Tuesday, 11 October 2011

(9.30 am)

PROFESSOR HOWARD THOMAS (Affirmed)

Questions by MS DUNLOP

THE CHAIRMAN: Yes, Ms Dunlop?

MS DUNLOP: Thank you, sir.

Good morning, Professor Thomas.

I want to begin with a little bit of biographical detail, if I may. Could we look firstly, please, at your curriculum vitae, which is PEN0171671.

This is, I suspect, a greatly abbreviated CV but I think we should design you as in the department of medicine. I see from your clinical appointment there, which is about half way down the page, "Honorary consultant, general physician and hepatologist at St Mary's Hospital in Paddington."

Would that still be correct?

A. That has really changed now, in that as of April this year, I reached 65 and retired. So now I'm an emeritus professor of Imperial College with teaching and research rights, but I don't do clinical practice any more.

Q. Until April this year, were you involved in clinical work at St Mary's Hospital?

A. Yes, I was.

Q. Thank you.

Could we just have a look at your degrees and qualifications first of all? I suppose what leaps out at us -- leaps out at me -- is that you did a PhD in Glasgow in 1974, in the 1970s. You are a fellow of the Royal College of Physicians of London and also a fellow of the College of Physicians and Surgeons in Glasgow, a fellow of the Royal College of Pathologists, a fellow of the Academy of Medical Science. We can see, outlined underneath, your past and present senior appointments.

You have explained to us your current appointment, the membership and offices you have held of and in learned societies: the Association of Physicians of Great Britain and Ireland, and then a number which relate to the liver, which is the Association for the Study of the Liver, European Association for the Study of the Liver, the International Association.

Indeed, of the first two you have been president, of the first two liver associations you have been president, the British Liver Trust, member of council of BSG -- we are guessing that that is the British Society of Gastroenterology. Is that right?

A. Yes.

Q. And a member of the council of the Royal College of Physicians. I take it that's in London. Yes.

A number of journals are listed. Again, we can see two relating to hepatology and indeed, you were a founding editor -- the founding editor or a founding editor of the Journal of Viral Hepatitis?

A. With one other person; the two of us founded it.

Q. And we see that that journal is still carrying on. Is that correct?

A. Yes, correct.

Q. That presumably has a worldwide circulation?

A. Yes.

Q. Then on to the next page, please. You have listed for us your membership of international committees, and again we see the liver featuring fairly strongly, and then national committees, Department of Health advisory group on viral hepatitis, chair of the Department of Health steering group on the Hepatitis C national strategy. Are all of these still true or have some of them come to an end?

A. They have really mostly come to an end in 2010.

Q. Right. So which of these that are shown as being "to the present" are still continuing as at today?

A. Well, I have ceased to have a role in these national committees as of 2010 -- January -- December 2010.

Q. Thank you.

Then there is a long list of academic distinctions.

Again, gastroenterology, virology and hepatology all featuring. You then tell us that you have published around 450 papers and reviews. You outline for us the main areas on which your research has been focused. Unsurprisingly, much of this relates to the liver and liver disease. We see, for example, the third bullet:

"Conducting the first European randomised control trials on the use of interferon in ... "

Is that chronic Hepatitis B and chronic Hepatitis C?

A. Yes.

Q. On to the next page, please.

Again, a lot of mention of hepatitis. I notice particularly the fourth bullet on this page:

"Contributing to the cloning of Hepatitis G virus."

I'm going to come back and ask you about that because I know you have a little addendum really on the topic of Hepatitis G:

"Determining host genetic factors influencing outcome of Hepatitis B and C. Identifying HCV-induced changes in the brain."

We will talk about that too. Then:

"Demonstrating the increasing incidence of cholangiocarcinoma in the UK."

Is that really bile duct cancer?

A. Yes, it is, and probably not related to Hepatitis C, as

far as we know.

Q. And then:

"Identification of genetic factors influencing alcoholism, drug-induced liver disease and NAFLD."

A. That's non-alcohol related fatty liver disease. Essentially fat in the liver related to obesity in type two diabetes, which puts you at risk of cirrhosis.

Q. Then current grant income. Are these research projects which have come to an end?

A. The MRC programme grant comes to an end in the next few days in fact. The rest have already ceased.

Q. Are you still the editor of the textbook "Viral Hepatitis"?

A. Yes, we are doing the fourth edition of that now.

Q. Right. At what point in your career, Professor Thomas, did you become a liver doctor?

A. Well, when I was a lecturer at the Royal Free, which would be around about the early 1980s --

Q. Right, and you gravitated towards the liver; the liver particularly interested you. What was it that you think caused the change or caused the move?

A. Up until then I had done general medicine and during my PhD I had become interested in induction of tolerance to orally administered proteins, essentially food proteins, and it turned out that the liver had a major role in

that induction of tolerance process. So as a result of that PhD really, I got the opportunity to go as a lecturer to the Royal Free Hospital, where I became interested in liver disease, really.

Q. And the --

A. I'm not sure of the precise dates of that. It would be at the end of the PhD actually.

Q. Right. And your interest in the medicine of the liver has continued to the present day?

A. Yes, and because I held the chair of medicine at St Mary's, I also had to do general medicine, acute medical take. So I was a specialist in liver disease but had a general knowledge of medicine and practised acute medical receiving, acute case receipt.

Q. Yes, and you had some involvement in work with HIV in the 1980s, I think, as well?

A. Yes, most of that interest really -- I really just supported Dr Janice Main, who was a member of my department at St Mary's from 1989 onwards, and she really dealt with that group that were co-infected with viral hepatitis and then HIV.

I had some early interest in HIV really, predominantly because of its involvement in the haemophilia patients, along with Hepatitis B and C, but outside that haemophilia setting I wasn't really

involved in the care of HIV-infected patients.

Q. I think, in fact, Professor Gazzard, for example, who has become a world authority on HIV, he actually moved into HIV, as I understand it, from a base in gastroenterology, because there were theories about HIV not -- I don't want to use the wrong language but having some sort of genesis in the gut, or having some kind of connection with the gut. Is that right?

A. Yes, I mean, many patients with HIV infection develop opportunistic infections and some of those affect the gut and also other organs of the body. So I think his interest really started as a result of managing those gastrointestinal complications, and of course, as drugs became available for treatment of the immunodeficiency state directed towards HIV virus itself, then, of course, he became interested in that aspect as well.

Q. Right. Thank you.

I think we can put your CV to one side and move to look at the report which you have provided for the Inquiry. That is [PEN0171071], and that will appear on the screen.

It's my intention, Professor Thomas, just to work through your report and ask you some questions as we go. You have asked for a white board. We have a white board, and if we need to use it, then please do so. We

may outline some particular arrangements for that if we come to use it.

You say at the beginning of your report that there are five main hepatitis viruses and I suppose conveniently they follow the first five letters of the alphabet. I wanted to ask you whether these viruses are all alike or whether their only common feature is that they cause liver disease?

A. They are all from different families of the virus kingdom, if you like, and as you have said, they come together because they all replicate in the liver cell and cause a form of hepatitis.

Two of them, Hepatitis A and Hepatitis E, cause a self-limiting infection. In other words, after two or three months, the liver function test will come back to normal. The virus will be eradicated and the person will have protective immunity for the rest of their lives against those two viruses.

Whereas Hepatitis B and C -- and I'll come to D in a minute. Hepatitis B and C are distinct in that they cause acute hepatitis but a proportion of those infected go on to chronic infection, and it's the chronic infection that puts you at risk of what we call "progressive liver disease", where there is a risk of developing cirrhosis, and it's the cirrhotic patients

who have the greatest risk of developing hepatocellular cancer, primary liver cell cancer of liver cells.

Q. I said we would briefly mention Hepatitis G and I think this is an appropriate moment. We have a passage in our preliminary report which relates to Hepatitis G and perhaps we could just, whilst leaving Professor Thomas' report open, go to the preliminary report.

The reference for that is [LIT0012310] at page 3. We will get the hard copy reference for that in a moment. I think it's page 19 for anyone who is working with a hard copy. Yes.

We can see that paragraph 2.10 on page 19 of the preliminary report deals with Hepatitis G. I wondered if you would perhaps bring us up-to-date on Hepatitis G, if you would, please?

A. It's a flavivirus and at the time, when we were involved, along with an American group, in identifying it and cloning it, we thought it did cause a form of hepatitis. It was found in about 20 per cent of people with chronic Hepatitis C and it was difficult to actually dissect how much of the liver damage was caused by the Hepatitis C and how much was due to Hepatitis G.

Subsequently, people with just Hepatitis G infection were identified and in the main they don't have liver disease. So I think now the position is that this is

not a hepatitis virus, it doesn't cause hepatitis. The main interest in it now is that it replicates in a type of lymphocyte, what we call the CD4 lymphocyte. That's the same cell as HIV replicates in. And when Hepatitis G infects those lymphocytes, it appears to slow down the replication and the development of problems due to HIV.

Michael Manns' group showed that some time ago and it has held up. So it's interest has been really as a modifying virus infection that modifies the course of HIV. Whether it modifies the course of Hepatitis C isn't 100 per cent clear but it probably doesn't make it any worse, nor any better.

Q. Does this virus have a different name now?

A. Yes. Two groups found this virus at more or less the same time and the other name for it was GBV-C and that, of course, didn't commit to being a hepatitis virus, and that's the one really that's probably best used now.

Q. GBV-C. I think we can guess what the V stands for but the "GB"?

A. There was a virus that replicated in marmosets, which was apparently transmitted from a surgeon whose initials I think were "GB", and his blood was shown to transmit this infection to the marmoset, another non-human primate. Those marmosets developed hepatitis.

Then the group at Abbott Pharmaceutical Company actually found out that GBV-C was in fact a member of a family of viruses. The other ones were GBV-A and B, and the one in humans was C.

It turns out that the one of major interest in relation to Hepatitis C is the one GBV-B, which doesn't infect man but does cause hepatitis in marmosets, initially severe acute hepatitis, but in a small proportion of marmosets it does cause a chronic infection. And that has been a useful model in some senses, allowing us to try and understand Hepatitis C.

Q. Right. So I think for our purposes we can just understand this as a case of mistaken identity?

A. Yes, or mistaken role, really.

Q. This virus is not a hepatitis virus.

A. Exactly.

Q. Right.

Can we go back to the report, please? And in your first paragraph you draw for us the distinction between modes of acquisition that Hepatitis A and E are enterically transmitted. So they come in through the digestive system, whereas B and C are parenterally transmitted, and you say that's by introduction of infected material through the skin or mucosal surfaces, and obviously for people with haemophilia, the virus in

that scenario would be injected into the blood?
A. Yes.
Q. And that's an example of parenteral transmission?
A. Correct.
Q. B and C may cause acute or chronic infection, and you say:

"It's the chronic infections that put patients at risk of hepatocellular carcinoma."

Would it be the case, Professor Thomas, that all chronic infections start as acute infections but not all acute infections progress to chronic?
A. Yes, that's true, and many acute infections may go unidentified; in other words, they are asymptomatic.
Q. Right. Just to talk a little bit about the difference between B and C, when we come to patterns of disease, could you explain for us, in relation to both these viruses, what the breakdown would be as between acute and chronic infection?
A. If we start with Hepatitis C, the break between acute and chronic is an infection that continues for longer than six months after the identification of the infection.
Q. Yes.
A. So it's often a diagnosis which is made in hindsight; in other words, you wait six months and then you can say

that this is not an acute infection; it is an acute which has progressed to a chronic infection.

After infection with Hepatitis C, around 30 per cent will clear the virus. They suffer an acute infection, they clear it within the first three to six months. The remainder, 70 per cent, go on to a chronic infection and those are the cases that are at risk of developing progressive fibrosis, ultimately cirrhosis and liver cancer.

With Hepatitis C it is only those that have cirrhosis that are at risk of developing liver cancer. As far as Hepatitis B is concerned, the proportion that develop an acute, as opposed to a chronic infection, varies with age. If you are infected at birth from your mother, then there is a sort of 95 to 100 per cent chance that you will become chronically infected. If you are infected after two years of age, right through to middle and late years of adult life, then 95 per cent will develop an acute infection and 5 per cent will develop the infection.

So the time of infection is important in Hepatitis B. The number developing the chronic infection diminishes the older you are when infection occurs.

There is another important issue too: of those that

have the chronic infection, the majority who develop cancer will already have developed cirrhosis; 70 per cent of those with hepatocellular cancer will have cirrhosis but 30 per cent will develop a cancer before the stage of cirrhosis, and that's a point of distinction between Hepatitis B and C.

Q. Yes. So with Hepatitis C cirrhosis is a necessary stop on the way to liver cancer. With Hepatitis B it is not a necessary stop on the way to liver cancer?

A. That has become of importance in explaining risk to patients and particularly emphasising the need to be treated before you get to the cirrhotic stage, which brings with it the risk of cancer.

THE CHAIRMAN: Ms Dunlop, Professor James is suggesting that we have got one of these points the wrong way round, and I think it is very important to get it right.

PROFESSOR JAMES: I think you may have misheard. It is true to say that hepatocellular cancer can occur in Hep B without cirrhosis but is extremely rare in Hep C without cirrhosis.

MS DUNLOP: I think that's what the witness said.

PROFESSOR JAMES: But it's not what you said, I don't think. I may be wrong and may have misheard, and if so I very strongly apologise.

THE CHAIRMAN: I think it's just a difference in language.

What you said was that Hepatitis C is a "necessary" step.

MS DUNLOP: I said:

"With Hepatitis C, cirrhosis is a necessary stop on the way to liver cancer; with Hepatitis B, it is not a necessary stop --"

PROFESSOR JAMES: I beg your pardon. I'm so sorry, I misheard.

MS DUNLOP: We are all singing from the same sheet.

PROFESSOR JAMES: I'm rather further behind the sheet than you were. Sorry.

THE CHAIRMAN: I just don't want any of these points to slip past.

MS DUNLOP: I'm also, as well obviously those above me, I'm dependent on those beside me to keep me right. I'm just looking at them to make sure that they know that, but they do.

THE CHAIRMAN: This is one of these points, where, as I once heard counsel say to a shorthand writer, "Take out that question", rather than the opposite. So we would like to take out that series of answers, Professor Thomas, but we will do it without changing the transcript.

MS DUNLOP: So I think we have established the important point of distinction about the role of cirrhosis in Hepatitis B and Hepatitis C, and obviously from the

percentages you have given us, the problem of chronic disease is much greater with Hepatitis C than with Hepatitis B.

A. That's true, unless of course with Hepatitis B you are infected at birth, when the higher proportion have chronic infection.

Q. I suppose epidemiologically that must be quite a small group, however?

A. No, as it turns out, I think there are about 350 million people with chronic Hepatitis B, whereas there is only around 170 million with Hepatitis C. These are guesstimate figures obviously, and three quarters of those that have chronic Hepatitis B are infected at birth, and the majority of these are in fact in China.

Q. Oh. In British terms, just, I suppose, being chauvinistic for a moment, chronic Hepatitis B, how much of a problem is that?

A. I think it's probably a smaller problem than Hepatitis C. It varies in different areas of the country and it's mainly people who are first generation migrants from the Far East or Africa or the Mediterranean, who have the high prevalence of Hepatitis B, whereas Hepatitis C at the moment is, apart from the haemophilia population, probably increasing in prevalence because it is transmitted through intravenous

drug use, which we have failed to gain control of really in our societies at the moment.

Q. Right. Another difference between the two is, as I understand it, that Hepatitis B is a DNA virus, whereas Hepatitis C is an RNA virus. Is that correct?

A. Correct, yes.

Q. And that just means that the genetic information for the B virus is contained in DNA, whereas for the C virus, it's contained in RNA. Is that right?

A. That's right.

Q. Another difference between them -- and we will come back to this -- but I understand from you that another difference between B and C occurs when one considers alcohol, and perhaps you could explain that to us as well.

A. Well, it's now an accepted fact from the basis of tissue culture work that alcohol increases the level of replication of Hepatitis C and as a consequence, the liver damage that you see in someone who has Hepatitis C and is in addition taking significant amounts of alcohol, those two factors are synergistic; in other words, they cause more liver damage than the sum of the damage due to the alcohol and the Hepatitis C, whereas when you come to Hepatitis B, the data suggests that alcohol does not synergise with Hepatitis B; in other

words, the liver damage in that setting is just the summation of that which is due to the alcohol and that which is due to the Hepatitis B.

Q. Right.

A. And that's again important because before we had ways of treating patients with Hepatitis C, one important thing to say was that you can slow down the progression of your Hepatitis C if you reduce your alcohol intake, and the ideal scenario would be that you would be abstinent from alcohol.

Q. Right, just for those of us for whom "synergistic" doesn't trip off the tongue every day, the notion of that is, as you have said, that the total damage is more than the sum of the parts?

A. Correct.

Q. Yes.

Having then looked at some of the key features of these two viruses, I would like to move on to the next section of your report, which outlines for us the discovery of the Hepatitis C virus.

We are very familiar, Professor Thomas, with the term "non-A non-B hepatitis", and I think we understand the concept that this was hepatitis for which Hepatitis A and Hepatitis B could be demonstrated not to be the cause, and that's because testing was available

for both these viruses. But I think, as you have explained, if one had been 100 per cent terminologically correct, the name would have been longer than "non-A non-B", and perhaps you could explain that too?

A. Yes, there are other parentally transmitted viruses, cytomegalovirus and Epstein-Barr virus are parentally transmitted. And technically speaking, since you are defining Hepatitis C by exclusion of these others, it should be non-A non-B, non-cytomegalovirus and non-Epstein-Barr virus. And there is another important component in the definition of non-A non-B hepatitis, which of course implied an infective aetiology, and that was that it should occur in a clinical setting, where you believed it to be an infective agent; and the settings that allowed you to make that deduction were: after a blood transfusion, after Factor VIII concentrate. Those are the two main ones.

Q. Yes.

A. And that differentiates it from non-A non-B hepatitis, that outside that infection setting might suggest that the hepatitis, which just means inflammation of the liver, might be due to a drug, for instance, ampicillin for example, or something like this.

Q. Yes. Again, if we were trying to be precise, it wouldn't be correct to say that non-A non-B hepatitis

was renamed "Hepatitis C". It's that our virus, which was named "Hepatitis C", was discovered and that virus explained the majority of cases of non-A non-B hepatitis, but not 100 per cent of them. Would that be an accurate way of putting it?

A. I think so. It's still a moot point as to whether there were a few post-transfusion hepatitis cases which might indicate another virus. I personally think that the evidence for that now is diminishingly small and that Hepatitis C does appear, for all intents and purposes, to explain most of the cases, if not all of the cases, of post-transfusion hepatitis.

THE CHAIRMAN: Can we deal with this practically by limiting NANB in some way by definition, to make clear that in the final report we are dealing only with transmission-related hepatitis or something? Is there some way one can put it that would be technically correct and at the same time simple to present?

A. Yes, I think it has tended to be shortened to "PT", post-transfusion, hyphen, non-A non-B hepatitis, which is probably the nomenclature which will help most.

THE CHAIRMAN: Thank you very much. I can see that helping because one can adopt that early on, as it were. Thank you.

MS DUNLOP: This paragraph in which you describe the work of

Mike Houghton and colleagues working at Chiron, perhaps could stand a little bit of development, Professor Thomas, because this is very difficult science for those of us who are not scientists. As I understand it, the work which was carried out depended on having at the outset a person who was ill with non-A non-B hepatitis. Is that correct?

A. That's correct. And where there was reason to believe that they had acquired that from a blood transfusion.

Q. Right.

A. Which would meet that criterion of it being PT, post-transfusion non-A non-B.

Q. And serum was taken from that person. By "serum" we should understand plasma with the clotting factors removed. Is that correct?

A. Yes, you could use either, though. It really is just material that -- from the patient's blood that you will subsequently show is infectious by injecting it into a chimpanzee. It's usually serum because the clotting factors create problems if clots form during the viral extraction procedure.

Q. I see. This substance is injected into -- I think in fact it was several chimps but to try and make it simple, it was injected into a chimpanzee who then developed non-A non-B hepatitis. Is that correct?

A. That's correct, and that was an essential step to remove any doubt about whether the episode in the patient was indeed due to an infectious agent.

Q. Right.

A. Because of course, all we had in the patient was an infusion and then two to three weeks afterwards, hepatitis, and that could have just been a coincidence. So when it was then shown that the patient's serum transmitted the same transaminase rise, or Hepatitis, to a chimpanzee, that was taken as evidence that it was an infectious agent.

Q. I have seen a reference in an English decision, I think it's a Court of Appeal decision, to the fact that the chimpanzee was called "Rodney", so if, for these purposes, we are imagining the one chimp, we can perhaps think of him as Rodney.

So he develops non-A non-B hepatitis and at this point a sample -- again, I think serum is taken from the chimp. Is that right?

A. Yes.

Q. And from that sample the RNA is extracted. Most of the RNA will be chimp RNA. I'm saying "is"; was extracted by those at Chiron. The hope was that they would also capture some viral RNA. Is that right?

A. That's essentially it but they didn't know whether it

was an RNA or a DNA virus, so they would be extracting in a way that allowed them to extract both RNA and DNA. But again, it would be true that that would include material from the chimp body as well as from a putative virus that may or may not be present.

Q. Having extracted the genetic material, then, if we call it that, to cover both RNA and DNA, they added reverse transcriptase, which is an enzyme that allows RNA to convert into DNA. Is that correct?

A. That's correct, and from that point on, they can handle the material as if it is all DNA, and indeed it is all DNA after that reverse transcription process.

Q. That material was then put into plasmids, and you have explained to me that a plasmid is a vehicle which will enable the expression of the DNA code. So it will facilitate replication of the DNA code of whatever is in the plasmid?

A. That's correct, yes.

Q. It can also be known as a "cloning vector". Is that right?

A. Yes.

Q. That product then goes into bacteria and in this case I think E. coli?

A. Yes.

Q. And the hope was that as the bacteria grow -- and this

is across, I suppose, a very large tray or many trays -- the DNA in those bacteria will be reproducing or will be coding, and most of that will be chimp DNA but some, it was hoped, would be viral DNA. Is that correct?

A. Yes, yes.

Q. So the injection into the bacteria is to facilitate multiplication and also, as I think you have explained, that was the only way in which the DNA could do its job, you know, could genetically reproduce. Is that an accurate way of putting it?

A. Yes, and it's the only way that the DNA could encode for the protein, which is the important part, because it's part of the structure of the virus, putative virus.

Q. Right.

At that point, after that has, I suppose, been going on for a period of time, you need a second patient, who is a patient who has had post-transfusion non-A non-B hepatitis and has recovered, so is presumed to have antibodies. Is that right?

A. That's right, yes.

Q. Yes. What role does that patient play?

A. Well, from that patient's serum, which you assume to contain an antibody directed against some component of the virus, you hope by either radio labelling or enzyme labelling that antibody, it will help differentiate

between proteins that are derived from the chimpanzee and proteins that are derived or encoded by the virus; because the majority of the proteins that will have come through that process that you described will be chimpanzee proteins.

Q. Yes.

A. You are just interested in the one needle in that particular haystack, perhaps one in a million, which will be a viral protein, as opposed to a chimpanzee-encoded protein, and the antibody is the way of sorting that out.

Q. Yes. At this point in the experiment, a ligand is used. I think we have had some explanation of the role of a ligand, when we heard from Professor Tedder.

A. It's a label, really. It's either a radioisotope or it's an enzyme that creates a coloured substrate, usually a peroxidase or an alkaline phosphatase.

Q. Yes, we heard about horseradish peroxidase.

A. That's right. You should just think of that as a label. So it is a labelled antibody, derived from a convalescent serum, that can differentiate proteins encoded from the virus or encoded from the chimp nucleic acid.

Q. Yes, and what you are hoping is that if an antibody to this mystery virus is contained in the convalescent

patient's serum, it will bond with a piece of virus which is contained in your tray and, because there is a signalling device, the fact that that reaction has occurred will show up?

A. Yes.

Q. Yes. And did it work?

A. It did work but many people, including myself and many people around the world, tried similar approaches and came up with nothing. And that, of course, then begged the question: was it that one had the wrong starting material; in other words, there wasn't an infectious virus in the material -- and I could go into why that might be the case -- or could it have been that this was an unusual agent and didn't evoke an antibody response? In other words, our detection system wasn't working.

So it was really an act of faith, since you knew you were neither certain about the starting material, nor the detection system. That's the worst possible situation really.

Q. So Chiron succeeded where many others had tried and failed?

A. Yes.

Q. And --

THE CHAIRMAN: Could I ask at that point: were the others around the world approaching the issue in the same way

as Chiron?

A. Yes, the advantage that the Chiron group had was that they had material that was what we call "well pedigreed". In other words, because of the constraints around using chimpanzees -- and the chimpanzee is the only non-human primate that allows replication of Hepatitis C -- there are only two or thee groups that had access to chimpanzees and could show that these human sera were indeed infectious; in other words, they transmitted hepatitis during passage. "Passage" means you go from the patient to the first chimpanzee and, then you take the material from the peak of the hepatitis in the first chimpanzee and inject it into a second chimpanzee and so on. And that passage shows, without any doubt, that it is a transmissible agent. The rest of us didn't have that advantage.

The other thing that the Chiron group were able to do was that they were able to titrate the amount of virus. In other words, between chimpanzee 1 and chimpanzee 2, they would dilute chimpanzee 1 serum many times until it no longer caused hepatitis and then they assumed they could calculate then how much virus they thought was in that specimen, in that first material.

Of course, they chose one where there was a relatively large amount of virus and that really was

the thing that opened it all up. And that was the work of a guy called Bradley at the Centre for Disease Control.

THE CHAIRMAN: It's just quite difficult to pick up the essence of the inventive step from the report of the litigation in England, where there is the most extensive, I think, debate on this. So from my point of view, and I think from everyone else's, we do not need to understand everything but it is helpful to be able to pin down just what it was that Chiron achieved that distinguished them from the rest of the world.

A. Yes. I think -- I mean, I was involved with that particular patent defence really, as an example of somebody who had tried and failed, if you like, and I think the only difference really was that there was very great uncertainty about the starting material and the detection system, to the extent that many people had given up, believing that there wasn't a virus; it was a chemical reaction that caused the transaminase rise, much in the way that a drug in medication can cause hepatitis. But I think this is why there hasn't been a Nobel Prize for the identification of Hepatitis C really, because this initial inventive step, you know, questions as to how inventive it is, apart from the legal patent issue, of course, which is important. And

of course, it was the first time that a patent was given for a natural sequence. Not a human sequence but a natural sequence of a living organism. So it was unique in that sense as well. But they got the patent.

Q. Yes, thank you.

Professor Thomas, you explained to us that the point of the plasmid, the cloning vector, is to access the protein synthesising capability, so it's a mechanism whereby whatever piece of DNA has been put into the bacterium can cause synthesis of proteins in the way that the virus would normally synthesise proteins. So you are looking for something that's synthesised by the genetic material that relates to the virus and not to the chimp?

A. Yes.

Q. And as I understand it, in the very small minority of these trays or samples -- that is, the ones that related to the virus and not to the chimp -- an antigen was synthesised and that then caused this antibody/antigen reaction, and I think the antigen was called "511".

A. Yes.

Q. It was christened 511. Is that correct?

A. Yes.

Q. And that is part of the virus but only a part of it?

A. Yes, it's one of the enzymes of the virus. It's what

would subsequently be called "NS4", which is a protease of the virus. I don't know whether it's helpful just to -- is there a pen? I might draw it on there.

(Pause)

THE CHAIRMAN: I'm sure it's helpful but from here I can't see it. I'll just come over so that I can see it.

A. So the RNA of the virus is positive strand and it encodes for what we call a polyprotein. This is the virus RNA, which would, of course, be in a virus particle and, when it gets into the cell, it would encode for this polyprotein, which is all the virus structural and non-structural proteins (inaudible). This polyprotein then has got to be clipped into fragments and --

THE CHAIRMAN: Physically or ...

A. Sorry?

THE CHAIRMAN: Physically clipped?

A. Physically clipped, yes, and that's done by a protease, and the virus makes its own protease. So it's actually done by the NS3 and the NS4 proteins. They then clip up the polyprotein into fragments and that allows them to form into the particles. What we were hearing is that the antigen that was recognised by the antibody in the recovered patient's serum was in this region, NS4, and that was termed "511".

Okay?

THE CHAIRMAN: Does 511 have any significance other than a number attached to it?

A. It is just a way of identifying the antigen really, it has no other significance, and, of course, it has been lost in time now. The only thing that's carried forth is NS4 because that is something which is a part of the virus and has been important subsequently. This isn't just scientific detail; these non-structural proteins are the target for the modern drugs of today.

So the proteases NS3 and NS4 are targeted by protease inhibitors -- and no doubt you will hear from others. These drugs now are useful. They increase response rate quite substantially.

NS5b is another enzyme, the so-called polymerase of the virus, that makes more copies of its RNA and that can also be inhibited by drugs.

So the only reason for this diagram is to show you where the antigen derives. It is from the NS4 protein and it is one of the antigens that evokes an antibody response at an earlier stage of the infection.

THE CHAIRMAN: I think the labelling process one can see in a sense at a superficial level quite easily, but you introduce something that has a particular characteristic impressed on it from another source and it will react

and give you a reading. But just exactly what's happening is not at all clear at that point.

A. I think how you need to think of it is that essentially you put a copy of the RNA. The fact that it has been reverse transcribed into DNA is a technicality. That DNA then results in the production of a protein. All of that is occurring in the bacterial cell.

The answer then is how do you identify the bacterial cell that has got this particular bit of viral RNA in it and everything that derives from that, how do you identify that as separate from the chimpanzee material? That purely relates to convalescence serum having a molecule in it called an antibody which can bind specifically to sites on the virus-encoded proteins.

That is either labelled with iodine 125, so that you can see where it is by radioactivity being tagged in the protein --

THE CHAIRMAN: Or the enzyme --

A. Or the enzyme system --

THE CHAIRMAN: -- such as the horseradish --

A. That's just a label. I wouldn't think of it as an iodine or an enzyme; just call it a label and a way of tracking where the antibody is bound.

THE CHAIRMAN: It is perhaps enough to know that it happens.

A. Yes, I think the detail of that probably is a little

irrelevant really, except for interest's sake, really. As you pointed out, the inventive step was the fact that they continued to do it, when many others gave up.

THE CHAIRMAN: Which is not or might not at that stage have been recognised as a particularly inventive process: persistence instead of --

A. Correct.

PROFESSOR JAMES: It might be called the Robert the Bruce moment. You know: try, try, try again, sort of thing. It's fair to say that they tried for millions of times over about five years before they got this result, isn't it, Howard, or maybe longer?

A. Yes. Most people were starting to say the hepatitis that occurs after Factor VIII concentrates or after transfusion of whole blood, maybe it's related to the chemicals that are present in the blood or the HLA proteins, you know, which are contaminating these coagulation factors. There were all manner of other explanations, which really just served to illustrate that it was no longer clear that there was a virus involved. People were beginning to doubt that.

I think that's the only point I would really need to make at this stage.

MS DUNLOP: Thank you for explaining it to us.

A. Or confusing --

Q. Well, we have the transcript and we can always go back and re-read it because it may not necessarily stick first time.

THE CHAIRMAN: I think it is very important that other people were giving up, even on the thought that a virus was involved.

MS DUNLOP: Yes.

A. That's an interesting key point really.

THE CHAIRMAN: And one is trying to get a picture of what was done and some sort of impression of whether something else might have been done, and if the process is of investigations or leading the vast majority of competent scientists to the view that they are following a false trail, that is important in itself.

A. There was one other thing that I think might serve to illustrate the uncertainty at the time and that was that, while it was still called "post-transfusion non-A non-B", we did a controlled trial, for instance, with interferon, in the belief that, were it a virus, the interferon would cause the transaminase abnormality, a measure of the hepatitis, to improve. We did it as a controlled trial because we knew that post-transfusion hepatitis is an intermittent disease. The transaminases may go up and then down and up and down. So we gave interferon to half the patients and no treatment to the

other half and were able to show that the transaminases fell in the group that received interferon.

What's the importance of the interferon? Well, it's a specific antiviral drug, again suggesting that there was a virus involved.

Q. Evidence?

A. So we did that in 1989, the year that the virus was discovered, and we were then able to go back and test our non-A non-B hepatitis patients that went into that trial and, sure enough, they were all Hepatitis C cases.

Q. When you say "we", this is your team at Imperial?

A. We were at the Royal Free at that stage.

Q. At the Royal Free, sorry.

A. And Jay Hoofnagle did a similar experiment but he didn't do it in a controlled way, so he didn't know whether the improvement was a coincidence or not, but in 1988/1989 there were two studies published showing that interferon normalised the transaminases in non-A non-B hepatitis, further illustrating that this was a virus because interferon, as far as we knew, only worked against viruses.

Q. I suppose the other thing we should take from this, Professor Thomas, is that what was identified in this breakthrough was not the whole virus?

A. Yes, exactly.

Q. And I think that has featured at a much earlier part of our inquiry because there are differences between genotypes. We are just going to come on to that. Because the first generation tests may have been only looking for a very small number of antigens or a small portion of the viruses, the variations between the different genotypes might make testing more successful with some genotypes than with others. Is that correct?

A. Yes, we didn't know about genotypes, of course, and the assumption, as we have pointed out, was that the antibody source which was going to be used as the detection system would be against a common antigenic component of the virus, but we didn't know that that was going to be the case.

So we could have had, for instance, an antibody from a genotype 3 case and if the virus being cloned was genotype 1 and it was in an area of sufficient variability, the antibody wouldn't bind. So that would be another reason why we would fail.

Q. Yes.

A. So ...

Q. I think the whole genome of the virus has subsequently been sequenced. Is that right?

A. Yes, yes.

Q. That's it; you have drawn it for us.

A. And that's what was done and they managed to identify the whole virus. Then Chiron said that then they could replicate the virus in tissue culture, and clearly they were looking at an artefact -- is the kind way of looking at it -- because this little fragment at the end here, called the "3 prime uncoded region" wasn't present on their RNA and that's essential for viral replication. So when they extended the patent to say that any system that uses this nucleic acid structure information should allow the investigator to generate a replication system and within that replication system you could then identify drugs, well, it didn't replicate in spite of what they said because this 3 prime is missing.

Q. I think we need to be sure that we have got this term, Professor Thomas, the "3 prime end"?

A. The 3 prime uncoding fragment. In other words, it's the tail end of the RNA molecule, that doesn't encode for amino acids.

Q. Right. The correct term for that is 3 prime, as in prime number?

A. Yes, 3 prime uncoding region.

Q. Uncoding region?

A. Yes.

Q. Right?

THE CHAIRMAN: And its function is the reproduction --

A. It allows the virus to make more copies of the RNA.
THE CHAIRMAN: And that's the right-hand element in the sketch of which we have a picture so that we can --
MS DUNLOP: And that's a necessary but not sufficient element in replication. Is that correct?
A. Yes, you would need the whole molecule for replication but if you just have this part, without the 3 prime uncoding, it won't replicate. So they were lucky to get that component of the patent.
THE CHAIRMAN: It could always be reduced for a lack of utility here.
MS DUNLOP: Is it still correct to say that no one has grown the virus in tissue culture?
A. No, the Japanese have now done that. They can replicate the virus in a particular cell line.
Q. How recent is that?
A. In the last five years, that sort of timeframe.
Q. Looking a little bit further down the first page of your report, if we could, please, we have another heading "The virus and its replication". You tell us that:

"HCV is a flavivirus ..."

And this, I understand, comes from the Latin for yellow, which is "flavus". You say it shares some properties with other members of the family including dengue, yellow fever and West Nile viruses. You say it

is a single positive-stranded RNA virus, which exhibits considerable genetic heterogeneity.

A. That just means sequence variation.

Q. Yes. So genetic diversity. I think you have already alluded to the fact that obviously this has been emerging knowledge since 1988/1989, that there are a number of different genotypes. You say:

"There are six major genotypes with additional differences between the strains found within a genotype."

I think they are labelled A and B, as necessary. Is that correct?

A. Yes, or A, B, C, D, however many.

Q. Yes, however many letters you need. So it did strike me when I was preparing for this that you can have a genetic difference between, say, 3A and 3B and that must be a smaller difference than the difference between genotype 3 and genotype 2?

A. Correct.

Q. And then those differences must be much smaller than between Hepatitis C virus and another virus?

A. Yes.

Q. Is it all a question of degree of difference?

A. Well, it is a question of degree of difference and there is an international convention. But having said that,

it isn't completely arbitrary because as it turns out, there are major biological differences between these different genotypes. So, for example, genotype 1 virus, when treated with interferon and ribavirin, we cure 40 per cent of those patients, whereas with genotypes 2 and 3, the same treatment, interferon and ribavirin, cures 70 or 80 per cent. So there are significant differences.

Q. So it's not just a difference in the make-up; it's a difference in the behaviour, if you like, the biological behaviour?

A. Yes, which is not surprising because that's, of course, encoded by the genetic structure of the virus. So the proteins are slightly different.

Q. And you go on to explain that even within an individual infected with a single inoculum -- so a person who has just one genotype -- the genetic sequence of each virus particle is different and changes over time. And I think you go on to discuss that in a little bit more detail. And you talk about the causes for those changes, which include the host's immune response and more recently exposure to potentially therapeutic drugs:

"HCV exhibits greater genetic diversity than most other viruses and this is a major contributor to the high rate of chronicity ... the difficulty in producing

a vaccine, and the rapidity of emergence of virus strains that are resistant to the new protease, polymerase and NS5a inhibitors."

Just to clarify, professor, the genotypes don't in some way change into each other?

A. No, they are sufficiently different from the onset of infection to be identified as separate genotypes but within a strain there will be significant changes in the virus, related to the fact that this NS5b, which is responsible for making more strands of the RNA of the virus, doesn't have what we call a "proofreading system". So when it's making a copy of this RNA strand, it keeps making errors. And normally, yours and my RNA -- the enzymes that replicate our DNA would actually check to make sure that they had replicated it faithfully; in other words, there was a proofreading system. The virus doesn't have that so it keeps on making errors, and that actually creates what's called a swarm of quasispecies: every virus particle in the patient is slightly different in its RNA sequence.

Q. So from the point of view of survival of the virus, the errors are quite handy?

A. They are very handy. There is an upside and a downside, because if it makes an error in something that's important to its replication, of course it becomes

non-viable, it can't replicate itself anymore. So within that constraint, the other mutations are actually of advantage because you have an infinitely variable population of virus particles. So whatever pressure the immune system puts on the virus, there will be a small number of quasispecies, just individuals variants, which have an advantage in that setting because their antigens will be slightly different. So it is a real advantage for the virus.

Q. You have given us a picture. Can we go a little bit further down? We can see it there and that's, as you say, a stylised representation of the virus, a virus particle. Can you just talk us through it a little bit, please?

A. Yes, the virus consists of lipid fat, which is derived actually from the cell which it's replicating within, and in that lipid envelope are stuck the envelope proteins, which in the case of this virus are E1 and E2. These virus proteins allow the virus, in a key and lock process, to bind to something on the surface of the cell. Remember, the virus can't replicate unless it's within the cell. It needs all the enzymes of the cell to replicate itself. So it has got to get in there and it does that with a key and lock process.

Q. And that's a handy metaphor because that's the door?

A. That's the door into the cell.
Q. Yes, and it gets into the liver cell, right.
A. Yes. And then within that envelope is a more robust core structure, and that serves to protect the RNA of the virus, the genetic information of the virus, and that's one of the reasons why this virus can live for a significant time outside the body. It's protected by this protein shell, particularly the core protein, and then stuck on to that RNA will be the RNA polymerase, this NS5b enzyme, and that's going to make copies of the RNA of the virus.

The other thing to point out here, of course, is that these envelope proteins themselves are hyper-variable, they change according to the antibody pressure that comes on them, and this is again a function of the fact that the replication enzymes of the virus are all the time making mistakes, so all these envelope proteins are slightly different on each virus particle, and therefore when an antibody is made against one type of the envelope, this will neutralise that virus and then a smaller variant will emerge with a different antigenic type, and this will not be neutralised initially until the new antibody against it is produced.

Q. So thinking of this stylised reproduction in 3D, what

has happened is it has been cut open to let us see the inside, and normally the outside would have these envelope proteins, which are antigens, and these are the red bits sticking out?

A. Yes.

Q. Yes.

A. And it might be pertinent here to mention that the molecule to which the virus binds on the surface of the liver cell is the same molecule as involved in taking fat into the cell. It's called the LDL receptor. So the virus has piggy-backed its entry process on to a normal receptor process that the cell uses to take fats into the cell, and if you look at the levels of virus in the blood after a fatty meal, they go up because --

Q. I want to come back to that. You mention that to us and you have alluded to the possibility of a pharmaceutical answer to that. So if we could come back to that perhaps, professor.

The second --

THE CHAIRMAN: The sort of docking system that we are talking about depends upon the characteristics of the cell that's being attacked and the envelope proteins on the virus?

A. Yes.

THE CHAIRMAN: Is it simply by chance that the viral proteins come equipped with appropriate key and lock devices or docking devices?

A. I think at the beginning of time -- it gets a little bit philosophical -- there must have been multiple different virus particles and they would only get into the cell, in which they ultimately were going to be able to replicate, if they had by chance a protein that bound to the cellular receptor, an appropriate docking system.

MS DUNLOP: So it's natural selection among viruses.

A. Yes.

THE CHAIRMAN: And Professor James has mentioned, at least to me, earlier that some viruses are species specific. Is that related to their capacity --

A. Yes, exactly. The receptors are different on each person's cells actually, and also between different species, but in the main the virus has -- if you look at viruses in general, they will have used a normal cellular receptor. So for Hepatitis C for instance, it enters the cell through something called "secretory piece", which is normally a method of transmitting one particular antibody across the gut. The herpes virus gets in through the FC receptor. These are all essential parts of the human physiology, if you like, and the virus has just found a way of using that.

Q. I'm sorry, I didn't quite catch that. The Hepatitis A virus comes in through the secretory piece, is that what you said?
A. Yes, the secretory piece is a docking mechanism on the lining cells of the intestine, so the virus Hepatitis A binds though that system, which exists normally to transport antibodies from the gut mucosa into the lumen of the cell -- into the lumen of the gut, rather.
Q. So this is, I suppose, a kind of opportunistic behaviour by viruses; they make use of what's already there for a different purpose?
A. Yes.
Q. Figure 2, I think we might all feel more comfortable with, Professor Thomas. We can recognise it.
A. It's just to illustrate how prevalent this infection is really. And this will become important later on because we are going to hear that Factor VIII concentrates were imported from the United States, which, as you see, has a higher prevalence, than, for instance, the UK. Prevalence in the UK is less than 1 per cent; in the US it's around 2 per cent. This is in the general population. Of course, the other issue is the difference between unpaid and paid donors, which we will come to later.
Q. Yes.

A. So that's the reason for showing this.
Q. It's very tempting, of course, to study the map, professor, and there are interesting variations within the continents. Of course, I had to check in South America but the red country is Bolivia. Why should it have such a high rate of Hepatitis C?
A. I think things like tribal behaviour, scarification techniques of the Indian communities and these sorts of things, plus the contribution that man has made are important factors. You have chosen Bolivia but if look at Egypt, for instance.
Q. I was coming to Egypt actually.
A. And there people were using a drug, which was given by an injection, to treat shistosomiasis. And they made this generally available and as a consequence they -- didn't use sterilised needles, and as a consequence they transmitted Hepatitis C, and 20 per cent of the Egyptian population have Hepatitis C, and it's all of one particular genotype, genotype 4, which is quite difficult to treat.

So there, an intervention by man to treat another condition, shistosomiasis, resulted in transmission of this virus. I suspect something similar may have happened in Central America.

Q. In fact there is a high instance, not quite as high as

Egypt, but a high instance in Libya as well?
A. You might say, "Why is it low in the UK," and this figure of less than 1 per cent, it is actually very low in the UK and that, I think, is partly related to the fact that we had a National Health Service from 45 onwards, where, you know, sterile equipment was provided in every hospital. In the continent, for instance -- you will see in France and Germany the prevalence is higher, and that was related to the fact that they didn't have a National Health Service. They used unsterilised equipment a lot of time and that spread the virus.
Q. I think we were under the impression that there was quite a high prevalence in Italy, but there doesn't look to be?
A. I think it is a high prevalence but particularly in southern Italy. I don't know whether that is green at the end of the boot of Italy but it's supposed to be.
Q. It's supposed to be green at the boot of Italy?
A. It should be, yes.
Q. Right. Well, perhaps something we can enjoy studying further at home.
You then give us another map, professor, and this is the geographic distribution of the different genotypes.
A. In the UK it's about 50/50 genotype 1 and genotype 2 or

3. The majority of the 2s and 3s are in fact 3. So it's about sort of 50/50. In the United States it initially was mainly genotype 1. And in the haemophilia population it has mainly been genotype 1, but added in subsequently has been genotype 3. And of course, the frequency with which each genotype is seen will be dependent upon the country where the Factor VIII concentrates were made, for instance.

Q. Yes. We can see exactly what you said a moment ago about the dominance of genotype 4 in Egypt. There isn't much reference to 5 and 6. 5 in southern Africa?

A. 5 is really South Africa and genotype 6 is Hong Kong and China.

Q. Can we just go back to the text, please, scrolling a little bit further down. I think you have covered this already, professor, talking about the two highly variable envelope proteins and its lipid coat. Hyper-variable regions. And this is the point about the virus evading its detector, as it were, isn't it?

A. Yes, and the immune system is always playing catch-up. It takes about ten days to produce the antibody after a new antigen appears and so the immune system is always ten days behind the antigenic variation generated by the mutations in the virus.

Q. Then a point which again you have already touched on

under HCV replication, that it gains entry:

"The virus gains entry to the liver by binding to lipid receptors on the liver cell surface."

You have said that these are the same receptors as take up fat from the diet. Yes.

The point you made a moment ago about levels of virus increasing after a high fat meal, does that mean that people with Hepatitis C should watch their fat intake?

A. I think it's a relatively small change but it is something that has been observed by Dr Bassendine and her group, in fact in Newcastle.

You mentioned the fact that, you know, there are drugs being developed now, or already exist, the statins, which influence the amount of LDL cholesterol and if you give a statin to somebody with Hepatitis C, the amount of virus goes down; not to the same level that you would see with the therapeutically useful drugs, in other words interferons and ribavirin, which can be curative, but the statins do cause a small reduction, which is one of the reasons why people started to suspect that the virus had piggy-backed on to some of the fat metabolisms of the body.

Q. I don't want people to get the wrong impression, Professor Thomas. Is there an upside to being on

a statin if you have Hepatitis C or are the interferon/ribavirin treatments really the route that should be followed?

A. The latter, yes. It's the interferons and ribavirins which are the only therapeutically useful manoeuvres. The statin were an interesting quirk. It may be in the medium term that something will come out of that but at the moment they are not useful clinically.

THE CHAIRMAN: Ms Dunlop, before you turn over the page.

MS DUNLOP: You would like a break? We would like a break. I think the next diagram is one that is going to cause us a certain amount of difficulty, given its scale.

(11.00 am)

(Short break)

(11.26 am)

THE CHAIRMAN: Yes?

MS DUNLOP: Thank you.

Just looking at the point in your report that we had reached, Professor Thomas. Essentially once the virus is in, so it has used its key in the lock and got in, it then hijacks the replication mechanism of the cell. Is that right?

A. Yes.

Q. To make more copies of itself?

A. Yes.

Q. Yes. And you say:

"New virus particles are then assembled and released from the liver to circulate in the blood stream."

Later in your report you tell us that about 10 to the power of 12 new virus particles are made each day.

A. Yes, and each one is slightly different, hence the capacity of the virus to evolve under the various selection pressures under which it comes.

Q. Can we turn the page, please, and look at the next diagram and it's getting bigger. I think it would be prudent if I simply asked you to walk us through this, please, if you would.

A. I think the main point of showing this diagram was really to illustrate how the virus is intimately involved with fat metabolism.

At the top left the virus is the orange particle with the mushrooms on its surface, which are the envelope proteins, and that's to represent the lock and key mechanism. And on the membrane of the liver cell, which is the brown structure, you can see there is a series of receptors, one of which is the LDL receptor, the lipid low density lipoprotein receptor. There are other receptors, we do not yet know how important or otherwise they are, but the one that we know allows the virus to get into the cell is the lipoprotein receptor.

Q. So it's the lock, really, for these purposes?
A. That's the lock, yes.
Q. And the mushrooms are the key?
A. The key, exactly.
Q. Yes.
A. And then within the cell, which is the main diagram, there is the positive-stranded RNA, which, because it's positive stranded, will be the template from which the polyprotein is produced. And the polyprotein is produced in the protein-synthesising machinery of the cell. So the virus is immediately using the apparatus of the cell to make its own proteins, to make virus proteins.
Q. And the polyprotein is the blue spaghetti?
A. No, the blue spaghetti is what's called the endoplasmic reticulum, and that's the area in the cell that's normally involved in production and secretion of protein.

So the virus is really just using this to make its own polyprotein, which is -- you can see, for instance, E1 and E2 and the core protein and then something called "2, 3, 4, 5," which are the other proteins, and the polyprotein is clipped up into those individual discrete proteins, which self-assemble; their physical properties are such that they come together as a virus particle in

exactly the right structure, and then those particles then are excreted from the cell in the same structures that are used to get rid of fat from the cell. So the uptake and the process within the cell all use the lipid pathway. That was the only point that I included this to illustrate.

Q. Right. So the exit, the back door, as it were, through which the virus leaves the cell again, is also something which exists --

A. It exists whereby the cell would normally get rid of fat, you know, from the cell.

Q. Right.

A. This becomes of some importance in that, if the synthesis of fat in the cell is altered, as, for instance, with a statin, then you alter the ability of the infected cell to export virus, and under some circumstances, particularly with genotype 3, you get an accumulation of fat in the liver cell, presumably because of an imbalance between the rate of synthesis and the rate of export of fat. And that accumulation of fat is one of the factors that causes progressive liver disease and is specific to genotype 3 and is probably related to why that virus is related to type 2 diabetes.

Q. Yes. We are slightly jumping ahead here, but it's convenient to do so. You have told us exactly that:

that genotype 3 is associated with accumulation of fat in the liver, for which the term is steatosis. Is that correct?

A. Yes.

Q. And type 2 diabetes mellitus. You have explained to me, before today, that it's more than an association. There is thought to be this causal mechanism as well.

A. Yes. Yes.

The other importance of mentioning fat in the liver, of course, is that when doctors see a report of fat in the liver, they think that it's often related to alcohol and, of course, we can't really tell the difference between fat which is accumulating through this virus-specific mechanism and fat that's accumulating because of genetically determined type 1 diabetes or fat accumulating due to alcohol.

Q. Right.

A. So when you start to see fat in the liver, you start to ask, well, is this something that is a mechanism whereby the virus is causing damage or is it that this is an individual who is also taking too much alcohol and has a more rapidly progressive liver disease because of that synergism that I was telling you about, between Hepatitis C and alcohol intake. Or greater than the sum of the parts, as you phrased it.

Q. So with diabetes, type 2 diabetes, the mechanism, as I understand it from you, is about the fact that accumulated lipid causes insensitivity to insulin. Is that right?
A. Yes. The insulin resistance starts to become a problem then. So it becomes a vicious circle.
Q. Can we go down to the text, please? I think you are explaining to us here that it's not the virus itself which directly damages or kills the liver cells, that the liver cells suffer because of the immune response to the virus?
A. Correct.
Q. Right. So in fact, because the immune system is trying to deal with the virus, it is releasing cytokines. Is that right?
A. Yes.
Q. And the purpose of cytokines is to kill infected cells?
A. Two things: to shut down the virus replication and also to kill infected cells, yes.
Q. Then you have given us some further details about the structure of the virus, the RNA is contained in the core, and then about how quickly HCV RNA can be detected. You tell us that only 30 to 40 per cent of people spontaneously clear Hepatitis C and the vast majority do so in the first six months.

A. And that's determined by how readily the immune system recognises the infected liver cells, which is in part related to the HLA proteins, which are the recognition proteins.
Q. Right. And those vary from person to person?
A. Exactly.
Q. Depending on an individual's genetics?
A. Yes.
Q. Yes.
A. So we know there are certain HLA types which make it more likely that an individual will develop an acute self-limiting infection than a chronic infection, for instance. We studied that as did several other groups, and that comes out quite clearly.
Q. I have seen some reference to the role of HLA, haplotypes in HIV as well. There seems to be some connection between your genetic make-up in that regard and your response to HIV.
A. Yes, and if you have -- you know, we have got two chromosomes. So everybody has two HLA proteins at each locus, and if you have two different HLA proteins, that puts you in a better position to present virus proteins to your immune system and clear the virus than if you are what we call homozygous for proteins at any locus, where both the chromosomes have the same gene, let's say

HLA1, as opposed HLA1 plus HLA7, which gives you a better chance of presenting.

Q. Then you go on to tell us that the level of viremia probably does influence the severity of the liver disease. That's simply the titre of viral particles. So your score of viral particles will influence how severe the disease is?

A. Yes, I mean, in people with HCV and HIV or in people, let's say, who have Hepatitis C and are immune-suppressed because they have a liver transplant, the levels of virus are higher, and those are the individuals who get more rapidly progressive disease.

Q. Yes. Perhaps we should define what we mean by "severity of disease", and you have just touched on this: to some extent you either have Hepatitis C or you don't?

A. Yes.

Q. So when we are talking about the severity of disease, we might be talking about such indicators as the rapidity of progression. Is that right?

A. Yes, we are really talking about the amount of fibrosis in the liver, which is a precursor of cirrhosis. That is graded on a scale 0 to 6, what we call the Ishak Scale.

Q. You had better tell us that. That's an acronym, is it?

A. No, it's the name of an American pathologist who

described it.

Q. Right, could you spell it for us, please?

A. I-S-H-A-K.

Q. Right.

A. And 0 is no fibrosis in the liver, a score of 6 -- or stage 6 -- is cirrhosis. And this becomes important in talking to patients because, once you have cirrhosis, we believe that this is irreversible in the main, and of course that puts you in the context of Hepatitis C at risk of hepatocellular carcinoma.

If we clear the virus before a patient reaches the stage of cirrhosis, then all the earlier stages of fibrosis, from 1 up to 5 -- if the virus is cleared that will regress; in other words the liver will ultimately remodel and go back to normal. So it's important to treat the patient before they have cirrhosis.

Q. So fibrosis can reverse and cirrhosis can't?

A. That's what we believe.

Q. Yes, then you tell us that:

"Outside of these settings, the level of viremia is not positively correlated with severity of liver injury or fibrosis and in any one patient may diminish as the disease progresses, possibly related to progressive reduction of the liver volume."

A. So there is less space for the virus to replicate in,

a smaller number of cells.

Q. Then you say:

"Severity of disease is not, as far as I know, related to the genotype or number of genotypes infecting the patient."

I should have said at the outset, Professor Thomas, we did send you a list of questions with some possible theories that had been suggested to us or some things we thought of ourselves. So sometimes this is in answer to points we have put directly.

It can, however, be relevant that a patient has more than one genotype. That can be relevant in the course of treatment, I understand.

A. Yes, I mean, it is particularly so in patients who have haemophilia because they may be carrying more than one, and also they may also have Hepatitis B as well as Hepatitis C, and there is such a thing as viral interference where the replication of one virus holds down a second virus --

Q. Yes.

A. -- to the extent that you may not realise that the second virus infection is there until the first virus is cleared, and then up comes the second virus. And we have reported one case, really, where Hepatitis B was there along with Hepatitis C and didn't become apparent

until six months after we had cleared the Hepatitis C.

Q. Right. So the pattern of viral interference between those two viruses is that C suppresses B?

A. Yes.

Q. Right.

THE CHAIRMAN: Common or rare?

A. Pretty rare, really, yes, because obviously it's the product of the instance of the two viruses, outside the context of haemophilia, where you are taking material maybe from 3,000 donors. It is exceedingly rare.

MS DUNLOP: But not rare amongst people with haemophilia -- or at a point maybe 20 or 30 years ago?

A. Yes, it's not uncommon, particularly -- different genotypes of Hepatitis C would be not uncommonly found in haemophiliacs.

Q. Right. Yes. A lot of different measures, of course, have been introduced to address the Hepatitis B risk with concentrates as well. So I suppose one would factor in all these other considerations in any assessment of how common the occurrence would be.

You go on to talk about other consequences of having the virus. We have covered the type 2 diabetes. You say:

"The virus may cause non-Hodgkins B cell lymphoma."

So is that essentially a type of cancer?

A. Yes, it's a cancer of the lymphoid system, and I think that association is fairly strong, to the extent that it is now fact that it is causatively related to Hepatitis C.
Q. I'm sorry, causally related to Hepatitis C?
A. Hepatitis C is causatively related to this particular tumour.
Q. A particular genotype?
A. No. Outside southern Europe the -- if you take a group of non-Hodgkin's B cell lymphomas, you very rarely find Hepatitis C, but in southern Europe it is commonly associated with Hepatitis C. You might say Koch's Postulates, we were talking about earlier, that they fall down there and you would say that, because you don't always see the infectious agent along with the disease, that would argue that the infectious agent doesn't cause the disease when you do see the two together. But the mechanism whereby the virus stimulates a particular receptor, CD81, on lymphocytes and stimulates the B cell to proliferate is established, and that is a fairly convincing way in which you can imagine B cell lymphomas would be caused.
Q. Why does it particularly happen in southern Europe?
A. We don't know the answer to that, is the answer. It is either that the host is subtly different, which is the

most probable explanation, because when we have looked at the virus -- and the whole virus genome has been sequenced in those with non-Hodgkins B cell lymphomas and no pattern comes out as causatively related to this particular tumour. So I think that's an open question.

Q. But in this country a rare risk?

A. It's a rare association.

Q. Right.

A. Most people with non-B cell lymphoma do not have Hepatitis C.

Q. And most people with Hepatitis C do not get non-Hodgkin's B cell lymphoma?

A. Yes.

Q. "Cognitive function, brain fog, and mood disorders are probably causatively related to HCV infection, supported by the observation that the virus can infect the brain."

I need to ask you firstly, Professor Thomas, to explain to us a little, "brain fog" as a term?

A. Brain fog is a phrase introduced by the Americans really, to just describe mild cognitive dysfunction; in other words a difficulty in concentrating and higher cerebral function really.

It is found in Hepatitis C and what is more, improves when the Hepatitis C virus infection is treated. The difficulty has always been, outside the

context of haemophilia, many of the people with Hepatitis C are using so-called recreational drugs, and they have an effect on cognitive function themselves. But -- and also, by the way, if you have severe liver disease, you develop what's called subclinical hepatic encephalopathy, where cognitive function is again suppressed. But if you look at non-drug using patients, who have minimal liver disease, they do have these cognitive abnormalities.

All this was fairly soft data until the virus was retrieved from the brain and found to have a different structure in the IRES, which is the region of the virus that is involved in production of the polyprotein, and that structure was also found in peripheral blood lymphocytes. So the same virus strain that infects the peripheral blood lymphocytes is present in the brain and it's different from what is found in the liver.

Q. What, for these purposes, do you mean by "virus strain". Is it something that has adapted slightly?

A. It is three adenine substitutions in the IRES. The IRES is a -- there is a structure with a three-dimensional configuration in the RNA, to which ribosomes bind in order to allow this RNA to encode for this polyprotein. So the ribosomes, which are the bodies which make protein, bind to the IRES and then reading the RNA, they

produce this polyprotein.

If you look at the virus that's found from the brain, then there are three regions where there is an adenine, the base adenine, which are not present in the virus that you can retrieve from the liver. And also, for the virus to replicate, it will also make negative-strand RNA. So the RNA positive strand gives rise to negative, the negative then gives rise to positive and so on.

If you can show negative strand present, it means the virus is replicating. And the negative strand, by a group at the Mayo Clinic, has been found in the brain. And my own group was able to show these adenine substitutions in virus retreat from the brain.

So there is no doubt that the virus replicates to low level in the brain. It probably has got there because of infection of monocytes, which are the phagocytic cells in the blood. They also may settle in the brain, and there they differentiate into specialised phagocytic cells, called microglial cells, which help clean up any dying cells in the brain.

So I don't know whether I have explained that adequately, but the bottom line is that the virus infects monocytes, those monocytes may give rise to microglial cells, and they are cells which are

present in the brain and have a very long half-life.

PROFESSOR JAMES: The point is that the brain fog and these cognitive disturbances are really independent of the severity of the liver disease.

A. Yes.

PROFESSOR JAMES: And that's kind of almost exemplified by these little structural changes that you have already alluded to.

A. Yes. This came out initially when -- there is something called magnetic resonance spectroscopy, which means you can look at the metabolism of the brain, and when we did that, the same abnormalities that previously had been described in HIV were found in Hepatitis C to a minor degree. And these changes suggested that there was a metabolic abnormality in the brain, which is why we cloned the virus from the brain post mortem material, and where we found these abnormalities. The group at the Mayo Clinic and a group in Hanover have now done similar studies. So I think it is now established that the virus is replicating in the brain.

Why is that important? Well, when you come to treatment, I think you have to consider this as potentially a sanctuary site, where the virus may not be readily cleared with interferons. Interferons don't cross the blood/brain barrier so readily.

Q. So the virus hides from the interferons by going to the brain?

A. Yes, aetiologically speaking, yes. And the ribavirin, which we know reduces relapse rate, is a very fat-soluble drug and probably goes to the brain and clears up this site of replication, which is why ribavirin doesn't alter the initial response to treatment; in other words, the rate at which the viral RNA falls in the blood. That's dependent on interferon's effect on the liver. What ribavirin does is stops the patient from relapsing because it clears up that second site.

Q. Right. Not everyone with Hepatitis C will get cognitive symptoms, though?

A. No, and recently we have been able to do PET scans, which are a way of looking at the brain, where you can use ligands, molecules that bind to the activated microglial cells, and when you do that, you can show that the microglial cells in the brain are activated, which is a consequence of infection. When those microglial cells are activated, they release chemicals which cause the cognitive abnormalities.

So mechanistically we now know what happens. It is important because it explains this symptom complex. And secondly, it's important because it may explain why you

need ribavirin to prevent relapse.

Q. And you refer not just to brain fog but also to mood disorders. What form would the mood disorders take?

A. When you compare Hepatitis C with Hepatitis B, with these standard test systems, there is a much higher prevalence of depressive disorders in the Hepatitis C patients compared to the Hepatitis B or in other liver disease groups. When microglial cells produce neurosteroids, they are involved in this depressive mood mechanism. So those are two important consequences of Hepatitis C virus infection, partly, as I have said, because they may explain why you need ribavirin to treat these patients.

Q. Yes.

A. I couched this cognitive issue in soft terms when I wrote this but I think now, with the Mayo Clinic's confirmation and the Hanover group's confirmation, I think this is now an established fact, really.

Q. So that is extremely recent research?

A. Over the last five or ten years. It takes a while for things to become established.

Q. Right.

Your next section is entitled "Mechanisms of HCV persistence". You explain what happens in acute hepatitis, so when someone who is fortunate enough to be

able to clear the virus in an acute episode is ill, that is because the body mounts an effective immune response to epitopes. Epitopes: the part of an antigen that is recognised by an antibody. Is that correct?

A. Exactly. Or a lymphocyte.

Q. Right. Derived from various virus-encoded proteins:

"In general, the stronger the CD4 and CD8 cellular response, the more likely recovery is to occur."

Does that actually mean that empirically the more ill the person is with Hepatitis C immediately after the infection, the more likely they are to clear it?

A. Yes, those that are jaundiced have a lower frequency of viral persistence than those that are non-jaundiced, because the jaundice is a reflection of the immune system killing liver cells, and the more effective that process is, the less likely the virus is to gain the upper hand and persist.

Q. You go on to talk about antibody response to the envelope proteins of HCV:

" ... but rapid antigenic shift occurs in the dominant quasispecies, presumably due to selection against variants recognised by the prevalent virus-neutralising antibody."

So in other words, the virus is discarding bits of itself, which antibodies can deal with. So it's

shedding its own weaknesses, as it evolves?

A. Yes, there are multiple different variations on the virus. There may be 10 to the 12 virus particles produced per day. They will all have different envelope proteins. So the antibody response will neutralise, let's say, 99.9 per cent of those variants, but there will always be one which doesn't have the epitope recognised by that antibody, and that variant there will become dominant until it is then seen by the immune system again and the immune system then says, "Ah-ha, this is an escaped variant. We must make another antibody," but this is ten days afterwards. And then it shuts down that antigenic variant. So it's a rolling process really.

Q. This is back to the catch-up point?

A. Yes.

Q. That the body's immune system is always playing catch-up with the virus.

A. And there is a phenomenon called "immune exhaustion", where the immune system says, "Oh, my goodness, I'm never going to catch this guy," and is then exhausted and starts to make less antibody.

Q. Right. You go on to describe characteristics of patients developing persistent infection. Perhaps we can just read that for ourselves. (Pause)

You say:

"Several studies have now indicated that the immune response may contribute to the outcome of interferon therapy. 50 per cent of patients show no response to interferon."

This presumably relates to interferon resistance:

"This may relate to inhibition of hepatocyte response to cytokines by Hepatitis C proteins, particularly the Hepatitis C protease, NS3."

A. That's now well established that this protease inhibits the production and the response to interferon.

Q. So what the body would normally do to deal with the intruder is inhibited by one of the proteins in the virus?

A. It would inhibit it by one of the host cytokines. And the viral protease will thwart that process, will stop that happening.

Q. Yes. So the cytokines are supposed to deal with the intruder but the virus in fact thwarts that intended mechanism?

A. Yes.

Q. Right. You go on to explain to us what I read as a description of a possible mechanism?

A. Yes, the -- I was telling you earlier about the monocytes or macrophages that are infected, which go to

form the microglial cells in the brain.

Q. So monocytes are a type of white blood cell and macrophages would normally gobble up the pathogen. Is that correct?

A. Yes. And those monocytes and macrophages in a specialised form, what we call antigen-presenting cells, the cells that present the viral proteins to the immune system, these are the dendritic cells. So if those monocytes and macrophages, and as a consequence the dendritic cells derived from them, are infected with Hepatitis C, and they are, then that compromises the cellular immune response, the lymphocyte response.

Q. Right. Another table is coming up, or another illustration, and this is the serological profile of acute and chronic Hepatitis C infection. You say:

"Chronic viral hepatitis is defined as infection persisting more than six months."

Is that, to some extent, arbitrary?

A. Yes, it is internationally agreed. It was agreed initially for Hepatitis B, to differentiate acute and chronic infection, and has been applied to Hepatitis C. It's statistically based on -- you know, that -- it was observed that if you were going to get better from Hepatitis C, you would have done so in the first three to six months after infection. If you were going to

develop persistent infection of many, many years, then you would still be positive at six months. So that was a break point, if you like.

Q. Yes. If we just look at these graphs, we can see that levels of Hepatitis C antibodies are following a similar path in the two. That's the navy blue, or in the second graph, purple line. Is that right?

A. Yes.

Q. ALT, again a very similar trajectory for the first six months but in the person developing chronic infection, it then zigzags about?

A. ALT is a measure of liver damage. It's an enzyme that is normally inside the liver cell and it leaks out when the liver cell is damaged. So in the top part you are seeing a discrete peak with return of the ALT to within the normal range by six months, indicating recovery. And in the second, the bottom part of the illustration, the transaminase starts to come down but then you see it fluctuating above the upper limit of the normal range, indicating chronic liver damage.

Q. And the red bar is there to illustrate when Hepatitis C virus RNA is detectable and in the person with the acute infection, it's detectable up to six months but, because their body has dealt with the virus, not thereafter. We then contrast the chronic infection, where Hepatitis C

virus RNA continues to be detectable indefinitely. Is that right?

A. Yes.

Q. What's the significance of the breaks in the second graph?

A. That really was just meant to illustrate that, depending on the sensitivity of the assay, it may become apparently undetectable from time to time, but it is still there. In other words, as the sensitivity of the assays have increased over time, you see very few, if any, breaks in what would be depicted by that red line.

Q. Right. Then the green bar relates to symptoms. So I suppose, given that the two green bars are the same in the two graphs, this is reflecting what we said earlier about all those who are chronically infected start with an acute infection?

A. Exactly, but I haven't captured the point that you put to me, that other symptoms, and particularly jaundice, are more severe in those that have an acute infection than in those that persist; that is the case and I haven't captured that in this diagram, if you like. Perhaps I should have put "Symptoms", two pluses on the top and "Symptoms" plus/minus at the bottom, something like that.

Q. I suppose, if the time axis was taken on for long

enough, the green bar would return?
A. Yes.
Q. Yes, varying from individual to individual?
A. Yes, I think symptomatic liver disease, you would expect to see maybe 20 or 30 years down the line, and the symptoms that you might expect when the patient developed cirrhosis would be lethargy, perhaps abdominal swelling due to accumulation of fluid, and even jaundice, yellowness of the eyes and vomiting of blood and these complications, really. But that would be at the extreme end of what we call decompensation of the cirrhosis.
Q. We are going to come back to that, Professor Thomas, because you have another table later on, or another figure later on.
A. Can I make one other point here?
Q. Yes.
A. That antibody is present in those that recover as well as in those that develop chronic infection.
Q. Yes.
A. And it's only antibody positivity in the absence of RNA which is the signature, if you like, of an acute self-limiting, cured infection.
Q. Yes, and in fact the top graph reflects the convalescent patient whose serum was used in the Chiron experiment,

if you like. That would be the pattern of their disease?

A. Yes, rather than anomalously, the antibody is present in the chronic infection as well, and it is often in higher titre in the chronic infection.

Q. It's just not working.

A. It's just not working, and that's because it's to an internal component of the virus, this NS3 protein, and not to the envelope. Had it been to the envelope, it would have neutralised the virus but because it's to a non-structural component, an internal component of the virus, it doesn't neutralise the virus.

Q. Right. Can we move on to the section entitled "Transmission of Hepatitis C"? You tell us something we know, that Hepatitis C will spread via the administration of unscreened blood or blood products from infected individuals prior to 1991. It can also be spread vertically, which is mother to baby, and sexually, but the rate of transmission is very low, less than 5 per cent in each case.

Then on to next page. You talk about drug use and also about the particular picture in Egypt. You go on to tell us that the higher the concentration of virus in the blood, the greater the risk of transmission, particularly via the sexual and neonatal routes.

I think we should ask you about your own experience of sexual transmission. Is this something you have seen?

A. It's very unusual. The figure cited in the literature is 5 per cent but in testing the spouses of known chronic HCV-infected individuals, I don't think I have ever found a spouse that has been positive. And indeed that, I think -- with the exception of those that are co-infected, that have HIV, where the Hepatitis C virus is replicating at 1 or 2 logs higher level than it is in the non-HIV infected individuals.

Q. Is that back to our 10 to the power 12 each day? So with HIV present it may be a higher number per day?

A. Yes, I mean, the number of virus particles being produced, minus the number that are cleared each day, gives you the level of viremia. In a normal HCV infection you are probably seeing a concentration of 10 to the 5, 100,000, or 10 to the 6, a million virus particles per ml. At these sorts of level, it's unusual for either sexual or neonatal transmission to occur but if you see the virus go to the levels that are found in Hepatitis B, which are around 10 to the 7 or 10 to the 8, you then start to see neonatal and sexual transmission fairly frequently.

Q. If we go back for a moment to Hepatitis B, that explains why Hepatitis B is much more readily sexually

transmitted. Is that right?

A. Exactly.

Q. Yes.

A. The same is true -- another illustration is there were cases of surgeons transmitting to their patients during operative procedures, and that's very unlikely if the level of virus -- and this is true of Hepatitis B and of Hepatitis C -- are around 10 to the 4 or 10 to the 5, but when they go up to higher levels, then you start to see transmission through perforation of bloods, et cetera. So infectivity is very much related, as I think logic would dictate, to the concentration of virus in the blood.

Q. You then come on to a section dealing with transmission by blood and blood products. You tell us that:

"Between 1970 and 1990, there was debate as to whether blood products derived from volunteer blood donations, prior to screening tests being introduced in 1991, were safer in terms of transmission of HIV and HCV than those derived from paid donors. In the case of HCV, where the prevalence of infection in the UK blood donating general community was around 0.5 per cent ... "

We have had discussion on a number of occasions with different witnesses, professor, about the prevalence in the UK, and of course it depends what population you are

looking at.

A. Yes, very much so, yes.

Q. Yes. So --

A. But I think -- well, carry on and then --

Q. Well, this figure is really back to the coloured world map, isn't it?

A. Yes.

Q. Yes. And it wouldn't therefore surprise you that much lower figures were found in the blood donating population in both England and Scotland in the first six months or a year after the introduction of screening?

A. Yes, and particularly repeat donations, where, you know, already the patients with the higher risk factors had been screened out. So the prevalence of infection in the established blood donor has gradually fallen to levels around 0.01, that sort of level. But 0.01 is still one in 10,000, so you would still expect to see some carryover into a Factor VIII concentrate if it's derived from 30 donors -- from 30,000 donors for instance.

Q. Yes. Of course, we understand that this is the problem with large pool concentrates, that very large numbers of donations were used to make each batch.

We do need to look a little more closely at some of the thinking on whether volunteer batches, if we can

call them that, were less infectious than batches of commercial donations. You say that:

"It transpired that the majority of batches made from volunteer blood donations were infected and the frequency of transmission was similar following use of both English NHS and Scottish NHS and commercial material."

If we could just have a little look at these references. I think perhaps we can look first at one that isn't mentioned there. It's an article from the BMJ in 1983 and it's [LIT0010239]. We have seen Dr Craske's name many times and we know that he tendered a lot of advice on hepatitis to haemophilia clinicians. I expect you recognise the other names. Dr Rizza, we know, was a haemophilia clinician, and actually if we scroll a little bit down the page, we can see that the patients involved in this particular study were those attending the Oxford Haemophilia Centre.

I think Dr Trowell is the liver specialist in this group. Is that right?

A. Yes.

Q. Perhaps if we could just look at the little abstract at the top. I expect you have seen this before?

A. Yes, this was one of the papers that alerted us all to the fact that non-A non-B was occurring after NHS

material as well as after commercial material.

Q. Yes. So 30 patients entered the study but we can see four patients and evidence of chronic liver disease before transfusion. So in fact they were eliminated from the study. At that point, of course, there wasn't a test for the virus; one had to use surrogate testing. Is that correct?

A. Yes, yes.

Q. So that the testing that was done here to ascertain if people developed hepatitis, was to measure serum transaminase levels. All of the nine patients who had not previously received Factor VIII transfusion developed non-A non-B hepatitis. Then four out of ten patients followed up for a year had persisting abnormalities of liver function. Then it goes on to say that:

"More than one serotype of non-A non-B hepatitis may be transmitted by Factor VIII concentrate prepared from volunteer donors in the UK."

That, I suppose, was a reasonable hypothesis at the time. Is the variability in retrospect explicable by different genetic make-up of the patients and possibly by different genotypes of the virus?

A. The variability in what respect?

Q. I think what they are saying in the abstract that the

pattern of illness suggests that more than one serotype of non-A non-B hepatitis --

A. Oh, I see what you are saying, yes.

Q. Yes.

A. Well, I think at the time there were also experiments in the United States using chimpanzees, and there were -- and also Ari Zuckerman did some experiments here in the United Kingdom -- where if you infused a Factor VIII concentrate into a chimpanzee and it developed an acute hepatitis and recovered, and you then infused a Factor IX concentrate, maybe six month later, then it developed a second episode of transaminase elevation, that was taken to indicate that -- assuming that after the first Factor VIII transmission with subsequent normalisation of ALT, that the animal had developed immunity to that particular agent. The fact that when you put the Factor IX concentrate in, it developed another hepatitis must indicate that that was a separate virus. We now know that that's probably not the case and that you can actually get second and third and fourth infections in someone who has recovered from a first infection with Hepatitis C.

Q. So this is a person who has cleared -- to use your term -- the virus on the first occasion. They can again have an acute attack?

A. Yes, and that was one of the confounding facts about this because we had all assumed that when someone had an attack of hepatitis and the surrogate of recovery, which was normalisation of transaminases, ALT -- when that reached normality, below the upper limit of normal, that that person would not be infected again, as the case was with Hepatitis A. You would never get a second infection of A. And you don't get a second infection with Hepatitis B.

So everyone thought a discrete episode with subsequent normalisation of the ALT must mean that you had immunity, or the chimpanzee had immunity to that strain or that isolate. And that was the reason for the haemophilia doctors thinking that when the same thing happened in patients, it was probably a second virus.

The other thing that was apparent was that the incubation periods were different. After a Factor VIII concentrate, the hepatitis usually occurred in two to three weeks, whereas after a Factor IX concentrate, it took about six to eight weeks, which again suggested it might be a different virus.

Q. What was the reason for the difference between Factor VIII and Factor IX?

A. Well, I mean, there are different methods of preparation and, you know, it was assumed that, you know, there

would be differing levels of robustness of the virus and that some of the purification techniques would destroy one virus but not the other, and we already knew that that happened with different viruses in tissue culture settings.

Q. The reason for people getting a second acute attack might be to do with the almost infinite variability of the virus.

A. Yes, in hindsight I think that probably is what was happening, you know, and that's how we now see in some haemophiliacs several genotypes and subtypes of the Hepatitis C in a single patient.

Q. Yes.

A. But that was an anomaly in virology, in that usually, when you are infected with one virus and you recover, then you cannot be infected with that same virus again.

Q. Yes. Just to look quickly at the text of the paper, there is this reference on the left-hand side to a kind of theory that product manufactured in the United Kingdom would be safer than product coming from the United States.

A. That was based on the observation that post-transfusion hepatitis, after infusion of discrete units of blood -- and most patients would have two or thee units of blood -- I think the frequency at which that occurred in

the United States was about 10 per cent of individuals, whereas I think in the UK it may be it was around 1 or 2 per cent. So it was assumed that the prevalence of infection, infective agents, was different and indeed I think it was different. The reason that you saw it after NHS concentrates as well as after commercial ones is because of the large numbers of donors.

Q. Yes.

A. Which made, you know, it irrelevant what percentage were infected.

Q. Yes. Staying on this page, there is, of course, a bit of description of what was done, and we can see from the passage headed "Design of Study" that patients were those who had not received Factor VIII in the six months before inclusion, and then further detail of the assessment procedure.

Then going on to the next page, there is a little heading "Hepatitis", and we can see that, as already mentioned, they defined a set of results, which would indicate non-A non-B hepatitis, and this is to do with transaminase levels, and then set out their results in a table.

Basically, the table shows what's in the abstract, that all nine patients who had not previously received Factor VIII developed non-A non-B hepatitis. So we can

see in the middle of the table that there is a two-part column, "Previous Transfusions". So you would be looking for the people with two zeros. Then reading along to the end -- sorry, I should have said there are nine of them. I know because I have counted. Reading along to the end, those nine all developed hepatitis, as indicated by their transaminase level.

The only thing which puzzled me slightly about this study actually comes in the discussion section, where the reference to nine has become:

"Nine patients who received NHS Factor VIII for the first time."

Do you see that sentence? I think it's seven lines in. It says:

"All nine patients who received NHS Factor VIII for the first time developed hepatitis."

I think actually there are only seven who were receiving NHS Factor VIII for the first time. It doesn't much matter because the point of this study is to show a very high rate of development of non-A non-B hepatitis in people given concentrates for the first time, and that that is true whether the concentrates are commercial or NHS. Is that right?

A. That's what was taken away from this study.

Q. Yes. You mention other work. The first reference is

the paper to which you contributed. Can we go on and look at that? That's [LIT0010800]. This is a paper from the British Journal of Haematology in 1985, although we can see that it was sent in in June 1984. I think it's fair to say, Professor Thomas, that this paper deals with incidence of non-A non-B hepatitis, rather than with severity of non-A non-B hepatitis. Is that right?

A. Yes.

Q. Yes. And in your study, nine out of nine British patients treated with USA-derived commercial products, and 10 out of 12 treated with British volunteer products, developed acute non-A non-B hepatitis. I should have said that this was a study in collaboration with Peter Kernoff and Christine Lee, who were haemophilia clinicians. Is that correct?

A. They were the haemophilia centre clinicians and Peter Karayiannis and I were hepatologists within the department of medicine. And the main focus really, was to see whether we could prevent infection with immune serum globulin, in that, through the haemophilia directors' meeting -- of course, there was a lot of discussions about both the NHS and the commercial concentrates transmitting hepatitis, and there were observations in the liver transplant setting that we

could prevent Hepatitis B by giving hyperimmune globulin at the time of the transplant. And there was some early data, if my memory serves me correctly, suggesting you might be able to do the same against non-A non-B. So what we were trying to do, bearing in mind we knew from Dr Craske and the Oxford group's data that, irrespective of whether we used commercial or NHS concentrate, we were going to see non-A non-B; could we prevent that by mixing in immune globulin from the general population in the hope that this might contain antibody to the virus and neutralise it and prevent transmission. So that was the main focus of this paper, which is, I think, reflected in the title, "Effects of Prophylactic Immune Serum Globulin".

Q. It wasn't a magic bullet?

A. No, except that -- you know, again the background was that we were thinking about two viruses: one more commonly seen with Factor VIII and one more commonly seen with Factor IX. And there was one patient who received NHS Factor IX with immune serum globulin, who didn't subsequently develop hepatitis, whereas when this batch of Factor IX had been used in other patients without serum immunoglobulin, it had caused hepatitis.

So we were wondering: well, could it be that there is an antibody to one of the viruses, that associated

with Factor IX concentrates, but not the more common, which is seen with Factor VIII concentrates. So that was the bottom line, really.

Q. That was the thinking.

A. The alternative could have been just that there was a smaller amount of virus and it didn't always transmit.

Q. Yes.

A. So that was what was behind this piece of work really.

Q. Right. There are, we can see in the summary, some tentative suggestions about what might be going on. You say in the fifth last line:

"Observed differences between concentrates might be attributable to their content of different NANB agents but dose-related effects could provide alternative explanations."

A. The other point that is made in the last sentence, of course, is that, because there was a high frequency, or high incidence of infection, both with NHS and commercial concentrates, when the inactivation procedures started to become a possibility, then if there were even one or two patients who didn't develop non-A non-B, then that would be significant, because we are seeing almost 100 per cent infection with the only concentrates that were available to clinicians at that time, whether they be NHS or commercial.

Q. Yes.
A. So that's the reason for that statement, that this data provides a basis for comparative assessment of new products with possible reduced infectivity. We thought we wouldn't need to do statistical evaluations because it's virtually 100 per cent infection. So if you had one with a reduced infectivity where, let's say, only half became infected, then it's highly likely that that would be an advance, and you wouldn't need to do control studies, which is the point we were trying to make.
Q. Right. You go on to say in the beginning of the article that:

"The quantity of Factor VIII concentrate fractionated from plasma ... "

That is plasma from volunteer donors in the UK:

"... is insufficient to meet demand."

We have had a lot of other evidence about this, Professor Thomas, and we do understand that there was a different picture as between Scotland and England, and Scotland was much closer to self-sufficiency, whatever quite that means, than England and Wales.
A. Yes, I think the ratio, in most of the English centres, was that over half -- probably two thirds of bleeding episodes in the moderate and severe haemophiliacs had to be dealt with by commercial concentrates because we only

had enough for about a third of those cases using NHS materials.

Q. Right. You say:

"Of the total Factor VIII used in the UK in 1982, commercial concentrate accounted for 63 per cent, NHS for 32 and NHS cryoprecipitate for 5 per cent."

That's from the UKHCDO?

A. And these are all patients who came in with active bleeding or were undergoing surgical procedures, so something had to be done to prevent them being infected really. So they had to have concentrates and when we knew that there was, following the Craske study, a high incidence of infection, we thought we would try immunoglobulin to see if that prevented infection, and subsequently, of course, heat inactivation processes were tried to stop transmission.

THE CHAIRMAN: Is the UK here inclusive of Scotland or exclusive of Scotland?

A. I don't know, I am afraid.

THE CHAIRMAN: It would make some difference to the split.

A. Yes. I can't answer that, I am afraid.

PROFESSOR JAMES: If the data is from the HCDO, it suggests that it's UK-wide.

THE CHAIRMAN: If that is so, then one has to amend the 63 per cent/32 per cent split if one is trying to get

a picture of what was happening in England and Wales, as against what was happening in Scotland.

A. Yes, it would be a higher percentage, wouldn't it, that was commercial in England and Wales?

THE CHAIRMAN: Yes.

MS DUNLOP: I think actually by this point you were referring to concentrate being used to treat bleeding episodes but I think we know that some patients were on home treatment, although I suppose most of them are using their Factor VIII at home for bleeding episodes as well, just so that they can --

A. I think, when they get pain in a joint, rather than coming up to the hospital, they would assume that that was the start of a bleeding episode. I think that was probably common practice.

Q. Then on to the next page. You say -- and we have touched on this already -- that:

"It is well established that the risk of post infusion hepatitis is higher after commercial than volunteer blood. The evidence that the same holds for clotting factor concentrates prepared from large plasma pools is less substantial. Acute post infusion hepatitis in patients treated with these products is usually of the non-A non-B type and there is a disturbingly high rate of progression to chronicity."

We will look at that in a little more detail later on.

A. And May Bamber, the author of that, was a member of our group, so we were studying non-A non-B in a non-haemophilia population.

Q. And then:

"The overall incidence of acute hepatitis in haemophilic populations has been reported to be only 2 to 6 per cent of treated patients per year, whether volunteer or commercial products have been used."

But you go on to make the point that there may be a degree of under reporting here because:

" ... a proportion of patients with acute NANB hepatitis remain asymptomatic and will therefore not be recognised unless their biochemical status is monitored prospectively."

Which one assumes for patients with haemophilia who weren't coming forward would be unlikely to be happening in the ordinary run of events.

You go on to say, at the conclusion of the next paragraph:

"The very high incidence of acute NANB hepatitis observed following concentrate therapy prompted a pilot clinical study of prophylactic immune serum globulin."

And that's the thinking that you have outlined to

us. And again, as we would expect, an explanation of the design of the study and the characteristics of the patients included in it.

A slightly larger group: 58 patients with congenital deficiencies of coagulation Factors VIII or IX, so 58 patients with haemophilia, although I think there are one or two in the table with --

A. This was before Professor Craske's study was published but, of course, he was a member of haemophilia directors and they always exchanged their data long before it was published in a journal. The gestation period would be a year or so. So Peter Kernoff knew of what was happening.

Q. Yes. I was just looking to see -- there were some who had von Willebrand's disease.

A. I think there were one or two.

Q. Yes:

"Only a minority of the patients were virgin. Although most needed infrequent treatment, a majority had received blood plasma or cryoprecipitate therapy before their first exposure infusions... Nine patients had been treated with blood products, cryoprecipitate, exclusively in the six-month period before their first exposure infusion. In these patients it was not possible to be certain that hepatitis which followed

concentrate therapy was necessarily attributable to concentrate. Since this seemed much the most likely possibility, however, it was assumed to be so in the analysis."

I think we can understand the logic of that, that if a patient developed hepatitis after concentrates, it was attributed to the concentrate rather than to a previous infusion of cryo.

You go on to describe the characteristics of the patients and the monitoring that was carried out and then to say at the bottom of the page -- we can see a section beginning in italics:

"The occurrence of acute post-transfusion hepatitis was the primary end point of the study."

And again you were relying on secondary testing really, to establish if post-transfusion hepatitis had developed.

On to following page, please. The therapeutic products are described:

"All cryoprecipitate and Factor IX concentrate was prepared by the NHS from volunteer donor plasma. Factor VIII concentrates, all described as being of intermediate purity, were either made by the NHS at the Blood Products Laboratory, Elstree, or bought from three manufacturers, the source of plasma in the latter

case being exclusively of USA origin. Donor pool sizes were in the range 1,500 to 5,000."

If we go on to the next page, we can see the results:

"Outcome in prospectively studied patients is shown in table 1 and figure 1. None of the five patients treated with cryoprecipitate developed hepatitis and no patient with hepatitis had serological evidence of acute infection with Hepatitis A, CMV or EBV. All nine patients treated with commercial Factor VIII concentrate and ten of the 12 patients with NHS Factor VIII concentrate developed acute NANB hepatitis."

Then for the Factor IX:

"All four treated with NHS Factor IX without the immunoglobulin contracted acute NANB hepatitis and one of these patients also subsequently developed acute Hepatitis B. Symptomatic acute NANB hepatitis was more common in patients treated with commercial Factor VIII than in those treated with NHS Factor VIII or Factor IX."

Then you introduce a note of caution, when you say:

"The apparent lower incidence of symptomatic hepatitis amongst NHS Factor VIII treated patients may have been influenced by the difficulty of detection of mild symptoms in infants."

Further down:

"The incubation period of acute NANB hepatitis was related to the type of product infused, being shorter in patients treated with commercial Factor VIII than in patients treated with NHS Factor VIII."

In retrospect, possibly to do with viral titre or viral load in the product?

A. Yes, although there was the background thought that we may be dealing with two agents.

Q. Yes:

"No apparent association between incubation periods and the dosage of Factor VIII or IX."

Then you go on to say:

"It was noticeable that the two patients treated with NHS Factor VIII concentrate who did not develop non-A non-B hepatitis, patients 20 and 21, had had the highest previous exposures in the NHS Factor VIII treated group and were treated with relatively small doses of concentrate for their first exposure."

And then some differences in the rates of progression to chronic hepatitis, and we can see all of this in the table, which is on the next page.

We can see that group between patients 20 and 25 who are shown as having no hepatitis, five of them who had cryoprecipitate and two of them who had NHS Factor VIII.

Patient 16 looks to have been an infant, who was first given cryoprecipitate and didn't develop hepatitis. But then, if we look further up, we can see that at the age of 27 months he was given NHS Factor VIII and did go on to develop hepatitis. Is that right?

A. Yes.

Q. Just so we are not confused by patient 16 appearing twice.

A. I think the haemophilia directors had actually concluded, as this was evolving, that they should use the cryoprecipitate whenever possible and particularly for the younger patients and, similarly, the NHS Factor VIII rather than the commercial Factor VIII should be used for the younger patients, but the caveat there was within the constraints of it being available.

Q. Yes. I want to come back to that, Professor Thomas, because in the 1980s there were obviously some difficult product choices to be made at different points.

THE CHAIRMAN: The other thing that it would be helpful to get some sort of flavour of is what you have mentioned before, that information was circulating among the haemophilia clinicians considerably in advance of publication of papers like this. The temptation, I think, for someone like myself is to take the date of

publication as the date of dissemination of information, but that might be wrong.

A. I think it is wrong. I don't know how many haemophilia centres there were in the UK but it must have been 10 or 12 or something of that order and they were a very well organised group of physicians dealing with a relatively small group of patients. They met regularly to try and work out what was going on and to agree priorities about which of the material should be used for which groups of patients.

One thing that happened, for instance, that you start to see in this study is that if a patient needed two or three treatments, they would try to use the same commercial Factor VIII concentrate; hence the reason for these batch numbers in the third or fourth column. That wasn't always possible. So you can see patients 2 and 3 got two batches but most of the other ones would have received all their treatment over a few days from the same batch and that might mean getting a similar batch from another centre so that that could happen. The younger patients, who had not had previous exposure, were the first up with a call on the cryo, for instance, when it became apparent that, probably because there were only eight or nine donors in a batch of cryo, this was a relatively safe preparation -- relatively safe in

terms of non-A non-B. Post-1983, of course, we also knew that the donors were -- because so few were involved, it was improbable that we would transmit HIV with cryo because that was occurring at a very low frequency in the population.

THE CHAIRMAN: Yes. I think it has gone slightly off where I started. I think the reference to 10 or 12 would be a reference to the reference centre rather than the total number of centres where haemophilia patients would be treated. There were a lot more of them, I think. But certainly, if we concentrate on those who would be the opinion formers, they would be the senior representatives of the profession.

A. Yes, and they met regularly. I know Peter used to come back and tell us what was happening, and John Craske, for instance, I know used to go to the haemophilia meetings.

MS DUNLOP: Faithfully. Every set of minutes he seems to have been there, and on their working party on hepatitis as well.

A. Yes.

Q. I think unusually, we have been told, for a UKHCDO working party, it was convened by Dr Craske and not by a haemophilia clinician, which all shows how very interested and aware of the topic he was.

We should also look in the table, professor, at the symptoms column. It is interesting, I think, to see how many of the patients had no symptoms. "S" is "Symptoms" and "SJ" is "Symptoms Including Jaundice". It does say at the bottom:

"J indicates the presence of clinical jaundice."

A. Although there isn't a statistical difference between the NHS and the commercial concentrates in this area. I think, when you look at the data -- and this comes through with most of the studies -- the severity of the hepatitis is worse in the commercial concentrates.

Q. Yes, severity of the acute attack?

A. Of the acute attack, particularly as evidenced by jaundice. You can see it here, I think. Four have "J" in that column, having jaundice, four out of nine, whereas only one of the NHS has a jaundice report. That must be related to the higher viral load in the commercial material, although there is enough, even in the NHS, to make sure everyone was infected.

Q. Yes.

THE CHAIRMAN: What's the zero?

MS DUNLOP: Zero is no symptoms.

THE CHAIRMAN: Is it? Then there is a great big blank half way down. That's just where there is no hepatitis?

MS DUNLOP: They didn't get hepatitis, yes. So the zeros

are asymptomatic hepatitis sufferers, yes. We can certainly see that some of those involved were pretty young. The youngest seems to have been four months. Four months, eight months.

I'm going to skip over the next two tables because I don't think we need to study them and move on to the discussion, which is two pages further on. Here we have it on the screen. In the seventh line:

"It is probable that a susceptible patient exposed to more than about 300 donor units of blood products will develop post-transfusion NANB hepatitis. Since clotting factor concentrates are usually prepared from pools of at least 1,500 donor plasmas, it's not surprising that the overall attack rate following a first exposure to these products should approach 100 per cent, whether they are of volunteer or commercial origin."

I think the highest number that we have seen for a plasma pool is 30,000 donations, but that was a commercial pool.

There is then a mention of the Fletcher paper, at which we just looked, and you and your colleagues suggested that:

"Previously reported lower attack rates in comparable groups of patients are probably mainly

attributable to reliance on symptoms rather than biochemical screening to detect hepatitis."

THE CHAIRMAN: Could I ask a question at this stage? One of the things I have noticed in the literature is that quite often there are quite different criteria applied in determining whether there is hepatitis. I think in some of the American papers I have seen reference to nothing but ALT measurements. You very carefully in this paper point to the three criteria -- I think it's at the beginning of this one, or is it Kernoff's paper? -- that were applied. Was there ever any generally accepted approach to presenting the data?

A. I think the thing that we thought should be in there was the context. The third criterion in Peter Kernoff's was that there should be no cause for the hepatitis other than blood products administration. So, for instance, if the patient were taking a medication -- let's say, an antibiotic -- which is known to cause hepatitis, then that would be included.

So I think the only difference really would be whether you used ALT, which is an enzyme that specifically arises in hepatitis, inflammation of the liver, as opposed to AST, which increases --

THE CHAIRMAN: Aspartate --

A. Aspartate transaminase, which increases, for instance,

after a pulmonary infarct or a heart attack, as well as after liver damage.

THE CHAIRMAN: It just means that one has to pay very careful attention to the criteria set out in the individual paper.

A. Yes. And that would have a minor effect, though, I think, on the incidence of hepatitis because you are not going to find in a transfusion setting, you know, people with myocardial infarctions or pulmonary infarcts really, unless, as in the American studies, of course, they were looking at post coronary artery surgery.

THE CHAIRMAN: As some of them were.

A. As some of them were, yes.

THE CHAIRMAN: Yes, thank you.

MS DUNLOP: Yes. You also comment, in relation to the group of patients who were studied retrospectively, that there reliance had been placed on the patient to report illness to his physician, and the detected incidence was even lower, at 12 per cent.

But, changing the theme, you go on to say:

"The absence of hepatitis amongst our cryoprecipitate-treated patients probably reflects their relatively low exposure, as none received more than 70 donor units."

So, to use language with which we have become a bit

more familiar, there are some false negatives in the concentrate-treated patients, particularly the retrospectively analysed perhaps because of the need to rely on reporting, but amongst the cryoprecipitate-treated patients the authors, you and your co-authors, are suggesting that that is probably a genuine finding and reflects their relatively low exposures. Is that correct?

A. Yes, and that's shown up by the need not just for a single ALT estimation but for multiple ALT estimations because we knew, as I showed you in one of the earlier diagrams of the acute and chronic infections, the ALT may fluctuate, returning to the normal range between episodes of hepatitis, and the probability of that occurring is much lower, of course, if you have half a dozen observations.

Q. Yes. A single measurement may not be as good a guide?

A. Yes, and that was the reason for following patients with repeated observations.

Q. Yes. The next part of the discussion is about ISG. But the concluding paragraph, on the following page, says:

"Whether prepared from volunteer or commercial donor plasma, clotting factor concentrates carry a very high risk of acute NANB hepatitis in first exposure recipients. Even substantial previous exposure to other

blood products may reduce this risk only marginally."

And you make the point you have made here today about the hope that safer products might be coming and the possibly of your data being used in a comparative exercise.

You also go on to say that many patients with mild bleeding disorders, who in the past might have been considered suitable for therapy with concentrates are now considered more appropriately treated with cryoprecipitate or DDAVP.

The other reference which you gave at this point in your report, Professor Thomas, was to a letter from Scotland, which bears the reference [LIT0013859]. It's the Lancet of September 2nd 1989. We can locate this in time by noticing that:

"The Lancet has recently reported that there may be a test for Hepatitis C which will detect antibodies to the major virus-causing post-transfusion non-A non-B hepatitis in patients receiving blood products derived from donors."

And the authors are reporting the prevalence of anti-HCV in patients with haemophilia who have received blood products manufactured exclusively from blood donors in Scotland by the Scottish National Blood Transfusion Service and in recipients of commercially

prepared Factor VIII.

61 patients have been studied and they all have either Haemophilia A or B or von Willebrand's disease. The Ortho ELISA test has been used. 48 of these patients had received non-heat-treated Factor VIII or IX before 1985. 41 of them were seropositive. On top of the 48, there were seven who had received only heat-treated concentrates and a few donations of cryoprecipitate and none of that group was positive. Six patients received only small amounts of cryoprecipitate or red cells and are anti-HCV negative and the results are set out in the table.

So in this little group 85 per cent of patients who would have had a history of NANBH are antibody positive, and that's the 41 who had had non-heat-treated product before 1985 and were seropositive.

Then, if we could go over the page, please --

A. Actually the previous article is also of interest because it looks at the frequency of HIV infection.

Q. Yes.

Excuse me a moment.

A. Antibodies to Hepatitis C virus in haemophilia. But they also look at anti-HIV and it just emphasises that in those with moderate haemophilia you start to see a lower frequency of HIV positivity, just reflecting the

fact that HIV was of relatively low prevalence in the UK, or in Scotland, and therefore, even with large donor preparations, if you are using modest amounts, there would be a reasonable number that would not be infected, whereas, when you look at the HCV data, the moderate and severe patients with inhibitors, the figures of anti-HCV positivity are very similar.

Q. Yes.

A. Which reflects the higher prevalence of this virus.

Q. Yes.

A. Of interest is why there is about a third who didn't become infected. You might have expected them all to be infected, bearing in mind that all Factor VIII concentrates would have contained the virus.

Q. Of course. The point that's being made to me is that this was the first generation of testing kits.

A. Exactly. So there may have been lower sensitivity.

PROFESSOR JAMES: We know now -- and we have heard evidence -- that those first generation kits were of --

A. Of low sensitivity.

PROFESSOR JAMES: -- low sensitivity.

MS DUNLOP: Yes. Just to get the detail of that letter, could we go back up the page, please? This is coming from France, I think, isn't it, this letter, via -- I don't want to say "Monsieur" because it may be

"Madame" -- coming from Noel and others. Can we go on to the end, please, just to see the end of this particular letter? In fact your paper is referenced in the French letter, I noticed.

In fact the authors of Edinburgh letter, that we looked at before, are wondering why all such patients are not anti-HCV positive, and the explanation may be in the kits:

"Perhaps they possess antibody but at a level below the detection level of the ELISA-or they may be HCV antigenaemic in the absence of specific antibody.

"Of great interest is the finding that all 7 patients who received only heat-treated Factor VIII/IX concentrates are anti-HCV negative."

Of course, it's not specific about what the heating protocol was, the extra heat-treated having come in in 1987. I suppose some at least of them might have had the extra heat-treated product. But at any rate, Professor Thomas --

THE CHAIRMAN: This is unfairly exchanging information you have not got, professor.

MS DUNLOP: No. I think what we can take from the two references, your paper and this letter, is exactly what you say, that overall there is a very high rate of infection and that the likelihood of infection doesn't

really vary much between commercial concentrates and NHS concentrates.

A. And against that high infection rate it's easy to see, when you have a therapeutic advance such as this early heat, where they are only looking at seven patients and where none of them became infected, even if only half had been infected, it would still be likely to be encouraging.

Q. Yes. Right. I think, sir, that's a good moment at which to pause.

(1.04 pm)

(The short adjournment)

(2.00 pm)

THE CHAIRMAN: Yes?

MS DUNLOP: Yes, thank you.

Professor Thomas, before lunch we were working our way through your report, which is [PEN0171071]. We had reached page 7, which is 1077, and we had just looked at the two references about two thirds of the way down the page. That's to the paper in which you were involved, and also to a letter from Dr Ludlam and others to the Lancet.

If we can just go down to the bottom of the page, we can see that you are dealing with the likelihood of people with haemophilia acquiring, respectively, HIV and

then going on to HCV from their treatment. As you say, the prevalence of HIV in the donating volunteer community was very much lower, and I think we all understand that.

The commercial or paid donor-derived material was more frequently infected than the volunteer material because of the higher HIV prevalence in this group, which often included IV drug users.

You say at the bottom:

"Thus, the frequent of serological evidence of HIV infection in treated patients with Haemophilia A or B was influenced by the severity of the haemophilia determining the frequency of the administration of Factor VIII or IX."

Then you go on to identify three factors which will influence the risk of blood-borne contamination of coagulation concentrates. I think you want to alter the reference there, which at the moment is shown as a reference to the Ludlam letter, and actually you wanted to refer to the letter which we saw immediately before.

A. Yes. It's Noel et al.

Q. It's by Noel and others. So it will, in fact, have the same reference because it's all part of the same document. So it's [LIT0013859], but it's that letter

from the French group that we looked at before lunch.

So just to look at these three factors, that the risk of blood-borne virus contamination was related to the number of donors used for each batch, the prevalence of each blood-borne virus in the donor population, and the severity of haemophilia, determining frequency of coagulation factor therapy, and therefore the number of batches to which each patient was exposed.

With HCV, of course, there is a different picture because if all the batches have some Hepatitis C in them, then there is a very high likelihood of infection, and that would be true for anybody treated with concentrates, even those rarely treated with concentrates. We saw some of the illustrations of that in the papers we looked at before lunch.

Then you go on to allude to some of the selection criteria for donors and to refer to a paper which I think we asked you to look at, which is one by Phil Minor and others in the Lancet. The reference for that is [SGF0011380]. Perhaps we could look at it just now. This is about respective levels of infection.

It's that letter which we can see beginning in the left-hand column, headed up "Antibody to Hepatitis C Virus in Plasma pools". The letter says that the authors are reporting the results of tests, I think it

is, with the Ortho Diagnostics anti-HCV ELISA on plasma pools, from which such products -- that's concentrates -- are prepared. We can see for ourselves the different pools that they sampled. The results are tabulated. Really quite a stark difference between the pools from the USA and the pools from the UK.

A. I think that's reflecting the lower proportion of the donor material being positive for anti-HCV and therefore that's diluted, and with limiting sensitivity, then there would be some undetectable.

Q. So it's really the two factors that we discussed before lunch: lower titres going in in the first place and possibly limited sensitivity of the test.

A. Yes.

Q. Interesting to note that statistic at the bottom:

"Two of 538 donations from UK sources were positive. A frequency of 0.4 per cent consistent with previously reported figures."

A. That's the figure that I used earlier on in my document really, saying that 0.4 per cent/0.5 per cent, I think I cited, of donations were positive, and Phil Minor, of course, is from what was the Central Public Health Laboratory, or the Centre for Disease Control, so he would be privy to the figures.

Q. NIBS and C, we have heard it called.

A. Yes.
Q. Actually one of the things that the authors say in their letter -- this is from the right-hand column -- is that:

"Another possibility is that the Ortho Chiron test detects antibodies induced by American strains of HCV more than it does antibodies induced by European strains."

Which is a good hypothesis?
A. Yes, I think were Peter Simmonds here, he would say that the assays were not equally sensitive for the different genotypes of the virus, so far as I understand it.
Q. Yes, we did look at some research that was carried out on the first generation assays and how successful they were at picking up, respectively, genotype 1 and genotype 3, and there was a difference, at least according to our understanding. But it does mention also, as a possibility, the US pools contain a very high proportion of strongly positive donations.

They say at the end:

"Our findings imply that the prevalence of positive donations in the American pools is very high, possibly approaching 100 per cent. This may reflect the fact that in the US, plasma for blood products often comes from paid donors. Examination of pools for HCV RNA is planned."

But I think the important point that we need to take from all of this is that even although the United Kingdom pools seem to have very much lower levels of virus, it's still over some kind of critical level at which infection of the pools will occur and the vast majority of recipients will acquire Hepatitis C at this time?

A. That's what I take from the overall data.

Q. Yes. Can we go back to the report, please? You say exactly that in your report, in your discussion of this paper.

Go a little bit further down the page, please, just to see that paragraph in which you discuss this letter.

(Pause)

Perhaps we can just read to the end of this section.

(Pause)

You say that:

"The haemophilia directors took the view ... "

Possibly slightly later than 1982/1983 but at any rate:

" ... took the view that NHS concentrates, heat inactivated, should be used because they were demonstrably less likely to transmit HIV while invariably transmitting non-A non-B HCV."

So the thinking in the group of haemophilia

clinicians would be, obviously, that NHS heat-treated concentrates were much safer from the HIV point of view, and therefore preferable.

A. Yes.

Q. You have then gone on, Professor Thomas, to deal with the changing perception of severity of NANB hepatitis, and you have talked about the conduct of liver biopsies. Liver biopsy in a patient with haemophilia is not a straightforward matter. Is that right?

A. Yes, I mean, they are at risk of bleeding however well it's done, and there were deaths in the haemophilia community, two worldwide.

Q. You tell us that between 1970 and 1985, liver biopsies taken from NANB haemophilia cases in Manchester, Oxford and London centres, showed mainly lobular hepatitis and chronic persistent hepatitis, usually indicative of a good prognosis. Could you just explain to us, please, what lobular hepatitis is?

A. I'll draw a diagram actually, if I may.

If that's what we call a portal tract, where the bile ducts, the hepatic artery and the portal vein come in to the liver. So that's the hepatic artery, the portal vein and the bile duct. And the blood then flows along the hepatic sinusoid to leave by the central vein. If there is inflammation just in the portal tracts, not

going outside the fibrous delineating plate, then that's call chronic persistent hepatitis, which is or was the benign prognosis.

If there was inflammation going into what we call the periportal area, which is scalloped, and there was piecemeal necrosis, which just means the liver cells around the portal tract were being destroyed, that was called chronic active hepatitis, and was associated with the risk of going to cirrhosis. If there were lobular hepatitis, it meant that the inflammation, rather than just being confined to the periportal area, as in chronic active hepatitis, it was spread throughout the hepatic lobule evenly, and that was called chronic lobular hepatitis, and again was said to be of a benign prognosis.

These prognostic indices, based on the liver biopsy, were really based on what we saw in Hepatitis B virus infection, and it was assumed that the same would be the case with chronic Hepatitis C. So chronic persistent hepatitis and chronic lobular hepatitis, which was seen in the early biopsies, were deemed to be indicative of a good prognosis. If there was any chronic active hepatitis with piecemeal necrosis, that would be a poor prognosis. And if there was bridging fibrosis, which means fibrous tissue going between either the portal

tracts to the central veins, or between the portal tracts, bridging fibrosis was an indication of the onset of the beginnings of cirrhosis. So that was really the basis for saying that initially this was a benign prognostic disease.

Q. Was that based on, the supposition that either chronic persistent hepatitis or chronic active hepatitis would not progress?

A. Would not progress, was unlikely. There were, however, cases in the literature with Hepatitis B where chronic persistent hepatitis did progress. So it's only -- it was only reflecting probabilities of this outcome. It isn't an absolute measure.

This was the reason for doing these biopsies really. It was the only basis that we had for giving a prognosis. Also, of course, on the basis of biopsy, you could give an Ishak score stage in the fibrosis of whether it was limited to just the portal tracts or whether it was spreading throughout the lobule, which would give a higher score on the Ishak score of fibrosis.

Q. Lobule is a section of the liver?

A. A lobule really is one functional unit, really determined by the blood flow coming in and leaving; coming in through the hepatic artery and portal vein and

leaving via the central vein.

Q. In retrospect, a supposition that chronic persistent hepatitis or chronic active hepatitis would follow the same course as Hepatitis B and not progress in Hepatitis C, was that wrong?

A. I think that was wrong, yes.

Q. Yes.

A. But the other confounding factor here was that we didn't know where we were in relation to the beginning of the illness, because the other variable which determined how much scarring there would be in the liver, how much fibrosis, would be how long the infection had been going; and as we discussed earlier, in many of the cases it would have an asymptomatic start but -- and rarely did it have a --

Q. A defined --

A. A defined start, yes.

Q. As you have said, the easiest is a patient who has had a blood transfusion on a known date, and you can then say that's likely to be the onset of the illness, but for other patients, particularly those with haemophilia, that's not possible?

A. Yes.

Q. I'm just needing to check the transcript. (Pause)

A. But even in the earliest papers, there were some of the

more severe lesions. So it wasn't, you know, all black or white. The reason for doing the biopsies was that those prognostic signs might be seen and that would give us an indication of what would be likely to happen in the future.

Q. Right. Can we just look at your report. You have said that:

"The initial biopsies showed mainly lobular hepatitis and chronic persistent hepatitis."

So in the progression, I should have put lobular hepatitis and chronic persistent together, and then chronic active is a deterioration?

A. Yes.

Q. Right.

A. And the reason for -- also in the biochemical data, if you -- what you expect to see with lobular hepatitis is an ALT, the aspartate aminotransferase, going up and then normal -- this sort of fluctuating pattern is what you see in chronic lobular hepatitis, and this is what we saw classically in the haemophiliacs, which I tried to depict in one of the serological diagrams I showed earlier on in the document.

So it was the biochemical picture which made us think we were going to see lobular hepatitis, which is spread of the inflammation throughout the lobule, and

indeed, that's what was seen in a significant number of these cases. But there were some that also unexpectedly had cirrhosis, already having gone right the way to cirrhosis.

Q. Right.

PROFESSOR JAMES: Could I add just two tiny things?

I'm sure Professor Thomas would agree that the problem with the liver biopsy is it represents only an absolutely minute -- I mean, less than 1 in 5,000th, or whatever, piece of the liver. So, in a way, there is a tremendous opportunity for what's called sampling error in the liver biopsy.

Perhaps the second thing to say is that the other centre that was doing liver biopsies that we are aware of, of course, and Howard too, is Sheffield. And they actually, as you remember, had a rather worse opinion of what the liver biopsies of haemophiliacs looked like and were slightly poo-pooed, for example, by the centres in Manchester and perhaps Oxford at that time. I don't know whether you would agree with that, Howard.

A. Yes, I do. The first paper in 1978, from David Triger and his group in Sheffield, already showed that some patients with Factor VIII concentrate-associated disease had cirrhosis.

But the trouble with that study and some of the

other studies was, of course, clinicians didn't biopsy so-called allcomers, they tended to biopsy, one suspects, those where they thought there would be, you know, a worse scenario. So there was what we would call case selection towards the adverse end of the disease spectrum. So that was another confounding, as well as the sampling error that Oliver has mentioned.

MS DUNLOP: I did want to go to Sheffield because I think you have the understated/overstated papers there, but I'm not there quite yet.

PROFESSOR JAMES: I beg your pardon.

MS DUNLOP: No, we are going to Sheffield.

PROFESSOR JAMES: I can't wait.

MS DUNLOP: Just to finish this page, you do refer, Professor Thomas, to different editions of Sheila Sherlock's textbook, and we know that this is a seminal work in the area. Is that right?

A. Yes, she was a really very famous physician and her textbook, really, was taken as an absolute truth almost.

Q. Yes. So in the sixth edition of her textbook in 1981, which, as you have pointed out, will be material prepared before 1981, obviously, she said that NANB hepatitis had a good prognosis but you say, on the basis of a study in the Journal of Clinical Pathology, views changed. I wanted to look at that. That's

[LIT0010759].

Can we look at the first page in, please?

This study, in which you were involved, looked at 12 serologically proven cases of non-A non-B hepatitis. The clinical course was mild in 11 patients. One patient presented in portal-systemic encephalopathy. You had better explain portal-systemic encephalopathy, please.

A. It's a cognitive dysfunction related to accumulation of ammonia-like compounds because the liver isn't working properly.

Q. Nine of the 12 patients continued to exhibit raised transaminase activities six or more months after the onset of the acute hepatitis. You go on to talk about the conduct of liver biopsies, and you say:

"Histological findings covered the whole spectrum of acute and chronic hepatitis and one patient had cirrhosis. One notable feature in these biopsies was the presence of fatty changes."

A. These were non-haemophilia patients because we, at that stage, didn't want to biopsy haemophiliacs, really.

Q. So these are likely to have been transfusion recipients?

A. These are transfusion recipients, or cases where there wasn't a transfusion history but on serological grounds they were designated non-A non-B and there was no

evidence of a drug toxicity.

Q. Right. The first point to note from the main text of the article is the reference in the second paragraph to the viruses, and by that you are meaning NANB agents, appearing to be a significant aetiological factor in chronic liver disease. You refer to findings varying from 12 to 25 per cent as a cause of sporadic hepatitis should we read that as equivalent to acute?

A. Yes, that was an acute sporadic hepatitis, but since -- we didn't have a transfusion event to mark the beginning of the event, so we didn't have any earlier specimens, we just had specimens that were during the established hepatitis, and that, therefore, made it difficult to determine whether this was an acute hepatitis or whether it was one of these sort of episodes of a flare-up of an existing chronic lobular hepatitis.

Q. You give a range of 23 to 46 per cent for rates of chronic hepatitis.

A. The other community-acquired so-called sporadic hepatitis would, of course, be Hepatitis A and B, and this was the group that were left after exclusion of those.

Q. Yes. Then the now familiar setting out of the criteria for inclusion in the study. Then on to the next page, please. We can see again the logic of excluding other

possible causes, including Epstein-Barr virus and cytomegalovirus. Oh, no, you say you couldn't exclude those due to insufficient serum but you excluded Hepatitis A.

A. And B.

Q. And B, yes.

A. Actually I should say, Epstein-Barr, of course, can occur sporadically but cytomegalovirus usually occurs in the context of somebody who is immuno-suppressed. So in a community study you wouldn't expect to see CMV contributing but Epstein-Barr virus could contribute.

Q. You go on to say:

"Albeit it was difficult to exclude those two serologically, and the clinical course of the patients was not consistent with either Epstein-Barr or CMV infection."

Then skipping past the methods of processing the specimens to the last paragraph on the left-hand side:

"The clinical histological diagnoses were ..."

Various different features. Then looking at the results, in fact of the 12 patients, six were women. All 12 patients were icteric during the phase of acute hepatitis. Then on to the next page, where you describe the eight patients who had liver biopsy within six months of the acute hepatitis. These results are shown

in the table there, table 2. Different features. Then you go on to say -- and this is a little bit further down. Yes, that paragraph beginning "in general":

" ... the hepatic histology was as described for other types of acute and chronic hepatitis, however, some features were regarded as unusual."

You go on to instance the fatty change. That's steatosis again?

A. At that stage, of course, that made us think -- steatosis always made us think of alcohol as part of the aetiology. We now know that's not the case. It's seen in Hepatitis C as well.

Q. Then you go on to discuss your results. You record that you had studied 12 patients who were considered, on serological grounds, to have had NANB hepatitis, and one of the patients had had a very serious illness in the acute phase. Is that right?

A. Yes, a dominant hepatitis, where essentially they develop hepatic encephalopathy indicative of liver failure.

Q. That's very unusual for Hepatitis C?

A. Very unusual. I think there is one described by a Dr Lee in the United States, and we saw one in the Royal Free actually, who was a serologically defined case of Hepatitis C-induced fulminant hepatitis, and she

went on -- a woman again -- to recover.

Q. And you say, in fact, that if it's going to happen, it predominantly occurs in females.

A. Yes.

Q. Just to look at a little bit of the biography of the patients.

A. One of the problems with these studies, of course, is that again -- and I hope the discussion illustrates that -- is that we are, all the time, trying to define a group by exclusion of other aetiologies, and the reason for wanting biopsies in these was the hope -- and it was just a hope at that stage -- that we might see something that was characteristic of this condition that would allow us to identify it as a specific disease entity rather than a rag bag of what was left after exclusion of the more defined problems.

Q. Yes. So you felt that, although there was obviously diagnosis by exclusion to some extent, there was still room for one other candidate to explain a certain number of the cases?

A. Yes.

Q. Yes. Then on the next couple of pages we can see for ourselves some of the liver biopsies, which I'm not going to ask you to explain. And you go on to tell us -- can we look to the next page, please, and the

right-hand side -- that the histological findings covered the whole spectrum of acute and chronic hepatitis. The features that were of interest were the fatty change, excessive cellularity of sinosoids in relation to the degree of necrosis. What should we understand by that?

A. That's really this business of the infiltrating lymphocytes spreading throughout the lobule.

Q. Right, and bile duct damage. You have referred to this paper, Professor Thomas, as indicating a shift in thinking on the severity of non-A non-B hepatitis, or the beginning of a shift in thinking perhaps?

A. Yes, and if you like, affirmation of what David Triger's group had described in 1978, where they were seeing some patients who already had cirrhosis, and I think, if I remember the results section of our paper, half of the patients had these poor prognostic features; namely chronic active hepatitis with piecemeal necrosis, rather than chronic persistent hepatitis or chronic lobular hepatitis, the indicators of what we thought would be a better prognosis. I think half of them, if I remember rightly, had chronic active CAH.

Q. Can we just go back, please, to page 4 of [LIT0010759] just to let you see that? I think this is the section that you are referring to.

A. Yes, the table there. If you see, there are -- with the established disease, in other words the chronic state, what, four have lobular hepatitis or persistent hepatitis but three have already chronic active hepatitis, two with moderate or severe severity and one established cirrhosis. So really that confirmed what David Triger had described back in 1978, that immediately after that had not been confirmed by particularly Italian and other groups.

Q. Yes.

A. So really there was a lot of controversy really over what the outcome was for these patients, and don't forget, these are very small numbers of liver biopsies because of the difficulty of obtaining tissue because of the risks involved.

Q. Can we go back to the report, please. Just to mention that we do actually have -- I'm not going to take you to it but we do have the particular passage from Professor Sherlock's book, and I think it's referred to in our preliminary report, that in the sixth edition she said:

"Non-A non-B hepatitis often progresses to a mild chronic hepatitis. The prognosis of this is, at the moment, uncertain but probably benign."

So she didn't commit herself completely perhaps to

the view that there was a good prognosis, but I take the point you make in your report, that the general sense of what she was saying was reassuring.

A. Then by the eighth edition really, which was being prepared in, let's say two or three years prior to 1989, she has changed her stance by saying 20 per cent develop cirrhosis over 20 years, which is, I think, what we currently believe, and if you wait 30 or 40 or 50 years, then that proportion with cirrhosis goes up progressively, as exemplified by what we see in Asian patients when biopsied in their 40s or 50s, and they are often infected in childhood.

So we are looking at patients maybe 30 or 40 years into the disease. Then the majority of these have cirrhosis. So it's a slowly progressive disease but if you wait long enough and the -- you know, 30/40/50 years would be what we are starting to see in the Asian community, then you do see the majority developing cirrhosis.

Q. Let's just jump to what she said in the eighth edition if we could, please. That's over the page. Just to let people see. Here we have it:

"By 1989, Sherlock, in the eighth edition of her textbook ... "

That passage. So, yes, results, I suppose, from

surveys of people infected in very early life must be the most valuable because they give you the longest period over which to monitor what happens.

Just to follow this chain of papers a little bit, can we go back to the bottom of the preceding page, please? You refer to studies from the United States, also reflecting the changing view, and one example is that reference Koretz and others from Los Angeles. That's [LIT0013738]. It's just an abstract, I think. What will this be? An abstract of a presentation or of a paper?

A. This will probably be at the American liver meeting and published as an abstract in Hepatology.

Q. Right. I suppose in the context of the sorts of sizes of studies we have looked at, Professor Thomas, this is not bad, 66 patients.

A. It's one of the bigger ones, yes.

Q. Yes.

A. They are seeing cirrhosis in around 6 per cent. After four to nine years of follow-up. So still relatively early on.

Q. And the overall incidence -- and this is from the middle of the middle paragraph:

"The overall incidence of chronic liver disease was between 35 per cent and 53 per cent."

And all they have done there is to take the known number, which is 23, and add on for the possible top number, the 12 patients who either died or were lost to follow-up. So these are the parameters of the group who developed chronic liver disease. It's between 35 per cent and 53 per cent. And, yes, you have said histologic confirmation of cirrhosis has been established in four. Then we can see the conclusions:

"NANB post-transfusion hepatitis commonly results in chronic liver disease. Cirrhosis has occurred in at least six per cent of those developing NANB post-transfusion hepatitis after four to nine years of follow-up."

Again, in retrospect, quite short period of follow-up given what you now know can happen over decades.

A. Yes.

Q. Yes. "Patients with NANB post-transfusion hepatitis should be followed for many years after the onset of disease if biochemical resolution fails to take place. Cirrhosis develops in a clinically silent fashion and usually only after years of activity."

A. Of course, the other thing that I think we will probably discuss later is that there are other accelerants of the rate of fibrosis, which we will come to later, which may

have been operative in the four who developed cirrhosis here, for instance.

Q. Part of this consideration of the changing perception does require that we look at some of the information from Sheffield. I don't know if it requires it so much as it is being notable for the catchy titles of the papers. It seems somehow balanced to look at the two articles which describe it respectively as an overstated problem and an understated problem. So that's what I plan to do. When I say "it", I mean, of course, liver disease in haemophilia.

I think the most sensible order is actually to look at the Manchester article from 1983, which is entitled "Liver Disease in Haemophiliacs: an overstated problem", published in the British Journal of Haematology in 1983 and having our reference [LIT0010008].

Quite a small number of patients, 12 multitransfused haemophiliacs, it says, from the Manchester area with persistently abnormal liver function tests. The tone of this piece is essentially reassuring, Professor Thomas, is it?

A. Yes, but I think the criticism, of course, is that, like our own studies, it's on very small numbers and, you know, you have to look at the overall picture really, putting it all together.

Q. Yes.
A. They are looking only at 12 cases; we only looked at half a dozen. So I think it's all -- in terms of getting a feel for the spectrum of lesions you might see in the overall population of patients, several thousand, this is only suggestive evidence really.
Q. Of course, lawyers are fond of pointing out that no evidence that X is the case is not equivalent to evidence that X is not the case?
A. Yes, exactly.
Q. Sorry. (Pause)

It's being pointed out to me that even within the group of 12, there is one patient with chronic active hepatitis and a further four with mild chronic active hepatitis. There is one patient with cirrhosis, sorry, and a further four with mild chronic active hepatitis.

In the narrative this article does in fact refer to previous reports of a high prevalence of abnormal liver function tests in multitransfused haemophiliacs, and one of the references is a Sheffield report. I just wanted to pause and, keeping this article open, look at that particular previous reference, which is Preston et al, 1978. The reference for that is [LIT0010387]. It's the Lancet of 16 September 1978.

We can see, just from the summary, what the tenor of

the results was. Abnormal liver function tests in 77 per cent of the patients studied:

"Percutaneous liver biopsy carried out on eight symptom-free patients under Factor VIII cover. A wide spectrum of chronic liver disease was demonstrated, including chronic aggressive hepatitis and cirrhosis."

A. What they don't say is how they selected the ones for biopsy from the overall population, and as I mentioned earlier, clinicians do not like doing biopsies unless they think they are going to find something significant.

Q. So there is a bit of a selection bias.

A. A selection bias, yes.

Q. Although they say, in their passage under the heading "patients":

"All patients had received Factor VIII replacement therapy on at least one occasion during the preceding 12 months. Apart from this, selection was random."

But I understand the point you make:

"The selected patients were well known to us and were considered to be intelligent and responsible."

I'm not sure quite how that affected their propensity to develop hepatitis, but anyway.

Perhaps we can just take a moment to look at the results ourselves. If we look on to the second page, we can see there is a table on the patients who had liver

biopsy.

THE CHAIRMAN: Can I blow it up a little, please?

MS DUNLOP: Sorry, yes.

THE CHAIRMAN: It's the bottom two.

MS DUNLOP: Yes. Actually that paragraph headed "Results" records that:

"Liver function tests were normal in only 11 of the 47 patients studied."

A. The difficulty with all these studies is being sure that what you are looking at is solely caused by Hepatitis C, because there are all the confounders of how much alcohol did they take. We will hear later that the age of infection, the duration of infection, are all factors that determine how rapidly fibrosis progresses, and in most of these studies, those other variables are not known. I mean, the one here with micronodular cirrhosis, you know, could have been someone who took a large amount of alcohol, for instance. Equally well, it could be due to Hepatitis C.

So it is difficult to be sure how much of this is due to Hepatitis C or non-A non-B, and that was the other reason for doing the biopsies, because if there were any fat in the liver biopsy, people would suggest that that indicated an additional alcohol factor, because we believed that fat in the liver usually meant

alcohol excess.

Q. I suppose it depends a bit on the question, doesn't it? I mean, if the question is how serious is the problem, then it may be, for the reasons you give, that the results are not generalisable -- a terrible word -- you can't extrapolate to generalities from these small studies for the reasons you have given: smallness of sample, possible other explanations and so on.

But if the request were to be is post-transfusion hepatitis a benign condition that we don't have to worry about, then these studies are of some assistance perhaps.

A. Yes, and the other factors are factors which are present in our society, and therefore you have to contextualise the dangers of post-transfusion hepatitis against the backcloth of what we are all doing, which is, you know, taking alcohol, putting on weight, so we are in danger of fatty liver disease to that end as well. So it doesn't mean that it isn't a problem, it just provides other reasons why there is variability, other than differing pathogenicity of the Hepatitis C virus.

Q. Yes.

THE CHAIRMAN: I wonder how one should look at -- these are very early studies, are they not?

A. Yes.

THE CHAIRMAN: I don't think any of them purports to be a statistically valid analysis of a relevant population that has been selected on a basis that a statistician would acknowledge as valid either.

A. No, exactly. It's just, you know, what's available, suggesting that the clinical course of this infection is not well established at this stage.

THE CHAIRMAN: Yes.

A. In fact, some would say, even now, we do not really know the factors that determine the rate of progression and, for instance, in Italy Hepatitis C has a much worse prognosis to what you see in northern Europe, for instance, and, you know, that's arguably related to all the other factors, you know, how much alcohol you take, the genetic factors, whether there is co-infection with other viruses, all manner of things.

So I don't think this uncertainty about the natural history that was prevalent between 1978 and 1985 has changed massively. I think we are still wondering: is it 20 per cent or 40 per cent that will develop cirrhosis? All we can deduce from these studies is that some people in the context of normal life, you know, where we eat and drink -- you know, some people have severe liver disease. But how many, that's an open question still because none of the studies, as you

pointed out, are statistically significant. There isn't a large enough sample of unselected cases.

THE CHAIRMAN: On the other hand, if one looks at it from a slightly different point of view, would a person continue to take great comfort from the sixth edition of Sheila Sherlock's book after data of this kind began to be published and made available?

A. No, I think they would start to be concerned.

THE CHAIRMAN: Because that's the other end of the spectrum of interest, isn't it?

A. Yes.

THE CHAIRMAN: It's not statistically valid, it doesn't paint a big picture, but it may just cause someone to pause.

A. Very much so, yes.

MS DUNLOP: Perhaps we should just look at the last page of this, just to see the discussion. We are not looking at all the published material, Professor Thomas. I don't think we could. There are quite a lot of studies and textbooks and so on, from this era and no doubt it's a terrible oversimplification but some are basically pessimistic and some are more optimistic or reassuring, and this is one of the more pessimistic ones.

A. Yes.

Q. Yes. They are pointing out that they have succeeded in

carrying out percutaneous liver biopsy in patients with haemophilia, albeit with Factor VIII cover and appropriate laboratory control. They say that they found -- and this is the middle of the second paragraph:

"A wide spectrum of chronic liver disease ... "

And they say --

A. I suppose it's worth asking how you would present this to a patient really, if you were now to make the arguments for and against, you know, having Factor VIII concentrate treatment. You would be presented with the dilemma of saying, well, you know, let's say it was an elective procedure, where you are thinking of undergoing surgery, you have to provide some level of protection and you have a choice of various coagulation factors that you can use. If you get the best protection, if you like, you would use concentrates but you would have to say that this carries a risk of transmitting, in the majority of cases, irrespective of whether you use commercial or NHS, non-A non-B hepatitis, where there is a variable outcome.

We don't really know what proportion will develop cirrhosis but cirrhosis is a disease that progresses over 10, 20, 30 years, not an acute illness, which is what is facing the patient when he is presented with this choice.

Q. Yes.
A. So, you know, I think with everything we know about the disease now, I think if a patient said to me, "Would I have a Factor VIII concentrate or not?" I think, you know, I would have to have it. You know, there is no choice really, as far as I can see.
Q. I suppose that, if you are in this example, if you are a patient with haemophilia, will depend on a lot of factors specific to you: what other treatments might be available.
A. Yes, it will depend on the severity. If you had very mild disease, then you would try to get by with vasopressin to stimulate our own production of Factor VIII. I accept that. You would have to, in the discussion that you had with the patient, integrate that information as well.
Q. Yes.
THE CHAIRMAN: I have to say that if the patient followed up your initial introduction by saying, "Well, just tell me what the range of potential outcomes might be," one would soon get into rather a mess, wouldn't one?
A. One would, yes. All you could say is, "Yes, there is a good chance, if you develop non-A non-B hepatitis, and the probability is that you would, we do not know what the outcome will be, but in the worse scenario, you

might develop cirrhosis." But if you look at the natural history of cirrhosis, I think there is a nice paper of Giovanna Fattovich, where she took people with existing, known Hepatitis C-induced cirrhosis -- and don't forget, only 20 per cent of the patients will have cirrhosis after around about 20 years, but even when they have got cirrhosis, then the mortality from liver-related pathologies is 2 to 3 per cent. So you are really looking at a high risk of chronic liver disease, which, you know, has a relatively good prognosis when seen against the context of the acute problems that you would be hoping to not get into, obviated by your coagulation therapy.

THE CHAIRMAN: And of course, the hypothesis is, or includes here, someone who is going for elective surgery that no doubt has some significant reason behind it.

A. Yes, yes, in an acute bleed, of course, the argument is even more strongly in favour but in an elective procedure, I think you would have a choice depending on what the elective procedure was.

THE CHAIRMAN: But if one were going to die, let's say, if the morbidity associated with the basic condition was high, the patient would have to measure against that the sort of morbidity factors that you have just been bringing out: very long term and very low rate.

A. And that's why, if you look at the haemophilia directors' use of the various concentrates, you know, they try to give to the youngest patients, who, you know, obviously have a greater life expectancy, those lower risk concentrates, such as the cryoglobulins.

THE CHAIRMAN: I know that things changed over time but at this early period when these articles were being written, had any haemophiliac died of complications of liver disease?

A. No, I think -- I read somewhere in the data that that was very low frequency, if any at all, actually. In fact, one of the authors of one of these papers says that there hadn't been any deaths. But that you would expect from what I said earlier. If you take people with cirrhosis, it's only a few per cent who over 15 to 20 years die a liver-related death.

PROFESSOR JAMES: We think the haemophilia centre directors published in around 1981 the fact that no haemophiliac had died of liver disease in the preceding five years, which took account of the fact that before that they had been dying of Hepatitis B but that had been obviated by the familiar screening and so on. So that led perhaps to an underestimation of the ultimate significance of non-A non-B just because they said, "Nobody is getting very ill with this".

A. Yes. All the problems are rear-ended, if you can use that phrase, really, 20 or 30 years down the line, and then at a relatively low frequency.

PROFESSOR JAMES: Yes.

MS DUNLOP: Having looked at that 1978 Sheffield paper, can we then go back to what I'm calling the Manchester article, which is [LIT0010008]? This is the 1983 piece in the British Journal of Haematology. It in turn refers back to that paper, Preston et al, on several occasions as being one of the publications indicating a more concerning picture, and perhaps we can just fast forward to the results. That's on page 3 of [LIT0010008].

We get some more percentages. Out of a total of 153 haemophiliacs attending the department of clinical haematology, Manchester Royal Infirmary, during 1982, 52 per cent were found to have abnormal liver function tests. Liver biopsy specimens were obtained in 12 cases and were reviewed by three independent pathologists.

The results are set out in table 1. So if we can look at that table, which is over the page, we can see set out there what we noted from the summary. Only one patient showing evidence of chronic active hepatitis, although a further four patients showed some evidence of mild chronic active hepatitis.

Sorry, I have done that before. The chronic active

hepatitis are patients 8 to 11, so four of those patients with mild chronic active hepatitis, and then patient 12 with chronic active hepatitis with progression to active micronodular cirrhosis.

A. The top seven cases have histological findings which we would interpret as indicative of a good prognosis. They have the lobular hepatitis, non-specific changes or chronic persistent hepatitis.

Q. So the tone of this paper, and even just given its title, is that it seems to be cautioning against exaggeration of the severity of the problem. Is that correct?

A. Yes, yes. You know, there are some worrying things in there but in the main, most of that histology is reassuring.

Q. Yes. They go on to say at the very end, if we look at the last paragraph, that they are suggesting that the true incidence of severe histological liver abnormality in multitransfused haemophiliacs may be less than previously reported but similar to the more recent results of 115 liver biopsies carried out worldwide, where the incidence of chronic active hepatitis and cirrhosis was 16 per cent.

Then in 1985 what, on any view, is the companion article in the Lancet, 29 June 1985, our reference

[LIT0010335]. "Progressive liver disease in haemophilia: an understated problem". In his own words Dr Hay told us that they were taking a pop at the previous group, and I suppose this must be to some extent a continuation of the work reported in 1978 in the Lancet. Certainly Preston, Underwood and Triger, had all featured in the paper in the Lancet in 1978. They were finding at least 17 patients with chronic progressive liver disease, eight having chronic active hepatitis and nine having cirrhosis.

They went on to say that:

"This suggests that chronic persistent hepatitis in haemophiliacs is not as benign as hitherto supposed. Symptoms and abnormal physical signs were uncommon in these patients."

In other words, they are pointing to this being, at least in its early stages, a silent problem. It's anticipated that liver disease in haemophiliacs will become an increasing clinical problem in the future.

A. I think this is a turning point, isn't it, where people are starting -- and this is the time when Sherlock is writing her eighth edition, to be published in 1989, when she changes her view really.

Q. Yes.

A. With all the caveats that it's a small number and all

the rest of it, that we have already discussed.

Q. Yes. They say in their "Patients and Methods" section that:

"Since 1977 [they] have been regularly screening haemophilic patients for clinical and biochemical evidence of liver disease."

We can perhaps look at the results for ourselves but highlight the initial observation in the discussion section on the next page, that progressive liver disease is a potentially serious problem in haemophilia. Perhaps we can just read on for ourselves to the next page, please.

THE CHAIRMAN: Before you go there, the second paragraph in the discussion says that the prevalence increased rapidly with the widespread introduction of Factor VIII and Factor IX. Do you know of any studies at all that dealt with the consequences of use of Cohn Fraction I by the English BPL development or by Scotland?

A. You mean how much of that --

THE CHAIRMAN: Whether there was any study and whether there are any results available. I'm interested because it's quite clear, I think, both from the writings of Dr Biggs and from work that was done in Scotland and reported in 1972, that from about 1956 here in Edinburgh, Cohn Fraction I was being produced and was being used,

involving pooling of material and fractionation according to the standard Cohn method, but I don't think we know anything so far about whether there was any hepatitis developing in the populations who were treated with that material.

A. No, and most of the albumin, of course, was prepared by a Cohn fractionation process, which involved alcohol precipitation of various proteins.

THE CHAIRMAN: The albumin, of course, is the final fraction. It's after a great deal of processing.

A. Yes, but I was going to say, the only thing I know is that the albumin is that final phase and that has never been reported to be causing non-A non-B. But I don't know, you know, what the earlier fractionations, you know, of that alcohol precipitation process, you know, whether they were used to any great extent. I don't know whether there is epidemiological data on the incidence of non-A non-B.

THE CHAIRMAN: I was just wondering if you did know because I don't think we have seen any at all.

MS DUNLOP: Of course, the albumin was pasteurised from a pretty early stage.

A. Yes. The other context -- the other person that might know something about that is Andrew Lever, who, when we were working together at the Royal Free, we described

non-A non-B associated with intravenous immunoglobulin, which was another product of the Cohn fractionation procedure, where people had diverted away from that because the alcohol exposure caused denatured proteins, and that caused the activation of complement, and all sorts of nasty side effects. And that moving away from that Cohn fractionation procedure, for the production of intravenous immunoglobulin, meant it was no longer safe. It was contaminated with non-A non-B, whereas the intramuscular material made by this fractionation process was free of non-A non-B.

THE CHAIRMAN: Following that reasoning, one might think that the first fractionation, which is subjected at that stage to just a straightforward ethanol procedure, with no pasteurisation, no other processes at all, might carry a higher risk, certainly than albumin, but possibly even higher than the immunoglobulins that came after a further process.

A. Yes.

THE CHAIRMAN: I was merely asking if you knew anything about any study that might bear on that.

A. No, I don't. I think the Elstree fractionation people kept detailed records of that and it will be in their documents, I suspect.

THE CHAIRMAN: The production has been published and Dr Cash

and others produced a similar study, a similar report of the volumes produced in Scotland from about 1956 on. It's not the production of it, it's just whether there is any data at all pointing to the infectivity of that material; and you don't know?

A. Not that I have seen.

THE CHAIRMAN: No.

PROFESSOR JAMES: We have looked very hard and not found any.

THE CHAIRMAN: Sorry, it was a diversion, I know, but if we look actually at what's here, the prevalence increased rapidly with the widespread introduction of Factor VIII. It almost provokes the question of what was the prevalence before when one was using what is referred to in England, I think, as "NHS Factor VIII", and in Scotland as -- well, it's not quite clear what it is in the document, but it's clearly Cohn Fraction I.

A. And since it hadn't attracted attention, presumably the incidence of ALT abnormalities, which they would have been doing throughout that period, must have been significantly lower.

THE CHAIRMAN: Or it may just be a question of time; that things hadn't had a chance to develop.

PROFESSOR JAMES: They attributed it to Hepatitis B, once HBV was discovered in the late 60s.

MS DUNLOP: I don't know, sir -- I mean, you obviously have information about this but I'm not sure how many patients with haemophilia were reached by the NHS product at that stage. It hadn't seemed to me that it was produced in anything approaching the same sort of quantity once the concentrate started to be produced, either commercially or by the NHS.

THE CHAIRMAN: Well, there are two sources of information about it and both of which have been referred to already. One is the Cash article, which gives quantities and a graph, and the other is what you have just disparagingly referred to as the proceedings of the Royal Society, which I seem to be interested in but no one else in this room has taken an interest in at all.

MS DUNLOP: It wasn't meant to be disparaging, I was anticipating ...

PROFESSOR JAMES: I think you are the only fellow in the room.

THE CHAIRMAN: I may be the only fellow in this room, but that's not an excuse. I don't know. We may just have to leave it that there is no evidence whatsoever of any adverse consequences of use of the original Scottish product.

MS DUNLOP: I am being referred to footnote 12, which is an

article called "Haemophilia, Hepatitis and HAA". I don't know whether that might be any use. We can certainly look for that. We would be able to recover that. I don't know, would you expect HAA to be Hepatitis A?

A. No.

Q. Because it does say "hepatitis". What do you think HAA might be, or do you not know?

A. Where are you?

Q. I'm looking at footnote 12, which is on the next page. It's an article from 1970 called "Haemophilia, Hepatitis and HAA".

A. I don't know whether that would be referring to -- sorry, I can't help there.

Q. Just at the very bottom of the page.

A. I can't help.

Q. No. We will recover the article and see if it assists in any way. I don't imagine that it relates to Scottish product but it may provide an interesting perspective as at 1970, certainly.

THE CHAIRMAN: Well, the production of the Scottish product is referred to in paragraph 5.36 of the preliminary report under a reference to the Cash and Spencely article. The proceedings of the Royal Society hadn't emerged as a significant feature at that stage.

MS DUNLOP: I did want to look at the end of this article, Professor Thomas. Hepatitis-associated Australia antigen, HAA. It might be worth looking at.

THE CHAIRMAN: The stenographer needs a break.

MS DUNLOP: Yes, indeed. I'm sure we all do.

THE CHAIRMAN: Is that convenient?

MS DUNLOP: It might have been better just to finish the article, actually. That would be neater perhaps.

If we just look at the page where the discussion concludes. Rather an ominous final paragraph. It is being suggested that the final paragraph is correct.

A. And of course, they had the superadded problem of HIV infection, which they were becoming aware of in the 1983/84/85 period.

Q. Yes.

A. Actually, the bottom of that page, you see the paper referred to in the references, Mannucci, Columbo and Rizzetto? They are studying Italian populations, and they were of the view that it was non-progressive as well, up to 1982, and that was based on liver biopsies.

Q. Yes. We have assembled, I think, a chronology, not me, but there has been assembled a chronology of different publications, and certainly that's one that is featured in it. But there does seem to have been, over the period from the mid-1970s, certainly towards the middle

and later 1980s, an ebb and flow between the publications of whether it was a serious problem or a less serious problem. Is that a reasonable, if very crude, summary?

A. Yes. And it is worth, actually, reviewing the paper by Fattovich, where she took, I think, 500 cirrhotic patients, and this is the one where the natural history of Hepatitis C-induced cirrhosis turns out to be relatively benign.

Q. Yes.

PROFESSOR JAMES: That's the liver mortality of 2 to 3 per cent a year?

A. Yes.

MS DUNLOP: That's one of the more reassuring of the publications.

A. Yes.

Q. And obviously to be noted because it's a much larger sample size.

A. It is a large cohort and it's looking at life expectancy rather than a predictive biopsy, which, as we have heard, for a variety of reasons may not be all it's hoped to be.

Q. Yes, right.

I think that's a convenient moment, sir, if you want to pause there.

(3.27 pm)

(Short break)

(3.47 pm)

MS DUNLOP: Professor Thomas, can you just give us the reference for the paper with the 500 samples, roughly -- well, the name of the author.

A. It's Giovanna Fattovich. I think it's published actually in Gastroenterology.

Q. Thank you. We will look for it. Just before we leave this topic of the changing perception, I wanted to ask you about the period 1985 to 1987, which is really plum in the middle of the changing perception period, in a way, I suppose. It's perhaps slightly closer to the end.

During that period, for people who were responsible for treating patients with haemophilia, there were dilemmas. By 1985 in Scotland, a product which had been adequately heated to inactivate HIV was available but there was nothing to suggest that the product was safe against hepatitis, non-A non-B hepatitis.

In England there was a more severely heated product and there was an emerging realisation that that might be safe against non-A non-B hepatitis, but there wasn't enough of it. Do you have any views as to what would have been, I suppose, the right treatment for a person

with haemophilia in that period, who had not previously received concentrate treatment but who needed treatment?

A. I think -- I mean, if it was a mild case of haemophilia, then obviously cryoprecipitate would be a way forward because that, as far as we can see, didn't have a high risk of transmitting non-A non-B hepatitis, and I don't think any cases of transmission of HIV were occurring.

If you are asking, you know, where would you position the 60-degree heated NHS concentrate, which, as you have said, still carried a risk of non-A non-B but not of HIV, I would give that one to the moderate to severe cases because, for the reasons I have said, the natural history of non-A non-B, it is a very slowly progressive disease, whereas HIV was much more feared and it would be considered a very important step forward that that preparation didn't carry the risk of HIV.

Q. Right.

A. I wouldn't have wanted to have used any concentrates that still carried the risk of HIV.

Q. Right. What about the answer to your suggestion of cryoprecipitate that might be given, that cryoprecipitate at this point -- this is 1985 to 1987 -- might still carry a risk of HIV?

A. I think, as far as we knew at that stage, the prevalence of HIV in the general community was very low indeed,

particularly if you were excluding the gay population, where most of the cases were occurring. So if that population were not involved in the sourcing of the plasma for cryoprecipitate, then I would have thought the risk of those cryoprecipitates transmitting HIV would be negligible.

Q. Is it relevant that from the autumn of 1985 -- I think in practice from September 1985 and officially from 14 October 1985 -- donated blood has been screened for HTLV III/HIV.

A. Yes, I had forgotten the precise time when the testing became available. It was in 1983, wasn't it, or that sort of --

Q. It's the autumn of 1985.

A. Yes.

Q. Yes. Is that relevant to the therapeutic choice?

A. If you are saying that the risk of HIV has gone from all the preparations, the commercial, the NHS and the cryoprecipitate, and all we are concerned with now is the likelihood of transmitting non-A non-B, or Hepatitis C, then the inadequately heat inactivated carried some risk of still transmitting non-A non-B, so its advantage over the non-heated material would be dependent on what the frequency of non-A non-B transmission was and I'm not sufficiently conversant

with the data really to comment on that. We know that the non-heat inactivated, we are seeing virtually all individuals becoming infected with non-A non-B/Hepatitis C. I'm not sufficiently aware of the data really to say whether they had a partial effect when they were heating it to 60 degrees, whereas they really needed to heat it to 70 for ten hours, to really get rid of the non-A non-B.

Q. Right.

A. Am I missing the point?

Q. No, I'm just interested in knowing, for the type of patient I'm describing, who is someone who has had no or minimal concentrate before, who presents --

A. What you give them.

Q. What do you give them?

A. I would have given them at the time the partially heat inactivated because it couldn't be any worse than the non-heat inactivated material, where we were seeing virtually 100 per cent infection, whether it was NHS or commercial.

So, with that as the worst scenario, anything that was potentially better than that would be preferably used, whether it was proven to be better or just possibly better. I think ethically that would be the material that you would want to use.

Q. What about that in a competition with cryoprecipitate?
A. Well, I'm not a haemophilia physician but, as far as I understand it, you can't really manage the severe haemophiliacs with cryoprecipitate. The volumes needed are too great. You really need to, in terms of adequate correction of the coagulopathy, use the concentrates. But if it were a mild haemophiliac, your question is would they be better off to have the cryo than the heat inactivated. Then, yes, I think they would be.
Q. Right.
THE CHAIRMAN: I'm not sure how it's going to work out, Ms Dunlop. I'm wondering, listening to it, whether it's perhaps necessary to specify the characteristics of the patient a little bit more, to see just what sort of person we are talking about and what sort of circumstances.

I take it that we can ignore the severe for this purpose at this stage -- or not?
MS DUNLOP: I'm not sure, sir. Certainly an important characteristic of the hypothetical patient is that they are a PUP or similar, a previously untreated patient.
THE CHAIRMAN: And therefore they are not severe normally?
MS DUNLOP: Yes.
THE CHAIRMAN: Right.
MS DUNLOP: The only situation, of course, in which they

might be severe would be a very young child.
THE CHAIRMAN: But there are other factors that then enter into it, aren't there?
MS DUNLOP: Yes.
THE CHAIRMAN: I'm just slightly concerned that it's too general at the moment. But it may be all we can do.
MS DUNLOP: Perhaps if we just go backwards a little bit, I think you have said, Professor Thomas, that in relation to such a person, if their haemophilia was mild, you would have been inclined towards cryoprecipitate. Is that correct?
A. Yes. That's partly from my own limited experience as an observer, if you like. I wasn't involved in the decision process; I was advising the haemophilia unit on how we might investigate the liver disease of these patients, but what I observed was that for the mild cases Dr Kernoff and Dr Lee would preferentially use cryoprecipitate, if it was available, and that was reinforced, if you like, by the paper that you spent some time going through, where we gave six mild haemophiliacs cryoprecipitate and none of them developed ALT abnormalities, suggesting that, because of the limited number of donors involved in the preparation of that material, they weren't getting infected.
Q. Yes.

THE CHAIRMAN: I think I see that but let's just change the hypothesis a little. One has a mild haemophilia patient, who has been treated very little or has always been treat with cryo, and he suddenly is confronted with the need for surgery. Could it be that the need for surgery would change one's perspective on what had to be used?

A. I'm not sufficiently au fait with haemophilia practice really to give you a professional opinion on that.

THE CHAIRMAN: I'm not sure that I really need you to. I just am trying to draw to your attention that perhaps the circumstances need to be rather more particularly defined before you can say very much.

A. Yes. The severity of the trauma, for want of a better word, that the patient is going to be subjected to is going to determine how much you need to correct the coagulopathy. If they are undergoing major brain surgery or liver surgery, for instance, you would have to get very good correction of the coagulopathy.

THE CHAIRMAN: That's what I had in mind. I didn't want the generality to be so wide --

MS DUNLOP: Yes, I appreciate that, sir.

I think the other point that we should just clarify, appreciating that these are to some extent generalities, is the other type of patient, the patient who is a young

child but who has severe haemophilia, so another untreated patient but who is severely affected by haemophilia. I think you said that you are aware, just from contact with haemophilia clinicians, of the difficulty of managing severe haemophilia with cryoprecipitate.

A. Yes, I got that impression, that they much preferred to use concentrates in that setting because of the difficulty of getting the Factor VIII level up to the good haemostasis level.

Q. Yes.

A. Because you get to a fluid overload position if you have you have to put in so large a volume to get it up to the level where haemostasis is occurring normally.

Q. Yes. So all sorts of factors might be relevant, as the chairman says: The presenting problem, which could be a very urgent need for major surgery or it could be a serious bleed; the degree of haemophilia from which the patient is suffering; and, possibly, even the size of the patient, because very small patients, very young patients, can't be overloaded.

THE CHAIRMAN: And not only that, there is the very small vessel into which the product has to be introduced. We have heard about as a factor.

MS DUNLOP: Yes.

A. And I would imagine there are aggregated proteins also in the cryoprecipitate. It's not a totally physiological material and if you get aggregates of proteins, then you get complement activation and all sorts of reactions, and they are greatest when you are infusing the larger amounts.

Q. Yes.

We still have bit of your report to work through, Professor Thomas. Can we go back to [PEN0171071]?

I think it is part of your expectation to return tomorrow, Professor Thomas, is it?

A. Yes, I put aside the time because I was asked to, if you needed it.

Q. I don't know, sir, might it be better to stop and come back tomorrow? I can keep going but I'm aware it has been quite a long day.

THE CHAIRMAN: I shouldn't comment on your capacity to keep going, Ms Dunlop, but I'm sure your judgment is correct. However, we have had a lot of very detailed material and I think it would help us to have a break, if you are able to tolerate that.

A. Yes.

MS DUNLOP: Yes, I would hope that we would still manage to finish by lunchtime and it would also offer all of the people in the front row the opportunity to ask questions

too.

THE CHAIRMAN: I'm sure they can't wait.

Tomorrow morning. I may be just a little late.

(4.03 pm)

(The Inquiry adjourned until 9.30 am the following day)

I N D E X