaps to attribute a cause to that continuing situation, if nothing could be measured.

A. I think that's true, yes.

THE CHAIRMAN: I don't know if that helps, Mr Di Rollo.

MR DI ROLLO: I think it does.

The situation is that it's one of these problems that it's very difficult to actually identify what is causing the trouble at that particular point, and it may or may not be related to the actual virus or the fact that there was a virus there in the first place.

A. Yes. What I was trying to say is it's a very complicated situation really. There is the pre-treatment problems. They may have additional problems, other worries, financial worries, you know, and doctors tend to find reassurance, since they are making very difficult decisions -- they find reassurance if there is something objective they can measure, which is the presence or absence of the virus by techniques

which are exquisitely sensitive really. And if, when you do that, you come up with a logic, something that you can understand -- when the virus goes down the patient feels better; when it goes up again, he feels unwell -- all that reassures the doctor that he is probably measuring something that's relevant.

Q. Can I just come back then to the issue of extra-hepatic manifestations, which I understand, obviously, is not the same thing. We are talking about a situation here where the liver is, one can see objectively, affected. But there are other things that are happening to the patient. Can you just describe for us what these other, or extra-hepatic manifestations are? Can you just go into some detail about each of them? They are referred to here as involving multiple organ systems, including renal, dermatological, haematological and rheumatological systems. Can you just go through that for us and just explain what they are?

A. The easiest ones to deal with are the renal and dermatological, in as much as there is a condition called "cryoglobulinemia", where the virus is complexed with antibody, and this complex, when the blood is cooled, precipitates out of suspension, and these immune complexes, the cryoprecipitate, will stick in small blood vessels, and the ones that are affected most often

are those in the kidney.

When you look at the cryoglobulin, depending on what antibodies it has got in it, you can classify it and, as you see here, it's the mixed cryoglobulinemias, which I think are a mixture of IGM and IGG antibodies, which I think are specifically involved here. There are other cryoprecipitates which have different classes of antibodies in them. The dermal complications can again be related to immune complexes deposited in the capillaries or small arterials in the skin so that you get small nodules and often they are on the lower limbs.

The other dermatological associations are these ones called -- this problem called "lichen planus", where I think really we have no idea as to why the infection should be associated with lichen planus. I think porphyria cutanea tarda is a metabolic disease where there's a genetic component and I think you could probably take that out of the list now as being causatively related to Hepatitis C.

The non-Hodgkin's lymphoma, I think, is, as we discussed yesterday, difficult because undoubtedly in the Mediterranean countries -- and by that I mean southern Spain, southern France and Italy -- there is a very high prevalence of Hepatitis C in non-Hodgkin's lymphoma, as opposed to Hodgkin's lymphoma, which is

a control group that was looked at in the same studies.

But if you look in northern Europe, the prevalence of infection in a non-Hodgkin's lymphoma is not significantly different from the normal population. So we don't have any epidemiological data for the virus being involved in non-Hodgkin's lymphoma in northern Europe. It's possible that a series of viruses in a particularly genetically pre-disposed individual could cause a non-Hodgkin's lymphoma and different viruses are operating in southern Europe to northern Europe, but that's a bit of a resort of the destitute really because we have no evidence for that.

Q. I think the table 3 that's -- if you go over to page 57, there are some other conditions referred to that that finishes there. But what I would really want to draw out from you is, from the point of view of the patient, these extra-hepatic manifestations, what would the patient suffer, taking them in turn: the renal, the dermatological, the haematological and the rheumatological problems or systems? How would that manifest itself as far as the patient was concerned, these extra-hepatic manifestations?

A. If you take the so-called autoimmune diseases, which are associated but not necessarily causatively associated -- if you take rheumatoid arthritis and autoimmune

thyroiditis, there is a genetic predisposition to those conditions. They usually have A1-B8-DRw3, one particular HLA pattern. If you have got those, you are more likely to have these autoimmune problems, and interferon makes those autoimmune diseases significantly worse.

Q. So the treatment makes them worse?

A. Yes.

Q. Right.

A. And we will screen patients prior to starting treatment for antibodies in their blood which tell us whether they have thyroiditis or rheumatoid arthritis and in those patients where the symptomatology gets worse during treatment, if you look at the pre-treatment specimens, they already have these conditions, it's just that the interferon has brought them out, made them worse, if you like. That is not an absolute contra-indication but it is something one would need to discuss with a patient. I have a patient whose arthritis got really extremely severe on interferon so that we had to curtail treatment.

Q. What about the dermatological problems? What extra-hepatic manifestation would you get? What is the skin trouble that one would have?

A. The one that's best causatively related to the

Hepatitis C is this cryoglobulin anaemia, where, over the lower parts of the leg, there will be thrombosed arterial -- little black nodules on the lower limbs, which look like purpura but they are actually thrombosed blood vessels, where the cryoglobulins, the immune complexes, have got stuck in the small blood vessels.

Why in the lower legs? Well, the circulation is slower in the lower legs and I guess it's more likely to precipitate there, and the lower legs are also colder than the upper limbs or the trunk, so the cryoprecipitate, which precipitates out of the blood with a falling temperature, is more likely to occur in the lower limbs.

PROFESSOR JAMES: And they are quite painful, aren't they? The nodules are quite uncomfortable if you have them?

A. Yes.

THE CHAIRMAN: Could I ask when these manifestations were known? For example, you say that you screened patients in advance for certain of these conditions. What timeframe should one have in mind for that?

A. In a historical sense?

THE CHAIRMAN: Yes. Is it recent or ...?

A. I guess we always knew that interferon stimulated the immune system. So I guess from the early 1990s we would be thinking about whether we made autoimmune diseases

worse. I think, with the licensing, probably in the package insert it will say that the interferons may make these autoimmune conditions worse. So that would allow you to fix a precise date. But it would be in the early 1990s.

THE CHAIRMAN: So it's not a very recent discovery?

A. No, no.

MR DI ROLLO: It sounds to me as though these manifestations are as a result, not of the underlying condition, but as a result of the potential treatment. Is that right?

A. No, the autoimmune conditions, initially we didn't know whether they antedated or were caused de facto by the interferon but, of course, now we know that they may occur, we test all patients, before they start treatment, for antibodies, to tell us whether they have got thyroiditis or whether they have got rheumatoid propensity. It makes sense really that interferon is probably making a pre-existing condition worse because of the genetic predisposition that we know exists. With the context of interferon treatment, there is a genetic predisposition to develop these diseases, if you have A1-B8-DRW3, one particular grouping of HLA proteins.

Q. So is this underlying condition as a result of the virus or is it as a result of the patient anyway having that underlying propensity?

A. It's in relation to the patient and the interferon boosting their immune system.

Q. I follow.

A. For instance, you could be giving interferon for treatment of Hepatitis B. With the same genetic predisposition and a different virus, the interferon will still cause these conditions to get worse. In hairy cell leukaemia, where interferon was used, similarly you would make these conditions worse. It's related, in a genetically pre-disposed person, to the chemical effects of the interferon stimulating your immune system.

Q. While we are on the subject of treatment, as we know, many of those who were infected with HIV through blood products also were infected with Hepatitis C through blood products. I just want to ask you what the effect of HIV infection has on the ability to treat Hepatitis C?

A. You need to actually consider both viruses. The issue has always been do you give highly active retroviral therapy first and then Hepatitis C treatment or do you do it the other way round? I think in the main patients are treated for their HIV first and then the interferon and ribavirin treatment would be added in. The reason for that is that, as we discussed, the progression of

Hepatitis C in the main is much slower than untreated HIV. So if you can unlink these problems, then you are going to be in a better situation. Also, don't forget, as a result of treating the HIV-related immuno-suppression -- in other words, by getting rid of the HIV or at least suppressing the virus -- you will see recovery of the immune response; the CD4 count will go up and the amount of Hepatitis C will come down anyway. Against that lower background, logic would suggest that you are more likely to get a sustained viral response with standard Hepatitis C pegylated interferon and ribavirin.

Q. Does having to treat both affect the outcome in the Hepatitis C? Does it mean you are more likely or less likely to treat effectively the Hepatitis C?

A. Yes. I think the overall data suggests that the sustained viral response rates are probably about half what you would otherwise see, so that in a genotype 1 you might see a response rate of maybe 20/25 per cent, instead of 40 per cent. How much of that is corrected by prior treatment of the HIV, I don't think we really know at the moment, but logically you would expect it to be improved.

Q. Presumably, also it means that the treatment takes longer if you are having to deal with both and therefore

the Hepatitis C has got a longer time to progress down the road. Is that fair or not?

A. Well, I think against the timeframe of progression of Hepatitis C -- and don't forget we have been discussing it going one stage every five years. Against that rate of progression, I think delaying long enough to get the HIV under control would be insignificant in terms of the progression of Hepatitis C. It is going faster in an HIV-infected person than in a non-HIV-infected person but even so it's not a rapidly progressive disease.

Q. I take it that throughout the 1980s it was the case that doctors did monitor haemophilia patients' ALT levels. That's what was done more or less as a matter of course. Is that right?

A. I think so, yes.

Q. And presumably that was because of concern about the potential for liver damage as a result of factor concentrates?

A. Yes, I think following that observation by Craske and colleagues -- I think it was in the Lancet, wasn't it? --

Q. Yes.

A. -- in 1978, I would have thought the majority of haemophilia patients would be getting their liver functions tested.

Q. Obviously, there was, as we saw yesterday, increasing concern about the non-A non-B as time went on, not only its incidence but also its severity?
A. Yes. As we were discussing, the timeframe of that is difficult to ascertain but in the period from 1978 through to 1985 it's becoming clear that it's a more serious --
Q. By 1985, however -- I think yesterday you used the word this is a "cut-off" or there was a sort of watershed?
A. Yes, I think summarised by just citing what I did about Sheila Sherlock's book. She summarised situations very well, and I think, as you heard, from edition 6 through to edition 8 she really changed her tune and said that she thought it was a more serious condition.
Q. All right. Thank you very much.
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, sir.
THE CHAIRMAN: Ms Dunlop, do you have anything to follow up?
Further questions by MS DUNLOP
MS DUNLOP: There is one question which I would like to ask just before we let Professor Thomas go.
It's just back to the sentence you have about acute infection. For the record, it's on page 11 of

[PEN0171071]. If you happened to know that a patient had been infected on a specific date -- I suppose it might be a patient who is a bit ill and has gone to see the doctor and has been tested and maybe it's after a blood transfusion or something. So you have the date of infection and you know you are within the first six months. Is there a dilemma there? Do you say to yourself, well, this patient may clear the virus spontaneously or, given that there is a 90 per cent success rate from administration of interferon in the first six months, do you move straight to giving them interferon?

A. I think nature has been a little bit kind to us, in that, if they are going to spontaneously clear, although the cut-off is taken as six months, very many will have already cleared by six months, and the results of using interferon in the first three months after infection, as opposed to between three and six, don't appear to be significantly different.

So I think what Jackel and Manns did in subsequent studies is take the very earliest ones, earlier than three months after infection and three to six months, and they really concluded, so long as you treated before six months, it was okay, you got the improved results.

I mentioned yesterday that sometimes Hepatitis C is

transmitted if a surgeon injures himself and a small amount of his blood goes into a patient, or vice versa: if surgeons operate regularly on haemophilia patients who have Hepatitis C and they become infected. In both directions we would screen the individual, the surgeon or the patient, at two-weekly intervals so that we picked up the viraemia as soon as it occurred and then we would, between three and six months, institute treatment.

Q. Thank you very much.

THE CHAIRMAN: Thank you very much, Professor Thomas.

Ms Dunlop?

MS DUNLOP: We have pencilled in the possibility of some discussion today about what should happen in the New Year. I think, however, it might be advantageous if counsel were able to talk about that among themselves for a short time first.

THE CHAIRMAN: I hope it would be advantageous if counsel talked about it first; I'm not confident.

Thank you very much. I don't think you need to be concerned about this stage.

MS DUNLOP: Maybe, if we plan to resume at two, I think that would allow time --

THE CHAIRMAN: I'm quite flexible about it. We will aim for two but if you were to benefit from an extra quarter of

a hour/half an hour, that would be all right by me; I wouldn't be concerned.

MS DUNLOP: We are obliged.

(12.27 pm)

(The short adjournment)

(2.15 pm)

Submissions by MS DUNLOP

THE CHAIRMAN: Ms Dunlop, has the time been profitably used?

MS DUNLOP: Yes, I'm grateful to you, sir, for allowing us a little bit more time. I'm keen to let others speak for themselves. So I think that amongst a number of issues one could usefully discuss at present, what I want to focus on is the whole idea of closing submissions.

As a result of discussions involving all counsel, we have a sort of embryonic plan, which, if I may, I'll just rehearse, and I'll no doubt be corrected if I get any of it wrong.

The idea is that each team, as it were, would use the period immediately after the New Year to try to define the issues or the questions which arise. That would be done by reference to the topics which have been examined in the oral hearings.

Plainly, some of the topics are themselves issues or could very easily be converted into questions. So

I think what's envisaged is that there would be at least one sublevel underneath a topic, so that one would start to say, "Well, a sub-issue is ..." For the purposes of discussion, it may be helpful to think of one we have just handled, which is B4, the introduction of the screening of donated blood for HIV.

One could envisage sub-issues along the lines of whether there was an independent effort to evaluate testing kits in Scotland, whether that was in some way thwarted and whether, if it had been allowed to proceed, screening could have been introduced in Scotland more quickly than it was.

I stress that is just an illustrative exercise but that is the kind of definition of questions that certainly I have in mind.

What is anticipated from the team of Inquiry counsel is that the preparation of these questions or issues would be led by the individual counsel who have led on a particular topic. We would hope that that statement would be ready perhaps by the third week of January, so a little before the end of the month. I think we would all envisage that there will be some liaison among all the counsel during January, just to see how everybody's mind is working. I think that would probably help.

Then there will probably be a further phase, where,

probably not Inquiry counsel but counsel for core participants, will work on answering some of these questions or some of these issues. So they will be advancing submissions on how they would suggest particular questions should be answered. That phase might take until around the middle of March and suggested resolution of these issues could be submitted in writing. I think we are still, as a group, quite open-minded on how much of this will require oral sessions or oral presentation.

THE CHAIRMAN: On the scheme so far, only Inquiry counsel would be preparing the initial submissions in January?

MS DUNLOP: Well, all parties would be working on their own versions of what the questions or issues are to be, and then these would be submitted before the end of January, perhaps the third week of January. And I think, as a result of the discussions we have had, it became clear that individual core participants are likely to want to go further, and at least in relation to some questions or issues, they would want to suggest what the answers should be.

So taking the example that I'm using as a working example, of screening, if a party, perhaps the families and the Haemophilia Society, wanted to suggest that screening could have been introduced more quickly in

Scotland, then they might submit a second round of submissions which will be trying to argue that that is the case. So they will identify parts of the evidence on which they rely in suggesting that screening could and should have been introduced more quickly in Scotland.

That seems to be a stage which would be sought, I think, by some of those representing core participants.

THE CHAIRMAN: In the second stage then that goes up to mid-March, do you envisage Inquiry counsel responding to the initial presentations by participants?

MS DUNLOP: I think we don't, sir. We, consistent with Inquiry counsel being neutral, the four of us wouldn't anticipate suggesting what the answers should be to some of the posed questions.

THE CHAIRMAN: That might lead on to oral hearings in due course but ...

MS DUNLOP: As I say, I should be corrected if I'm getting any of this wrong, but I think that is really the synopsis of the discussions that we have had on the whole topic of closing submissions.

For what it's worth, the separate matter of a closing statement is something on which Inquiry counsel really would see themselves as being

disinterested, and I don't think I can envisage circumstances in which Inquiry counsel would want to make a closing statement but others, I think, will want to make a closing statement of some sort.

THE CHAIRMAN: Do you have any understanding yet of what that might be?

MS DUNLOP: I think they need to tell you themselves, sir, and I think really from the perspective of Inquiry counsel, those are the only matters which I would want to mention today, but if you will allow me a moment, sir, I will check I haven't forgotten anything. (Pause) I'm reassured I haven't.

THE CHAIRMAN: Mr Di Rollo?

Submissions by MR DI ROLLO

MR DI ROLLO: Thank you, sir.

As far as the procedure of identifying issues and thereafter presenting, in written form, a submission in relation to such issues as is thought to be appropriate, I can confirm that that was really discussed between us and we think that that procedure should be followed.

THE CHAIRMAN: Can I just check on your understanding of and agreement to the timetable implicit in that.

MR DI ROLLO: Indeed.

THE CHAIRMAN: Does that involve agreeing that your initial written statement, whether it's submissions or

otherwise, I'm not really exercised -- should be available by the end of the third week in January.

MR DI ROLLO: I'm content with that. What I am more troubled by is the timescale between January and the middle of March to produce detailed, as it were, material or submission in respect of answering the questions that are posed.

THE CHAIRMAN: I'm sorry, why?

MR DI ROLLO: What concerns me is being able to process the information and consult with a number of different individuals, at least to get some input, all within that period of time.

THE CHAIRMAN: Has any processing of the information been done?

MR DI ROLLO: Well, some.

THE CHAIRMAN: Speaking for myself, I know that it has been a hard job to try to analyse the evidence and keep it up to date, but I would like to think that I have done most of it, and I don't like to think that counsel haven't.

MR DI ROLLO: Well --

THE CHAIRMAN: So if you are telling me that you need an appreciable period of time to do basic analysis, that concerns me a bit.

MR DI ROLLO: You must -- I'm sure you do -- bear in mind that we have to absorb the material for the first time

in the course of the --

THE CHAIRMAN: I have tried to make it clear that I have had to absorb quite a lot of the material for the first time too.

MR DI ROLLO: You say that but the Inquiry team, and indeed yourself, have had the opportunity of a number of months before we started.

THE CHAIRMAN: Mr Di Rollo, I'm not reaching any view on this sort of thing at the moment but I really do want it to be understood that the process mustn't go on forever, and I need a fair assessment with rational basis, when you get round to it. If you are going to ask for an extended period, I have to know why.

MR DI ROLLO: I'm trying to tell you.

THE CHAIRMAN: Yes, but the generality is that you could give an answer to why you need an hour for a motion instead of ten minutes.

MR DI ROLLO: I fully accept that we should not be given a very lengthy period; I'm just indicating a concern that the middle of March may be a bit too soon to complete all of the work that we would want to complete --

THE CHAIRMAN: What do you suggest?

MR DI ROLLO: I would look for at least to the end of March for that purpose.

THE CHAIRMAN: Well, that's infinity. It starts today and ends at least at the end of March; that's no help at all. What about an envelope?

MR DI ROLLO: If you are going to press me on it, sir, I would say that we should have until 31 March.

THE CHAIRMAN: Yes, okay. Clearly, these proceedings are not bound by any firm protocol that really cannot be altered. So no decisions that I take in the light of this discussion will be so final that you can't come back and ask --

MR DI ROLLO: I appreciate that.

THE CHAIRMAN: -- for more. But I really just want to have as tight a framework as I can get.

MR DI ROLLO: I fully accept that there is a need to impose tight deadlines and that we should try our best to work towards those.

The other two matters, one which has already been raised, which is the issue of the closing statement.

The purpose of making a closing statement on behalf of patients, relatives and the Haemophilia Society is really to make a public statement in the course of this public process, drawing together the threads of certain matters which have emerged in the course of the hearing, the hearings on evidence.

What I have in mind mainly is to do with the

information given to patients and the effect that the infection with HIV and HCV has had upon them. That is the main topic which we would wish to address in the course of a closing statement.

THE CHAIRMAN: On the evidence that will have been heard by then?

MR DI ROLLO: Obviously we have dealt with B4, B5 and B6, and we will have by then have dealt with C5 and C6, and the purpose of making a closing statement is essentially to point out the patient perspective on these matters.

THE CHAIRMAN: Well, that may be what you do in due course. My concern at the moment is not whether you express anger, satisfaction or otherwise, Mr Di Rollo; it's merely to ensure that what we are talking about is closing statements on the evidence and not an attempt to introduce fresh evidence.

MR DI ROLLO: No, it's simply on the evidence. I would say that, in making such a closing statement, I would wish not to be confined to what is contained in the material that has actually been given at the hearings; in other words, I would wish perhaps to refer to material contained in statements to the Inquiry.

THE CHAIRMAN: That is perfectly proper, I think that that's correct. I would wish to have those materials available to myself, and there is no way I would deny you the

opportunity to refer to them.

MR DI ROLLO: Such a closing statement would not be lengthy, and when I say that, I would wish to make it orally, obviously, but I don't envisage it taking longer than an hour.

THE CHAIRMAN: That's a very modest estimate. I think that what everyone has to understand is that if we get to oral closing statements of that length, everything is fine. If they were to extend to days, they become counter-productive, and I think they end up as discussions rather than statements that one would listen to, and if it's that sort of statement you have in mind, I have no questions to ask you at the moment. I think it seems reasonably clear.

MR DI ROLLO: Very well.

The other matter I think I have to raise is an issue which became apparent on receipt of an email from, I think, the deputy solicitor to the Inquiry, which indicated that there would not be an opportunity to comment upon a draft of the report before it's issued.

THE CHAIRMAN: A draft of the whole report, yes.

MR DI ROLLO: I think it would be fair to say that an expectation has been created that there would be an opportunity to comment on a draft of the report because of remarks made by the chairman on 15 March.

THE CHAIRMAN: In what context?
MR DI ROLLO: In the context of the deaths. I'm sure you are aware of the passage that I have in mind.
THE CHAIRMAN: Yes, indeed.
MR DI ROLLO: Can I just leave aside the issue of the deaths for a moment, because there is a discrete issue there which is of importance.
THE CHAIRMAN: Leave the deaths aside. You are going to tell me you want to see the whole report and trawl through it line by line and make comments on it from the individual word up to the whole note?
MR DI ROLLO: What I'm going to say is that it would be of value, I think, in this process to allow parties the opportunity of considering a draft in advance of publication.
THE CHAIRMAN: Why?
MR DI ROLLO: There are a number of reasons. One reason, I think, is that the material which the Inquiry has had access to is vast and we do not have access, I think, necessarily to all of the material that the Inquiry is considering.

More importantly, I think, because of the vast nature of the material, it would be useful to see what material is being relied on in coming to final conclusions about matters and, as part of that process

I think it would be helpful, in allowing participants to feel included in the final process, to allow them an opportunity to comment, or to make comment, on what the report contains before it's issued.

THE CHAIRMAN: Tell me what I would do with these comments.

MR DI ROLLO: Take them into account.

THE CHAIRMAN: Change any impressions given in the draft and appear to the public to be altering my opinion?

MR DI ROLLO: Not necessarily.

THE CHAIRMAN: Not necessarily, but is that the objective of making the submissions?

MR DI ROLLO: It isn't the objective.

THE CHAIRMAN: Then what is the objective? To strengthen the preliminary views expressed?

MR DI ROLLO: Heaven forbid but your Lordship may make the odd error.

THE CHAIRMAN: I'm sure I will, but I'm not sure they will matter.

MR DI ROLLO: Even from that point of view it might be of use or value to have some sort of input in relation to that.

THE CHAIRMAN: Do you remember Lord Justice Scott's report and the effect on him of trying to accommodate every exchange that parties thought fit to make in the course of revising a final report, where --

MR DI ROLLO: The only thing I remember about him was that he used to ride a bicycle.

THE CHAIRMAN: Well, he probably wasn't fit to ride a bicycle as a result of the intervention of parties in relation to his draft report for quite a long time, Mr Di Rollo.

What I must do is to intimate to parties, who are likely to be subject to criticism of a particular kind, what the proposed criticism might be and to give them an opportunity to answer it.

That's what I'm required to do. There will be areas where I might be inclined to go beyond that, and the deaths raise issues, perhaps of that kind. But you will have to persuade me that in what is likely to be a very long report, dealing with vast amounts of material, there is any advantage at all to be obtained in exposing the whole of the draft to the critical examination, and uncontrolled critical examination, of a vast number of people.

That's what you are perhaps setting out to do, Mr Di Rollo, and that's what you have got to do if you are going to make this a substantial submission. Otherwise, it's an open-ended invitation to take an indefinite tract of future time to involve each and every party in textual criticism that has got no

constraints built in, is unregulated and is likely to cause nothing but further discord.

MR DI ROLLO: You have, sir, obviously an example of where that opportunity has been given and it didn't prove to be a success. I have drawn attention to what possible advantages there may be.

THE CHAIRMAN: Have you drawn my attention to any case other than Lord Justice Scott's in which it has been done?

MR DI ROLLO: I don't think I can and I appreciate that it is not something which ordinarily happens in ordinary court procedure, or even under the Fatal Accident Inquiries --

THE CHAIRMAN: These aren't ordinary court procedures.

MR DI ROLLO: Indeed not. The standard, however, is not to allow for comments on drafts but the difficulty that arises -- and this is a real difficulty, I think, that needs to be considered and taken account of -- is that when writing the report, there may be material which has not been focused on or emphasised or looked at in the public course of the evidence.

I can give you an example of unfinished business, as it were, which we are not coming back to; the issue of statistics.

Our understanding of the situation in relation to that is that that is a matter on which enquiries are

going on and are to be completed. We won't have seen that material.

THE CHAIRMAN: That's a very particular problem and I'm not limiting this comment to statistics. There is a very particular problem that there may be reference to material that has not been discussed in the public domain. I think, if you were to make a submission that if I were to use, in any material way, documents or other sources of evidence that had not been exposed to examination in public, I ought to give parties an opportunity to comment on that. That's a different issue. That doesn't involve sending you the whole report or anything else. It involves acknowledging the fact that a public Inquiry is not a complete public Inquiry if some parts of it haven't taken place in public.

MR DI ROLLO: Quite so.

THE CHAIRMAN: I see that as a different point altogether.

MR DI ROLLO: It may be that allowing us to comment on the whole report is the sledgehammer --

THE CHAIRMAN: The trouble is I'm the nut, Mr Di Rollo, and I'm the one who is likely to be broken on the anvil as you wield the sledgehammer.

MR DI ROLLO: I have no desire for that to happen, of course, and I would hope that if a solution, which takes

into account the concern that I have expressed, can be devised, then that would take --

THE CHAIRMAN: I'm sure if you give me your particular concerns.

MR DI ROLLO: I think I have. I have tried to do so in the context of material that will be referred to by you which has not been rehearsed in public.

THE CHAIRMAN: Well, there are one or two bits that I would think I wouldn't bother letting you see and at the risk of upsetting Ms Dunlop again, let me mention the document that no one has been prepared to bring to my notice, the joint College of Surgeons/Royal Commission report. That actually sets out a lot of the history of the production of the pre-PFC Factor VIII. As I have tried to indicate, I have an interest in whether there was in Scotland exposure of the haemophilia population to a product from pooled plasma prior to PFC, and what the implications of that might have been.

I don't think it's going to come out in the evidence. I just don't think it is. But it seems to me a possibility that both in the Southeast of Scotland and in the area serviced by Elstree in England, there was throughout the 1960s really, and into the early 1970s, the supply of a factor concentrate from Cohn Fraction I, which was substantially fibrinogen with a relatively

high Factor VIII content in it, of really the crudest version of Cohn fractionation, and one then goes into a period, starting in 1974/1975, when there is the production of a more refined product.

It has seemed to me to be a potentially interesting question whether, in the case of haemophilia patients in that part of Scotland and in England, they may have been developing hepatitis before 1974. They weren't getting cryoprecipitate all the time, in fact, we all know in Scotland they only got that from a considerably later date, according to Cash and Spencely.

So there are areas there that I might refer to, but since no one has taken up something that I have trailed persistently, I don't see any sense in asking people to comment on it again. You all know that it's something I have been interested in and none of you have taken it up. Why should I expose the issue afresh?

So there would be things like that where I think, as a matter of judgment, everyone has had an opportunity and has or has not taken it. I think there is no unfairness to you if I don't give you a chance to comment on what I might say about the data that one finds in that document or about the inferences that one might draw from Cash and Spencely itself, because the article is referred to in the preliminary report.

It's a simple problem.

MR DI ROLLO: It may not be a simple problem but it's one that we have to leave, to some extent, to your discretion, because if the process is one of filtering through the report and determining whether or not in writing the report, there are aspects that require or may require some comment for the reason of fairness, as it were, one has to depend on your judgment in relation to that because there is no other way we can do it, unless, of course, the whole draft report is provided and then we run into the difficulties that you have indicated.

THE CHAIRMAN: It's an endless process if one does that.

You know, just envisage what happens. So something that's not central to an issue that you are particularly interested in, which I would expect to know from your submitted list of issues.

MR DI ROLLO: Indeed.

THE CHAIRMAN: But it's something that divides you and Mr Anderson or you and Mr Johnston or you, as against Mr Anderson and Mr Johnston or whatever, we could have a very long process, a wholly unregulated process, no prescription at all as to what the rules might be of exchange of submissions and counter submissions on matters that were not sufficient to exercise your mind

when you came to draft the list of issues. I can't let that happen, I don't think. So I think you do have to think very carefully what you are asking me to do.

MR DI ROLLO: One matter before I move on from the draft report issue, if I can put it like that, is there is a discrete issue that arises in relation to the deaths, and I think the context of your remarks was in relation to, potentially at least, a particular matter arising out of one of the deaths.

THE CHAIRMAN: It's Tamburrini and drink.

MR DI ROLLO: Indeed.

THE CHAIRMAN: I'm not sure that there is anything else, but you may know of some things that I haven't identified, but clearly in relation to alcohol and Mr Tamburrini, there is a possible issue.

MR DI ROLLO: I think an indication has been given that an opportunity will be given to me to see what's going to be said in advance.

THE CHAIRMAN: Yes. Because there has been a lot of evidence.

MR DI ROLLO: I had rather hoped that such an opportunity would be given.

THE CHAIRMAN: This is a public Inquiry into a death and you will have to bear that in mind, that I was asked to do it. I didn't select it. I didn't choose to do it. It

was put before me by the Secretary of State, following representations to her. You will bear all that in mind. But I know there is an issue. How it's resolved, let's wait and see.

MR DI ROLLO: If I might, what I would be quite keen to have is an understanding, if I may, that before the report is issued in relation to that specific matter, we would be given an opportunity of considering what's going to be said.

THE CHAIRMAN: You can put the question of alcohol in Mr Tamburrini's death into the issues. I think that's the straightforward way to do it. I think you are going to have to identify in relation to each of the deaths what you say the issues are that arise on the evidence. And if you do that, the mechanism has been started, as it were. And that should lead on to the development of those submissions by the end of March. It will be squarely before me and it's something I don't see that I could avoid looking at.

So it's going to be there. The issues can be debated at that stage perhaps, if you wanted an opportunity to have oral submissions on it. Whether that meant that you then had to have an opportunity to look at the draft report, might depend on circumstances that I would rather not try to anticipate and prescribe

in advance, because I'm still open to a flexible resolution of issues, rather than an over-prescriptive and narrow, single way of dealing with things, Mr Di Rollo.

MR DI ROLLO: Well, I --

THE CHAIRMAN: I'm not going to give you a promise. In fact, I'm not going to give you any decision here today at all, but I think it's unlikely that I would give you a promise before I knew what the format of the statement of issues was and what the content of the representation was.

MR DI ROLLO: So should I understand it that you are departing from what was said on 15 March 2011?

THE CHAIRMAN: If you construe it the way you do, yes.

MR DI ROLLO: Right. I don't think I have anything else to add at this stage in relation to the matters that have been identified. Thank you very much.

THE CHAIRMAN: Mr Anderson?

Submissions by MR ANDERSON

MR ANDERSON: Yes, I'm obliged, sir. Turning firstly to the question of submissions. Clearly I'm in broad agreement with what has been discussed but it may be helpful just if I articulate my personal understanding of matters.

What, as I understand it, is envisaged by the third week in January is that each of the core participants

plus the Inquiry team will seek to identify those questions which have arisen, which might be said possibly to be still matters of controversy; so that by the end of that process, by the third week in January, what one will have is a composite list, as it were, to which each of the core participants and counsel to the Inquiry has contributed. So it shouldn't be --

THE CHAIRMAN: Sorry, you see it as a single document, then?

MR ANDERSON: I had thought so, yes.

THE CHAIRMAN: That's my misunderstanding then.

MS DUNLOP: I hadn't envisaged it as a single document either.

THE CHAIRMAN: There is a big difference because, if it is to be single, then I think all the parties really have to agree on what goes into it, and that might take a considerable period of time, Mr Anderson, I don't know.

MR ANDERSON: That's the reason I sought to dig deeper, as it were, and go behind it because I'm just anxious to ensure that before we leave this building today, we all do understand precisely what's happening. The misunderstanding is clearly mine. I had thought that there would be a single. I was simply seeking to point out that notwithstanding it was on a single document, it shouldn't be taken that each party agreed that these

were necessarily issues. If there are going to be separate documents, that flies off. So that deals with that.

I'm in agreement that it should be possible by the middle of March for parties to have responded to those questions as they see fit. As I would envisage it, it may be that there are certain questions raised that some parties do not feel the need to make specific submissions or comments upon.

THE CHAIRMAN: I would hope so.

MR ANDERSON: Again, I specifically mention this in the hope that this discussion will perhaps prevent any misunderstandings, since we have identified one already.

Sir, I think that's all that I have to say, sir, in relation to the question of submissions.

In relation to a closing statement, for my part I would not seek to make any closing statement. I had understood that before this Inquiry started, an application had been made by those for whom my learned friend Mr Di Rollo represents, to make an opening statement, and that was not allowed.

THE CHAIRMAN: That's correct.

MR ANDERSON: It, respectfully, seems to me, sir that, consistent with that, you should disallow any closing statement. It's difficult, I have to say, for my part

to see whether that is either necessary or appropriate at an Inquiry of this sort, but I fully accept it's a matter entirely for you and within your discretion.

But I simply have a fear, I have to say, that it may --

THE CHAIRMAN: So have I. That's why I was pressing Mr Di Rollo on whether it was wholly on the evidence that we have heard. And I understand him to say that there would be no fresh evidence introduced at that stage.

MR ANDERSON: One would hope not, but the difficulty I have with that is that, if it's on the evidence, then really it seems to me that that's part of the submissions, and I fail to see how one gains anything by making a statement which is wholly referable to the evidence, that can't be dealt with in submissions in the more traditional manner. And I just have a fear that, with the best will in the world, there may be some element of grandstanding, or whatever, in relation to any closing statements.

THE CHAIRMAN: Mr Di Rollo effectively invited you to take that view by talking about it as an opportunity to express people's anger.

MR ANDERSON: Precisely, and in my submission that simply is not either necessary or appropriate, but I leave the

matter in your hands, sir.

The third and final matter is that of a draft report. Notwithstanding the comments that I have heard from you, I would also encourage you to produce a draft report, for this reason, that after the preliminary report, which was in itself the result of very considerable industry, those instructing me produced a document entitled "Errors and Omissions", which I understand was well received, and the purpose of it, of course, was not to engage in any special pleading but simply to seek to correct any errors and omissions, and --

THE CHAIRMAN: It was very long.

MR ANDERSON: I make no comment on that, sir. But it's simply that the same process might usefully, it is thought, be gone through again.

THE CHAIRMAN: I think it's different now, Mr Anderson, because what we have had is evidence on oath or on affirmation from a large number of witnesses, and my job at this stage has changed its character; it is no longer setting out how I read documents and how I interpret them, it involves issues of assessment of credibility and reliability. There are significant areas here where I have to or may have to exercise that discretion and I consider that it is absolutely inappropriate that my

views on credibility and reliability should be subjected to critical analysis by individual parties and made the subject of representations.

MR ANDERSON: I'm entirely in agreement with that, sir. There would not be any attempt to influence the way in which you should deal with the evidence. The only purpose would be in the hope that it would be of assistance and that would be to correct any factual inaccuracies because, notwithstanding your industry and Professor James's expertise, it would be very surprising if, after an Inquiry lasting over such a period and with such a wide subject matter over such a long period of time, there were not certain inaccuracies, and that would be the whole purpose.

THE CHAIRMAN: I'm sure that's so but since I neither pretend to omniscience nor infallibility, having a few errors would merely accord with my own general expectation of my own performance, Mr Anderson.

Really, picking up casual errors is of no real significance. What matters in an inquiry of this kind is whether the substantial issues have been addressed. They are often going to depend on judgment at this stage in the Inquiry. I don't think that I am over well disposed to the notion of opening up to your clients now an opportunity for textual criticism. I do, of course,

remind you that you had ample opportunity throughout the evidence to correct the errors that I no doubt demonstrated by some of the interventions I made. But if this is what you are inviting me to do, to allow all parties the opportunity to look at the draft report, to make helpful comments in support of the correction of errors and omissions or something like that -- of course it has to be everybody.

MR ANDERSON: I accept that but, as I say, I had sought to assure you, sir, that it wasn't to deal with textual criticisms.

THE CHAIRMAN: I can envisage you applying your mind to every line of it, Mr Anderson, from beginning to end, to ensure that I have not committed any error of any kind, grammatical or choice or of language or otherwise, in your usual way.

MR ANDERSON: The offer has been made and if declined, so be it.

THE CHAIRMAN: I have not declined anything yet and I'll treat it as an offer and thank you for the offer.

MR ANDERSON: I have nothing to add.

THE CHAIRMAN: Mr Johnston?

Submissions by MR JOHNSTON

MR JOHNSTON: In relation to submissions and the date by which the draft list of issues should be prepared by

each party, I don't think I can usefully add to anything that others have said. I'm quite content with the procedure that's envisaged and also that it will be possible to prepare the list of issues by late in January and any submissions by mid-March or the end of March, depending on what date seems appropriate.

THE CHAIRMAN: You feel you can do it by the mid-March. It's really a question of whether I accommodate Mr Di Rollo or not.

MR JOHNSTON: That's correct, yes.

So far as the closing statement is concerned, I cannot at present envisage circumstances in which I should want to make one, not least because I would plan to deal with anything I wish to say in the written submissions.

THE CHAIRMAN: If I may say so, measured by your intervention in the course of Inquiry, one would be very surprised at a very lengthy and detailed involvement in it.

MR JOHNSTON: Well, one might think brevity is the soul of wit, no doubt. At any rate I cannot imagine making even a short closing statement.

THE CHAIRMAN: So it is not of significant interest to you at this stage?

MR JOHNSTON: That's correct. Clearly I'll fall in line

with whatever procedure is decided on.

In relation to the draft report, I don't think there is anything I can usefully contribute. All the points have been aired and I'm content simply to leave it where it stands.

THE CHAIRMAN: Thank you all very much.

Ms Dunlop, is there anything that you think you can help me with at this stage?

MS DUNLOP: I would only refer to one matter, sir, which is that I should have said that certainly what I envisage is that the identification of issues would relate to the B and C topics. I did endeavour at the end of the evidence on the deaths to take a morning to deal with the evidence that we had heard on the deaths and to identify what from my perspective were the systemic issues raised by the deaths. I would, I think, perhaps be slightly uncomfortable at the idea that I would have to go back over all the deaths because that's evidence that was heard some time ago.

THE CHAIRMAN: I don't know that you are. In your submissions? I don't want you to do that.

MS DUNLOP: All right.

THE CHAIRMAN: No, not at all. I think I have got your position in a relatively straightforward way, but I'm conscious that, arising out of it, in one death in

particular there is a continuing issue and I would feel very uncomfortable if Mr Di Rollo didn't have the opportunity to address that.

MS DUNLOP: I see.

THE CHAIRMAN: I really do think, Mr Di Rollo, that I would be surprised to find other issues of the same kind elsewhere because I don't think any have had any real debate or discussion or exploration. But in that one case I know, and I think that it would be inappropriate not to allow Mr Di Rollo the opportunity in some way to deal with that.

MS DUNLOP: I see.

THE CHAIRMAN: But I don't think you need to have a rehearsal of Ms Dunlop's position; it's there in the record.

MR DI ROLLO: I think I may want some input from Ms Dunlop at some point in relation to that particular --

THE CHAIRMAN: I'm not sure I know why but it's now for me and not for Ms Dunlop.

MR DI ROLLO: No, but in the course of discussions leading up to the conduct of that particular matter certain indications were given as to what would be discussed or not.

THE CHAIRMAN: Yes, and, to the best of my recollection, Ms Dunlop didn't ask a single question that could be

interpreted as going beyond what had been discussed. The problem here arises not from Ms Dunlop's questions; the problem arises from the expert testimony that was given by people whose evidence I can't ignore, or may not be able to ignore.

MR DI ROLLO: Yes, but there are issues arising out of this which do concern me very much, I have to say, because certain evidence that could have been led was not led on Mr Tamburrini's behalf.

THE CHAIRMAN: If you had led it, I would have been put in an astonishingly difficult position and it would have been so hurtful to people, and I trust actually that all of those involved will appreciate that at this stage, when you focus on the issues that necessarily involve reference to credibility and reliability, the potential for the report to do untold damage exists, and it's a big problem that everyone who has to take a decision has to confront.

As far as litigation is concerned, we know about it, we do it, we don't like it, but if some of these more contentious issues don't have to be raised, it's an advantage. If they are raised, they carry with them risks for everybody. If you want to submit some documentary evidence to say that Mr Tamburrini didn't drink, which I gather is the nature of part of it, for

particular areas, do it and I'll look at it. But be very careful because, on the objective clinical evidence available, it might be necessary to say that some of that evidence is wholly unreliable, which will not help the family at all. That is just a bit of advice, to be careful what you do in this context. That's intended to be helpful, Mr Di Rollo. I'm not going to silence you in any way and you will take your own professional decision in due course but I think sometimes it's necessary to exercise a wise discretion.

Maybe you should have a word with Ms Dunlop, if she is prepared to talk to you, but I think there are phases in the life cycle of Mr Tamburrini that may be material in this context.

Anyway, it's not for me to say anything else at the moment. If you wish to focus it at a particular issue, if you wish to suggest that there is further evidence that ought to be heard, then make a motion, put it in writing and ask for a direction -- and do it now, please, because one of the reasons for sending out emails and letters recently has been to try to bring all of this to a head.

MR DI ROLLO: I had thought that the solution to this particular problem had been identified and given to me, which is that I would have an opportunity of commenting

on the draft report.

THE CHAIRMAN: Yes, well, I'm just now saying that that is not necessarily the way to do it. There may be a better way to do it. If you ask me to allow you to comment on the draft report at a stage at which no further evidence can be led, what good does that do? You are not going to be able to tell me that I'm in some way barred from dealing with the subject. That would hardly work. If there is something you feel must be brought out in all the circumstances, then the way to do it, which is what I tried to outline last time I commented about procedure, is put in an application, tell me why and ask for a decision.

We have got between now and the end of the year, Mr Di Rollo. I would rather face up to a problem like that, with respect, now, than in the course of next year.

MR DI ROLLO: I certainly would like to know where I am. I thought I did and now I'm not so sure, and that's the problem.

THE CHAIRMAN: There is one way to find out: Draft a nice application, put it in, ask me to do something and we can debate it and I'll give you an answer. Then I think you will know where you are.

MR DI ROLLO: All right.

THE CHAIRMAN: There is no single mechanism that solves all the problems in an Inquiry like this, absolutely not.

Well, ladies and gentlemen, thank you all very much. I'll ponder on these things. It's a distraction, mind you, it will mean that I don't get on with analysing the evidence, but that's no doubt not a problem for you.

(3.09 pm)

(The Inquiry adjourned until 9.30 am the following day)

I N D E X